Clinical Gastroenterology
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Ramona Rajapakse *Editor*

Inflammatory Bowel Disease

Pathogenesis, Diagnosis and Management

Humana Press

Clinical Gastroenterology

Series Editor:

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ISSN 2197-7399 ISSN 2197-7704 (electronic)
Clinical Gastroenterology
ISBN 978-3-030-81779-4 ISBN 978-3-030-81780-0 (eBook)
https://doi.org/10.1007/978-3-030-81780-0

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This Humana imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

In a world where obsolescence is in hot pursuit of the breakthrough, the field of inflammatory bowel disease (IBD) is one of the frontiers. The past couple of decades have seen a rapid expansion in the understanding of IBD. Unraveling of disease pathogenesis and pharmacogenomics is allowing the development of new medications and their nuanced use in a personalized model of medicine for the patient. Although the practice of good medicine has always been part art and part science, we are beginning to better understand the interplay of patient and non-patient related factors and how they affect treatment and prognosis in different patient populations. Along with this, we have seen the demise of the Leviathan textbook, and information is now squeezed into shorter and shorter missives.

In this climate, the objective of this book is to provide a concise, comprehensive update of scientific and clinical knowledge on IBD, to cover standard issues, and also to bring into focus new thinking on the different facets of care. It is intended for medical personnel interested in expanding their knowledge of IBD. Topics covered in this book include an update on the pathogenesis; diagnosis and management of IBD; extraintestinal manifestations (following the dictum of Occam's razor); problems of special populations such as juniors, seniors, and females; updates on screening protocols and endoscopic therapies; infectious complications; alternative therapies; the role of surgery (especially when to consider a re-do pouch); and the cost of care including the concept of an "IBD home" model. The COVID-19 pandemic struck during the writing of this book and has had an indelible impact on the psychosocial, economic, and healthcare status of our society. It is an evolving field, but we include a chapter on what is known currently about IBD and COVID-19. A unique aspect of this book is the account, by a physician, of a personal journey with IBD in the setting of limited access to subspecialist care. Her reliance on virtual healthcare, before its current popularity, provides insight into the travails faced by patients such as herself that we, as caregivers, are rarely privy to.

I am grateful to the authors, experts in their field, who have struck a balance between remaining concise and yet providing highly relevant accounts of the latest thinking and concepts in IBD. The referenced texts, together with abstracts and keywords, allow the reader to easily access material for further reading. It is hoped

that this book will be a useful addition to a medical library and act as a stepping-stone for the reader in search of information about this complex disorder.

A special note of thanks to my colleague Dr. David Schwartzberg for his support in this endeavor, and to my family who patiently gave up their time with me, so that I could work on this project.

Port Jefferson, NY, USA Ramona Rajapakse

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Chapter 1
Advances in Our Understanding of the Pathogenesis of Inflammatory Bowel Disease

Catiele Antunes, Karolina Dziadkowiec, and Aline Charabaty

Introduction

What causes an individual to develop an inflammatory bowel disease (IBD)? The answer to this simple question has puzzled researchers and clinicians for many years. According to the evidence available so far, the answer is complex and the etiology multifactorial, with several genetic, immunologic, and environmental factors affecting each other and promoting the development of IBD in an individual (Fig. 1.1). It has been established that both Crohn's disease (CD) and ulcerative colitis (UC) are immunologically mediated chronic inflammatory diseases that develop in genetically susceptible individuals as a consequence of the complex and multidirectional interactions between genetics, environmental triggers, the gut immune system, and gut microbiota.

Historically, IBD was thought to be a disease predominantly affecting North American and European populations, Caucasians, and individuals of Ashkenazi Jewish descent, putting a focus on genetics as the main driver of the disease. In the last half of this century, the incidence of IBD has increased in the Westernized world, including in African-American and Hispanic minorities possibly explained by improved diagnosis but also likely driven by changes in environmental factors [1,

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R. Rajapakse (ed.), *Inflammatory Bowel Disease*, Clinical Gastroenterology,
https://doi.org/10.1007/978-3-030-81780-0_1

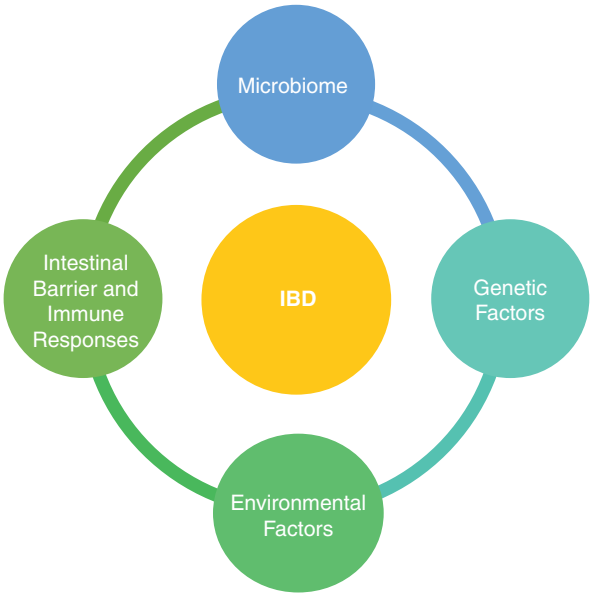

Fig. 1.1 *Complex relationships in the pathogenesis of IBD*. Genetics, gut microbiome, intestinal immune response and intestinal barrier, and environmental factors play a role in the pathogenesis of IBD

2]. At the other end of the spectrum, areas of the world traditionally known to have a low prevalence of IBD (such as China, India, and the Middle East) have also seen an increased incidence of IBD over recent years. Finally, in first-generation immigrants from areas with low incidence of IBD to the United States, the incidence of IBD has increased to reach that of the new country [3]. Dietary changes, with increased consumption of a Western diet (low in fiber, rich in processed foods, saturated fat and added sugar), environmental influences such as pollution, stress, decreased physical activity, urban living, antibiotic exposure, and increased hygiene are all potential factors that could explain this change in IBD epidemiology. Most recently, a great deal of attention is being given to the role of the gut microbiome and the concept of dysbiosis, i.e., a microbial imbalance in diversity and functionality leading to maladaptive interactions between the gut microbiome and the intestinal immune system.

In this chapter, we will explore the knowns and unknowns of the etiology and pathophysiology of IBD, exploring the mechanisms behind known associations and the understanding of modifiable risk factors. We will describe the role of genetics, microbiome, and pharmacological agents and also explore the role of environmental and lifestyle factors that are now emerging as key drivers of inflammation.

Genetic Factors

The role of genetic predisposition in developing IBD was highlighted with studies examining the higher prevalence of IBD within ethnic and family groups. Between 2 and 14% of patients with CD and 7 to 11% of patients with UC report a family

history of the same disease [4]. The risk of developing IBD is estimated to be up to tenfold higher in those with a first-degree relative with an IBD diagnosis compared to those in unaffected families [5]. The risk to an individual is highest when both parents have IBD, reaching 33% by age 30 [6]. The risk for first-degree relatives is further increased in individuals of Jewish heritage. While the relative risk of developing IBD for a non-Jewish first-degree relative is around 5% for CD and 2% for UC, the relative risk rises to 8% and 5.2%, respectively, for a family member of Jewish heritage.

Studies in twins, albeit few in number, have also been important in understanding the relative contribution of inherited and environmental factors in the etiology of IBD. In short, if a disease is entirely due to genes, then its concordance in identical (monozygotic) twins should approach 100%, and in non-identical (dizygotic) twins, it should approach 50%. On the other hand, if the disease is dependent on extrinsic and acquired factors, its concordance should be similar in both dizygotic and monozygotic twins. Interestingly, large European studies have identified a concordance rate for CD in monozygotic twins between 20 and 55%, while that number dropped to less than 10% in dizygotic twins brought up in the same environment (Table 1.1). A high concordance rate for the presence of extraintestinal manifestations and for the extent of colon involvement in CD and UC has been demonstrated in twin studies as well [7]. One of these studies, with over 38,000 identified twins in Denmark, showed a concordance rate among monozygotic pairs of 58.3% for Crohn's disease but only 18.2% for ulcerative colitis. Among the dizygotic pairs, the numbers dropped to zero and 4.5%, respectively [8]. Collectively, all this family data suggests a stronger genetic influence for CD than for UC.

Over the last few decades, significant advances in the understanding of genetic contributions to IBD have been made. Thanks to advances in genetic testing and genome-wide association studies (GWAS), multiple single-nucleotide polymorphisms (SNPs) have been identified. Up to now, more than 200 IBD susceptibility loci have been identified, but this number is likely to keep rising [14]. Approximately 30% of all IBD-related loci identified so far are shared between CD and UC, suggesting that these diseases engage some common pathways [15]. Many IBD loci are also implicated in other immune-mediated diseases such as ankylosing spondylitis and psoriasis [15, 16]. Most of the genes and genetic loci identified so far are involved in intestinal homeostasis, including barrier function, epithelial turnover,

Table 1.1 Concordance rates for Crohn's disease (CD) and ulcerative colitis (UC) according to international twin studies

	Monozygotic twins		Dizygotic twins	
	CD	UC	CD	UC
Thompson (England, 1996) [9]	20% ($n = 25$)	16% ($n = 38$)	7% ($n = 46$)	3% ($n = 34$)
Halfvarson (Sweden, 2003) [10]	50% ($n = 18$)	19% ($n = 16$)	4% ($n = 26$)	0% ($n = 20$)
Orholm (Denmark, 2000) [8]	50% ($n = 10$)	14% ($n = 21$)	0% ($n = 27$)	5% ($n = 44$)
Jess (Denmark, 2005) [11]	55% ($n = 9$)	14% ($n = 21$)	4% ($n = 28$)	5% ($n = 44$)
Spehlmann (Germany, 2008) [12]	35% ($n = 31$)	16% ($n = 37$)	3% ($n = 58$)	2% ($n = 63$)
Halfvarson (Sweden, 2010) [13]	27% ($n = 33$)	14% ($n = 41$)	2% ($n = 50$)	6% ($n = 49$)

microbial defense, autophagy, adaptive immunity, and metabolic pathways associated with cellular homeostasis [15].

NOD2 (nucleotide-binding oligomerization domain containing 2), located on chromosome 16, was the first susceptibility gene identified for CD, approximately 20 years ago [17–19]. NOD2 belongs to the family of intracellular NOD-like receptors and is involved in autophagy, bacterial replication control, and antigen presentation. NOD2 mutations have been associated with several inflammatory diseases suggesting that balanced NOD2 signaling is essential for the maintenance of immune homeostasis [20]. The association of NOD2 with CD has been replicated in many studies, but the exact role of NOD2 variants has not yet been fully elucidated [21, 22]. Three main NOD2 polymorphisms have been identified and linked to susceptibility to CD: R702W (Arg702Trp) on exon 4, G908R (Gly908Arg) on exon 8, and Leu1007fsX1008 on exon 11. The first two are single amino acid changes or missense mutations; the latter is caused by a deletion causing a reading frameshift that ultimately leads to a loss of 33 amino acids [20]. In patients with CD, NOD2 is strongly associated with disease location (ileocolonic > colonic, ileal > colonic), early age at diagnosis, stricturing, and non-perianal fistulizing behavior [23, 24]. The frequency of mutant NOD2 haplotypes is 2.1-fold higher in ileum-specific disease than that restricted to the colon and 1.6-fold higher in ileocolonic disease [25]. CD patients with two NOD2 mutations have 10.1 times the odds of having ileal disease than those with one mutation or wild-type alleles [24]. Interestingly, though sequence variations within the NOD2 gene are strongly associated with CD, that is not the case for UC, reinforcing the notion that these two diseases have distinct pathogenetic pathways leading to chronic inflammation of the bowel.

GWAS have also implicated interleukin receptors and their signaling components including STAT3, JAK2, and IL10 itself [15]. The transcription factor STAT3 and kinase protein JAK2 also function in other contexts, including signaling of IL-6, IL-22, and IL-23. These genetic studies have led to a better understanding of disease pathways and, therefore, to the development of IBD therapies.

Over 130 loci have been identified via GWAS with association to risk for UC [26]. An important association identified so far is with the major histocompatibility complex (MHC) genes, particularly HLA class II genes DRB1*0103 and DRB1*15 [27, 28]. DRB1*0103 is found in 8–10% of UC patients but only in 2–3% of controls and has a strong association with extensive UC disease and with the need for colectomy. There are a few loci containing genes such as IL2, CARD9, and REL that are shared between UC and primary sclerosing cholangitis (PSC) [29, 30]. This overlap may help to identify UC patients at risk for PSC and advance research for new therapies.

We have presented here a brief summary of what is known thus far in terms of IBD genetics. This field is constantly evolving and a comprehensive review of all genes and loci involved is beyond the scope of this chapter. Although there is strong evidence that genetics plays an important role in the genesis of IBD, it is estimated that the variants identified so far only explain up to 20–25% of all IBD cases [15, 22]. This indicates that genetics alone cannot explain IBD pathogenesis. In addition, some of these variants may be present in healthy individuals, further reinforcing that epigenetics and nongenetic factors, including environmental factors, play an essential role.

Gut Microbiome

There is growing evidence that the gut microbiome plays a significant role in the overall health of humans and in intestinal and non-intestinal disease process. The gut microbiome is part of an ecosystem that is involved in many aspects of host health including digestion of food, maintenance of intestinal barrier integrity, and protection against pathogens. Therefore, it seems reasonable that disruptions of the gut microbiome would have significant effects on the gut immune system and could lead to dysregulation of the gut immune response.

The gut microbiome plays a crucial role in the development of the host's immune system. The gut microbiota induces accumulation of several different lymphocyte populations at the mucosal site and particularly modulate regulatory T cells (Tregs) and T helper (Th) cells [31, 32]. Germ-free mice (deficient in gut microbiota) have impaired immune development, with immature lymphoid tissue, decreased numbers of intestinal lymphocytes, and low levels of antimicrobial peptides. Because of a deficient mucosal immune system, germ-free mice are more susceptible to infection by intestinal pathogens compared to wild-type mice. Interestingly, once the germ-free mice microbiota is reconstituted, those immune abnormalities are reversed [33]. Additionally, gut microbiota also seems to modulate inflammatory status. A study using a mouse model of colitis showed that daily administration of probiotics containing bifidobacteria and lactobacilli modulated inflammatory status, likely by induction of Tregs cells [34]. Another study using *E. coli* DNA and the probiotic VSL#3 given by the intragastric or subcutaneous route was able to inhibit dextran sodium sulfate (DSS)-induced colitis in normal mice but not in mice lacking Toll-like receptor 9, a class of proteins that plays a role in the innate immune system [35]. These studies further reinforce the role of the gut microbiome on the maintenance of a balanced gut environment and immune responses.

IBD patients' microbiome is characterized by a depletion of anti-inflammatory microbiota and an overabundance of pro-inflammatory microbiota (Fig. 1.2). IBD patients also have a marked reduction in gut microbiota diversity. These differences are more pronounced in CD patients, while UC patients' microbiota resembles more that of a healthy individual [36]. Overall, there is a higher presence of Enterobacteriaceae (such as *E. coli*), *Fusobacterium*, and *Ruminococcus gnavus* and a decline in *Clostridium* groups, *Bacteroides*, *Bifidobacterium*, and *Faecalibacterium prausnitzii* [33, 37, 38]. *F. prausnitzii*, among others, has been reported to have anti-inflammatory properties due to the production of butyrate. Short-chain fatty acids (SCFAs), such as butyrate, are metabolic end products of carbohydrate fermentation by the gut microbiome and have an important role in the modulation of host immune response. The decreased production of SCFAs affects the differentiation and expansion of Tregs cells and affects the growth of epithelial cells, which is important in maintaining intestinal homeostasis. Also, *Desulfovibrio*, a sulfate-reducing bacterium, is seen at higher levels in UC patients. It results in increased production of hydrogen sulfate that leads to intestinal epithelial damage and induces mucosal inflammation.

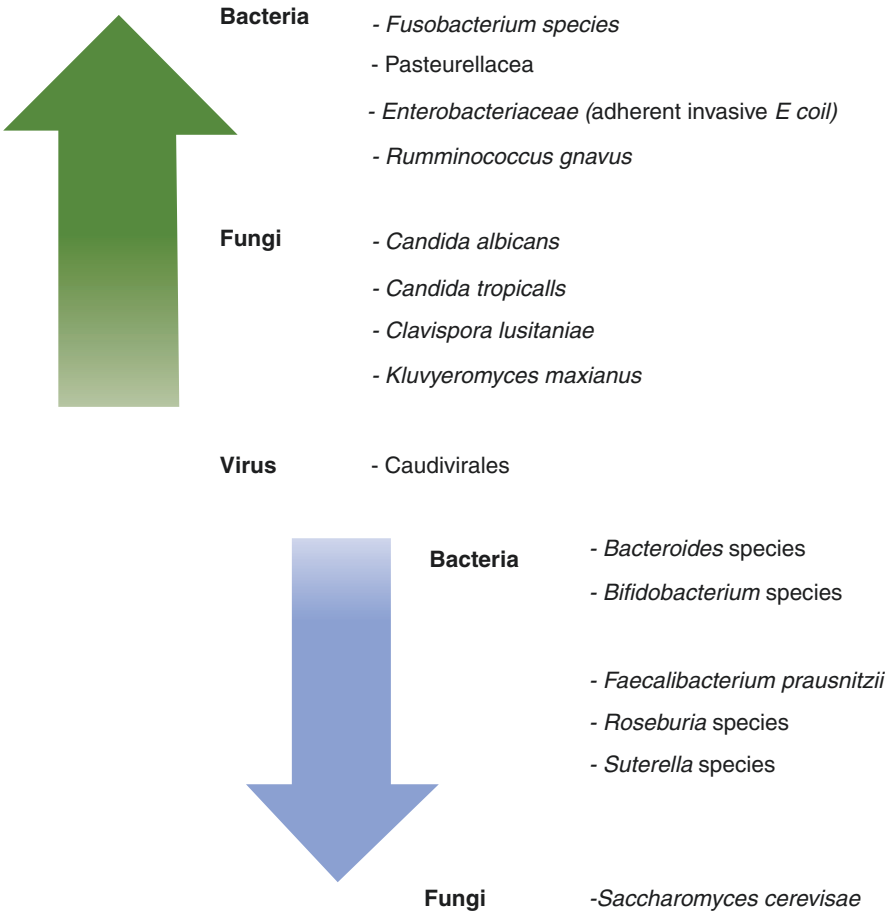

Fig. 1.2 *Microbiota changes associated with IBD*. The microbial composition in patients with IBD is altered compared with that in healthy control subjects. Specific changes have been identified in the abundance of various bacteria, fungi, and viruses. Above, green and blue arrows show some of the gut organisms that have been established to be increased or decreased in IBD patients. Many butyrate-producing bacteria are markedly decreased in IBD, including *Faecalibacterium prausnitzii*, a known beneficial bacterium with anti-inflammatory properties

The imbalance in the gut microbiome in IBD patients also extends to fungi and viruses. Fungal microbiome corresponds to only 0.02% to 0.003% of the fecal microbiome but is also altered in IBD patients, with a lower presence of *Saccharomyces cerevisiae* and a higher presence of *Candida albicans*, *Candida tropicalis*, *Clavispora lusitaniae*, and *Kluyveromyces marxianus* [39]. The richness and diversity of the mucosal fungal community is positively associated with expression of TNF-α and IFN-γ and negatively associated with IL-10 levels. Interestingly, fungal diversity is also higher in areas of active inflammation [40]. The idea that fungi could be involved in the pathogenesis of IBD is plausible as many of the genes involved in antifungal responses are also IBD susceptibility genes (such as CARD9 and RElA).

As described here, dysbiosis has been documented in IBD patients. However, strong evidence for the existence of specific pathobionts, i.e., commensal microorganisms that, under specific environmental and genetic influences, cause IBD, is lacking [41]. Some agents have been investigated: adherent-invasive *E. coli* (AIEC) as the cause of ileal mucosal disease, *Mycobacterium avium* subsp. *paratuberculosis* for its ability to cause granulomatous enteritis in sheep and cattle, and *Fusobacterium nucleatum*, after highly invasive strains were isolated from UC patients [36, 41]. All of these studies have described associations, but none of them were able to prove causation. In IBD models of intestinal inflammation, the role of the microbiota ranges from protective to causative. Caution, however, is needed when interpreting these data as animal studies have several limitations. The question of whether dysbiosis precedes inflammation or reflects an altered immune and metabolic environment is still waiting to be answered.

Lifestyle

Diet

Most of the epidemiological studies of diet in IBD have focused on macronutrients. Despite some heterogeneity, fiber has been the most consistent negative association. Pediatric patients newly diagnosed with Crohn's disease had a markedly lower intake of fruits and vegetable on dietary logs from the year prior to diagnosis when compared to healthy controls [42]. Another important study highlighting the potential impact of diet in IBD comes from the Nurses' Health Study (NHS), a prospective study that began in 1976 and enrolled 122,701 female nurses who were asked to complete dietary questionnaires every 4 years [43]. This study showed an association between high consumption of fiber, particularly vegetables and fruits, and a low risk of developing CD [38]. On the other hand, high intake of red meat was associated with an increased risk of UC [38]. A large prospective cohort study from France (67,581 participants and 705,445 person-years) investigated the correlation of protein intake and development of CD and found that a high animal protein consumption was associated with a high risk of developing CD (HR, 3.03; 95% CI, 1.45–6.34) [44]. The effect of animal protein on disease activity has also been demonstrated in animal studies, where red meat intake exacerbated colitis in DSS mice. Mice on a red meat diet had consistently high histopathological scores, higher disease activity, and mortality [45]. The evidence so far suggests that dietary hemoglobin from red meat consumption can form reactive oxygen species ultimately leading to damage to the colonic epithelium. Most recently, a systematic review and meta-analysis of nine studies tried to assess the role of the Western diet – characterized by high consumption of processed grains, red meat, animal protein and, low consumption of vegetables and fruits – in the development of IBD. The results showed that a western dietary pattern was associated with a relative risk (RR) for IBD of 1.92

(95% CI, 1.37–2.68). The effects were higher for UC with an RR of 2.65 (95% CI, 1.61–4.36) [46]. In animal models, mice on a Western diet were more susceptible to DSS-induced colitis and had increased inflammation compared to mice on a control diet [47].

Interestingly, some beverages can also affect the risk of IBD. In a meta-analysis including studies done in Asian populations, consumption of tea seems to be protective against UC (RR, 0.69; 95% CI, 0.58–0.83) [48]. Even though a complete biological explanation for this effect is still under investigation, studies in mice have shown that polyphenols present in green tea have anti-inflammatory properties [49]. On the other hand, the consumption of soft drinks was associated with an increased risk of UC (RR, 1.69; 95% CI, 1.24–2.30) [48, 50]. More studies still have to be done to clarify these associations.

It is likely that the effect of diet on the pathogenesis of IBD is due, at least partially, to changes on gut microbiome. Even acute changes in diet, for example, from a primarily animal-based to a plant-based diet, can alter the gut microbiome within 24 h [51, 52]. Studies have reported that subjects on an animal-based diet had increased levels of bile-tolerant microorganisms such as *Bacteroides* and decreased levels of Firmicutes that metabolize plant polysaccharides. Wu et al. demonstrated that when healthy volunteers were challenged with a high-fat, low-fiber diet, a noticeable change in the bacterial environment occurred within 24 h and persisted over the 10 days of the study [52]. Clearly, diet can strongly and quickly affect the gut microbiome composition (Fig. 1.3).

Over the past few years, several dietary interventions have been evaluated as therapeutic options for patients with IBD. Enteral nutrition with an elemental diet (ED) and semi-elemental or polymeric diets have been used as a first-line therapy to induce steroid-free remission in CD, mainly in children, and have been associated with clinical and mucosal healing [41]. The leading hypothesis behind the effects of these diets is that by altering the number of luminal antigens, the gut microbiome and its metabolome are also altered [53, 54]. Diets not only affect the gut microbiome composition but also serve as a substrate for microbial synthesis of metabolites and consequently have a significant impact on mucosal integrity and immune function.

Smoking

Multiple studies have investigated the role of environmental factors and the risk of IBD [50, 55]. Cigarette smoking has been consistently linked to an increased risk of CD, with first reports dating back to the 1980s [50]. A recent meta-analysis established the risk of IBD in current smokers compared to never smokers: there are an elevated risk for CD (OR, 1.76; 95% CI, 1.4–2.22) and a decreased risk for UC (OR,

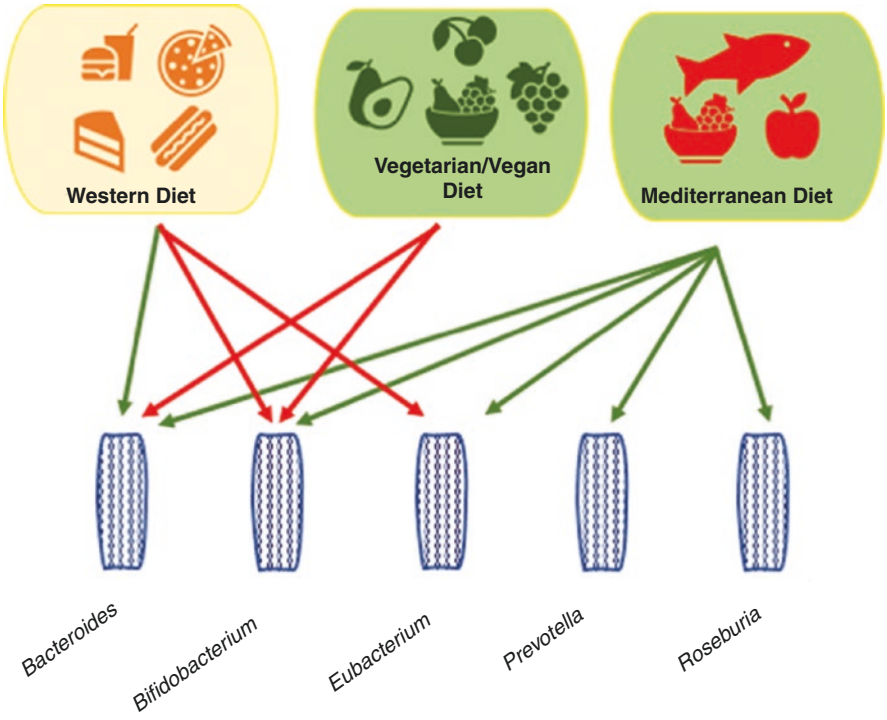

Fig. 1.3 *Diet effects in the microbiome.* Different diets seem to have different effects in specific components of the microbiome. Green arrows demonstrate a positive relationship (increased levels), while red arrows demonstrate a negative relationship (decreased levels). Much is still unknown about the significance of these effects

0.58; 95% CI, 0.45–0.75) [50]. The effect seems to be dose dependent and also strongly modified by genetic factors and ethnicity, with most of the associations being observed in non-Jewish White individuals. The underlying mechanisms seem to be related to the effects of smoking on the innate and adaptive immune responses, including cell apoptosis, chemokine expression, and T-cell recruitment [55]. Smoking also decreases microbiome bacterial diversity, with a predominance of *Bacteroides-Prevotella* (38.8% vs. 28.3% in non-smokers) and a reduced presence of *Faecalibacterium prausnitzii*.

Smoking has been linked to histological changes in the intestines of patients with established disease. CD patients who smoke have an increased number of lymphocytes and increased levels of pro-inflammatory cytokines such as TNF-α, IFN-γ, and TGF-β [55]. Among patients with CD, those who smoke have more clinical relapses, higher surgery rates, and poorer response to treatment compared to those who do not smoke [56].

Physical and Emotional Stress and Mental Health

There is increasing evidence that stress, lack of sleep, and physical inactivity adversely affect the gut microbiome and the gut-brain axis by altering intestinal mucosal permeability and cytokine secretion [57, 58]. Stress, anxiety, and depression can induce low-grade chronic inflammation in the gut. The vagus nerve is thought to have anti-inflammatory effects. Stress decreases vagus nerve efferent outflow and increases sympathetic tone, ultimately inhibiting immune cell function and leading to intestinal inflammation. In rats, stress has been shown to increase intestinal permeability, allowing bacteria to cross the epithelial barrier and activate mucosal immune responses. In humans, depression correlates with elevated levels of TNF-α and CRP [58]. Patients with IBD have a two- to threefold higher rate of depression and anxiety than the general population, and these conditions frequently precede the diagnosis of IBD [58]. In 79% of IBD patients with mood disorders, the first episode of depression occurred more than 2 years before the onset of IBD [59]. In a Danish nationwide cohort study, use of anti-depressants after a diagnosis of IBD was associated with a lower incidence of disease activity [60].

Environmental Factors

Pollution

Air pollution-mediated inflammation has been implicated as the cause of a number of disease processes. It is believed that the pro-inflammatory cascade related to pollution may be associated with the development of IBD and other similar diseases [61]. The incidence of IBD in westernized or industrialized countries has increased over the last century, mainly in urban areas, and now we are witnessing rapid disease emergence in newly industrialized countries and in developing countries, where IBD was previously uncommon [1, 62].

The mechanisms by which air pollution may influence the development of IBD are mostly hypothetical. The leading hypotheses suggest that the adverse health effects associated with exposure to air pollution, either through inhalation or ingestion, may incite an inflammatory process that is believed to be in part related to the pathogenesis of IBD [61]. A recent study has demonstrated that young adults and children are at an increased risk of developing IBD if they lived in regions with higher concentrations of pollutants (OR, 2.31; 95% CI, 1.25–4.28); when all age groups were combined, air pollution did not increase the risk of IBD [63]. Thus, further studies are needed to explore this association and examine gene-pollutant interactions.

Low Vitamin D

Some studies show an increased incidence of IBD with increasing latitude, suggesting that decreased sun exposure and subsequently decreased vitamin D production are a risk factor for IBD. Vitamin D plays an integral role not only in electrolyte homeostasis and bone health but also in immune function and reduction of inflammation. As a result, the deficiency of this essential vitamin has been associated with inflammatory diseases, including IBD, through an impairment of mucosal immunity and integrity in the gut [64]. In 2010, the Institute of Medicine (IOM) defined vitamin D deficiency as a serum concentration of 25-hydroxyvitamin D less than 20 ng/mL (50 nmol/L) [65]. The prevalence of vitamin D deficiency in the general population is reported to be between 30% and 47% [66–68]. Patients with IBD appear to be especially at risk of developing vitamin D deficiency as a result of impaired nutrient absorption in the gastrointestinal tract, restricted dietary intake, and, in some instances, medical advice to avoid sunlight exposure when taking certain immunosuppressive therapies [69].

In addition, recent studies have suggested a strong correlation between vitamin D deficiency and more pronounced disease activity [70–73]. Vitamin D deficiency has also been implicated in the development of colorectal cancer in those suffering from IBD [74]. In a large study by Ananthakrishan et al. that included 2809 IBD patients, deficiency of vitamin D was associated with an increased risk of cancer (OR, 1.82; 95% CI, 1.25–2.65), and increased levels were associated with reduction in colon cancer [74]. Further research on the effects of vitamin D deficiency and its role in IBD and colorectal cancer is warranted.

Hygiene Hypothesis

The hygiene hypothesis and its relationship with allergic and autoimmune disease were first introduced in 1989 [75]. This hypothesis was developed as a potential cause for the development of IBD after observations were made of an increased incidence of IBD coinciding with improvements in physical hygiene in the last century [76]. The improvements in hygiene are not limited to access to clean water, advanced filtering sewage systems, and improvements in waste disposal but also include less crowded housing [77]. The basis of the hygiene hypothesis lies in the postulation that a person may be overprotected from exposure to common antigens in the environment owing to improved hygiene and, when exposed later in life, an inappropriate and exaggerated immunologic response may occur leading to inflammation. Exposures to common antigens are thought to be necessary for keeping the immune system of the gut “in check” and establishing an immunological balance between pro-inflammatory cells and their response to microbes and other antigenic

stimuli [78]. A recent meta-analysis found varying levels of evidence to support factors associated with increased risk of IBD, including urban living among others [49]. Although evidence supporting the hygiene hypothesis appears possible, the quality and strength of the evidence vary; carefully designed prospective studies are needed to evaluate the plausibility of these findings.

Pharmacological Agents

NSAIDs

Many patients with IBD suffer from extraintestinal manifestations such as arthritis and seek pain relief using non-steroidal anti-inflammatory drugs (NSAIDs). Although effective for pain control, NSAIDs are not without risk. With prolonged use, there is serious concern for the development of gastrointestinal injury, including mucosal damage in the form of erosions, ulcers, bleeding, mucosal scarring with stricture formation, and rarely perforation [78]. The mechanisms responsible for NSAID-induced gastrointestinal toxicity include increased mucosal permeability, increased enterohepatic drug circulation, and depletion of intracellular adenosine triphosphate (ATP) [79].

Several studies have suggested an association between NSAID use and the onset or exacerbation of IBD [80–83]. A recent study evaluated clinical signs and objective measurements of fecal calprotectin in patients with IBD and demonstrated that NSAIDs were associated with a 17–28% relapse rate within approximately 9 days of administration [84]. Several other studies have shown that NSAIDs are associated with an increased risk of new onset of IBD and were associated with an overall increase disease activity [85–87]. NSAID use in patients with IBD warrants significant consideration and careful monitoring due to the potentially increased risk of gastrointestinal toxicity and risk of IBD exacerbation in certain patient populations. However, it remains unclear as to whether NSAIDs are indeed directly implicated in causing flares or new onset IBD.

Antibiotics

The relationship between IBD and antibiotics is complex and paradoxical. Antibiotics can modulate gut inflammation by altering the gut microflora via several mechanisms: decreasing bacterial concentrations and allowing more favorable bacteria to flourish, decreasing bacterial translocation and reducing bacterial enzyme activity [88–91]. A meta-analysis published in 2011 found antibiotics to be superior to placebo in the induction of remission of active Crohn's disease (RR, 0.85; 95%

CI, 0.73–0.99) [92]. A meta-analysis from 2012 included patients with CD that were treated with broad-spectrum antibiotics and noted clinical improvement in 56.1% of patients in the antibiotic group vs. 37.9% of patients in the placebo group (OR, 1.35; 95% CI, 1.16–1.58) [93].

Current American College of Gastroenterology (ACG) guidelines for the treatment of UC and CD do not include antibiotics as a part of a routine treatment protocol, unless there is concern for infection or abscess [94, 95]. In patients with CD, there is some evidence for antibiotics (metronidazole and ornidazole) reducing incidence of endoscopic recurrence after surgery when compared to placebo-treated patients [95].

Conversely, antibiotic use has been implicated as a risk factor for developing CD. Several observational studies have found an association with the use of antibiotics in childhood or adulthood and a subsequent increased risk of developing CD. A meta-analysis of 11 observational studies demonstrated a pooled odds ratio of 1.74 (95% CI, 1.35–2.23) for the development of CD in patients exposed to antibiotics [96]. In addition, the risk of developing IBD following antibiotic exposure seems to be cumulative, increasing with the number of antibiotics used [97]. An association between antibiotic use and risk of developing UC was not noted.

Whether it is the antibiotics themselves that trigger the development of CD (likely by affecting the gut microbiome) or the infections for which the antibiotics were prescribed that lead to an immune dysfunction, or even the presence of an underlying immune system dysfunction that promotes a shared susceptibility to infection and IBD, the exact association is still unknown and remains to be elucidated.

Oral Contraceptives

In 1984, a study showed that the prevalence of oral contraceptive use was significantly higher among patients with colonic CD compared to those with ileal CD and UC [98]. A meta-analysis published in 2008 showed that current use of oral contraceptives was associated with a nearly 50% increase in the risk of CD compared to no use (RR, 1.46; 95% CI, 1.26–1.70), but although there appeared to be an increased risk, this was no longer statistically significant after adjusting for smoking [99]. Finally, a large study including 232,452 women without IBD enrolled in the Nurses' Health Study I (NHS I) and II (NHS II) evaluated current use of oral contraceptives and demonstrated an increased risk of CD (HR = 2.82, 95% CI, 1.65–4.82) but not UC (HR = 1.22, 95% CI, 0.74–2.07) [100]. Therefore, the association, despite not being consistent across all studies, seems to be stronger for the development of CD.

The precise mechanism by which oral contraceptives may increase the risk of IBD is unknown. Some experimental data suggests that estrogen may modulate the immune system and affect intestinal barrier functions [101, 102].

Vaccines

Several studies have evaluated a potential link between vaccines and IBD. In the mid-1990s, few studies suggested a possible link between MMR vaccination and an increased risk of IBD, especially CD [103–105]. However, those findings were later refuted as subsequent studies did not confirm those findings [106–108]. A potential association between poliomyelitis vaccine and IBD was also reported in small studies; however, the heterogeneities between these studies, their small size, and the unaccounted confounders dramatically limit the interpretation of their results [108]. It is important to remember that timeline association does not equal causation, and vaccines prevent infectious diseases that can otherwise lead to irreversible life-altering and life-threatening complications. Finally, there is no evidence that vaccines lead to a change in disease course or trigger an IBD flare. Subsequently, gastroenterological society guidelines recommend age-appropriate vaccination in all IBD patients, with the exception of live virus vaccines in patients on immunosuppressive drugs.

Surgeries

Appendectomy

Multiple studies have investigated the relationship between prior appendectomy and the development of IBD. Many studies have shown an inverse relationship between prior appendectomy and the development of UC [109, 110]. Conversely, a review of meta-analysis showed increased risk for CD following appendectomy [50]. Researchers have investigated whether appendectomy affects the natural course of patients with IBD, but the evidence so far suggests that it does not [111, 112]. Currently, there is no evidence to support prophylactic appendectomy to prevent IBD or alter the course of the disease.

Tonsillectomy

Tonsillectomy remains a poorly established risk factor for the development of IBD. A recent meta-analysis involving nearly 20,000 patients suggests that there may be a correlation between tonsillectomy and an increased risk for developing CD (OR, 1.37; 95% CI, 1.16–1.62) [113]. This study did not find an increased risk for the development of UC after adjusting for confounding factors. Further prospective studies are required to confirm the validity of these findings.

Early Life Events

Cesarean Delivery

Cesarean delivery may be a risk factor for the development of IBD, potentially by disturbing the normal bacterial colonization of a newborn's intestine that occurs with vaginal delivery. In 2012, a study using the Danish National Patient Registry found that rates of childhood-onset IBD were increased in those delivered by cesarean delivery compared to those delivered vaginally, but the effect was very small [114]. A meta-analysis published in 2014 supports the hypothesis that cesarean delivery is associated with an increased risk of CD but not UC [115].

Breastfeeding

Breastfeeding has been described as having protective effects against CD. In a recent meta-analysis, being ever breastfed was associated with a lower risk of CD (OR, 0.71; 95% CI, 0.59–0.85) and UC (OR, 0.78; 95% CI, 0.67–0.91) [50]. The longer the duration of breastfeeding, the higher the benefit. The ORs for CD associated with breastfeeding for 3, 6, and 12 months was 0.62 (95% CI, 0.39–0.97), 0.56 (95% CI, 0.31–0.69), and 0.20 (95% CI, 0.08–0.50), respectively [116].

The effect seems to be greater in Asians compared to Caucasian populations, suggesting that an interplay with genetic factors and ethnicity may occur [50, 116]. Lack of breastfeeding has been associated with colonization with *Clostridium difficile* and immune-mediated diseases, suggesting that the protective effect of lactation may be related to improved mucosal immunity through microbiome interaction [50] (Table 1.2).

In the above table, factors reported in the literature that are associated with an increased or decreased risk of IBD are summarized. Of note, the strength of the epidemiological evidence for each factor listed above is not being assessed for the purpose of this chapter. Please review individual references for further information.

Table 1.2 Risk factors and protective factors for CD and UC

	Crohn's disease	Ulcerative colitis
Risk factors	Smoking [50], urban living [50], tonsillectomy [50, 113], cesarean birth [115], oral contraceptive (OCP) use [100]	Soft drinks [48, 50], urban living [50], OCP use [100], meat consumption [46]
Protective factors	Physical activity [50], *H. pylori* infection [50], breastfeeding [116], fiber and fruit consumption [38]	Tea consumption [48], *H. pylori* infection [50], smoking [50], breastfeeding [116], appendectomy [105, 109], fruit and vegetable consumption [38]

Summary

It is our current understanding that IBD pathogenesis involves complex and multidirectional interactions of several immunological, microbiota, and environmental factors, leading to a chronic inflammatory disease of the gut in a genetically susceptible individual. In this chapter, we reviewed the factors that are potentially involved in the pathogenesis of IBD as described in the literature. The interplay between the gut microbiome and the environment in modulating the gut immune response is the center of current research. It can shed light on how to prevent IBD in susceptible individuals or on how to change the natural history of IBD by implementing interventions on modifiable risk factors.

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Chapter 2
Diagnosis and Monitoring in Inflammatory Bowel Disease: Who, When, Where, and How

Anthony Passarella, Prabhsharn Grewal, and Raluca Vrabie

Pathogenesis

As there is no universal test for IBD, there is also not a known universal causative agent. Genetics, the environment, and the microbiome populating the digestive system seem to interact in such as a way as to bring forth this disease state.

Genetics

Genes tell only part of the IBD pathogenesis story. Monozygotic twins have a 20–50% concordance for Crohn's and 14–19% for ulcerative colitis [6], indicating that genes are not solely accountable for IBD. The relative risk of developing IBD for first-degree relatives of a patient with Crohn's disease is estimated to be around 5% in non-Jewish and 8% in Jewish patients, with the corresponding risk for ulcerative colitis being 1.6% and 5.2%, respectively [7].

Two hundred independent genetic risk loci have been associated with IBD since the onset of genome-wide association studies in the early 2000s, but none of them account for the majority of IBD cases. The genetic risk loci for IBD identified thus far only explain approximately 13% of CD and 7.5–9% of UC cases. The majority

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R. Rajapakse (ed.), *Inflammatory Bowel Disease*, Clinical Gastroenterology,
https://doi.org/10.1007/978-3-030-81780-0_2

of these genetic loci have been discovered using the Immunochip project, which is a chip aggregating all the known loci related to immune diseases, in a largely European cohort. New loci were added when this project was expanded to include Asians, a population that we subsequently learned has a completely different set of loci associated with autoimmunity [8].

The earliest gene associated with IBD was NOD2, which is located on chromosome 16. Mutations in the NOD2 gene cause reductions in alpha defensins and Toll-like receptor overstimulation, which lead to inflammation and bacterial translocation. Being homozygous for NOD2 confers a 20–40-fold increased susceptibility to Crohn's, and heterozygosity leads to a two- to fourfold higher risk. Other important genes related to IBD are IL23R, which is thought to regulate immune response, and ATG16L1, which is involved in autophagy. IL23R binding with IL23 leads to activation of the JAK-STAT pathway and increased formation of proinflammatory cytokines. Variations of this gene are thought to lead to inappropriate responses to the gut bacteria and dysregulation of the microbiome. Variations in ATG16L1 can lead to decreased removal of pathogens and increased inflammation. An IBD subgroup thought to have a strong genetic component was the Very Early Onset IBD (VEO-IBD), which is defined as presenting before 6 years of age. The genetic contribution, in even this highly specific subgroup, was underwhelming, with only 10–20% of these patients noted to have a defect in the IL-10 signaling. Defects in IL-10 signaling pathway are thought to contribute to several autoimmune conditions as well as chronic granulomatous disease and B-cell lymphoma [9].

Microbiome

The interplay between our microbiome (the bacteria that live within our digestive system) and the host is extremely complex [10]. Through the secretion of mucus, IgA production, and antimicrobial peptides, the gastrointestinal (GI) tract regulates the microbiome that lives within it. The microbiome in turn potentiates the development of a healthy mucosal layer and normal epithelial repair as well as ensures immune tolerance. The bacterial composition of our GI tracts varies longitudinally (it is different in the duodenum than in the transverse colon) and transversely (more oxygen-tolerant species live closer to the mucosa, more anaerobic ones in the midst of the fecal stream). Fecal samples are therefore poor proxies of the complexity of the system they presume to represent. Most microbiome studies are also cross-sectional rather than prospective, so the evolution of bacterial colonies over time in response to specific interventions is hard to ascertain. Many species of bacteria are anaerobic and therefore difficult to grow in culture. It is also hard to be specific about strains within bacterial phyla using the more commonly used 16S ribosomal RNA tagged sequencing, which is not as precise as metagenomics with deep sequencing. With these caveats, the fecal samples of IBD patients have a decrease in the relative abundance of Firmicutes and an increase in Enterobacteriaceae

compared to normal controls. It is at this point unclear to our knowledge what the role of viruses and fungi are on the microbiome in IBD, as bacteriophages and antifungals seem to impact inflammation.

Dysbiosis, which is defined as a decrease in the normal diversity of intestinal flora, is both causative of IBD, and more recently thought to develop as a response to IBD as well. A dysbiotic environment is thought to be less versatile than a healthy one in terms of responding to an insult, such as a pathogenic foreign organism or systemic inflammation. Areas of bacterial stasis, such as the ileum and the rectum, seem to have a higher incidence of IBD than other, more rapid-transit areas of the GI tract. Similarly, diverting the fecal stream is often the solution for severe perianal and at times even intestinal IBD, leading to the concept that the microbiome itself is pro-inflammatory in these instances.

Early life factors that are thought to contribute to this decreased microbiome diversity are cesarean delivery, formula feeding, and antibiotic use. More longitudinal factors including NSAID use, air pollution, low-fiber diet, low exercise, low education level, poor sleep, stress, smoking, and even appendectomy have also been proven to negatively impact microbiome diversity and subsequently be associated with IBD [11, 12].

Dietary factors associated with increased IBD risk include a diet rich in n-6 polyunsaturated fatty acids (PUFAs). Conversely, a diet high in n-3 fatty acids, fruits, and vegetables is thought to be associated with a decreased risk of developing IBD [13]; supplementing with these nutrients after an IBD diagnosis is made has not been proved, to our knowledge, to confer clinical benefits, however.

Epidemiology

IBD affects between 1.6 and 3.1 million Americans [14], and the global incidence is increasing. A recent noteworthy and concerning trend is that Crohn's incidence is rising disproportionately in the pediatric population on a global scale [15].

IBD can present at any age. The disease was traditionally thought of as bimodal in terms of age distribution, but this has not been seen in the majority of the epidemiologic studies conducted [16]. It is more correct to say that the peak age of onset of Crohn's is the second decade of life and ulcerative colitis in the third decade. Children tend to be diagnosed more with Crohn's and the elderly with ulcerative colitis [17].

The clinical course of Crohn's disease is thought to be milder in patients who are diagnosed later in life [18, 19], with younger patients (16–40 at diagnosis) having more immunomodulation, more surgery, and more disease progression as compared to the elderly [20]. Ulcerative colitis in the pediatric population is also more aggressive than in the elderly. Children see more disease extension; 60% in one study after a median follow-up of 6 years [21], compared to 10–28% after 10 years in another study of an elderly population [22]. Early intervention can restore base line function, while delays can lead to permanent structural damage [5].

Though the male to female ratio for this disease is overall 1:1, pediatric males have more Crohn's than age-matched females, and conversely, adult and geriatric females have more Crohn's than their male counterparts. The shift seems to occur at puberty, adding sex hormones to the list of potential contributors to IBD pathogenesis [15].

IBD is a disease of industrialization. Initially described in the Western European medical literature in the 1850s (UC) and in further detail by Dr. Burrill Bernard Crohn in JAMA 1932, it was originally thought as a disease of Western countries (the United States, Canada, Europe, Australia, and New Zealand). With the rise of global industrialization, the incidence (number of new cases/100,000 person-years) and prevalence (total number of cases/100,000 person-years) are increasing in Asia, the Middle East, Africa, and South America [23].

The pattern of disease distribution for IBD is changing as well, likely because of global migration trends. Immigrants to the West from less industrialized countries tend to have a lower rate of IBD than the host country in the first generation of immigrants, but the rate increases with the second generation and at times surpasses the host country rates. This varies with ethnic group and disease type, with UC incidence mimicking the host country before CD, especially among South Asians. Also, younger age at migration correlates with increased IBD risk [24].

In the United States, IBD has traditionally been thought of as a disease of Ashkenazi Jews in particular and Caucasians in general. More recently, incidence and prevalence rates have been noted to increase in ethnic and racial groups, with Asians and Hispanics having more pancolonic disease, Asians having higher hospitalization rates, and African Americans having higher emergency department admission rates [25].

Clinical Presentation of Inflammatory Bowel Disease

IBD is a chronic relapsing illness, with periods of flare and remission. These disease is more recently thought of as a disease continuum with distinct features [1]. These diseases have a significant impact on quality of life but do not seem to shorten it. The presenting signs and symptoms are often connected to the affected area of the bowel but can also present with extraintestinal manifestations. The severity of these symptoms also correlates with the severity of the disease. Due to the variety of symptoms and complexity involved in making the diagnosis, there can be a delay of about 9.5 months from symptom onset [2–4].

Clinical Features of Crohn's Disease

Crohn's disease causes transmural inflammation in a discontinuous pattern anywhere from the mouth to the anus, with rectal sparing. Typically, CD presents with abdominal pain, weight loss, and fever with the most common symptom being chronic diarrhea [26].

The clinical features of Crohn's depend greatly on the disease location. In a population-based cohort of 200 Crohn's patients in Europe, 27% were found to have exclusive involvement of the ileum, 45% were found to have only colitis, and 26% had involvement of both the ileum and the colon [27].

Small Bowel Crohn's

Small bowel inflammation can lead to diarrheal losses of specific electrolytes, including potassium, magnesium, phosphorus, zinc, iron, as well as various vitamins.

Potassium functions in many physiological processes. It affects resting membrane potentials within neuronal and muscle cells, thereby controlling diverse physiologic processes including cardiac activity, vascular tone, and gastric motility. Deficiencies of potassium can therefore present as muscle weakness, cardiac arrhythmias, and even renal impairment from the changes in blood flow to this organ.

Deficiencies of magnesium affect metabolic processes such as insulin-mediated carbohydrate absorption into cells, neuronal signaling, and calcium homeostasis. Hypomagnesemia can present as increased insulin resistance, tremors, weakness, ventricular arrhythmias, and hypocalcemia.

Phosphate is important in the formation of adenosine triphosphate (ATP) and bone mineral homeostasis. Hypophosphatemia can present as metabolic encephalopathy, various digestive dysmotilities such as dysphagia and ileus, ventricular arrhythmias, and bone metabolism disorders, namely, rickets and osteomalacia [28].

Zinc deficiency can lead to anosmia, hypogonadism, decreased axillary hair, and dermatitis [29].

B vitamins are micronutrients that work as coenzymes in cellular processes facilitating the creation of the cellular fuel, ATP. These vitamins are water soluble and eliminated in the urine. Side effects are more common from deficiency rather than excess as toxic levels are prevented by increasing urinary excretion.

Thiamine (B1) is an important cofactor in energy generation and serves a separate role in initiating nerve propagation impulses. Thiamine deficiency presents clinically as infantile or adult beriberi, as well as Wernicke-Korsakoff syndrome. Infantile beriberi is associated with thiamine deficiency early in life and results in cardiac as well as neurologic complications and long-term developmental deficiencies. Adult beriberi develops later in life and can be described as dry (neurologic) and wet (cardiac) in symptomatology. Dry beriberi presents as a symmetrical, motor, and sensory neuropathy affecting mostly the distal extremities. Wet beriberi presents as cardiomegaly, cardiomyopathy, high output cardiac failure, tachycardia, and edema [30]. Wernicke-Korsakoff syndrome presents as a triad of confusion, ophthalmoplegia, and ataxia. Both beriberi and Wernicke-Korsakoff syndrome have been described with sudden precipitous weight loss, particularly in adolescents.

Riboflavin (B2) [31], niacin (B3), pantothenic acid (vitamin B5), and pyridoxine (B6) rarely lead to clinically significant deficiencies, but when they do,

the symptoms are nonspecific and include gastrointestinal and neurologic symptoms [32]. A noteworthy exception is niacin deficiency, also known as pellagra (raw skin), which presents as dermatitis of sun-exposed areas, diarrhea, and dementia.

Folate (vitamin B9) and cobalamin (vitamin B12) deficiency do have clinical significance in IBD. Often patients restrict intake of folate-rich foods due to concerns of "irritating the bowel," and B12 absorption can be impaired by bacterial overgrowth in the small bowel or terminal ileum inflammation. B12 and folate deficiencies most classically present as macrocytic anemia, which can help differentiate this nutritional deficiency from other IBD-related anemias (iron-deficiency anemia is microcytic and anemia of chronic disease is normocytic). A means of distinguishing these two vitamin B deficiencies is measuring the levels of metabolic intermediates homocysteine and methylmalonic acid (MMA). In B12 deficiency, only MMA is elevated, whereas in folate deficiency, both homocysteine and MMA levels are high. Apart from anemia, folate and B12 deficiencies can also present as jaundice or (more often for B12 than for folate) neurological symptoms ranging from paresthesias to psychosis [33].

Apart from the B vitamins, other water-soluble vitamins essential for nutrition are biotin and vitamin C. These are rarely deficient in IBD patients, however, being found more often in scenarios of profound starvation from famine.

Clinical manifestations of small bowel inflammation can also be thought of as related to the specific segment of intestine involved. The small bowel is comprised of three main sections: duodenum, jejunum, and ileum. Approximately 80% of Crohn's patients have involvement of the small bowel with one-third having only ileitis. Duodenal disease can lead to malabsorption of iron leading to a microcytic anemia. Fat is absorbed within the jejunum and the ileum. Malabsorption of fat leads to steatorrhea and fat-soluble vitamin (A, D, E, and K) deficiencies.

Vitamin A plays three roles in the eye: prevention of xerophthalmia, phototransduction, and cellular differentiation (all the cells of the conjunctiva and retina have retinol-binding proteins). Vitamin A deficiency therefore can cause xerophthalmia (dryness of the conjunctiva and cornea), xerosis (corneal dryness), keratomalacia (clouding and softening of the cornea), and Bitot's spots (focal keratinization of the cornea, often with bacterial colonization and metaplasia of the conjunctival epithelium) [34].

Vitamin D can be derived from dietary intake or absorbed cutaneously from sun exposure. This vitamin plays an important role in bone calcium homeostasis and can present as hypocalcemia, rickets, and osteomalacia [35].

Vitamin E works as an antioxidant scavenging free radicals. Vitamin E deficiency can present as myopathy, neuropathy, retinopathy, or anemia [36, 37].

Vitamin K deficiency can lead to bleeding via defects in the coagulation cascade leading to a prolonged prothrombin time and an increased international normalized ratio (INR) [38].

Prominent ileal involvement can prevent adequate absorption of copper and bile salts.

Copper deficiency can lead to peripheral neuropathy, impaired vibration and proprioception, and upper motor neuron symptoms such as spasticity and a positive Babinski sign [39].

Malabsorption in the ileum can also be caused by extensive surgical small bowel resection. When less than 100 cm of small bowel has been resected, decreased bile acid absorption leads to higher than normal levels of bile salts in the GI lumen and subsequently a bile salt diarrhea. Decreased ability to absorb bile at the level of the gallbladder leads to both a relative reduction of bile acid and a higher level of cholesterol, which might precipitate into gallstones [40]. When more than 100 cm of the terminal ileum (TI) is affected by CD (either disease or surgery), there is a systemic bile salt deficiency (the liver is unable to keep up with the luminal bile salt losses) and subsequent fat malabsorption. The unabsorbed fatty acids in the GI tract bind to calcium (a process called saponification), decreasing the availability of calcium to bind to oxalate and thereby excreting it in the GI tract [40]. The inflamed intestinal lumen has increased permeability to oxalate, leading to higher levels of reabsorption. In addition, the diarrhea leads to dehydration and loss of bicarbonate, causing acidosis and reduced excretion of citrate. Excess oxalate in the GI lumen, unbound to calcium, leads to surplus oxalate being absorbed into the bloodstream and brought to the kidneys, where the acidic environment allows it to precipitate out of solution in the form of calcium oxalate kidney calculi [41, 42].

CD has been shown to cause a reduction in growth in pediatric patients through chronic caloric losses due to protein malabsorption and anorexia. Therefore, the diagnosis of IBD in children often is initiated by the pediatrician noting the child's falling off the growth curve. Inflammatory mediators can lead to an increased basal metabolic rate. IGF-1 directly mediates growth via upregulation by growth hormone (GH), and both GH and IGF-1 are significantly reduced in patients with CD. TNF-α and IL-6 are linked to direct inhibition of GH. In a systematic review of pediatric CD patients around the world, 10–56% of patients were found to have growth failure at the time of diagnosis (where growth failure was primarily defined as height less than third percentile for age) [43].

Perianal Crohn's

Perianal CD is defined by inflammatory lesions at or around the anus. The most common structural findings are skin tags or fissures but can also consist of skin tags, hemorrhoids, fissures, fistulas, and abscesses.

Penetrating phenotypes (found in some studies in up to 60% of CD patients) are strongly correlated to perineal disease. In a cohort of over 500 CD patients in Sweden, 37% had perianal involvement.

Skin tags are small bumps in the perineal area caused by lymphedema (Fig. 2.1, image a). They increase in size during a Crohn's flare but are benign. In a cohort of 200 CD patients in the USA, 37% had skin tags [44].

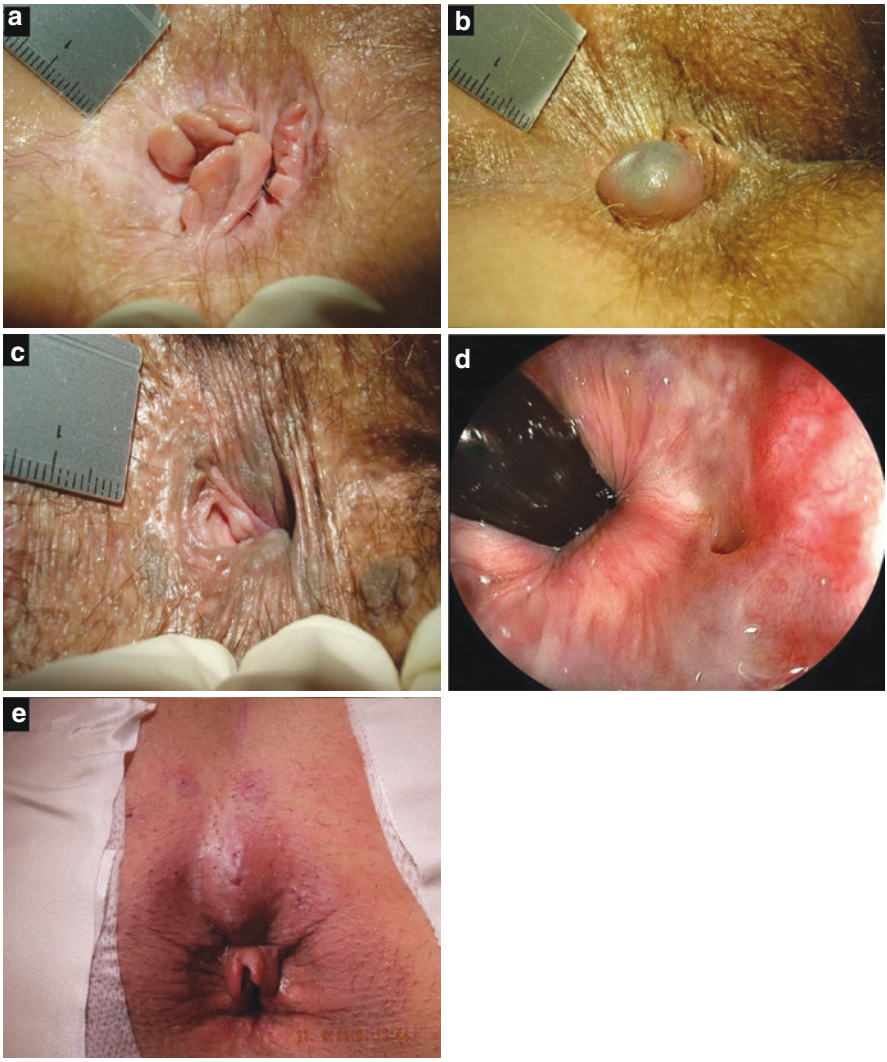

Fig. 2.1 (**a**) Perianal skin tag – small leathery pedunculated lesion [45]. (**b**) Thrombosed hemorrhoid – swollen purple protrusion perianally [45]. (**c**) Perianal fissure – heaped up edge [45]. (**d**) Rectovaginal fistula observed on retroflection of colonoscopy [50]. (**e**) Perianal abscess [51]

Hemorrhoids (Fig. 2.1, image b [45]) are dilated veins that occur from increased pressure within the anus. Hemorrhoids can be further classified into internal hemorrhoids (proximal to the dentate line) and external hemorrhoids (distal to the dentate line). Hemorrhoids can present with rectal bleeding, and thrombosed hemorrhoids can be painful. In a cohort of 200 CD patients in Europe, hemorrhoids occurred in 15% of patients [44].

An anal fissure is a linear tear or sore in the anal canal that is very painful – patients describe it as passing glass through the rectum. They are associated with increased resting anal pressures [44] (Fig. 2.1, image c [45]).

Fistulas are abnormal passages between two hollow organs. These can be categorized as originating in the rectal canal, in which case they are referred to as perianal, or abdominal cavity. Perianal fistulas are an abnormal connection or tract between the anus and the perianal epithelium (Fig. 2.2). In an observational cohort in Minnesota, fistulas were reported in 10–26% of patients, out of which 54% were perianal, 24% were entero-enteric, and 9% were rectovaginal [46]. Perianal fistulas can be classified by their location with respect to the external and internal anal sphincters as superficial, intersphincteric, trans-sphincteric, suprasphincteric, and extrasphincteric. Superficial fistulas track inferior to the external anal sphincters. Intersphincteric fistulas track from the anal canal in the intersphincteric plane to the perianal region. Trans-sphincteric fistulas pass through both the internal and external sphincters prior to exiting to the skin. Suprasphincteric fistulas pass through the intersphincteric space superior to the puborectalis and through the levator plate. Extrasphincteric fistulas pass outside of the external anal sphincter from the perianal skin through the levator muscle [47].

Fistulas originating in the abdominal cavity cause abnormal communications between nearby organs. These connections can arise between loops of small bowel, also known as entero-enteric fistula, and most often occur as ileo-ileal. Fistulae that occur between small bowel and the colon are entero-colonic and often form between the terminal ileum and the sigmoid colon Fistulae within the genitourinary system can make connections to the urinary bladder (entero-vesicular), and the female reproductive system (rectovaginal or entero-fallopian). Enterocutaneous form connections between the bowel and the skin. Rarely, connections between the transverse colon and the greater curviture of the stomach known as entero-gastric fistula can form [48].

Entero-vesicular fistulas present most commonly with pneumaturia. Other symptoms are dysuria, fecaluria, UTI-type symptoms, and passing urine per rectum. Men

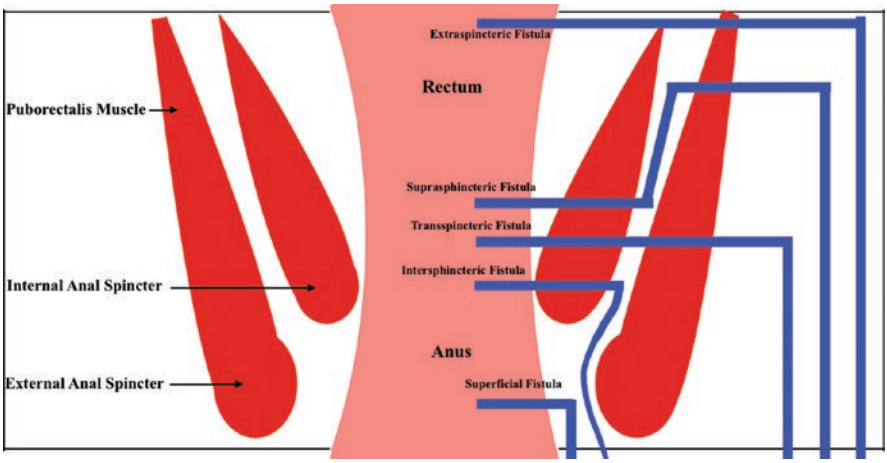

Fig. 2.2 Diagram of perineal fistula location

(who also get these fistula types more often than females, as there is no reproductive system shielding the rectum from the urinary bladder) might report seeing vegetable matter in the urine stream.

Rectovaginal fistulas are a type of trans-sphincteric fistula that tracks anteriorly from the rectum to the vaginal orifice. These can present with abdominal discomfort, dyspareunia, and feculent vaginal discharge. This is a very hard symptom to elicit, as female patients are often recalcitrant to disclose this aspect of their sexual experience. Rectovaginal fistulas occur in 5–23% of patients [49] (Fig. 2.1, image d [50]).

Enterocutaneous fistulas are a rare sight in the age of biologic therapy. These involve a loop of inflamed bowel eroding into the abdominal wall, creating a sinus tract through which serosanguineous discharge, pus, or more rarely feces can drain. The majority of these fistulas are postoperative rather than de novo and originate from the small bowel. These can also lead to dehydration if they are high output fistulas.

Patients with Crohn's disease are at an increased risk of squamous cell carcinoma and adenocarcinoma of the anus. The incidence of developing cancer was 0.7% over a 14-year period [44].

Perianal abscesses are a collection of pus that is built up adjacent to the anus (Fig. 2.1e [47]). The most common presenting symptoms are fever, pain, and dyschezia. On physical examination, the perineum is indurated, is tender to the touch, and can have a fluctuant mass. Abscesses begin to form from plugging of anal crypt glands allowing for bacterial growth. In a European cohort of 200 patients, 26% had an abscess in their lifetime [44].

Inflammatory nodules and sinus tracts can also be a presentation of hidradenitis suppurativa (HS), which is a chronic inflammation of the sweat glands that occurs from follicular occlusion from hyperplasia and hyperkeratosis. HS occurs in the axillary, inguinal, perianal, pubic, and scalp areas. A systematic review suggests that there is a statistically significant association between IBD and HS, with odds ratios linking the two conditions between 2 and 10 [52].

Colonic Crohn's

Crohn's disease with exclusive involvement of the colon was found in 45% of patients in a European retrospective study [27]. While the symptoms of colonic involvement tend to be diarrhea and pain, they can progress to more serious conditions such as hemorrhage or fulminant colitis. Diarrhea, one of the principal symptoms of CD, is multifactorial and occurs due to persistent inflammation leading to dysregulation in electrolytes, impaired epithelial barrier function, and increased susceptibility to infections. Hematochezia generally occurs due to deep ulcerations within the intestinal wall. This bleeding can be further exacerbated by derangements in vitamin K absorption. Severe hemorrhage is one of the most rare complications of colonic CD, with an incidence noted to be from 0.6% to 4% in a systematic review of CD patients worldwide [53]. Patients with CD may also present with

fulminant colitis, which is an acute severe episode of inflammation of the colon. These patients may exhibit diarrhea, hematochezia, fever, and tachycardia [54].

Upper Tract Crohn's

Involvement of the upper tract is rare in adults, with a population-based cohort of European adults noting that only 4% had upper gastrointestinal involvement at the time of diagnosis. However, it is more commonly found within the pediatric population [27]. A retrospective study of over 200 children in Scotland found more than half of the patients had involvement of the upper GI tract at the time of diagnosis [55]. Involvement with the esophagus can present with dysphagia or odynophagia. Gastroduodenal lesions can present as dyspepsia. Dyspepsia in CD occurs from inflammatory mucosal changes, tissue swelling, outflow obstruction, and delayed gastric emptying without obstruction [56]. The dyspepsia of CD is often refractory to proton pump inhibitors (PPIs). Occasionally there can be gastric outlet obstruction from strictures, which can present with nausea, vomiting, early satiety, and abdominal distension post-prandially.

Extraintestinal Manifestations

While extraintestinal manifestations (EIMs) will be further discussed in Chap. 5, they are important to recognize as they may be the initial presenting symptom of IBD. A large population-based study of over 10,000 CD patients in Denmark found that 37.8% had at least one EIM prior to their diagnosis of IBD and 30.8% presented with EIMs more than 1 year prior to their diagnosis of IBD [57]. The broad variety of symptoms and their intensity may play a factor in the diagnostic delay of CD. The pathogenesis of EIMs is thought to be associated with a triggered immune response on shared epitopes of other organ systems [58]. EIMs most commonly affect the skin, joints, eyes, and liver.

Dermatologically, IBD-associated EIMs are pyoderma gangrenosum and erythema nodosum. Pyoderma gangrenosum appears as painful papules or pustules that rapidly ulcerate. These lesions exhibit pathergy (minor trauma can lead to lesion progression) [58]. Erythema nodosum presents as erythematous nodules with a darker periphery and lighter center on the dorsal surface of the upper and lower extremities [54]. Erythema nodosum lesions relapse and remit in parallel to IBD flares, a phenomenon which does not occur with pyoderma gangrenosum. Psoriasis, another skin condition often associated with IBD, is caused by excessive growth of the epidermal layer of skin from premature maturation of inflamed keratinocytes. This leads to an inflamed erythematous rash with overlying white plaques [59].

Rheumatologically, IBD patients can present with psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis. Psoriatic arthritis occurs from upregulation of

T helper 1 cells (Th1) and T helper 17 cells (Th17) [54]. Psoriatic arthritis causes an asymmetrical oligoarthritis that can affect the metacarpophalangeal joints (MCPs), the proximal interphalangeal joints (PIPs), and the distal interphalangeal joints (DIPs). It can also affect the nails, causing a separation of the nails from the nail bed known as onycholysis and hyperkeratosis. Rheumatoid arthritis presents as a symmetrical polyarthritis that affects large joints as well as the MCPs and PIPs [57]. Ankylosing spondylitis is inflammation of the spine and pelvis that occurs via TNF and IL-1. It often presents as pain of the hip and back with decreased mobility of the lumbar spine.

Ophthalmologically, patients can present with episcleritis, scleritis, or uveitis. Uveitis presents with pain and erythema of the uvea. Episcleritis is inflammation of the outermost layer of the sclera just below the conjunctiva. This usually presents as a painless erythema. Scleritis is inflammation of the sclera layer below the episclera. This can present with erythema or edema of the scleral layer. Typically, the presentation is a deep boring pain of the eye. Scleritis is the most concerning ophthalmic IBD complication, requiring urgent ophthalmological examination and intraocular steroids as it can lead to necrosis and permanent vision loss [58].

Hepatologically, IBD is associated with primary sclerosing cholangitis. Primary sclerosing cholangitis (PSC) is a progressive autoimmune inflammation of the biliary tract. The classic radiographic appearance is that the biliary tree appears beaded by sacculations and strictures caused by inflammation leading to fibrosis. This can present as jaundice, pruritus, steatorrhea, and darkening of the urine. PSC can progress to an acute cholangitis or liver failure and is also associated with cholangiocarcinoma [60]. The majority of PSC patients (90% in some studies) also have IBD (usually ulcerative colitis, though this PSC has also been seen in CD), but the reverse is not true, with a minority (approximately 5%) of IBD patients having concomitant PSC.

Clinical Features of Ulcerative Colitis

Ulcerative colitis is a chronic immune-mediated inflammation of the large bowel. It is characterized by continuous superficial inflammation that starts in the rectum and can extend in a retrograde fashion throughout the colon. The severity of the disease is correlated to the extent of bowel involvement. UC can present with proctitis, left-sided colitis, or pancolitis. A systematic international review of UC patients noted 29.4% of patients to have proctitis (inflammation of the rectum) at the time of diagnosis [61]. These patients generally experience tenesmus and urgency. Left-sided colitis is commonly found at the time of diagnosis. In the same review, 40.1% of patients had this at presentation [61]. These patients experience diarrhea, hematochezia, and anemia. Of the UC patients, 30.5% were found to have extensive colitis [61]. These patients present with more extensive diarrhea, hematochezia, anemia, and toxic megacolon with fever, abdominal pain, and substantial acute distension.

The rate of progression from proctitis to left-sided colitis, proctitis to extensive colitis, and left-sided colitis to extensive colitis was 28–30%, 14–16%, and 21–34%. The overall 5-year risk of progression in this international study was 13% [61]. While UC is typically confined to the colon, about 10–20% of patients will have inflammation in the terminal ileum, which is also known as backwash ileitis [62].

Many scoring systems have been developed to stratify and categorize the extent of ulcerative colitis. One of the most commonly used is the Truelove and Witts Severity Classification (Table 2.1). Truelove and Witts takes into account the frequency of stools, frequency of hematochezia, temperature, pulse, hematocrit, and erythrocyte sedimentation rate (ESR) [63]. While simple, this scoring system excludes extraintestinal manifestations, quantitative measures, and endoscopic severity [63, 64]. The Mayo Score (Table 2.2) and the Simple Clinical Colitis Activity Index (Table 2.3) account for endoscopic disease activity, and have also demonstrated responsiveness to therapy well [64, 65].

Diagnostic Evaluation

Laboratory testing does not definitively establish a diagnosis of inflammatory bowel disease, but it can be a helpful complement in sorting through differential diagnoses as well as evaluating the patient's disease status.

The fecal biomarker calprotectin has emerged as the most useful tool in the diagnosis and monitoring of IBD due to its superior sensitivity and specificity, compared to other disease markers. Fecal calprotectin (FC) is an antimicrobial manganese sequestration protein complex that binds to calcium within neutrophils. Its presence in stool indicates neutrophilic migration from the blood to the luminal GI tract, a phenomenon which does not occur under normal physiological conditions [66].

Fecal calprotectin can be helpful in differentiating irritable bowel syndrome (IBS) from IBD. A large systematic review and meta-analysis of patients around the world found calprotectin to have a sensitivity of 88% and a specificity of 79% for IBD, with a normal reference range of 6–280 μg/g when compared to the gold standard, colonoscopy [66].

Table 2.1 Truelove-Witts ulcerative colitis severity classification

	Mild	Moderate	Severe
# of stools per day	<4	>6	>10
Hematochezia	Intermittent	Frequent	Continuous
Temperature (°C)	Normal	>37.5	>37.5
Pulse (beat/min)	Normal	>90	>90
Hematocrit (%)	Normal	<75	Transfusion
ESR (mm h)	<30	>30	>30

Adapted from Truelove and Witts [63].

Table 2.2 Simple clinical colitis activity index

Stool frequency	Nocturnal bowel frequency	Urgency	Hematochezia	Well-being	Extraintestinal features
0 = 1–3 per day	0 = 0	0 = none	0 = none	0 = very well	1 per manifestation
1 = 4–6	1 = 1–3	1 = hurry	1 = trace	1 = slightly below par	
2 = 7–9	2 = 4–6	2 = immediate	2 = occasionally frank	2 = poor	
3 = 9+		3 = incontinent	3 = usually frank	3 = very poor	
				4 –terrible	

Adapted from Walmsley et al. [64]

Table 2.3 Mayo score

Stool frequency	Hematochezia	Endoscopy	Global assessment
0 = Normal	0 = no blood	0 = Normal/inactive	0 = Normal
1 = 1–2 > Normal	1 = streaks <½ time	1 = mild (erythema, mild friability, decreased vascular pattern)	1 = mild
2 = 3–4 > Normal	2 = gross blood most of the time	2 = moderate (marked erythema, lacks vascular pattern, friable, erosions)	2 = moderate
3 = >5 than normal	3 = blood without stool passed	3 = severe spontaneous bleeding and ulcerations	3 = severe

Adapted from Schroeder et al. [65]

Calprotectin correlates to disease activity, so it may be utilized for disease monitoring [67]. An international systematic review and meta-analysis of over 2000 patients found calprotectin to have a sensitivity of 88% and a specificity of 73% in the diagnosis of IBD [68]. International studies have shown that FC is correlated to remission, response to therapy, and relapse. In a retrospective chart review in the USA of 68 UC patients, a value of <60 μg/g predicted deep histological remission with a sensitivity of 86% and a specificity of 87% [69]. A Korean cohort of 181 patients with IBD found that a value of <187 μg/g for FC indicated complete mucosal healing with a sensitivity of 85.7% and a specificity of 89.1% [70]. FC rising to a value greater than 321 μg/g in clinical remission predicted a risk of relapse in 6–12 months [71]. Calprotectin can also be utilized to monitor for recurrence of CD with a value of >160 μg/g having a sensitivity of 91.7% and a specificity of 82.9% for flare [72, 73], thereby substituting for colonoscopy in resource-limited or time-sensitive clinical instances.

Lactoferrin is another fecal biomarker that has been studied in IBD. It is a globular glycoprotein secreted in the mucus layer overlying most mucosal surfaces. It is a major component of the secondary granules secreted by neutrophils in response to pathogens. In a systematic review and meta-analysis of over 2000 IBD patients around the world, the sensitivity and specificity of lactoferrin were determined to be

82% (95% CI 0.73–0.88) and 79% (95% CI 0.62–0.89), respectively. Lactoferrin utilization is therefore limited due to its lower stability and less data compared to calprotectin [68].

Another study utilized in IBD is the mannitol-lactulose permeability test. This test utilizes two non-metabolizable sugars (the absorption of which should be very low if the mucosa is intact) and compares the ratio of their urinary excretion to assess for intestinal permeability (the ratio, rather than the absolute amount, is used in an attempt to standardize for differences in absorptive surfaces between patients). Patients fast 8 hours prior to the exam and empty their bladder immediately before the exam. They then ingest a solution of 5 g of lactulose and 2 g of mannitol, and their urine is collected over a 5-hour period. The normal percentage of excretion of lactulose, mannitol, and the lactulose-mannitol excretion ratio (LMER) is 0.3550 (range 0.0204–1.8030), 12.300 (range 1.4800–43.7500), and 0.0317 (range 0.0029–0.2510), respectively [74]. A case-control in France of 100 healthy adults compared to 47 patients with CD reached the highest sensitivity values (67% for lactulose and 86% for the lactulose-mannitol ratio) for the active disease subgroup only, making this cumbersome to perform test less useful in clinical practice, where the important clinical distinction is between quiescent and incipient disease activity subgroups [75].

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are nonspecific markers that are elevated in a variety of conditions that cause systemic inflammation.

ESR is measured by the distance the erythrocytes of a blood sample fall until they settle in a standardized vertical column. Since this can vary with alterations in plasma concentration and hematocrit, it is not the most reproducible test [76]. ESR also reflects systemic inflammation, limiting its usefulness as a clinical marker for a specifically gastrointestinal disease process.

CRP is produced in hepatocytes in response to cytokines such as interleukin-6 (IL-6), IL-1β, and tumor necrosis factor α (TNF-α) that are released in inflammation. CRP has a sensitivity of 70–100%, and ESR has a sensitivity of about 50–60% in diagnosing IBD. An elevation of CRP can correlate to active UC in 50–60% patients. However, in less severe cases of UC, the ESR or CRP maybe normal in up to 34% of patients [77]. These tests are nonspecific and should be used only in conjunction with other tests in determining the severity of IBD.

Initial evaluation of a patient with IBD should include complete blood count (CBC) and iron studies. Chronic slow bleeding can cause anemia, which can be assessed on CBC. Iron deficiency anemia (IDA) is usually defined as low iron and ferritin, but ferritin may be falsely elevated as it is an acute phase reactant. The elevation in inflammation is presumed to have developed as a defense mechanism to prevent iron utilization by pathogens and tumors [78].

Ferritin is an intracellular protein that regulates iron stores. It can be elevated in the setting of increased red blood cell turnover, liver disease with damage to hepatocytes, infection, malignancy, and inflammation. The elevation of ferritin can be a confounding factor when trying to diagnose IDA. A study of 250 hospitalized patients in the United States with anemia or disorders of iron metabolism found that

of the patients without iron deficiency anemia, the mean ferritin level was 180 ng/mL, but in 43%, ferritin was greater than the upper normal limit of 300 ng/mL [79]. The most common cause of the elevation was inflammation, with mean ferritin of 305 (range 10 ng/mL to 1650 ng/mL) [79]. More recently, ferritin has also been found to be elevated in COVID-19. In Wuhan, China, Wu et al. reported that 78.5% of their 201 patients with COVID-19 had elevated ferritin ranging from 315 ng/mL to 1266 ng/mL with a median of 599 ng/mL [80]. When the measured ferritin was less than 45 ng/mL, the sensitivity of diagnosing IDA was maximized. A ferritin threshold value of less than 45 ng/mL has a sensitivity of 85% and a specificity of 92% for IDA [81]. It is recommended to use this reference range for the diagnosis of IDA, but for patients with inflammation, co-testing with C-reactive protein (CRP) or transferrin can help diagnose IDA. IBD can cause anemia but it may not always present as a typical iron deficiency anemia, but rather as anemia of chronic inflammation or a combination of both diseases. Additionally, if there is B12 or folate deficiency as well, the anemia might also have a macrocytic component, further obscuring the clinical picture.

Serologic antibody testing can be useful in the evaluation of IBD, but it is not recommended for establishing a diagnosis or for prognostication. The two most commonly used antibody tests for IBD are anti-neutrophil cytoplasmic antibody (ANCA) and anti-*Saccharomyces cerevisiae* antibody (ASCA).

Anti-neutrophil cytoplasmic antibodies (ANCAs) are autoantibodies that target antigens within the cytoplasm of neutrophils. Cytoplasmic ANCA (c-ANCA) targets proteinase 3 (PR3). Perinuclear ANCA (p-ANCA) targets myeloperoxidase (MPO). MPO is an enzyme that produces acid for antimicrobial activity and bactericidal permeability protein (BPI). BPI binds to lipopolysaccharides and activates the immune system. ANCAs are positive in many inflammatory diseases such as microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis. The perinuclear ANCA (p-ANCA) is the most prevalent in IBD, being present in 6–20% of CD and 50–70% of UC [82].

Anti-*Saccharomyces cerevisiae* antibody (ASCA) is an antibody directed against mannose residue from phosphopeptidomannan of the cell wall of this specific yeast. ASCA was found to have a prevalence of 50% to 70% in Crohn's, but only 5–15% in ulcerative colitis. ASCA was found to have a sensitivity of 50–70% and a specificity of 80–85% for IBD [82]. ASCA is also found to be positive in Behçet's disease and celiac disease.

Additional serologic tests for IBD include antibody to various components of bacteria and fungi such as outer membrane porin, antibodies to *Pseudomonas*, and anti-carbohydrate antibodies (anti-laminaribioside carbohydrate, antichitobioside carbohydrate, and anti-mannobioside carbohydrate). This correlation between potential pathogens and IBD-specific antibodies points again to the importance of the microbiome in the pathogenesis of this disease process, as well as to our so far nebulous understanding of the complex interplay between our immune system and the organisms that reside within us.

Outer membrane porin C (OmpC) was a protein that was first noted in the outer membrane of E. coli. IgA antibodies to OmpC (anti-OmpC) have been found in

patients with IBD. Anti-OmpC was found to have a prevalence of 37% to 55% in Crohn's and 2% to 11% in UC. The sensitivity was 20–55%, and the specificity was 88.5% for IBD [82].

Antibodies to *Pseudomonas fluorescens*-associated sequence I-2 (anti-I2) were isolated in the lamina propria of mononuclear cells. They were noted to have a prevalence of 54% in CD and 10% in UC. The sensitivity was 42% and the specificity was 76% for IBD [78]. Anti-I2 has also been noted to be positive in infectious colitis, radiation proctitis, and shigellosis.

Flagellin (Cbir1) found in the enteric microbial flora of mice is detected in 50% of CD and less than 5% of UC.

Anti-carbohydrate antibodies such as anti-laminaribioside carbohydrate (ALCA), antichitobioside carbohydrate (ACCA), and anti-mannobioside carbohydrate (AMCA) are anti-glycan antibodies. Glycans are saccharide polymers; when combined with proteins, they also create glycoproteins [82]. ALCA targets laminarin found in the cell wall of fungi and yeast. The prevalence of ALCA in CD and UC is 17.7% to 27% and 4% to 7%, respectively, with a sensitivity of 18% and a specificity of 93%. ACCA targets chitobioside, which is found in chitin insects and the cell wall of bacteria and yeast. AMCA targets mannobioside, which is a component of mannan (found in fungi and yeast). The prevalence of ACCA is 20.7% to 25% in CD and 5% to 15% in UC with a sensitivity of 21% and a specificity of 85%. The prevalence of AMCA is 28% in CD and 18% in UC with a sensitivity of 28% and a specificity of 82% [82].

Since the sensitivity and specificity of individual serologic markers is so low, studies have focused on using combinations to improve the sensitivity and specificity. There may be some utility for monitoring with ASCA and p-ANCA, but there is not enough data to support utilization for differentiating inflammatory bowel disease based on these. In comparing IBD-U to CD, the sensitivity was 33% and the specificity was 83% for p-ANCA−/ASCA+. IBDU vs UC had 65% sensitive and 66% specific for p-ANCA+/ASCA−. In comparing CD to UC with p-ANCA+/ASCA−, the sensitivity was 65% and the specificity was 77%, which was lower than previous reports. Finally, p-ANCA−/ASCA+ for differentiating CD and UC was 33% sensitive and 97% specific [83].

A panel that was commercially produced by Prometheus Laboratories utilized seven serologic tests that consist of ASCA IgA, ASCA IgG, anti-CBir1, ANCA, anti-OmpC, p-ANCA, and DNAse-sensitive p-ANCA. Two statistical models found this panel to have 92% accuracy and 93% sensitivity, 95% specificity, 96% positive predictive value (PPV), and 90% negative predictive value (NPV). The initial study was funded by Prometheus and had some inherit biases. Subsequent studies reevaluated the panel but found less useful results for the purpose of screening. A retrospective study of 394 pediatric IBD patients tested with IBD found great variation in the results in the testing with a sensitivity of 67%, a specificity of 76%, a PPV of 79%, and an NPV of 49% [84]. The study also evaluated the utility of adding anti-CBir1 to a panel (IBD7), which only showed a sensitivity of 60% and a specificity of 92%. This serologic panel can also be very expensive without providing a significant benefit diagnostically. When comparing the panel to CBC demonstrating anemia

Table 2.4 Laboratory test summary

Serologic marker	Sensitivity	Specificity	Differential diagnosis
Calprotectin	88%	79%	Gastrointestinal inflammatory disorders
CRP	70–100%		Malignancy, inflammatory disorders
ESR	50–60%		Malignancy, inflammatory disorders
p-ANCA	65–70%	80–85%	Microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis
ASCA	50–70%	80–85%	Behçet's disease, celiac disease
Anti-I2	42%	76%	Infectious colitis, radiation proctitis, and shigellosis
Anti-OmpC	20–55%	88.5%	
AMCA	28%	82%	
ACCA	21%	85%	
ALCA	18%	93%	

Adapted from Peyrin et al. [82]

and ESR co-testing, CBC and ESR had better sensitivity, specificity, PPV, and NPV and a lower cost. The sensitivity was 83% and the specificity was 96% [84]. Table 2.4 summarizes the sensitivities, specificities, and other common diseases associated with the serological markers.

Imaging

Radiographic imaging can be used noninvasively to determine the extent of involvement and the severity of the disease and to detect disease-related complications and extraintestinal inflammatory bowel disease (IBD) manifestations [85]. Imaging is much more important in Crohn's disease, with its segmental distribution and extraluminal complications, than in ulcerative colitis, where serial endoscopy is the mainstay of diagnosis as well as surveillance.

The earliest attempts to use radiology in IBD management were small bowel follow-through (SBFT) and small bowel enteroclysis (SBE) [86]. These are fluoroscopic examinations that use liquid contrast containing either iodine or barium to evaluate the small bowel. SBFT involves the ingestion of the oral contrast agent, followed by radiologic imaging. SBE requires the insertion of a nasoduodenal tube until the fourth part of the duodenum, through which the barium contrast is instilled. SBFT was preferred as it was less invasive and better able to demonstrate gastroduodenal involvement. These examinations are operator dependent, with the technician having to position the patient and the x-ray source in various angles to achieve optimal image quality. Due to the ionizing radiation exposure, failure to most capture extramural complications, and decreased accuracy compared to other cross-sectional imaging, the utilization of these modalities has decreased gradually over the last 30 years [87]. The sensitivity for the detection of active SB Crohn's disease

was 82% for CTE and 65% for SBFT, and the overall accuracy was 85% and 79%, respectively [88].

Computed tomography enterography (CTE) is a type of CT examination performed with intravenous contrast material after ingestion of approximately 1.5–2 L of neutral oral contrast that helps in producing high-resolution images of the small intestine. As with all CT examinations, ionizing radiation is utilized. Different body tissues absorb these x-rays in different amounts, which are then transmitted to a computer forming 2-D and 3-D images. CT enterography can exquisitely demonstrate active CD features including mucosal hyperenhancement, wall thickening, mural stratification with prominent vasa recta (comb sign), and mesenteric fat stranding [89].

Limitations and disadvantages of CT enterography include exposure to ionizing radiation, inability to visualize the GI luminal tract in obese patients, and subtle disease.

Magnetic resonance enterography (MRE) is a noninvasive imaging examination used for the assessment of small bowel. It uses MRI following the ingestion of a neutral oral contrast agent, which distends the small bowel. MRE does not use ionizing radiation; instead, it uses radio waves. MRE uses powerful magnets to create an electromagnetic field that aligns the hydrogen atoms present in the body with the magnetic field. Then radio waves are passed through the body, which spins these protons out of equilibrium. Once the radio frequencies are shut off, these protons realign with the magnetic field, which releases energy that is captured by MRI sensors. The amount of energy and the time taken to capture the image allow the radiologist to differentiate between normal and diseased tissues. This technique provides high-contrast resolution images and a detailed evaluation of bowel wall changes, allowing for monitoring of disease activity and localization. The acquisition time is approximately 30–45 minutes.

MRE is also useful in the classification of CD into three subtypes, based on inflammatory activity: active, fistulizing/perforating, and fibrostenosing. It has further been proven useful in monitoring relapses and planning future interventions [90].

MRE and CTE use contrast materials to improve the quality of images produced. Both oral and intravenous contrast is used. Oral contrast are given about 30–45 minutes before the procedure to help distend the small bowel. Barium sulfate (with other additives) is the most commonly used oral contrast agent as it allows better opacification of the bowel. In CT, iodinated intravenous contrast is used, while in MRE, the intravenous contrasts are gadolinium based. Table 2.5 below differentiates between these two commonly used contrast agents.

Acute kidney injury (AKI) occurring subsequent to administration of iodinated contrast is called contrast-induced AKI (CI-AKI). It is mainly a clinical diagnosis base on rising creatinine 24–48 hours after contrast administration, which can rarely progress to oliguria [91, 92].

Patients with severe kidney disease who are being administered gadolinium may develop nephrogenic systemic fibrosis [93]. The rate of adverse events associated with these contrasts is very low.

Table 2.5 The advantages and disadvantages of different imaging examinations summarized

Imaging tests	Advantages	Disadvantages
Ultrasound	No radiation; may show terminal Ileal disease well	Operator and patient dependent; Comprehensive examination is not Possible; time consuming
CTE	Fast (<5 min); greater spatial resolution Than MRE; multiplanar reformats are Possible; mural and extramural Complications are seen	Radiation burden; early disease is Not well seen; cine imaging is Not possible
MRE	No radiation; high soft tissue contrast; Multiplanar ability; shows mural and Extramural complications; defines activity Of disease; cine imaging is possible; Can combine with perianal imaging	Longer scan time than CTE (20 min); Early disease is not well seen; Suboptimal distention of proximal Small bowel
Capsule endoscopy	Evaluates small bowel mucosa	Cannot use in stricturing disease; Battery exhaustion; poor localization; Extramural complications are not Assessed

Reference: Griffin et al. [114]

CTE and MRE are both very useful modalities for diagnosing small bowel inflammation in CD. A recent global meta-analysis showed that sensitivity and specificity were 87% and 91%, respectively, for CTE and 86% and 93%, respectively, for MRE [94]. Disease monitoring is usually required for an extended period in IBD patients. A standard CTE delivers an effective radiation dose of approx. 18 mSv, which is equivalent to around 180 transatlantic flights [95]. In this regard, MRE is a preferred method in disease monitoring in CD. MRI has other advantages over CT such as improved ability to determine active inflammation using submucosal enhancement and better visualization of fistulas and perianal disease [96].

Limitations of MRE include contraindications if there are cardiac vascular implantable electronic devices (CIED) implanted <6 weeks before the MRI (as there is increased risk of dislodgement), surgically placed permanent epicardial leads [96], cochlear implants, and certain metal coils in blood vessels. However, a recent study on the effect of MRI on Olympus EZ clips having ferromagnetic properties showed that they may be safe for MRI [97]. Other MRI limitations are obesity, claustrophobia [98], and pregnancy, as the gadolinium contrast is absorbed into the fetal circulation [99, 100].

Video capsule endoscopy (VCE) is a photographic imaging technique in which a patient ingests a pill containing a wireless camera. The camera takes images as it progresses through the upper GI tract, up to the ileocecal valve. It generates two to six frames per second over 8 to 12 hours. The images are then transmitted to a

recording device. A literature review suggests that cardiac pacemakers, left ventricular assist devices, and implantable cardioverter-defibrillators (ICDs) do not interfere with capsule endoscopy or vice versa [101]. In a recent study involving over 100 capsule endoscopy patients, 63% had pacemakers, 25% had ICDs, and 12% had left ventricular assist devices. The functionality of these devices was checked before capsule endoscopy, and no evidence of arrhythmias was determined [102]. The technical data of PillCam (Given Imaging) demonstrate that the maximum transmission power is below the permitted limits for cardiac devices, so any interference is not expected [101]. Despite the evidence, the US Food and Drug Administration and manufacturers recommend not using capsule endoscopy in patients with implantable cardiac devices. In spite of the limitations of this technology, approximately 30% of CD patients have small bowel involvement; thus, we incorporate capsule endoscopy routinely in diagnostic testing for IBD, as it allows direct visualization of the small bowel mucosa [103]. Capsule endoscopy has a high negative predictive value of 96% [104]. The most common complication in patients undergoing capsule endoscopy is capsule retention [105], which is 0–5.4% in patients with suspected CD and is higher in patients with known disease [106]. Using a patency capsule (or small bowel imaging) before capsule endoscopy reduces the risk of retention [107–109]. A patency capsule is around the same size as the video capsule (26 × 11mm) and is made of barium sulfate and lactose anhydrous. The patient is instructed to be on a liquid diet the day before and stop drinking or eating after 10 pm. The following morning, the patency capsule is ingested, after which the patient is advised not to drink or eat for 2 hours. The patient undergoes an abdominal radiograph approximately 30 hours after patency capsule ingestion. Patency is confirmed if the capsule is not detected on the radiograph. The patency capsule is biodegradable and would dissolve even if its passage was obstructed by strictures after 40–80 hours. VCE is superior to small bowel barium examination, CT enterography, and ileocolonoscopy in patients with suspected CD, with an incremental yield of diagnosis of 32%, 47%, and 22%, respectively [103]. This technique does have limitations, which include patients with known or suspected strictures, fistulas, and obstructions [110]; pregnant women (due to lack of studies done on the safety of VCE in this population) [111]; wireless telemetry (which can interfere with the recording of images generated from video capsule endoscopy) [101]; and patients with swallowing disorders, gastroparesis [101], or cognitive dysfunction [112].

In a prospective, blinded study of multiple small bowel imaging modalities, comparing small bowel capsule endoscopy (SBCE), CTE, and MRE performed after ileocolonoscopy in 93 patients with suspected or established Crohn's disease, the sensitivity and specificity for terminal ileum Crohn's disease were 100% and 91% for SBCE, 76% and 85% for CTE, and 81% and 86% for MRE, respectively [113]. A summary of the indications for radiographic imaging can be seen in Table 2.6.

Table 2.6 Indications for radiographic examination

Indications for radiographical evaluation in patients with ulcerative colitis
1. Exclude small bowel disease in patients with IBD, unclassified type (IBD-U)
2. Exclude alternate etiologies for symptoms and extraintestinal IBD manifestations
3. Identify disease complications (toxic megacolon and perforation)
4. Evaluation of the ileoanal pouch function and anatomy
5. Emerging potential indications Predict the need for colectomy Evaluate response to therapy Bone health assessments

Reference: Deepak and Bruining [85]

Unique Radiographic Findings in Inflammatory Bowel Disease

Perianal lesions affect approximately one quarter of the global CD population, with 18% of the case presenting as penetrating lesions: fistulas (Fig. 2.3) or abscesses (Fig. 2.5). For the development of perianal fistulas, the cumulative probabilities are 16.9% and 28.3% at 10 and 20 years from diagnosis, respectively [115]. The prevalence of perianal fistulas in Crohn's disease varies according to disease location, with fistulas being least common in isolated ileal disease (12%) or ileocolonic disease (15%) and most common in colonic disease (41%), particularly in cases with rectal involvement (92%) [116].

The "comb sign" (Fig. 2.4) is seen in CD. It is due to fibrofatty proliferation and perivascular inflammatory infiltration on the mesenteric side of the colon forming multiple tortuous opacities. The increase in vascularity seen here appears like a comb's teeth on CT. Another radiographic finding related to the same inflammatory phenomenon is creeping fat (Fig. 2.6).

Intra-abdominal abscesses occur spontaneously in 10–30% of patients with Crohn's disease 10–20 years after their diagnosis [117]. The common feature seen in CT is rim enhancement, which, when greater than 50% of the circumference of a collection, is 54% sensitive, 71% specific, and 62% accurate for diagnosing an abscess [118]. On imaging, abscesses are frequently surrounded by fat stranding. MRI has superior soft-tissue resolution compared to CT, but because of its higher costs and longer scanning time, CT is the preferred option in detecting an abscess.

Population-based cohort studies have shown that out of the 80% Crohn's disease patients with penetrating disease, 5–28% have a stricturing pattern of inflammation [119–124]. These patients develop strictures within 10 years of their diagnosis [125–126]. A stricture (Fig. 2.7) is a narrowing of the intestinal lumen. Strictures are classified into inflammatory or fibrotic lesions based on chronicity. Computed tomography enterography (CTE), magnetic resonance enterography (MRE), and bowel ultrasound (US) are the three most commonly used cross-sectional imaging modalities used in the identification of strictures. All three imaging techniques have high accuracy for evaluation of strictures affecting the small bowel or the colon: for

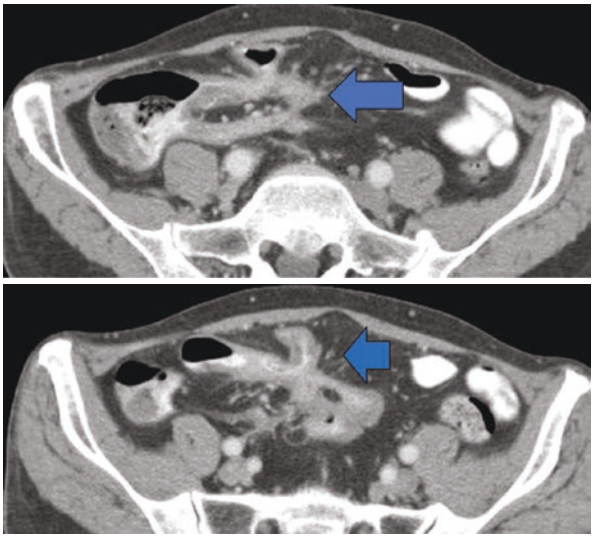

Fig. 2.3 CT Images of the upper pelvis/lower abdomen demonstrate fistulae between loops of distal ileum and the appendix, in a middle-aged patient with active CD. (With permission granted by Dr. Douglas Katz)

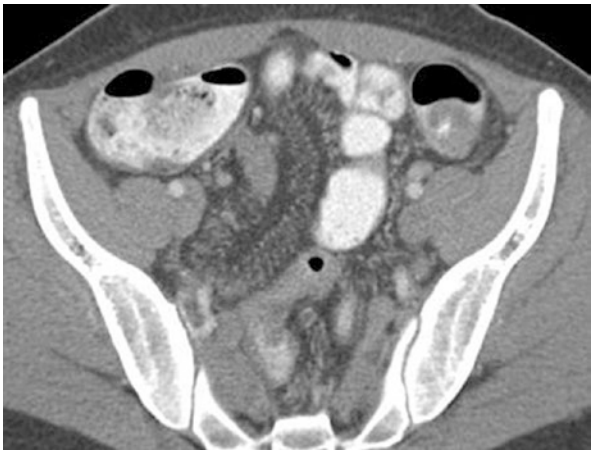

Fig. 2.4 Comb sign on CT scan, in a patient with chronic CD involving the terminal ileum. There is associated creeping fat. (With permission granted by Dr. Douglas Katz)

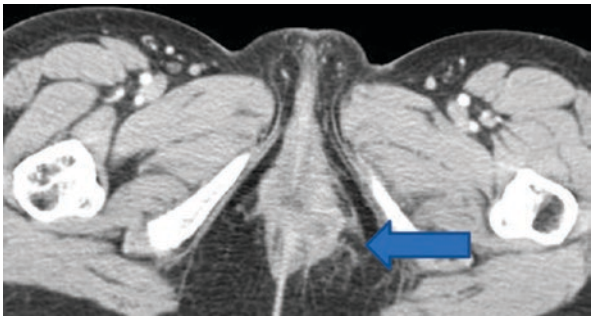

Fig. 2.5 Perianal abscess. Pelvic CT scan shows a left small perianal abscess with adjacent inflammation in the left ischiorectal fossa fat (arrow). (With permission granted by Dr. Douglas Katz)

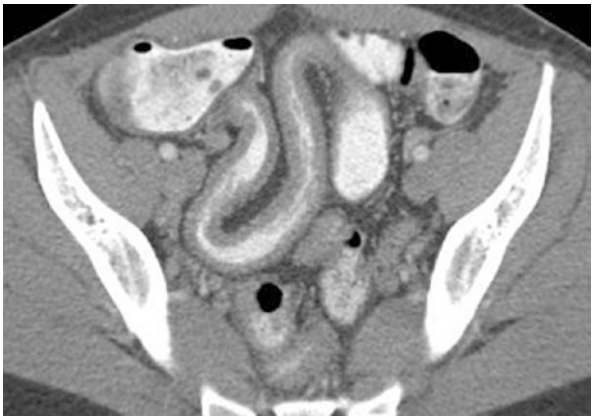

Fig. 2.6 Creeping fat on CT scan. There is terminal ileal diffuse thickening, prominent adjacent fat, and prominent adjacent vessels, in a young adult with active CD. (With permission granted by Dr. Douglas Katz)

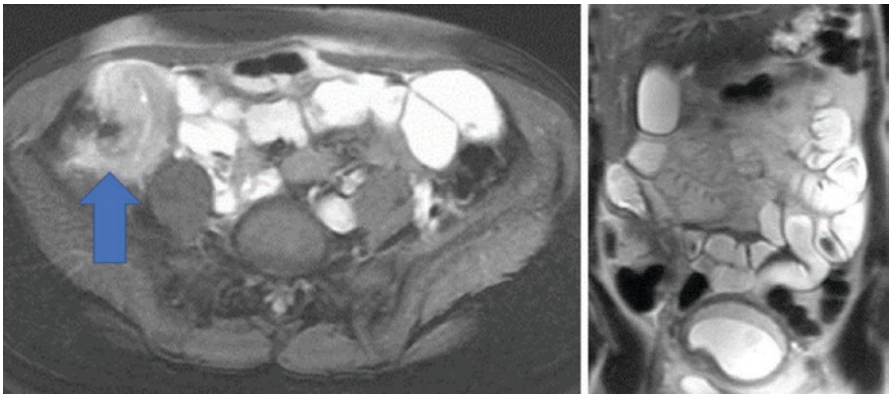

Fig. 2.7 Strictures on MRI. Axial (left image) and coronal (right image) T2-weighted MR images in a young teenager shows mild distension of the more proximal small bowel, and marked thickening, luminal narrowing, and associated inflammatory changes of the terminal ileum (arrow). (With permission granted by Dr. Douglas Katz)

CTE, the sensitivity is 89% and the specificity is 99%; for MRE, the sensitivity is 89% and the specificity is 94%; for US, the sensitivity is 79% and the specificity is 92% [127].

Endoscopy

Endoscopy is a minimally invasive procedure to visualize the hollow organs in our bodies, in this case the digestive tract. It uses a long thin tube equipped with a camera, a light source, and a biopsy channel. The type of endoscopic examinations most commonly used in IBD are colonoscopy and esophagogastroduodenoscopy (EGD). In colonoscopy, we examine the mucosa of the large bowel and terminal ileum, while in EGD, we examine the upper GI tract from the upper esophageal sphincter

to the second portion of the duodenum. In IBD patients, endoscopy plays a vital role in determining the diagnosis and prognosis, assessing disease-related complications, guiding therapeutic options, and assisting in early detection of dysplasia and preventing colorectal cancer [128]. The major limitation of diagnostic imaging is not being able to provide a tissue sample that is required to make a diagnosis of IBD, which is directly addressed with endoscopy. Consequently, colonoscopy with mucosal biopsy is considered the gold standard for the diagnosis of IBD as well as differentiating between CD and UC [129]. In a prospective study of more than 350 patients with IBD followed for more than 22 months, the index colonoscopy was accurate in distinguishing CD from UC in 89% of cases [129].

During the initial evaluation of IBD, the American Society for Gastrointestinal Endoscopy (ASGE) recommends that a full colonoscopy with intubation of the ileum is performed unless there is a contraindication. It is preferred that two biopsies are obtained from five different sites of the examined bowel, including the rectum and ileum in particular [130]. The specimens should be taken from both the diseased and the normal-appearing mucosa [131]. For the bowel preparation, the patients should be advised against using NSAIDs and sodium phosphate-based bowel cleansing agents as they cause mucosal changes that may mimic IBD [132]. Colonoscopy has a very low rate of adverse events (1/300) but is contraindicated in settings of acute inflammation or suspected toxic megacolon [133].

Endoscopic findings strongly suggestive of ulcerative colitis include continuous inflammation starting at the anal verge and extending proximally, loss of vascular markings of the mucosa, friability, and granularity of the mucosa, erosions, shallow but extensive ulcerations, and spontaneous bleeding.

Many of the endoscopic findings of ulcerative colitis are also seen in CD; three major endoscopic findings that help in differentiating CD from UC include the presence of aphthous ulcers (these are small, shallow lesions that develop on the mucosal surface of the GI tract, be it mouth, gums, or bowel, due to submucosal lymphoid follicle expansion), cobblestoning (these are deep, longitudinal ulcers separated by normal mucosa, which occur late in the disease or after severe inflammation), and discontinuous or skip lesions [130]. Terminal ileum involvement in UC usually occurs in the setting of pancolitis; it is defined as backwash ileitis (meaning the colon inflammation extends proximally), whereas isolated involvement of terminal ileum in the absence of colitis is highly suggestive of CD [134]. The findings during the endoscopy can be classified and is supported by the Revised Montreal Classification. See the table below.

Revised Montreal Classification

Upper GI tract involvement occurs in around 16% of CD patients, and it can involve any part of the upper GI tract from the mouth to the ligament of Treitz. The most common findings seen in EGD include aphthous ulcers, erythema, strictures, and fistulous openings [135]. Upper endoscopy in the setting of adult-onset UC or CD is recommended in patients presenting with upper GI symptoms including

Table 2.7 Revised montreal classification

Ulcerative colitis		
Classification	*Definition*	*Maximal endoscopic involvement*
E1	Proctitis	Limited to rectum
E2	Left sided	Limited to colonic mucosa distal to splenic flexure
E3	Extensive	Extends proximal to splenic flexure
Crohn's disease		
A: Age of onset	*L: Location*	*B: Behavior*
A1: </=16 y	L1: Ileal	B1: Non-stricturing, non-penetrating
A2 = 17–40 y	L2: Colonic	B2: Stricturing
A3: >40 y	L3: Ileocolonic	B3: Penetrating
	L4: Isolated upper GI	. + p: Perianal disease is present

Haskell et al. [134]

dyspepsia, abdominal pain, vomiting, or findings of nutritional deficiency. Ideally, at least two biopsies should be taken from the following site: esophagus, stomach, and duodenum, if there is a suspicion of IBD [135] (Table 2.7).

There are two endoscopic scoring systems developed for Crohn's disease to assess the severity of mucosal involvement in the colon and terminal ileum. These are the Crohn's Disease Endoscopic Index of Severity (CDEIS) and the Simple Endoscopic Score for Crohn's Disease (SES-CD) [136, 137]. SES-CD is more convenient to use and has been included in several commercial endoscopic reporting systems. It has shown excellent intra- and inter-rater reliability [137, 138]. The presence and size of ulcers, the proportion of surface covered by ulcers, the proportion of surface affected by disease, and the presence and severity of stenosis are the four endoscopic variables used in SES-CD. These variables are scored from 0 to 3, and the total is calculated and is reported accordingly: 0–2 (in remission), 3–6 (mild endoscopic activity), 7–15 (moderate endoscopic activity), and >15 (severe endoscopic activity). A sample table is given below on how to score for the SES-CD.

UC Endoscopic Index of Severity (UCEIS) and Mayo Clinic endoscopic subscore has shown to provide a constant objective assessment of the severity of the mucosal disease activity in ulcerative colitis patients [139]. UCEIS incorporates three items—vascular pattern, bleeding, and erosions, quantifying each on a scale of 0–3 (0–2 for vascular pattern) for a total score ranging between 0 and 8. A UCEIS score of >/=4 usually leads to treatment escalation [140]. It demonstrated excellent correlation with disease severity [141] and good intra- and inter-observer reliability [141, 142]. Mayo score takes into account the stool frequency per day, rectal bleeding, mucosal appearance at endoscopy, and the physician's global assessment. For the endoscopic subscore, 0 = normal mucosa, 1 = mild activity (erythema, decreased vascular pattern, mild friability), 2 = moderate activity (marked erythema, loss of vascular patterns, and erosions), and 3 = severe activity (spontaneous bleeding and presence of large ulcers).

Table 2.8 Summary of the endoscopic guidlines of the American College of Gastroenterology (ACG) and the American Gastroenterological Association (AGA)

Society	Surveillance intervals
ACG (UC) 2019	Every 1–3 years for UC of any extent beyond the rectum Every year for patients with PSC and concomitant UC (based on previous colonoscopies and combined risk factors: Duration Of disease, younger age at diagnosis, greater extent of inflammation, and the first-degree relative with CRC)
AGA 2010	Every 1–2 years with extensive or left-sided colitis Every 1–3 years after two negative examinations More frequent surveillance is needed if there is ongoing endoscopic or Histologic inflammation or history of CRC in a first-degree relative or Anatomic abnormality, i.e., foreshortened colon, stricture, or inflammatory Pseudopolyps Every year for patients with PSC and concomitant UC

Rubin et al. [144]

If a patient is in clinical remission, a routine endoscopy is not recommended unless it would likely change the management [143]. Patients with IBD are at increased risk for colorectal cancer than the general population, so colonoscopy is also used for colorectal cancer surveillance. The colorectal cancer surveillance guidlines are summarized in Table 2.8.

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Chapter 3
Ulcerative Colitis Diagnosis and Management: Past, Present, and Future Directions

Keith Sultan and Noah Becher

Epidemiology and History of Ulcerative Colitis (UC)

Currently, the Centers for Disease Control and Prevention (CDC) estimates the US prevalence of adult inflammatory bowel disease (IBD) at 1.3%, or over 3 million individuals [1]. Among these, half or more are believed to have ulcerative colitis (UC). Regional variation has also been noted within the United States, with higher rates in the northeast. Similar high IBD rates have been reported in the countries of northern and western Europe [2]. A variation of prevalence has also been noted across racial and ethnic groups, with the highest rates for whites and Ashkenazi Jews and lower rates among traditional minority populations [3, 4]. Much as we are witnessing an increase in the rates of IBD among minority groups in the US population, so too are we observing increasing rates internationally [5].

While the history of IBD appears to parallel the history of industrialization and westernization, it should be noted that UC leads the way, typically decades ahead of Crohn's disease (CD) within a population [6]. Though likely present in some form throughout history, the recognition of UC as a distinct disease entity coincided with the observed microbial association with many diseases, followed by the observed *lack* of this association with a form of chronic colonic inflammation. The advent of sigmoidoscopy lead to the first formal descriptions of what we now call UC in the 1800s [7, 8]. Following those initial reports, rates of UC in the west continued to

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R. Rajapakse (ed.), *Inflammatory Bowel Disease*, Clinical Gastroenterology,
https://doi.org/10.1007/978-3-030-81780-0_3

rise and somewhat level off into the current era. Though many decades behind, this pattern is repeating itself in previously low-risk regions around the world such as Southeast Asia and the Far East.

Early Medical Therapies: The Pre-Biologic Era

Unfortunately, many decades passed between the recognition of UC as a distinct disease entity and the first effective treatments. It is worth briefly noting some of the milestones along the road that transformed UC from an untreatable and often fatal illness to one for which most patients find a safe and effective medical (or surgical) treatment.

The first and perhaps still the greatest breakthrough in the management of UC came with the identification, isolation, and eventual production of corticosteroids (CS). Isolating hormones from the adrenal cortex of thousands of slaughtered cattle, Philip S. Hench (rheumatologist) and Edward C. Kendall (biochemist) first used "Compound E" to treat a 29-year-old female patient hospitalized with rheumatoid arthritis at the Mayo clinic [9]. The patient recovered in 3 days. Fortunately, at around this time, Lewis Sarett, a chemist working for Merck, devised a chemical process to synthesize Compound E, renamed corticosterone, in 1946. Further clinical use of corticosterone demonstrated similar dramatic results in 14 more arthritis patients, with Hench and Kendall sharing the 1950 Nobel Prize for Medicine with the Swiss scientist Tadeus Reichstein [10, 11].

Not even a decade later in 1954 the first randomized and blinded trial of cortisone was conducted by Truelove and Witts [12]. They randomized patients to either cortisone 100 mg daily (approximately equivalent to prednisone 20 mg daily) or "dummy" drug. They included only those patients who would "normally require at least 6 weeks treatment in hospital" and excluded those with regional colitis or ileitis. They included 210 patients (109 cortisone, 101 placebo), with remission defined as one to two stools/day and no blood. At 6 weeks, they observed remission in 41.3% of cortisone-treated patients vs. 15.8% for those receiving placebo. Overall, there were 15 deaths including five (4.6%) for the cortisone-treated patients vs. ten (9.9%) for those receiving placebo. Looking back from the present day, the study appears familiar in design to those common today, while providing a stark reminder of the devastating toll that untreated UC can reap.

Another major advance in the treatment of UC took place with the development of sulfasalazine. Nanna Svartz, a Swedish physician, began using sulfasalazine, an azo bonded combination of sulfapyridine (a known antibiotic) and 5-aminosalicylic acid (5-ASA or mesalamine) for the treatment of arthritis. In addition to its benefits for arthritis, she noted an improvement of bowel complaints for those patients also suffering from UC [13]. Since the compound reaches the colon largely intact and is

subsequently split by colonic bacteria, the question remained as to which was the therapeutic component. The question was later answered in a blinded trial by Azad et al. randomizing patients with sigmoidoscopy-confirmed UC to receive enema therapy with either sulfasalazine or 5-ASA alone or sulfapyridine alone [14]. The improvement in the sulfasalazine and 5-ASA groups, but not the sulfapyridine group, confirmed 5-ASA as the therapeutic component. The following years saw the development of 5-ASA/mesalamine preparations without sulfapyridine, which were able to provide the therapeutic benefit of 5-ASA without the sulfapyridine-related side effects [15, 16].

Though management of moderate to severe UC increasingly centers around the use of biologic therapies, it is worth remembering that the era of immunosuppressant use did not begin with the US approval of infliximab for UC in 2005, 8 years after its approval for CD. Bean et al. first demonstrated the efficacy of mercaptopurine (6-MP) and its precursor azathioprine (AZA) for the treatment of UC in the early 1960s [17, 18], followed shortly thereafter by Korelitz and Wisch [19]. First developed as a chemotherapeutic agent, 6-MP inhibits cellular proliferation by acting as purine mimic. This effect is most pronounced on rapidly dividing cells such as inflammatory cells, which are associated with UC. While neither 6-MP or AZA, together referred to as the thiopurines, is currently recommended as agents to induce clinical remission for UC, they are both still commonly used and recommended as maintenance therapy for patients with a response to corticosteroids [20]. As with the earlier discovery and clinical use of corticosteroids, the developers of 6-MP were also awarded a Nobel Prize in 1988 [21].

Diagnosis of UC

The diagnosis of UC is based upon a combination of factors. Though there is not a universally accepted "gold standard" of diagnostic criteria or specific checklist of required characteristics to be met, there is broad agreement on the features that make for an accurate diagnosis. Given the increasing complexity of medical therapies, as well as the possibility of surgical management decisions with lifelong consequences, accuracy of diagnosis is paramount. While the endoscopic examination may be the most important part of this workup, endoscopic findings typically can and *must* not exist in isolation of other parts of the workup including:

- Clinical presentation
- Laboratory evaluation
- Endoscopic examination
- Microscopic findings
- Imaging studies

Clinical Presentation

The most common presenting complaint associated with UC is rectal bleeding [22]. Bleeding either as the sole abnormal complaint or associated with other symptoms occurs in upwards of 90% of patients. While not always the case, bleeding often occurs with other notable changes of bowel habit, especially increasing frequency of stools, decreasing formation, and bouts of urgency, often with abdominal pains and cramps. Though signs of more advanced disease such as weight loss and nocturnal bowel complaints (i.e., awakening from sleep with urgency with or without bowel movement) may more immediately suggest a UC diagnosis – as opposed to irritable bowel syndrome with hemorrhoidal bleeding – these findings may not accompany an initial UC presentation and should not delay an appropriate diagnostic workup. While UC is typically associated with diarrhea, it is important to remember that some patients with severe distal disease may present with constipation or severe urgency without significant bowel movements, i.e., tenesmus [23]. To better understand the severity and frequency of a patient's complaints, it is important to not just ask how many stools a patient has each day, but how often the patient will seek out the bathroom with the urge to move their bowels.

As with most medical conditions, even for patients with a known UC diagnosis, a detailed history is needed to help select the appropriate workup and intervention. Elements of the history such as a family history of IBD and prior tobacco use may statistically increase the likelihood of a patient developing UC, but far more important for the individual patient is the time course of the complaints. Again, while there is no specific standard in this regard, the longer that the complaints have occurred and the greater the consistency of these complaints, the greater the likelihood of IBD rather than infectious or functional bowel disease. Particularly during this earlier period, it is important to obtain an accurate history of new medications (even those that may have already been discontinued), including over-the-counter medications and dietary supplements. Nonsteroidal anti-inflammatory medications (NSAIDs) may mimic or possibly exacerbate both UC and CD, and a large number of medications (e.g., metformin) list diarrhea as either a possible or frequent cause of gastrointestinal complaints [24, 25]. Though the role of the acne therapy transretinoic acid as it relates to cause/exacerbation of UC, remains controversial, newer immune therapies such as the checkpoint inhibitors may trigger a UC-like illness, often necessitating a similar diagnostic and therapeutic approach to UC [26–28]. Other immune suppressing medications such as mycophenolate may also cause diarrhea as well as a true colitis [29, 30]. Of course, a detailed travel and sexual history is needed, as certain chronic infections such as ameba and chlamydia may cause symptoms which can mimic UC. A few quick questions may also elicit a history of extraintestinal disease manifestations such as arthritis and ocular or skin complaints that might tip the balance toward proceeding with a workup and, if positive for UC, might have significant impact on the timing and type of therapy used. Similarly, a quick but comprehensive physical exam may reveal some of these ocular or skin findings, along with signs of wasting and abdominal tenderness, which

are often present with more severe disease presentations. Rectal findings such as stenosis, fistulae, or skin tags might prompt a more extensive workup for CD, while rectal prolapse or hemorrhoids might at least temporarily redirect the patient to colorectal surgery for evaluation.

- Rectal bleeding is the most common presenting UC complaint.
- Loose stools or diarrhea is common but not required to suspect UC.
- Remember that medications may alter bowel habit, and some even cause colitis.
- Thorough history and physical exam is needed to best select patients for further workup.

Laboratory Testing

Laboratory testing for suspected or known UC consists of a combination of blood and stool testing. There is currently no single test or combination of tests that can substitute for an endoscopic evaluation to confirm an initial diagnosis, though as with the patient history and physical exam the laboratory testing can suggest a UC diagnosis as well as disease severity. Abnormalities associated with routine blood testing that might favor a UC diagnosis include anemia, thrombocytosis, iron deficiency, electrolyte abnormalities, and low serum albumin. Blood inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) will also be elevated in most cases but are often normal in cases of mild disease [31, 32]. Though commonly used in clinical practice, expert opinion still does not support the use of serologic testing such as ASCA, ANCA, and newer genetic/serologic panels for either the diagnosis of UC or CD [33, 34]. Additionally, it may be prudent, even on a first visit, to test for tuberculosis with QuantiFERON-TB Gold, as well as to check hepatitis B serologies, as abnormalities on these tests may impact the ability to quickly and safely treat with immunosuppressant or biologic therapies.

Stool testing is also needed for accurate diagnosis of suspected UC, mainly to rule out infectious etiologies. It is worth keeping in mind, however that isolating and treating a pathogen does not exclude the possibility of UC, as patients may present with infections supra-imposed on underlying UC. Conversely, for those with an established UC diagnosis, it is important to retest patients with apparent disease flares before automatically altering or escalating UC therapy. At minimum, stool testing should include an investigation of common pathogens either with traditional cultures and staining or with the newer stool polymerase chain reaction (PCR) tests. Ameba testing should also be considered in appropriate circumstances. All results, however, need to take into account the context of the clinical presentation. Given the sensitivity of the newer PCR testing, an abnormal finding does not necessarily exclude UC but may reflect colonization rather than infection [35]. This dynamic has been best studied in the case of *Clostridium difficile* (C-diff). C-diff testing is recommended for all suspected cases of UC, as well as for all those with

exacerbation of known UC. However, the high sensitivity of testing with PCR may reveal as many cases of colonization as clinically relevant infections. As such, it is suggested that toxin assays continue to be employed for known UC patients to help distinguish colonization from infection, though there is no current consensus on best diagnostic/therapeutic algorithm [36].

Though stool inflammatory testing such as lactoferrin and staining for white blood cells (WBCs) have long been available, these have been increasingly replaced by the more sensitive fecal calprotectin (FC) test, which reflects activity of bowel neutrophils [37, 38]. FC, however, is not specific to IBD-related bowel inflammation and may also be elevated in cases of enteric infections. The greatest utility for FC may be in helping to distinguish inflammatory vs. functional complaints, both for those with new presentations and for those with an established diagnosis. FC is a useful marker for response to treatment, though it is still unclear how well the level of elevation correlates with severity of disease activity. Anal swabbing for sexually transmitted diseases may also be appropriate for some patients, particularly for those with complaints limited to blood and mucus per rectum. Also, while stool testing for cytomegalovirus (CMV) may be available, its value may be limited to deeply immune-suppressed patients who are not candidates for an endoscopic examination.

- Blood testing may suggest UC but never alone diagnoses UC.
- ESR and CRP elevation is frequent but is often absent in milder disease presentations.
- Isolation of stool pathogens does not rule out UC; reassess post-treatment.
- FC is not specific to UC or IBD, and degree of elevation may not correlate to disease severity.

Endoscopic Examination

At a minimum, examination by sigmoidoscopy with mucosal biopsies is required for the initial diagnosis of UC. A diagnostic first examination will not just confirm mucosal inflammation but can be used to assess the extent and severity of disease, which are necessary to guide effective and appropriate therapy. Though relatively common in the pediatric population, cases of gross rectal sparing of UC are rare in untreated adults [39, 40]. The classic presentation of UC involves gross inflammation beginning just above the anal verge and continuing in a continuous/circumferential pattern proximally. In cases that involve less than the entire colon, it is common to observe a sharp cutoff between abnormal and normal appearing mucosa. Extent of disease is typically described by the Montreal Classification as proctitis (limited to the rectum), left-sided disease, or extensive colitis (any length of extension proximal to the splenic flexure) [41]. Severity of inflammation may range from mild erythema, granular mucosa, and contact bleeding to severe mucosal edema, ulceration, and spontaneous bleeding.

Particularly for sicker patients, a full colonoscopy may be too risky and is not needed for an initial diagnosis. At some point, however, a complete colonoscopy with biopsies is required to both assess for disease extent – which has implications for future disease surveillance – and examine the terminal ileum for signs of CD. Biopsies of normal appearing colon segments should be taken as well [33, 34]. With a full colonoscopy, it is important to accurately identify atypical patterns of UC that are not regarded as CD. An appendiceal "patch" of inflammation in the cecum may be found in cases of limited left-sided UC [42, 43]. Also, inflammation may be found in the terminal ileum in cases of severe pancolitis, termed backwash ileitis [44, 45]. Neither of these findings requires a more extensive evaluation of the upper gastrointestinal (GI) tract for CD, though imaging or capsule endoscopy evaluation may be appropriate if there is clinical suspicion for disease proximal to the colon. Surveillance colonoscopy considerations will be discussed later in the chapter.

- Sigmoidoscopy is adequate for an initial UC diagnosis.
- Biopsy protocols should include grossly normal appearing colon segments when identified.
- Recognize atypical patterns of UC to avoid misdiagnosis as CD.

Microscopic Examination

A variety of histopathologic findings may occur in UC and may be dependent upon the timing of tissue sampling as it relates to disease course and therapy. Again, while there is no single finding that is required for a UC diagnosis, at least some form of abnormality must be identified. Current guidelines recommend at least two biopsies obtained from five segments around the colon and ileum [34]. Early UC is characterized by findings of basal plasmacytosis with preserved crypt architecture and a neutrophilic infiltrate, while later findings include cryptitis, crypt abscesses, crypt architectural distortion, and mucosal atrophy [46]. As noted earlier, a number of medications can cause colitis mimicking UC, and it is important to provide relevant clinical information to the interpreting pathologist to avoid a misdiagnosis.

- No single histopathologic finding defines UC.
- Microscopic findings may differ relative to the time of disease progression.

Radiographic Imaging

For most cases of suspected or known UC, there is no imaging routinely required. Imaging, which increasingly means computerized tomography (CT) scan (standard or enterography) and/or magnetic resonance (MR) enterography, has steadily

replaced prior modalities such as plain abdominal x-rays, small bowel series, and contrast enema examinations. Imaging is appropriate for those patients with worsening abdominal pain and distention to rule out colonic dilation/megacolon as well as to exclude perforation or other pathologies. In less critical situations, upper GI imaging may be appropriate to investigate for evidence of CD such as with patients complaining of bloating or vomiting suspicious for small bowel disease, or generally where the clinical complaints/severity do not seem to match the endoscopic findings. Other imaging modalities not directly related to defining bowel inflammatory activity are also commonly used for UC management. Bone density testing is routine following UC diagnosis and is especially important for those with a history of corticosteroid use. Imaging of the axial spine may be needed to confirm comorbid sacroiliitis and spondylitis, as well as abdominal sonogram for suspected fatty liver, cholelithiasis, and cholecystitis, which are all more common among UC patients. Finally, evaluation of abnormal bloodwork may suggest the need for MR cholangiopancreatography (MRCP) to exclude primary sclerosing cholangitis, which is a diagnosis with significant therapeutic and clinical impact.

– Upper GI imaging is not required for typical/uncomplicated UC.

Management of Ulcerative Colitis

The recommended management of UC is based upon a combination of disease extent and severity. The disease extent, divided into proctitis, left-sided colitis, and pancolitis, as previously defined, provides both a guide to the suitability and type of "topical," nonsystemic therapy that can be utilized as well as toward prognosis. Disease severity, based upon clinical signs and symptoms, endoscopic appearance, or both, is typically used to guide whether escalation to systemic therapy (i.e., oral or intravenous CS, thiopurines, biologic therapies) is warranted.

The utilization of clinical and/or endoscopic scoring of disease severity is most clearly referenced in the many new clinical guidelines [33, 47–49]. The use of formal disease activity scores is a requirement in the research setting such as clinical drug trials, though it is less of a presence in the course of day-to-day clinical practice which tends to follow an informal physician global assessment model. For the purposes of the following review, we will be dividing treatment recommendations along the lines of the proposed categories of *mild*, *moderate/severe*, and *fulminant* disease found in the latest ACG guidelines [33]. These categories are themselves a modification and combination of the traditional Truelove and Witts criteria, incorporating newer testing such as FC, as well as endoscopic measures of disease severity as outlined by the Mayo endoscopic subscore and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) (Tables 3.1 and 3.2) [50–54]. Notably, the patient's own sense of well-being and the lifestyle impact of their disease may be less or greater than suggested by the formal disease scoring models. Patient-reported

Table 3.1 Mayo endoscopic score

Mayo Endoscopic Score [1]	Disease activity	Endoscopic findings
0	Normal or inactive	None (normal)
1	Mild	Erythema, decreased vascular pattern, mild friability
2	Moderate	Marked erythema, absent vascular pattern, friability, erosions
3	Severe	Spontaneous bleeding, ulceration

Table 3.2 Ulcerative Colitis Endoscopic Index of Severity (UCEIS)

Ulcerative Colitis Endoscopic Index of Severity (UCEIS) [2]		
Descriptor	Finding (score)	Definition
Vascular pattern	Normal (0)	Normal vascular pattern with arborization of capillaries clearly defined, or with blurring or patchy loss of capillary margins
	Patchy obliteration (1)	Patchy obliteration of vascular pattern
	Obliterated (2)	Complete obliteration of vascular pattern
Bleeding	None (0)	No visible blood
	Mucosal (1)	Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope, which can be washed away
	Luminal mild (2)	Some free liquid blood in the lumen
	Luminal moderate or severe (3)	Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intraluminal blood, or visible oozing from a hemorrhagic mucosa
Erosions and ulcers	None (0)	Normal mucosa, no visible erosions or ulcers
	Erosions (1)	Tiny (# 5 mm) defects in the mucosa, of a white or yellow color with a flat edge
	Superficial ulcer (2)	Larger (>5 mm) defects in the mucosa, which are discrete fibrin-covered ulcers in comparison with erosions but remain superficial
	Deep ulcer (3)	Deeper excavated defects in the mucosa, with a slightly raised edge

Mild disease: UCEIS 2–4
Moderate to severe disease: UCEIS 5–8
Fulminant disease: UCEIS 7–8
Schroeder et al. [53]; Travis et al. [54]
[a]UCEIS total combined score is used to classify the severity of disease

outcomes (PRO) in turn will also impact decisions on types of therapy [55]. An understanding that assessment of treatment outcomes should not only reflect objective markers of disease activity but also patients' perceptions of disease activity and satisfaction with treatment has led to recent interest and regulatory requirements for the development of PRO measures into clinical trial design.

The following review is focused on basic principles/pearls of clinical management. For a more detailed review, we recommend accessing the updated guidelines and clinical source material as referenced.

Mild Disease

ACG UC Activity Index

- *<4 stools/day, intermittent bleeding, mild occasional urgency*
- *Normal Hgb, ESR < 30, elevated CRP, FC > 150–200*
- *Mayo endoscopic subscore 1.*
- *UCEIS 2–4*

Arguably, the most important distinction for guiding UC treatment is that between mild disease and all other levels of severity. Though the line may be blurry, the distinction between mild disease and greater levels of severity typically separates the focus of treatment between the worlds of mostly topical/non-immune therapies versus treatments that suppress or "modify" the immune system. "Topical" therapy refers to the primary site of action (mucosal) of these medications, rather than the oral or rectal route of drug delivery.

The mainstay of topical therapy is the 5-ASA/mesalamine formulations, both orally and rectally administered. The oral mesalamines are themselves updated versions of the older sulfasalazine. Removal of the sulfa component of the drug succeeded in improving tolerance without impacting efficacy. To a great extent, these newer formulations, some with approval for once-daily dosing, have become the standard for treatment of mild UC. Currently, the preferential use of sulfasalazine is more frequently limited to those patients continuing long-standing therapy or those with limited or no prescription insurance coverage.

For mild disease limited to the rectum, current guidelines recommend mesalamine suppository once daily. For those not responding or intolerant to mesalamine, a trial of rectal CS may be considered. Ideally, this should involve budesonide MMX foam, but hydrocortisone suppositories may also be used. Though all CS preparations have some systemic absorption and effect, these preparations are believed to act mostly at the topical level. For whatever therapy is used, a trial of several weeks should be attempted before deciding upon the success or failure of treatment. For patients responding to topical mesalamine, therapy may be continued indefinitely for maintenance. There is currently no consensus upon duration of therapy or discontinuation/tapering of treatment. Also, though it may be disappointing to encounter a patient with mild/limited rectal disease who fails local therapy, the classification of disease extent/severity should not limit escalation of therapy for those who fail to respond to topical therapy alone.

For those with disease extending proximal to the rectum, therapy will need to incorporate an oral mesalamine preparation and perhaps mesalamine enemas. Though results and tolerance to enemas may vary, if taken properly, they can provide treatment well into the sigmoid colon. While mesalamine enemas alone may be sufficient to control disease symptoms, trial evidence has shown superiority of combining oral mesalamine and rectal mesalamine [56, 57]. Unlike the enemas, oral mesalamine preparations are approved for a range of doses, typically from 2.4 grams and 4.8 grams, and either once daily or multiple daily dose regimens. Despite the recommendation of a dose range, there has been little demonstrated benefit for the higher doses either for induction or maintenance of response. Similarly, there is no benefit to multiple daily doses, and there is evidence that single daily dosing may in fact improve compliance and clinical outcomes [58, 59]. At this time, no single mesalamine preparation is considered superior to any other [60]. Failure or intolerance to one preparation is generally regarded as a class effect. That is, switching from one preparation to another does not typically improve response, though patient-specific/anecdotal experience may suggest otherwise. As with more limited disease, long-term maintenance with mesalamine is recommended.

For mild disease not responding to mesalamine, the use of CS is recommended. When available, current guidelines support the use of budesonide MMX (9 mg/day), though prednisone (starting at 40 to 60 mg/day) may be used as well. Though less effective than prednisone, budesonide MMX is associated with less systemic side effects [61]. Currently, there is no standard tapering regimen for either, though there is broad consensus that neither should be used for long-term maintenance therapy. There is also a lack of consensus with regard to the appropriate maintenance therapy for those patients with mild disease following CS response. For those previously failing but tolerant to 5-ASA, another course may be reasonable. For all others, failure of corticosteroid tapering or relapse should prompt consideration of immune therapies.

- *Suppositories treat the rectum, while enemas may be effective through the sigmoid colon.*
- *Oral mesalamine 2.4 g daily is as effective as 4.8 g daily.*
- *Daily mesalamine dosing is as effective as multiple daily doses.*
- *For those requiring CS, budesonide MMX is preferred.*

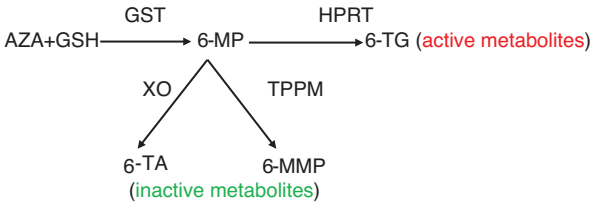
Moderate to Severe Disease

ACG UC Activity Index.

- *>6 stools daily with frequent blood, urgency often*
- *Hgb <75% of normal, ESR > 30, CRP elevated, FC > 150–200*
- *Mayo endoscopic subscore 2–3*
- *UCEIS 5–8*

Moderate/severe disease is more than just an increasing frequency of bowel movements and more frequent passage of blood with bowel movements. Moderate to severe disease is characterized by the presence of worsening objective clinical markers of disease activity (ESR/CRP, FC, anemia, thrombocytosis, tachycardia, wasting), which typically mirror findings on endoscopic examination (e.g., more extensive disease, deeper ulcers, spontaneous bleeding). Though the recommendations provided are meant for outpatient management, it is important to distinguish severe disease from fulminant disease for which hospitalization is recommended and which has specific management strategies.

In the immediate pre-biologic era, management of moderate/severe UC heavily relied upon the use of CS and thiopurine therapy, 6-MP, or AZA. There is no current evidence to support a role for methotrexate monotherapy for treatment of UC [62]. Though current guidelines strongly favor biologic therapies as first line for moderate/severe disease (both for induction and maintenance therapy), they still allow for a CS/thiopurine-based approach. In this type of scenario, clinical response and ideally remission are achieved by CS induction at a dose of prednisone 40–60 mg daily. There is no evidence to favor multiple daily CS doses over single daily dosing, though patients may anecdotally report benefit to one approach or another (e.g., avoiding evening use to lessen insomnia). Following successful induction, a thiopurine is initiated on a weight-based dosing regimen while proceeding with CS taper. In this method, the thiopurine is utilized as the maintenance agent [20, 63]. Thiopurine dosing is typically not initiated until phenotype testing for thiopurine methyltransferase (TPMT) activity to identify those patients for whom either a lower starting dose is needed due to impaired TPMT activity (8.0% of the population) or avoidance of therapy completely due to absent TPMT activity (0.3%) would be appropriate [64] (Fig. 3.1) [65]. Once initiated, frequent laboratory monitoring with CBC and chemistries are recommended to check for common toxicities such as leukopenia and elevated transaminases. There is currently no evidence to support the use of thiopurine monotherapy for induction without the use of CS.



AZA:Azathioprine
GSH: reduced glutathione
GST:Glutathione-S-transferase
6-MP: 6-Mercaptopurine
6-TG:6-Thioguanine
HPRT:Hypoxanthine-guanine phosphoribosyltransferase
6-TA: 6-Thiouric acid
6-MMP:6-Methylmercaptopurine
XO: Xanthine oxidase
TPMT: Thiopurine methyltransferase

Fig. 3.1 Thiopurine metabolism. (*AZA* Azathioprine, *GSH* Reduced glutathione, *GST* Glutathione S-transferase, 6-*MP* 6-Mercaptopurine, 6-*TG* 6-Thioguanine, *HPRT* Hypoxanthine-guanine phosphoribosyltransferase, 6-*TA* 6-Thiouric acid, 6-*MMP* 6-Methylmercaptopurine, *XO* Xanthine oxidase, *TPMT* Thiopurine methyltransferase)

- *Prednisone use for induction should never exceed 60 mg daily.*
- *The thiopurines are only indicated for maintenance therapy following CS response.*
- *TPMT testing is recommended prior to initial weight-based thiopurine dosing.*

In contrast to the thiopurines, biologics may be used both for induction and maintenance of response/remission in moderate to severe disease. In this role, they offer several advantages over the CS/thiopurine approach including avoidance of CS side effects, ease of use and monitoring, and the ability to induce and maintain with a single agent. Currently, three classes of biologics have approval for UC treatment: TNF-alpha inhibitors (infliximab, adalimumab, golimumab), the anti-integrin therapy vedolizumab, and the interleukin 12–23 (IL-12/23) inhibitor ustekinumab. All are approved and regarded as acceptable first-line biologic therapies for mild/moderate UC. That is, a patient does not need to fail CS or CS/thiopurine therapy first. However, recent data from network meta-analysis, attempting to compare response rates across different clinical trials, has suggested a superiority of infliximab for induction therapy [66]. Additionally, VARSITY, the first head-to-head trial of two different biologics for UC has been reported, demonstrating the superiority of vedolizumab over adalimumab for induction therapy [67]. As such the most recent AGA guideline has specifically supported the use of either infliximab or vedolizumab for UC for those patients without prior biologic exposure [47]. For those patients achieving response/remission with biologic therapy, all guidelines suggest continuing the same treatment indefinitely for maintenance.

It is worth noting that while current guidelines do not provide recommendations for duration of immune suppressing or biologic therapy, there is evidence of risk of malignancy with their use. Specifically, the use of thiopurines even after their discontinuation has been associated with an increased risk of squamous cell skin cancers, and TNF-alpha inhibitors have been associated with an increased risk of melanomas [68–70]. Cervical cancer risk, likely related to human papillomavirus infection, has been associated with IBD, but its relationship to either immune suppressant or biologic use remains unclear [71, 72]. Further, thiopurines and TNF-alpha inhibitors appear to carry a significantly increased risk of lymphoma, which appears to be associated mostly with active rather than past exposure [73–75]. The increased relative risk of lymphoma has been noted to be two to three times greater than an individual's baseline, though the absolute risks remain small, approximately one case per 1000 person years [74]. The decision regarding the continuation of thiopurines and/or TNF-alpha inhibitors in the face of this risk is a highly personal one that needs to be a routine part of the conversation between patient and physician.

Beyond the guidelines, the choice of biologic therapy typically takes into account other patient-specific factors. As an example, those favoring convenience may opt for a medication with at-home subcutaneous administration such as adalimumab or ustekinumab and possibly vedolizumab in the near future [76]. Conversely, there are those patients and physicians who may prefer a medical facility and the security and documented compliance of intravenous dosing. Additionally, given the limited UC and CD indications, those with additional diagnoses such as arthritis or

psoriasis may be better off skipping the bowel selective vedolizumab as first line. A history of heart failure or frequent infections might also suggest a choice other than TNF-alpha inhibitors as first-line treatment. Also, while not contraindicated, there appears to be no benefit to continuing oral mesalamine therapy in those responding to biologic therapy, with current guidelines advocating their discontinuation [77].

For those patients not achieving an acceptable response to biologic therapy (primary failure), or having disease recurrence after an initial response (secondary failure), the options include switching to another biologic, thiopurine, or tofacitinib therapy. For those patients failing TNF-alpha inhibitors, particularly either infliximab or adalimumab, it is important to distinguish primary vs. secondary failure, ideally utilizing currently available therapeutic drug level and antibody level testing. In either a primary or secondary failure, the drug and antibody level tests may be used to guide an approach of switching within the same drug class (for those who have lost response due to drug-specific antibody formation) vs. escalating the dose of the current medication (for those with inadequate drug trough levels) vs. switching to an entirely new class of medication (for those with adequate drug trough levels and an absence of neutralizing antibodies) [78]. Recent network meta-analysis data suggests that patients with prior failure of infliximab might not be as responsive to second line vedolizumab as other biologic failures, though the use of vedolizumab as second-line therapy is not prohibited [66].

Though mostly used as monotherapies, all of the currently available biologics may be used in combination with a thiopurine both for induction and maintenance. Though the recent guidelines encourage this approach, they do acknowledge that this is mostly supported by study evidence for infliximab in combination with thiopurine. The recommendation to combine any biologic with either a thiopurine or methotrexate is largely extrapolated from this infliximab/thiopurine data, demonstrating clinical benefit through prevention of anti-infliximab antibody formation [79, 80]. Despite these recommendations, there is no direct evidence supporting a similar mechanism of benefit for non-infliximab biologic therapy. Moreover, the risks of lymphoma observed with either active use of thiopurine or TNF-alpha inhibitors as monotherapy are increased further with active combination therapy [74]. This risk appears to be especially high in young males with greater than 2 years of combination therapy [81, 82].

In cases of failure or loss of response to a biologic, the latest option for induction and maintenance therapy is the new "small molecule," tofacitinib. The category of small molecule IBD therapy is, loosely, anything that is not a large molecule/biologic. Patients and practitioners need to appreciate that tofacitinib's oral dosing and/or its status as a non-biologic therapy does not imply a greater level of safety, as suggested by its current position as a second-line agent following biologic failure. It is a broad immune suppressing therapy as exemplified by its use for rheumatoid arthritis, as well as its potential infectious complications, such as herpes zoster, which may occur in as many as 5% of patients [83]. Zoster vaccination is recommended (but not required) for all patients at risk for zoster before initiating tofacitinib therapy. An observed increase in thrombotic complications prompted a lowering of the recommended dose for RA to 5 mg BID. Though currently not

prohibited for prolonged use at an UC induction dose of 10 mg BID, it is recommended that all responding patients try decreasing the dose after 8 weeks to 5 mg BID. However, doses of 10 mg BID may be continued for as long as 16 weeks if needed to achieve maximal therapeutic response, with a recommendation to discontinue at 16 weeks if an adequate response is not achieved (similar dosing recommendations for the daily extended release formulation of 21 mg induction, 11 mg maintenance). Dose escalation back to 10 mg BID may be used in those failing maintenance at 5 mg BID. Unlike biologic therapies, a combination of thiopurine and tofacitinib is not recommended, and there is no data to support a role for tofacitinib in combination with methotrexate for UC.

- *All UC biologic therapies are approved for first-line use for moderate/severe UC.*
- *All UC biologic therapies are approved for induction and maintenance.*
- *There may be an advantage to infliximab or vedolizumab as first-line biologic therapies.*
- *Patient-specific health factors and preferences may influence the choice of biologic.*
- *Tofacitinib is specifically a second-line therapy for those with prior biologic failure.*

Fulminant UC

ACG UC Activity Index

- *>10 stools daily, continuous bleeding, continuous urgency*
- *Transfusion required, ESR > 30, elevated CRP, FC > 150–200*
- *Mayo endoscopic subscore 3*
- *UCEIS 7–8*

Though patients themselves may be more or less reluctant to seek hospitalization, those with more than ten bowel movements a day, a majority with blood, as well as signs of systemic toxicity such as fever, tachycardia, anemia, and elevated ESR/CRP should be directed toward hospitalization. Though therapies have improved with time, it is worth remembering that patients meeting these criteria have a 20% short-term colectomy rate [84].

Once hospitalized, particularly if the patient is admitted to a general medical service, it is important that the gastroenterologist directs treatment consistent with the medical evidence and current guidelines, which may be counter to the instincts of the admitting team. Though all patients should be tested for superimposed bacterial infections, especially C-diff, antibiotics should not be given routinely as they have no proven benefit for the treatment of UC at any stage. Both for C-diff and other bacterial findings (particularly in the setting of PCR-based testing), it is important to try and distinguish infection from colonization when deciding upon

choice and duration of antibiotic [36]. Also, given the high risk for venous thromboembolism in this population, pharmacologic prophylaxis is recommended. This may seem to be contraindicated for patients already anemic and bleeding, though the evidence of risk in this setting is mixed [85, 86]. When pharmacologic prophylaxis is not to be used, mechanical means such as sequential compression devices should be employed. Also, while it is common for patients' diet to be restricted to liquids or even NPO, there is no data to support improved outcomes with bowel rest. Along with this, while there may be individual patients for whom total parenteral nutrition (TPN) may be needed, there is no role for bowel rest with TPN support in the setting of fulminant UC. In addition, though it may seem counter to the goals of admission, i.e., improvement of colitis activity with more aggressive medical management, we highly recommend consultation with an experienced IBD surgeon for all patients from the beginning of admission. Fulminant colitis is a potentially fatal illness. Saving the patient's colon if possible is important, but saving the patient's life is the true primary goal of admission.

Additional workup typically involves abdominal imaging, increasingly with abdominal CT scan, though current guidelines stress that this should be reserved for cases of suspected alternate diagnoses or suspected complications of fulminant UC such as megacolon and perforation. While imaging findings may be incorporated into disease severity assessment (e.g., thumbprinting, colonic dilation), "mild" findings on imaging should not limit aggressive management when other markers for disease severity are present.

CS remain the standard for first-line treatment, at a methylprednisolone dose equivalent to prednisone 40 mg to 60 mg daily [87]. There is only limited data to support the superiority of intravenous (IV) CS over oral, though the IV route is most commonly used. There is currently no evidence for the superiority of multiple daily doses or higher total daily doses. In general, a 3- to 5-day trial is considered sufficient to assess for response. The use of CS following 7 days of non-response has no clinical benefit and only serves to delay necessary rescue therapy. Of note, many patients admitted for UC may have recently begun treatment with a mesalamine preparation. This should be stopped, as cases of severe drug sensitivity and clinical decompensation have been reported. For those with long-standing use of a mesalamine preparation, continuation should be decided on a case-by-case basis, though there is no evidence of continued benefit in this setting.

For those patients failing CS but not yet requiring emergency surgery, sigmoidoscopy with biopsy is recommended prior to rescue medial therapy. Sigmoidoscopy is preferred over full colonoscopy to reduce the risk of perforation. While the procedure may reveal an unexpected but associated diagnosis such as dysplasia or colon cancer, the main purpose is to rule out a co-diagnosis of CMV colitis. A finding of CMV colitis does not mean a cessation of UC therapy but rather an addition of antiviral therapy along with UC therapy [88].

Though there have been recent interest and case reporting for the use of high-dose tofacitinib for fulminant UC, current recommended medical rescue therapy involves either cyclosporine or infliximab [89–91]. The choice of one over the other is largely based on physician preference and experience, as well as availability.

Particular patient scenarios might dictate the use of one over the other (e.g., cyclosporine for those with prior infliximab failure/allergy).

Cyclosporine is dosed by continuous IV infusion. Initially studied at a starting dose of 4 mg/kg, treatment has evolved to a lower recommended starting dose of 2 mg/kg, with similar efficacy and lower side effects [92]. Drug levels may be monitored on a daily basis with a goal level of 150 to 250 nanograms/ml. Close monitoring for side effects is critical, with rates of nephrotoxicity 6.3%, seizures 3.6%, anaphylaxis 0.9%, and death 1.8% reported [93]. Those clinically malnourished may be at higher risk for these side effects. Response rates of as much as 80% have been reported within 7 days, with colectomy-free survival of over 50% at 5 years [94, 95]. Cyclosporine is however, only a bridge therapy, with responders discharged home on oral cyclosporine (typically at double the cumulative daily IV dose) and overlapping treatment with the intended maintenance therapy. Traditionally, this has meant a thiopurine, though recent reports have been encouraging for the use of vedolizumab in this role [96, 97]. Of note, Pneumocystis pneumonia (PCP) prophylaxis is recommended along with cyclosporine use, both during hospitalization and for the duration of oral therapy.

Infliximab is the primary alternative for inpatient rescue therapy and likely preferred for most given the wider familiarity of use and availability outside referral centers. Infliximab has been shown to have equivalent efficacy to cyclosporine for short-term rescue, with similar rates of colectomy-free survival [98, 99]. Unlike cyclosporine, infliximab serves as its own maintenance therapy for responders. Optimal dosing of infliximab for rescue remains a source of controversy. Though efficacy for rescue has been demonstrated at the standard 5 mg/kg dose, it is well known that those with severe colitis may "lose" infliximab in the stool and/or generally have a higher inflammatory burden that might benefit from a higher dose. Uncontrolled studies comparing 5 mg/kg dosing to higher doses have not generally shown a benefit, though the non-randomized nature – with possible selection bias favoring the use of higher doses in sicker patients – means that this issue remains to be settled. Also, the use of a rapid second rescue dose for those with a suboptimal response to a first dose has become more common. Commonly referred to as an "accelerated induction," there is again no prospective evidence of increased benefit for patients generally. A recent meta-analysis of retrospective studies has however observed a similar response to standard induction despite a tendency toward the use of accelerated induction in sicker patients, again suggesting a hidden benefit for some [100].

For those failing either cyclosporine or infliximab, the question remains whether it is safe to try the alternate therapy (i.e., cyclosporine following infliximab failure and vice versa). The main argument against this approach has been one of safety rather than efficacy. Most of the recent guidelines specifically discourage this approach, citing cases of serious infections and death [101].

- *An experienced IBD surgeon should be consulted for all patients.*
- *Antibiotics without an identified pathogen are not recommended for fulminant UC.*

- *Pharmacologic venous thromboembolism prophylaxis is recommended.*
- *Limited liquid diet, bowel rest, or TPN is not broadly recommended.*
- *CS therapy beyond 7 days without clinical improvement is not indicated.*
- *Cyclosporine and infliximab appear equally effective for rescue therapy.*
- *There is mixed evidence to support higher or accelerated infliximab dosing schedules.*

Goals of Therapy: The Evolution of Treat to Target (T2T)

Traditionally, the goals of IBD treatment have focused on clinical outcomes. Simply put, in the clinical practice setting when patients reported improvement or resolution of their symptoms, clinicians considered that the desired goals of treatment had been met and that further escalation of therapy was not indicated. Endoscopic healing of the mucosa has long been assessed in clinical practice and formally "scored" in therapeutic drug trials (e.g., Mayo endoscopic subscore), but healing itself was not widely regarded as a goal of treatment.

The main challenge to the traditional approach has been the observation that despite the medical advances made in IBD treatment, the natural course of the disease observed in population-based cohort studies has not substantially improved along with therapeutic advances [102, 103]. This has led researchers to pay more attention to the consistent observation that achieving mucosal healing appears to be a more reliable marker for improved long-term outcomes such as avoidance of colectomy [104] and hospitalizations [105]. This has led to the initiative to not *just* treat symptoms and passively observe for mucosal healing, but to make the achievement of mucosal healing a primary "target" of therapy. Thus, the paradigm of treat to target (T2T) for IBD was conceived. Such an approach had already been shown to achieve better long-term patient outcomes in hypertension [106], hyperlipidemia [107–112], diabetes mellitus type 1 diabetes [113] and 2 [114], and rheumatoid arthritis (RA) [115, 116]. Instead of solely relying on patients' reported symptoms, the RA strategy proposed in 2010 [117] used clear-cut end points such as validated composite measures of disease activity to assess disease status. Clinicians use these validated tools to establish which patients are in remission and which patients require escalated treatment despite feeling well. A systematic literature review in 2016 found that the T2T approach in RA "leads to less comorbidities and cardiovascular risk and better work productivity than conventional care." [115] The success in treating RA was of particular interest to the IBD community as both diseases are due to dysregulation of the immune system.

Using this model, a steering committee comprised of 28 IBD specialists released the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Guidelines in 2015, outlining a T2T approach tailored to the management of IBD [118]. The primary goals of treatment classified as the "composite end point" included both clinical remission *and* endoscopic remission. Clinical remission was defined for UC as "resolution of rectal bleeding and diarrhea/altered bowel habit,"

and endoscopic remission was defined as "a Mayo endoscopic subscore of 0–1" (image of Mayo score tissue samples). This combination of both clinical and endoscopic remission is commonly referred to as "deep remission." In practical terms, this means that even patients reporting a resolution of symptoms should undergo an endoscopic exam to reassess the mucosa and that those with a Mayo subscore >1 should escalate therapy and be reevaluated until endoscopic remission is achieved. Serum inflammatory markers such as CRP and FC were also suggested as adjunctive measures of inflammation, but not treatment targets. Histologic remission was also discussed as a possible adjunctive goal of treatment.

Though there is little debate that mucosal healing is a desirable outcome [119], it is less clear that specifically targeting mucosal healing will yield improved outcomes. To date, there is very little evidence to support the benefits of a T2T strategy, and most is retrospective. A small trial of 60 UC patients was able to observe that escalating therapy in patients with endoscopic disease activity could achieve higher rates of mucosal healing. However, over 80% of these patients were also experiencing clinical complaints, which themselves would drive an escalation of therapy [120]. Another prospective study found that escalating treatment based on target inflammatory biomarkers combined with clinical symptoms in CD patients has led to better clinical and endoscopic outcomes [121].

In addition to sparse supporting data, there are several challenges to employing the T2T model. Physicians must be willing to recommend, and patients must be willing to take tests and medications that are often time-consuming, invasive, and expensive and with potential risks, all while they are feeling well. In addition, the increased long-term benefit associated with escalating treatment may need to be more firmly established if patients and/or insurance companies will be expected to pay for them [104, 122]. While the T2T strategy has been integrated into the ACG IBD treatment guidelines [33, 123], it is unclear if this approach is being used as the standard of care in IBD. Further prospective studies are needed to evaluate the efficacy and long-term benefits of a T2T strategy in IBD.

Colonic Dysplasia and Cancer Surveillance

Patients with long-standing UC are known to have an increased risk for colonic dysplasia and colon cancer. This risk has been observed to increase with disease duration, disease severity, and disease extent [124–129]. Risks of colon cancer in the UC population have been noted to be decreasing, but at this point, it is unclear to what degree this is related to a greater availability of more effective drug therapies versus improvements in surveillance techniques [125, 130]. The rationale for surveillance has not changed over time: early detection of mucosal dysplasia and/or colon cancer with the ultimate goal of reducing colon cancer-related death. An evolution of methods and management recommendations has broadened this goal to one of reduction of colon cancer deaths without colectomy. The core questions remain:

- Who should undergo surveillance?
- When should surveillance start and at what intervals?
- What is the best method of surveillance?
- When dysplasia is detected, what is the appropriate management?

While all patients with a colon, with or without UC, will eventually become candidates for a screening colonoscopy, the application of UC surveillance protocols refers to the process of more frequent colonoscopy examination, often at a younger age than the general population. Since there is currently little evidence that those with disease limited to proctitis are at an increased risk of cancer, current UC guidelines are focused on the surveillance of those with left-sided (proctosigmoiditis) or more extensive UC. Of note, all UC surveillance recommendations involve the use of colonoscopy [33, 34, 131, 132]. Alternate methods such as CT colonoscopy and fecal DNA testing are not considered acceptable alternatives.

Most current guideline recommendations focus on the initiation of surveillance 8 years following either the diagnosis of UC or the first signs/symptoms of UC [33, 34, 131, 132]. Surveillance interval recommendations for those without dysplasia vary, ranging from 1 to 5 years, related to physician preference, disease severity, and family history of colon cancer in a first-degree relative under the age of 50. The most notable agreement concerns those with a co-diagnosis of primary sclerosing cholangitis (PSC). These patients have the highest risk for colon cancer despite a generally/relatively mild colitis disease course. Colonoscopy surveillance is recommended to commence annually following diagnosis of PSC.

As imaging has improved over time from fiber optic to low-definition white-light colonoscopy to high definition, observers have noted an increase in "visible" dysplastic lesions (i.e., those seen and biopsied or removed) and a corresponding decrease of findings of "invisible" dysplasia found on random biopsies. Current evidence suggests that only 10% of all dysplasia is found by random biopsies and that the yield for dysplasia on random biopsies may be as low as one in 1000 [132]. Most current study interest centers around the appropriate utilization of chromoendoscopy to enhance dysplasia detection. Chromoendoscopy involves the application of dye (e.g., methylene blue or indigo carmine) to the entire colonic mucosal surface to better define mucosal irregularities suspicious for dysplasia. Evidence suggests a superiority of directed biopsies/removal of visible lesions with chromoendoscopy over the traditional directed biopsies/removal of visible lesions and random biopsy technique using standard definition white-light colonoscopy without chromoendoscopy. While evidence is emerging, less data is available to suggest a similar benefit for chromoendoscopy examinations using high-definition instruments [133, 134]. Though expert guidelines have increasingly moved in the direction of recommending chromoendoscopy for all surveillance examinations, questions remain regarding the effectiveness of chromoendoscopy outside of expert centers/study environment, as well as concerns regarding the unknown clinical impact of finding additional dysplastic lesions [135, 136]. That is, are we truly impacting the ultimate goals of colon preservation, cancer prevention, and improved mortality?

Perhaps the greatest evolution over time has been the management of dysplasia once detected. It was once common practice to refer any patient with dysplasia (particularly invisible high-grade dysplasia or multifocal low-grade dysplasia) for immediate colectomy [137, 138]. Historically, rates of colorectal cancer detection following colectomy in those with high-grade dysplasia have been reported at 50% or more, with rates as high as 22% for those with low-grade dysplasia [128, 139, 140]. These numbers, of course, have to be taken into context, as most of these cases of dysplasia were detected by random biopsies without the identification of a removable lesion. Even those with visible lesions did not typically undergo endoscopic resection. Previously, the identification of a dysplasia-associated lesion or mass (DALM), regarded as a distinct entity from a sporadic adenoma, was regarded as an indication for colectomy [138].

The term DALM is no longer considered standard when referring to visible lesions found during a UC surveillance colonoscopy. Neither are the descriptors adenoma-like or non-adenoma-like. The critical distinction is whether or not a lesion can be resected endoscopically, as is the current practice for those in the general population. For those with visible lesions completely removed during colonoscopy, current guidelines advocate for narrowed surveillance intervals with the use of chromoendoscopy on follow-up examination.

Though the value of random biopsies with either high-definition colonoscopy or chromoendoscopy is increasingly questioned, the guidelines continue to address the management of invisible dysplasia found by such biopsies. The 2015 SCENIC International Consensus Statement regards referral for colectomy as acceptable but recommends referral to an endoscopist with expertise in chromoendoscopy first [132]. The goal is for a second look to try and define an endoscopically resectable lesion at the site of the invisible dysplasia. Resection of the lesion would permit such patients to remain in a surveillance protocol and avoid colectomy. The authors however note that even if a lesion is not subsequently detected, even in cases of invisible high-grade dysplasia, subsequent management can be "individualized" to continued surveillance vs. surgical referral.

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Chapter 4
New Developments in the Management of Crohn's Disease

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Introduction

Crohn's disease (CD) can occur in any part of the gastrointestinal (GI) tract, with small bowel being the most frequent site. It is marked by a variable course with periods of remission and exacerbation. Active disease and chronic inflammation lead to complications such as scarring, stricturing, abscesses, and fistula formation. CD exhibits different phenotypes: penetrating disease-causing fistulas and strictures and non-penetrating or inflammatory disease. Inflammatory disease can become stricturing and penetrating if there is continued or recurrent inflammation. The goal of therapy in CD is to prevent disease progression and long-term intestinal damage and to improve health-related quality of life (HRQOL). The challenge is to find the "right medication, for the right patient, at the right time."

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R. Rajapakse (ed.), *Inflammatory Bowel Disease*, Clinical Gastroenterology,
https://doi.org/10.1007/978-3-030-81780-0_4

Currently Available Therapies

5-Aminosalicylates (5ASAs), Antibiotics, and Steroids

5-ASAs have a limited role in the management of CD. As per American College of Gastroenterology guidelines, sulfasalazine may be used for the treatment of patients with mild to moderate colonic CD. Oral mesalamine has not been shown to consistently produce mucosal healing in patients with CD compared to placebo and should not be used for the treatment of active Crohn's [1].

Metronidazole and ciprofloxacin should not be used as primary therapy for luminal CD. Metronidazole can be used for simple perianal fistulas and may be used in combination with infliximab for complex fistulous disease.

In moderate to severe disease, oral corticosteroids may be sparingly used to alleviate signs and symptoms because they have not been shown to produce consistent mucosal healing. Intravenous conventional steroids should be reserved for severe/fulminant disease in the hospitalized patient. Ileal release budesonide can be used for mild to moderate ileocecal CD [1].

Immunomodulators

6-Mercaptopurine/Azathioprine (6-MP/AZA)

6-MP and azathioprine have been in use since the 1980s for the maintenance of remission in inflammatory bowel disease following induction with corticosteroids. With the development of biologic agents that have a more rapid onset of action and possibly fewer side effects, these drugs have fallen out of favor as monotherapy for maintenance of CD but are still used in combination with biologic agents for patients with severe disease, both for therapeutic effect and also for prevention of immunogenicity. It is now recommended that all patients are tested for the enzyme thiopurine methyltransferase (TPMT) prior to starting 6-MP/AZA and that they are monitored on a regular basis with lab work including complete blood count (CBC), chemistry, and hepatic panel [1]. CBC's are particularly important because of the propensity for leukopenia with these medications.

Objective therapeutic targets should be followed during the course of therapy. Levels of metabolites are not routinely checked in the asymptomatic patient in remission. If there is evidence of ongoing disease or loss of response, the active metabolite of 6-MP, 6-thioguanine (6-TG), can be checked and the dose of 6-MP adjusted accordingly. Metabolite levels can also be useful in the setting of abnormal liver function tests in order to determine if they are related to 6-MP/AZA. In this situation, 6-methylmercaptopurine (6-MMP) may be significantly elevated [2].

Patients should be closely monitored for potential side effects including bone marrow suppression, hepatitis, pancreatitis, non-melanoma skin cancers, and infectious complications especially shingles.

Methotrexate (MTX)

MTX is an antimetabolite long used in the treatment of arthritis. It is a second-line immunomodulator used for the treatment of CD and may be useful in patients who have had an allergic or adverse reaction to 6-MP/AZA. It may be used for the maintenance of remission in CD, but evidence for efficacy in induction of remission is lacking [3]. It may also have a role in patients who have both CD and arthritis and may be used in combination with biologics to prevent immunogenicity. Potential adverse effects of treatment should be discussed with the patient prior to commencing on this medication, and cumulative dosing as well as liver function tests should be monitored. In addition, it is absolutely contraindicated in pregnant patients. Therefore, young women should confirm contraception prior to receiving this medication.

Biologics

Biologic medications are genetically engineered proteins derived from living organisms used to target specific parts of the immune system. They were first used for the treatment of IBD in the late 1990s and are used for both induction and maintenance of remission in CD.

With the emergence of different classes of biologics with varied clinical characteristics, we now have choices between biologic agents. Advances in laboratory technology have allowed us to monitor disease progression, follow drug levels and antibodies, and measure treatment success. The different classes of biologics also afford the clinician the ability to personalize therapy based on demographic parameters, comorbidities, disease characteristics, and personal preferences. Unfortunately, the lack of head-to-head studies comparing biologics in the treatment of CD still leaves large gaps in our knowledge.

Anti-Tumor Necrosis Factor

The first biologic to be used for the treatment of CD was anti-tumor necrosis factor (anti-TNF). Medications belonging to this class target cells expressing TNF or soluble TNF, which are responsible for initiating numerous pro-inflammatory

processes, including increasing permeability of membranes and apoptosis [4]. The first anti-TNF to come to the CD landscape was infliximab (IFX), a chimeric IgG immunoglobulin that targets TNF [4]. IFX was FDA approved for the treatment of CD in 1998. Data behind its use has been favorable with the ACCENT trials demonstrating its efficacy [4, 5]. Given its pharmacokinetics, IFX is administered intravenously and is dosed at different intervals depending on whether a patient is in the induction versus maintenance phase of treatment. [1] Induction is undertaken with a dose of 5 mg/kg at 0, 2, and 6 weeks followed by maintenance infusions at 5 mg/kg every 8 weeks. The drug dose and intervals should be adjusted based on patient response and results of drug and antibody levels. Typically, these levels are checked up to a week prior to the infusion in order to obtain the trough level. Escalation of dose, by increasing the mg/kg or the frequency of administration, is performed for patients with ongoing inflammation and inadequate IFX levels, or for those with low levels of antibodies, in an attempt to override them. In severe cases, higher doses of medication may be used for both induction and maintenance [5].

Following the introduction of IFX, adalimumab (ADA) and certolizumab (CZP) were approved for the treatment of CD. ADA is a humanized anti-TNF molecule, while CZP is pegylated. These medications are administered subcutaneously with induction and maintenance protocols. Although subcutaneous administration was a concern in terms of possible bioavailability issues and the development of immunogenicity, this feature allows for personalization of therapy. For patients who need or want to travel, these medications are more convenient and thus preferred [4]. Multiple trials, including CLASSIC-I and CLASSIC-II, have demonstrated the ability of ADA to induce and maintain a clinical response in patients [6, 7]. ADA induction is with 160 mg at day 0, 80 mg at day 15, 40 mg at day 29, and every 2 weeks thereafter. Maximum current dosing is 40 mg per week.

Although CZP is within the same class of biologic therapies, it is different from the other anti-TNFs in that its structure does not contain an Fc region, a feature that can potentially reduce various cytotoxic effects and reduce its ability to cross the placental barrier in pregnant patients [4, 8]. Induction is with 400 mg at weeks 0, 2, and 4, followed by 400 mg subcutaneously every 4 weeks. Although all of these agents are within the same class, the differences among them allow healthcare providers to tailor therapy to the specific needs of their patients. Individual factors, such as whether the patient is a primary or secondary non-responder, has personal limitations, or is pregnant, allow physicians to be more particular in their drug choice within an entire class of medications [4, 8].

With regard to perianal disease, several randomized controlled studies have established anti-TNFs as the cornerstone of therapy [5, 9, 10]. However, a substantial portion of patients do not achieve perianal healing with anti-TNFs alone. There is some evidence that higher serum levels of drug and combination therapy with antibiotics, immunomodulators, or surgical intervention may increase healing rates, but further studies are needed [11].

Biosimilars

Biologic therapy is partially responsible for the high cost of IBD treatment. Anti-TNF biosimilars are a group of medications similar in amino acid sequences to the anti-TNFs but with possible variations in glycosylation molecules. They are therefore highly similar but not identical to the parent products. As the patents for the original medications ran out, biosimilars were developed in an attempt to reduce cost of treatment through competition and reduced pricing. There were concerns regarding efficacy and interchangeability. Of the FDA-approved biosimilars, only Renflexis and Inflectra (infliximab biosimilars) are marketed in the United States. These two agents are in use for the treatment of CD, but switching between the original drug and the biosimilar is not recommended [1]. The ADA biosimilar is currently in patent litigation until 2023.

New classes of biologics that target different parts of the immune cascade have expanded the gastroenterologist's armamentarium. These include integrin and IL-12/23 inhibitors. These agents have been developed in the hope of mitigating some of the side effects of anti-TNF medications, improving responsiveness, decreasing incidence of primary and secondary non-response, inducing deep remission, and increasing the capability of personalization.

Integrin Inhibitors

Anti-integrin biologics target the leukocyte recruitment arm of the inflammatory cascade. Pro-inflammatory cells typically obtain access to the site of injury via migration through the endothelium [12]. Integrin proteins are vital elements of the cascade; these receptors are expressed on the surface of leukocytes and bind with various affinities to cell adhesion molecules (CAMs) [12]. Binding, leading to the subsequent inhibition of integrins, has been demonstrated to inhibit the migration of leukocytes to areas of inflammation [12]. Currently available anti-integrins for CD include the monoclonal humanized antibodies, natalizumab, an α4 integrin inhibitor, and vedolizumab (VDZ), an α4ß7 integrin inhibitor, the latter being approved for use in CD and UC in 2014 [12]. Studies have demonstrated that natalizumab can interact with cellular adhesion at the level of the central nervous system and, as a result, increase the risk of progressive multifocal leukoencephalopathy, an opportunistic infection caused by the JC virus (John Cunningham virus). It is therefore not routinely used for the treatment of CD.

VDZ, on the other hand, does not cross the blood-brain barrier and is significantly more specific to the gastrointestinal tract [12]. Several trials have been performed investigating VDZ in both UC and CD patients, including Gemini I–III, GEMINI LTS, and VERSIFY, all of which have demonstrated the ability of VDZ to

induce and maintain adequate disease remission and produce mucosal healing [12]. VDZ is administered as an intravenous infusion: Induction is with 300 mg by intravenous infusion at weeks 0, 2, and 6, followed by maintenance infusions of 300 mg every 8 weeks (similar dosing schedule to infliximab). With regard to perianal disease, a recent multicenter cohort study revealed a low rate of success with intravenous VDZ in the treatment of active perianal disease and a one-third recurrence rate in patients with quiescent disease [13].

Ustekinumab (Stelara)

Ustekinumab (UST) is a monoclonal antibody that was approved for the treatment of CD in 2016. It binds to the p40 subunit common to both IL-12 and IL-23 [14]. Both of these cytokines are critical elements of the inflammatory cascade with the former involved in T_h1-related pathways and the latter involved in T_H17-mediated pathways, all of which are responsible for driving the pro-inflammatory state [14]. When compared to VDZ, UST has shown very favorable responses in both treatment-naive and refractory CD patients, as demonstrated in the UNITI trials [14, 15].UST has been studied extensively in patients with psoriasis and may serve favorably in patients who have both psoriasis and IBD [14]. UST is administered in weight-based dosing as an intravenous infusion at week 0 for induction followed by 90 mg subcutaneously every 8 weeks for maintenance. A recent study from France showed promising results with the use of UST in perianal disease [16].

All of the above biologic agents have several common potential side effects, including allergic type reactions, increased infection risk, lymphoma risk, and cancer risk. Anti-TNFs use should be avoided in patients with heart failure or multiple sclerosis. All biologics should be avoided/used with caution in patients with cancer. Hepatitis panels and a Quantiferon should be checked prior to commencing on therapy.

Small Molecules

Whereas the pro-inflammatory cascade is initiated by cytokine release, intracellular signaling is mostly relayed by a series of Janus kinases. These proteins are part of a larger pathway known as the JAK-STAT pathway through which cytokines, including IL-2, IL-6, IL-12, and IL-23, transmit their signals [17]. These pathways are integral in the pathogenesis of transmural inflammation in patients with CD. JAK inhibitors, such as tofacitinib, have been designed to inhibit the transmission of signals from these pro-inflammatory cytokines. Tofacitinib is a small molecule that globally inhibits all JAK pathways without any specificity in order to reduce inflammation and induce disease quiescence and remission. Although trials have not demonstrated tremendous efficacy of tofacitinib in the induction of remission in CD patients, they have shown reduction in inflammatory markers, specifically fecal

calprotectin and serum C-reactive protein (CRP) [17]. The chemical composition of tofacitinib allows it to be manufactured in tablet form, making it convenient and easy for patients to use. Although studies have demonstrated improved efficacy in patients with refractory UC, further research needs to be performed to determine the role of JAK kinase inhibition in patients with CD [17].

Choice of Therapy

The choice of therapy for a patient with CD depends on many factors including patient factors (patient preference, lifestyle, age, gender, place or state of residence), disease-specific factors (extent and duration of inflammation; presence or absence of complications such as strictures, fistulas, abscesses, and perianal disease; presence of extraintestinal manifestations), comorbidities, and cost. More than almost any other chronic illness, CD lends itself to personalized medicine. The concept of personalized medicine is not a new one. Physicians have been tailoring care to individual patients for decades. However, the ability to tailor therapy based on objective criteria is a relatively recent development.

Personalized medicine or precision medicine refers to a medical model where therapy is tailored to the individual patient depending on many factors including lifestyle issues and comorbidities, risk of disease progression, likelihood of response, and prognosis. For example, a young patient with CD who is planning to become pregnant may be served better with CZP due to its large size and the fact that it does not cross the placenta in the third trimester [4, 8]. Preconception counseling has become an important part of the clinical discussion in managing young women with inflammatory bowel disease. Fertility and pregnancy issues are also an important determinant factor and are discussed elsewhere in this book. Similarly, a patient with CD and psoriasis may be served better with UST, which has a long track record of therapeutic efficacy in psoriasis. Anti-TNFs have proven benefit in perianal disease as well as arthritis and other extraintestinal manifestations. In addition, a patient with acute CD who is hospitalized may benefit from an anti-TNF induction and maintenance. If rapid onset of action is required, anti-TNF or UST would be preferred over VDZ. However, in an elderly patient with an increased risk of infection, VDZ may be preferred for its gut selectivity.

In the past, a step-up approach was used for the treatment of CD, starting with the lowest level treatments such as mesalamine products and advancing therapy based on clinical response. This left some patients with ongoing symptoms and the development of complications. On the other hand, the top-down approach aimed to treat patients early with biologics in order to modify disease course and prevent complications. However, this strategy allowed for overtreatment of patients.

We have since learned that one size does not fit all in CD management. The first step in treatment is to assess the clinical prognosis in the individual patient. High-risk prognostic factors include young age at diagnosis, smoking, longer disease duration, early need for steroids, perianal disease, and early need for surgery, as

well as biochemical markers such as low hemoglobin and low albumin [18]. Patients without these features are considered low risk. High-risk patients should be considered for a top-down approach, with early use of biologics and, in severe cases, in combination with an immunomodulator such as 6-MP or methotrexate. The SONIC trial evaluated the efficacy of combining a biologic with an immunomodulator [19]. Immunomodulators 6-MP/AZA and MTX may be used in conjunction with biologics to induce remission in treatment-naive patients or to mitigate the development of immunogenicity [20, 21]. Although the SONIC trial did show the efficacy of combination therapy over monotherapy, a post hoc analysis by Colombel et al. suggested that this may not be necessary in all patients, as it is important to consider the malignant potential of combination therapy, particularly in vulnerable patient populations [19, 20]. Addition of an immunomodulator to the regimen of a patient who is on a biologic and has developed antibodies is commonly seen in clinical practice. Studies have demonstrated that this can be an effective approach to decrease immunogenicity and allow continued use of the chosen anti-TNF agent [21].

There are concerns regarding the potential for hepatosplenic lymphoma with the use of combination anti-TNFs and 6-MP/AZA in young males [22, 23]. Using objective evidence such as mucosal healing determined by endoscopy, in tandem with markers of inflammation such as fecal calprotectin, C-reactive protein, and erythrocyte sedimentation rate (ESR), helps to optimize therapy and prevent over- or under-treatment of patients. This approach requires close clinical follow-up with regular monitoring of patients, as well as a multidisciplinary team including other specialists, nutritionists, and psychologists.

The development of specific biomarkers that will consistently allow risk stratification of patients into those who will have an aggressive course and therefore need early treatment with biologics, compared to those with slower disease who may not need early aggressive treatment, will allow greater personalization of care.

Medication intolerance, lack of response, or loss of response poses a particularly difficult problem in CD. While new biologics are under investigation, there are also other modalities under investigation that may be helpful alone or in combination with currently available treatments. These are discussed later in this chapter.

Therapeutic Targets

Given the availability of different classes of IBD medications, as well as the ability to monitor both the patient and drug levels, providers are now tasked with choosing appropriate therapeutic targets for their patients. Mucosal healing as the treatment target is preferable to clinical response alone because there is a disconnect between mucosal healing and clinical symptoms [24]. For example, some patients with significant objective inflammation have minimal symptoms, and others with severe symptoms may have very little inflammation. Studies have shown that patients who have evidence of mucosal healing have lower rates of hospitalization, decreased risk for bowel resection, higher quality of life scores, and overall better long-term outcomes [25].

The SONIC trial highlighted the importance of choosing targets by demonstrating that 50% of individuals who reported clinical remission still had either biochemical or endoscopic evidence of inflammation [19]. Mucosal healing can be assessed with endoscopic procedures.

However, in the future, transmural healing (TMH) may become the target of therapy since transmural inflammation is what causes complications in CD. Imaging, particularly magnetic resonance imaging (MRI), which has the ability to distinguish acute inflammation from scarring, may be particularly helpful in this regard. In office, bedside ultrasound modalities may become a disease monitoring tool in the future [26, 27]. In addition, stool calprotectin (especially in tandem with endoscopic findings), ESR, and CRP can all be used to monitor disease activity (as detailed in other chapters). The optimal intervals for monitoring of patients on biologics for mucosal healing are yet to be defined, with much debate about proactive vs. reactive drug monitoring [28].

Health-Related Quality of Life (HRQOL)

HRQOL is a subjective measure of a person's physical and psychological well-being. CD is a chronic illness, often diagnosed at a young age during the most productive time of life. Although mucosal healing and objective and subjective measures of inflammation are an important target in any chronic disease, the ultimate measure of success of any treatment plan has to be quality of life for the patient. The assumption is that mucosal healing will automatically result in a better quality of life. This may or may not be the case, and there is insufficient literature on the subject.

In one study, the main stressors that affect QoL were found to be physical symptoms usually produced by ongoing inflammation. These include abdominal discomfort, bloody stools, diarrhea, loss of appetite, weight loss, need for long-term use of immunomodulatory medication, and hospitalization or surgery. Increased perceived stress, decreased social support, higher number of relapses, and, possibly, female sex may be associated with worse HRQOL in patients with IBD [29].

Although routine clinical visits do not incorporate QoL measures, this may be an important goal post for the future.

Therapeutic Drug Monitoring

We now have the ability to test the serum concentrations of some biologics and their antibodies. The challenge has been in determining how to use this information in order to maximize therapeutic effect. Most data are available for monitoring of anti-TNFs. The ideal is to achieve sufficient concentrations of the drug in serum and tissue to produce neutralization of excess TNF. Too little drug would be insufficient

for neutralization, and too much may neutralize the small amounts necessary in the body for host defense. In addition, the optimal drug concentrations may vary from patient to patient depending on pharmacokinetics and can also vary between labs. Thus, the lab-provided target levels can only be used as a guide.

In recent years, there has been debate between proactive and reactive drug monitoring for biologics. As there is variation between labs, the ideal therapeutic target values are still being evaluated and have to be aligned with clinical findings. However, it is clear that targeting therapy to trough levels in patients on IFX allows more efficient use of the drug [30].

Reactive drug monitoring refers to a strategy where when there is active disease such as failure to induce remission or primary or secondary loss of response to a biologic, drug levels and antibodies are checked, and the drug dose is adjusted accordingly. In proactive monitoring, drug levels and antibodies are checked in patients who are in clinical remission, the aim being to ensure that adequate drug levels are reached in order to prevent a flare of disease. If low drug levels are found, medication dosing or the frequency of delivery is increased; low titer antibodies may be transient and non-neutralizing, so medication dose can be increased to maximize trough concentration; if the antibody titers are very high, especially in the setting of low or undetectable drug levels, then the appropriate strategy may be to switch out of class. European trials indicate that a proactive strategy may be more cost-effective. However, recent US guidelines favor reactive over proactive monitoring, although the evidence to support this is of low quality. Thus, further studies are needed to elucidate the benefits of these strategies [31].

Commercial assays for monitoring UST and VDZ are available, but their role in clinical management has not been defined [32].

De-escalation of Therapy

How long should a patient in remission remain on a biologic or combination therapy? This is a frequently asked question by patients and the subject of much debate. The major concerns for long-term treatment have been risk of infections and lymphoproliferative disorders/cancer. The risk is increased with combination therapy. In addition, de-escalation can also produce cost savings.

Many factors have to be taken into account when deciding whether to withdraw or de-escalate therapy in a patient who is in remission. These factors include patient factors and preferences (such as females, pregnancy, and other comorbidities), cost and insurance issues, and cumulative side effects and toxicity. Four randomized controlled trials have evaluated the withdrawal of immunomodulatory monotherapy in clinical remission in CD patients and found higher relapse rate in the withdrawal group [33]. In the European Consensus, the presence of high trough levels of infliximab and lack of perianal disease and normal biomarkers appeared to predict successful discontinuation of immunomodulators in patients on combination therapy [34]. The STORI trial (Infliximab diSconTinuation in CrOhn's disease patients in

stable Remission on combined therapy with Immunosuppressors) was a multicenter, prospective study specifically designed to assess the risk of relapse and to identify predictors of relapse following anti-TNF maintenance therapy withdrawal in patients with luminal CD (perianal disease was excluded). The relapse rates at 12 and 24 months were 43.9 ± 5.0 and 52.2 ± 5.2%, respectively, with a median time to relapse of 16.4 months [35]. Until there is more data available, de-escalation of biologics is a decision that has to be made by the physician and patient, on a case-by-case basis, with a full understanding of the dynamics and prognosis of CD in the individual patient.

Prevention of Postoperative Recurrence

Approximately one-fourth of patients who undergo surgical resection will require further surgical intervention later in life, and a significant proportion will continue to have endoscopically active disease [36]. This leads to questions of how to prevent postsurgical recurrence with the above array of pharmacological therapy, when to start the therapy, and how to effectively monitor for disease recurrence.

The POCER trial evaluated 18-month endoscopic recurrence in CD patients after bowel resection. Patients were randomized to colonoscopy at 6 months with step-up treatment for endoscopic recurrence versus "standard care" with no 6-month colonoscopy. At 18 months, 49% of patients in the active arm had endoscopic recurrence compared with 69% in the standard arm ($p = 0.03$) [37]. To date, the most convincing evidence for prevention of postoperative recurrence is with the use of infliximab. In the PREVENT trial, clinical and endoscopic recurrence was lower in the infliximab group [38].

The American Gastroenterological Association (AGA) has developed guidelines on the postoperative prevention of CD recurrence and recommends immediate initiation of pharmacological therapy, preferably with an anti-TNF, following surgical resection in certain high-risk patients [36]. Major risk factors for recurrence include young age, smoking history, prior bowel operations, and penetrating disease [36]. Postoperative management in patients who are in lower-risk categories can be driven by findings on surveillance endoscopy, which is recommended at 6–12 months following surgical intervention [36]. An endoscopic recurrence scale, the Rutgeerts score, enables an objective assessment of inflammation although critics point to the fact that the lower end of the scale may reflect postoperative ischemic changes rather than Crohn's recurrence [39]. Pharmacologic therapies can also be tailored to personalized targets as well as biochemical markers including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and fecal calprotectin. There is no consensus on exactly how to use these inflammatory markers. However, they can be used in conjunction with the overall clinical picture to help steer therapy and frequency of endoscopic surveillance [40].

The management of IBD is constantly evolving. The treatment of this chronic condition is highly personal and patient specific, which emphasizes the importance

of shared decision-making. The therapies discussed above form the foundation of current CD care, and still more immune modulators that target different parts of the immune cascade are under investigation.

Orally administered small molecules including selective JAK inhibitors (filgotinib and upadacitinib), sphingosine-1-phosphate receptor 1 (S1PR1) agonists (ozanimod and etrasimod), and selective IL23 inhibitors (risankizumab and brazikumab) are undergoing trials [41–43].

In addition, the field has many exciting new developments that serve as adjunctive treatments to fulfill an unmet need in patients who are failing immune modulation in spite of dual therapies and close drug monitoring. From stem cell therapies to fecal microbiota transplantation, in the rest of this chapter, we will discuss the many additional options currently under investigation, highlighting the complicated nature of the inflammatory cascade responsible for this chronic condition.

Therapies Under Investigation for the Management of Crohn's Disease

Nutrition

In the pediatric IBD population, exclusion diets and exclusive enteral nutrition have had positive results. There are several studies evaluating the efficacy of Crohn's disease exclusion diets (CDED) and partial enteral nutrition (PEN) in adults with mild Crohn's ileitis. In one study, Sigall-Boneh et al. treated 22 patients, 11 of them adults, who had failed dual therapy or had disease refractory to biologics, with CDED and PEN using polymeric formulas. They reported a remission rate of 60% with a decrease in CRP [44]. Several other studies have shown positive results with good remission induction rates, mostly in pediatric patients, allowing steroid sparing [45]. There are criticisms that can be made about methodology, patient selection, and results, and the fact that the diet does not allow for a maintenance strategy because it is difficult to tolerate in the long term is a problematic issue. Studies in adults have been plagued with problems. Although the concept of a nutritional therapy is exciting, its role in the induction and maintenance of remission in adults with CD remains to be elucidated.

Hematopoietic and Mesenchymal Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) has been utilized in numerous disease processes since the late 1990s [46, 47]. Since consensus guidelines were established outlining its use in pathologies outside hematologic malignancies, the use of

HSCT has exponentially increased in the treatment of vasculitides, systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis [46–48]. First investigations into the use of HSCT in autoimmune disease were in the setting of concurrent disease in those patients with known hematologic malignancy [46, 48]. Since then, our understanding of this versatile treatment has tremendously improved, and so has its applications.

Pluripotent stem cells can be derived from somatic, embryonic, or induced pluripotent cells. The latter two are not frequently used in therapeutics at this time due to the potential for oncogenesis with pluripotent cells and numerous ethical issues involved in embryonic cell uses [49]. Current stem cell therapy is derived from somatic cell lineages and is a complex process that involves several stages [49]. These include the identification of type of transplant, the recruitment of cells, conditioning of both the graft and recipient immune system, and final transplantation [46]. The type of transplant can be divided into autologous and allogeneic transplants. Autologous transplants involve the infusion of one's own apheresed recruited stem cells, whereas allogeneic transplants involve transplanted cells from a matched donor [46, 48]. Although autologous transplants are more commonly used, allogeneic cells are believed to harbor a greater curative potential [46, 48]. Donor stem cells may possess genetic elements that may change the initial predispositions that produced the underlying autoimmune process [48, 50]. These cells can be obtained from either bone marrow (via marrow punctures and aspiration), umbilical cord blood, or peripheral blood samples, with the latter being most prevalent [51]. Mobilization of the stem cell graft is undertaken with combination of cyclophosphamide and granulocyte colony-stimulating factor [46]. Once these cells are obtained, the recipient's immune system is conditioned to receive the transplant in a process of lymphoablation. These regimens involve the combination of total body irradiation, cyclophosphamide, and various combination chemotherapy regimens, all depending on the disease process being treated [46, 51].

To understand the role of HSCT in the management of IBD, one first has to understand the genetics of CD. As a result of advancements in genome-wide association studies, we know that genes such as NOD2, CARD15, and ATG16LI play a major role in the pathogenesis of this disease [52]. Mutations in NOD2/CARD15 have been associated with a more complicated disease course given the resulting disequilibrium in functionality of the innate immune system [48]. Further evidence can be seen in the case report by Barone et al., outlining the course of a patient who underwent HSCT that was harvested from a matched sibling with CD [53]. Following transplantation, the patient developed signs and symptoms consistent with IBD [53]. Although the pathogenesis is unclear, this case potentially supports the notion of a set of genetic mutations that lead to IBD and which can potentially be transferred from one host to another [53].

Given the genetic nature of the disease and the involvement of the various components of the immune system, one can deduce that treatment geared toward

irradiating defective cells and infusing ones with new potential can offer a new start to patients, thus potentially curing patients of the disease [48, 50]. Given the stepwise approach of HSCT, the question remains as to whether the HSCT itself is responsible for delivering the positive therapeutic endpoint or if it is the lymphoablative conditioning regimen or a combination of both [48, 50]. Ideally, a randomized controlled trial would help further elucidate the therapeutic effects of HSCT in the management of IBD. To date, only one such study, the ASTIC study, has been carried out, and other studies looking at the benefits of HSCT are currently in progress, although one of them has been terminated due to some reported adverse effects. In one particular study, Hawkey et al. randomized a total of 45 participants to receive either HSCT with standard CD treatment or standard therapy alone [49, 54]. In their analysis, 23 patients were included in the primary endpoint analysis from the experimental arm, and 22 patients were included from the control arm [54]. There was a failure to demonstrate statistical significance between the two arms of the study, and thus, HSCT was not deemed superior to conventional therapy [54]. Moreover, numerous serious adverse events including death were reported. Although the ASTIC study failed to demonstrate true statistical significance, certain clinical benefits were identified in the HSCT + conventional therapy group [54]. This has led to the initiation of other randomized trials aiming to look at the benefits of HSCT; however, there is no published data as of yet.

Besides HSCT, other cells have also been explored in the treatment of CD, particularly in the management of fistulizing disease. These are known as mesenchymal stem cells (MSCs) [55]. Similarly, these cells can differentiate into numerous cell types including neuronal cells, chondrocytes, and adipocytes and can be retrieved from marrow, adipose, muscle, and umbilical cord as well as from endometrial polyps, fallopian tubes, and the cruciate ligament [55]. These cells have unique anti-inflammatory properties via various signaling cascades, although the true mechanism is not fully elucidated [55]. A meta-analysis by Ciccocioppo et al. demonstrated that MSCs have tremendous therapeutic potential when locally injected into fistulas, demonstrating established healing in over 60% of patients [55]. One randomized double-blind controlled trial performed by Panés et al. demonstrated that local MSC injection into perianal fistulas, when added to existing therapies, led to significant therapeutic effect that was demonstrated by the closure of the fistulous opening [26]. The mechanism underlying the therapeutic benefit has not yet been described.

HSCT and MSC therapies have spawned a new era of CD management. Not only are we able to suppress various elements of the inflammatory cascade with biologic therapies, but now we are able to alter either the local or systemic immune composition entirely (Fig. 4.1*)*. Although the field of stem cell therapeutics in inflammatory bowel disease is new, clinical benefit has been shown in some limited cases. As more studies are implemented in this field, we will see whether stem cell therapy will become essential to the management of refractory CD.

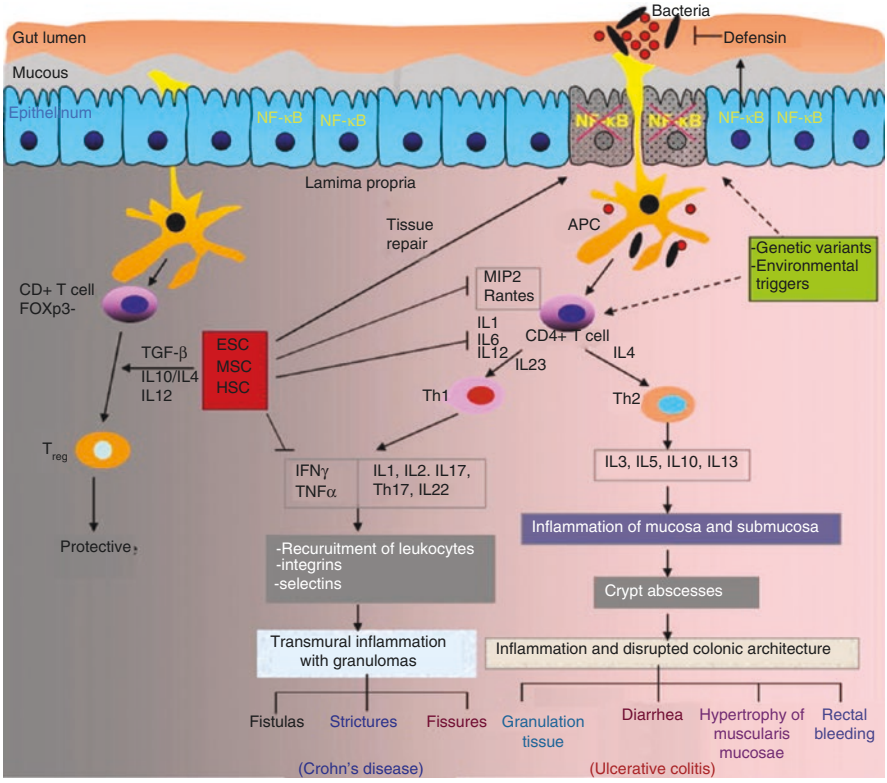

Fig. 4.1 Inflammatory targets of hematopoietic and mesenchymal stem cells in inflammatory bowel disease. HSC can form endothelial precursors, and they can migrate to the site of injury and can differentiate into the elements that are unique to the intestines, leading to tissue recovery and restoration of normal mucosa. (Singh et al. [56])

Restoring the Microbiome: Fecal Microbiota Transplantation, Prebiotics, and Probiotics

Over the course of the last several years, fecal microbiota transplantation (FMT) has become a mainstay in the management of severe *Clostridium difficile* infection (CDI). Numerous trials have demonstrated its efficacy and have shown significant decline in associated morbidity and mortality. Although described as far back as the fourth century, its uses as a directed therapy had only started to be explored in the mid-1950s [57–59]. Theories associated with its mechanism of action in altering gut microbiota and underlying immune system have carried over into its applications toward other disease processes, such as IBD, particularly in managing severe refractory ulcerative colitis (UC). Although limited, some studies have also demonstrated its use in CD.

The relationship between the gut flora and the human host is incredibly complex. Our understanding to date has led us to isolate two main phyla that dominate the microbiome: Bacteroidetes and Firmicutes [60, 61]. In their work, O'Toole et al. demonstrated that the microbiota dominant in the gut changes as individuals age, particularly with a decline in diversity [62]. Some reasons for this may include changes to diet as well as an exposure to antibiotics that are used in the elderly for other reasons [62]. Such alterations have been demonstrated to cause weakening of the immune system and contribute to inflammation [61, 63]. As in a number of other pathologies including HIV and hepatitis B, the gut microbiome is altered in patients with IBD [61]. While there is a predominance of Firmicutes and Bacteroidetes in healthy adults, patients with IBD experience a loss of diversity among bacterial flora, particularly with a decline in Firmicutes [61]. The clear interplay between gut microbial homeostasis and the immune system, as well as clear evidence of alteration in gut microbial species in the inflammatory state, supports the possibility of re-populating the gut with microbiota to restore homeostasis.

Like stem cell transplantation, FMT requires a complex process of obtaining a viable donor and delivering the transplanted material [64, 65]. Donors can be either related or unrelated and must be healthy adults without any major immune-related pathology [64, 65]. Fecal material is obtained, processed, and prepared with the option of different mediums as diluents (such as normal saline, water, milk, and yogurt) [64, 65]. Studies have demonstrated variable success rates with different mediums [65]. In their literature review, Gough et al. describe varying success rates with water versus normal saline as mediums for fecal material. However, results are inconclusive with regard to which medium is better, specifically when applied to the resolution of symptoms in CDI [64, 65]. Options for delivery of fecal material are broad and can be accomplished either endoscopically, through nasogastric/jejunal feeding tubes, enemas, and/or rectal catheters [64, 65]. The selection of the method of delivery depends on the site of disease activity and the indication for therapy [64]. Gough et al. identified diminished rates of resolution of symptoms following nasojejunal tube or upper endoscopic methods of transplant delivery when compared with direct delivery via rectal catheter or colonoscope [65].

Although FMT has been extensively studied in patients with CDI and UC, no major studies have been performed to assess its true efficacy in CD [66]. In the pediatric CD population, Suskind et al. demonstrated that FMT delivered via nasogastric tube with parental donors was a safe therapeutic option that delivered clinical improvement to most enrolled patients [67]. However, the study is very small with only nine patients receiving FMT, all limited to the pediatric population. Suskind et al. also described a number of biases that may stem from the nature of an open label study [67]. In a study of 30 individuals with moderate to severe CD who were included in the final analysis, clinical remission was achieved in approximately 60%, and improvement in overall clinical status was achieved in approximately 83.3% of individuals [68]. In a comprehensive meta-analysis by Colman et al., only four papers were published and included in their analysis on FMT use specifically in CD, further highlighting the scarcity of evidence and lack of randomized trials [69]. They determined a pooled clinical remission rate of 60.5% among

patients with CD receiving FMT [69]. Given the current evidence, FMT remains a promising therapeutic strategy in the management of CD. It is clear that more randomized trials need to be performed in order to truly evaluate this option and safely offer it to patients. As our understanding of the interplay between the host and the microbiome improves, so will our understanding and utilization of FMT in the wide clinical setting.

As with FMT, other forms of gut bacterial repopulation have been proposed, which include prebiotic and probiotic therapies. The former is a bacterial substrate that allows for proliferation and secretion of various anti-inflammatory entities [70]. Examples of prebiotics include psyllium, fructose, and galactose oligosaccharide [70]. Dissimilarly, probiotics are very specific live bacterial strains that are thought to have restorative, anti-inflammatory potential [70]. Mechanisms of action of these agents range from synthesizing anti-inflammatory agents (such as hydrogen peroxide) to producing short-chain fatty acids that affect the overall acidity of the local environment and potentially shift species predominance [70]. Probiotics have also been shown to affect the NF-kB pathway and affect secretion of various pro-inflammatory cytokines [70]. (Table 4.1)

Although in vivo studies have demonstrated some positive effects, many studies lack adequate sample sizes and use different cultures. One study by Gupta et al. investigated the role of *Lactobacillus rhamnosus* GG on pediatric patients with CD [71]. Following a 6-month administration, they demonstrated clinical symptom improvement with a reduction in the Pediatric Crohn's Disease Activity Index and noticed effects very early in their work [71]. Another study by Guslande et al. evaluated a total of 32 patients with CD and investigated maintenance regimens with the combined use of probiotics [72]. They divided groups with one receiving

Table 4.1 List of the most commonly used prebiotics and probiotics

Common prebiotics and probiotics used in the management of IBD
Prebiotics
Inulin
Psyllium
Fructose oligosaccharides
Galactose oligosaccharides
Germinated barley food stuff
Starch-derived oligosaccharides
Cocoa-derived flavinol
Probiotics
Lactobacillus rhamnosus GG
Lactococcus lactis
Saccharomyces boulardii
E. coli Nissle
Bifidobacterium longum
VSL#3
Clostridium butyricum

mesalamine three times daily versus another group receiving mesalamine twice daily plus *Saccharomyces boulardii* for a total of 6 months [72]. Approximately 6% of the patients in the 5-ASA/probiotic combination group relapsed compared to much higher rates in the 5-ASA group [72]. In contrast, Bourreille et al. performed a study involving 165 patients and randomized them into a placebo group and a group receiving *Saccharomyces boulardii* [73]. In their analysis, approximately 47% of patients in the probiotic group relapsed, whereas approximately 53% relapsed in the placebo arm [73].

Although many of these studies demonstrate some effects, they are not robustly powered. In fact, a Cochrane review by Limketkai et al. did not recommend probiotics in patients with CD [74]. This is a consequence of poor study design, lack of well-powered studies, and lack of randomization with different studies using variable methods (such as different cultures and/or combining them with various prebiotics) [74]. As with probiotics, little evidence exists in great support of prebiotic use in the clinical setting. Although certainly having some benefits, studies are not standardized with the type and quantity of prebiotics to make the data generalizable [75].

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy (HBOT) is a therapeutic modality that has been utilized for many years [76]. Pressurization of 100% O_2 at 2–3 atmospheres increases the partial pressure of O_2 in the blood. This alters the local and systemic inflammatory pathways, which affords this modality numerous therapeutic applications from diabetic wound ulcer healing to applications in inflammatory bowel disease [76, 77].

As other therapies described in this chapter, HBOT may be considered in patients who are either non-responders to conventional options or to help augment adequate clinical response. With a very low adverse event profile, this therapy significantly alters the concentration of cytokines and helps to downregulate the underlying inflammatory process. Al-Waili et al. described a decrease in levels of IL-1, IL-6, and TNF and increases in levels of VEGF, thus facilitating the healing process [77]. With the formation of reactive oxygen species, there is also an effect on stem cell recruitment to the site of inflammation and injury [76] (Fig. 4.2).

Although the exact mechanism of HBOT is not clearly elucidated, there is a potential therapeutic benefit in patients with CD. Brady et al. originally reported the significant healing potential of refractory perineal disease in a patient with CD [79]. In their systematic review of HBOT in IBD, Dulai examined 17 studies that discussed HBOT in patients with IBD [80]. They analyzed 286 patients with CD but noted that the majority of the articles did not clearly document endoscopic data before and after HBOT [80]. They reported that approximately 91% of the patients who had pre- and post-follow-up had perineal disease and 48% had fistulizing disease [80]. Of these patients, approximately 43% had complete healing of their fistulizing/perineal disease [80]. The reported adverse event incidence was reported to be approximately 10/10000, which included ear perforation and psychological effects [80].

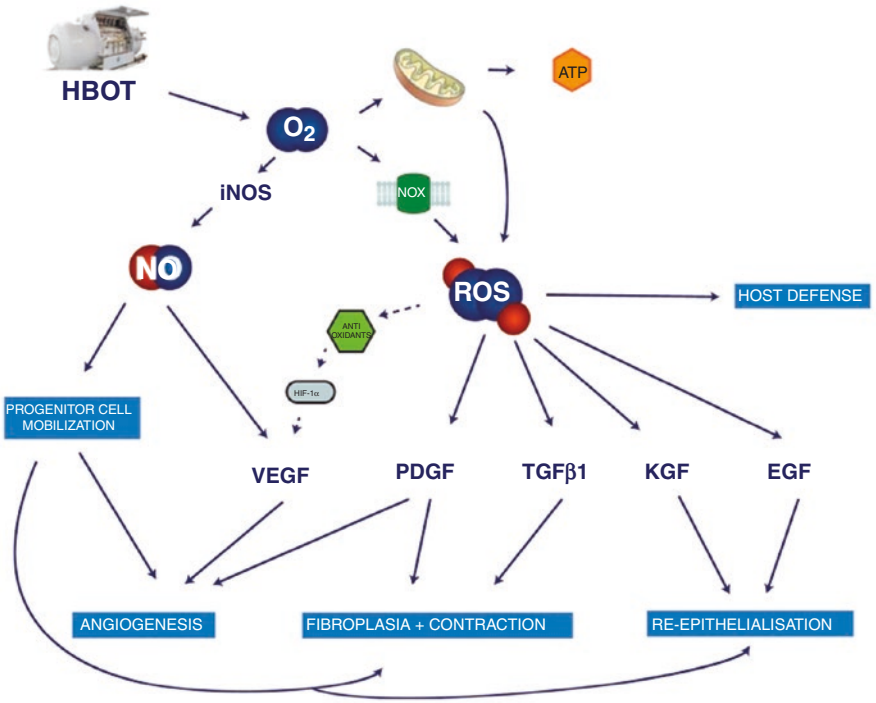

Fig. 4.2 Direct (solid line) and indirect (dashed line) mechanism of action of hyperbaric oxygen therapy (HBOT). Reactive oxygen species production enhances wound repair by promoting angiogenesis, fibroplasia, and reepithelialization. (André-Lévigne et al. [78])

HBOT is a promising therapy that can be used in conjunction with known biologic and immunomodulatory therapies. Although we have some understanding as to how this therapy works, there is still limited availability and significant cost associated with it [79]. There needs to be more research on HBOT with conventional medical therapies in an effort to find a combination that can lead to faster and longer remission times.

Leukapheresis and Extracorporeal Photopheresis

Leukocytapheresis (LCAP) and granulocyte-monocyte apheresis (GMA) are the two major cataphoresis techniques utilized in IBD, functioning to selectively remove cellular components from the blood [81–83]. With numerous applications in medical practice, these techniques have only recently come into use in the management of IBD. To date, there have been very few large-scale studies of CAP in patients with CD. Studies are limited by sample size and lack of standardization. However, LCAP and GMA have been used in managing patients with UC, and these studies have shown positive outcomes.

The premise of LCAP and GMA is to apherese the blood or to remove cells that function to either directly or indirectly promote the release of various pro-inflammatory cytokines that are thought to be involved in IBD [81–83]. In LCAP, filtration is performed using a leukocyte reducing column, which ultimately leads to the removal of approximately a fraction of platelets, lymphocytes, and nearly 100% of all granulocytes [84]. In GMA, apheresis is typically performed using the Adacolumn [81]. This device is a chamber through which blood can flow and come into contact with cellulose acetate beads that act to adsorb cells of interest. In this approach, adsorption favors the removal of granulocytes although not to the same degree as in LCAP. [84]

As Saniabadi et al. demonstrated using electron micrography, the cellulose acetate medium allows for the adsorption of monocyte and granulocyte cell types [81]. Numerous mechanisms explaining the anti-inflammatory effects have been described in the literature, which include reduction in overall inflammatory cytokine concentrations and the turnover of immature granulocytes [85, 86]. The proposed mechanism for the reduction of inflammatory cytokines during LCAP can be explained by its ability to enhance the bodies' lymphocytes to be able to produce IL-4 (an anti-inflammatory cytokine) and decrease the release of IL-6 (a pro-inflammatory cytokine) as well as to increase the production of IL-10 (which inhibits its production of pro-inflammatory cytokine IL-1) [84].

Although there is a significant lack of literature on the use of Adacolumn in CD, Sands et al. performed a feasibility study looking into apheresis in UC and CD patients [85]. In their work, they had a UC and a CD arm, with both enrolling 15 patients [85]. In the CD arm, ten patients were classified by their Crohn's Disease Activity Index (CDAI) to have moderate disease, and four had severe disease [85]. The majority of the patients undergoing apheresis experienced tremendous benefit and improvement in their CDAI [85]. Patients also did not experience any major adverse events during the course of the treatments [85]. This is in accordance with other work that has demonstrated very few overall side effects, with some of the most common being headache, fevers, chills, and nausea [83]. In another study, Fukuda et al. performed a prospective open label investigation into the effects of Adacolumn leukapheresis on patients with moderate or severe CD [87]. Their work was limited in the sample size (only 21 patients were enrolled) and an uneven distribution of male to female patients (14 males and seven females) [87]. Inclusion criteria included a CDAI of at least 200 [87]. A little over 50% of the patients undergoing therapy responded with improvement in their CDAI following therapy [87]. Analysis also revealed that following therapy, there was a significant increase in the number of CD10 (−) neutrophils in the blood [87].

Although the true mechanism of how apheresis delivers its positive effects is unclear, some studies have suggested that there is an improvement in overall CDAI following treatments. The protocol, with regard to length of treatment sessions, number of sessions needed, and the right time to initiate this adjunct mode of therapy, is yet to be clearly elucidated. Although studies have shown symptom improvement and remission, they had very small sample sizes. Preliminary work suggests this to be a promising new therapy, and it is clear that more research needs to be

done to determine the place for this treatment modality in today's personalized care approach of the IBD patient.

Conclusion

Continuous advancements in our understanding of CD and its pathophysiology have led to new developments in its management. The primary goals of treatment are to achieve mucosal and perhaps transmural healing as well as improved quality of life. In an effort to do so, we have developed new methods to monitor disease activity and response. We can also measure drug and antibody levels and, in the future, be able to fine-tune the appropriate drug levels necessary to obtain clinical and histologic remission. Biomarkers are being developed in order to personalize care further by being able to identify patients with more aggressive disease and target them for early advanced therapies. A multidisciplinary approach is paramount to good care of patients with this chronic illness. New immunomodulators are under investigation, and we are also developing other modalities such as stem cell therapy with which we now have the potential to alter the body's immune composition. With the broadened use of FMT, as well as the addition of prebiotics and probiotics, we can attempt to restore the body's bacterial microbiome. The added use of HBOT allows for faster wound healing and shorter recovery times for patients with fistulizing disease. And with the use of cataphoresis, we have the potential to expel unwanted cells that lead to the release of the inflammatory cascade. These new advancements in the treatment of CD may be coupled with existing treatment modalities to meet the needs of patients who have failed standard treatment.

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Chapter 5
Extraintestinal Manifestations in Inflammatory Bowel Disease

Rashmi Advani and Ramona Rajapakse

Key Points

- Extraintestinal manifestations (EIMs) is a term used for inflammatory processes that manifest outside the gastrointestinal tract.
- Ophthalmologic, dermatologic, rheumatologic, and hepatobiliary complications are the most commonly affected sites outside the intestinal tract.
- Certain EIMs can mimic or parallel disease activity of the underlying inflammatory bowel disease, while others are independent.
- Pathogenic mechanisms of EIMs such as antigenic cross-reactivity, upregulation of tumor necrosis factor, and aberrant lymphocyte homing have been considered and proposed as the underlying pathophysiology in EIMs.
- Other organ systems can also be involved including the renal system and pulmonary system as a consequence of the underlying inflammatory bowel disease.
- Secondary manifestations may include side effects related to medical and/or surgical treatments of the underlying inflammatory bowel disease.

Introduction

Inflammatory bowel disease (IBD) is a term used to describe the clinical entities of Crohn's disease (CD) and ulcerative colitis (UC). These disorders are characterized by a systemic inflammatory response that primarily affects the intestinal tract. On a

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R. Rajapakse (ed.), *Inflammatory Bowel Disease*, Clinical Gastroenterology,
https://doi.org/10.1007/978-3-030-81780-0_5

molecular level, marked genotypic and pathophysiological changes coupled with environmental exposure lead to varying phenotypic expressions and account for the main clinical differences between CD and UC. However, both disorders are systemic in nature and may therefore have manifestations outside of the intestinal tract that can lead to complications. These manifestations are known as extraintestinal manifestations (EIMs) and can occur in 25–40% of patients with IBD.

Common sites of EIMs include ophthalmologic (uveitis and episcleritis), dermatologic (erythema nodosum, pyoderma gangrenosum, and stomatitis), hepatobiliary (primary sclerosing cholangitis), and rheumatologic (arthritis and spondyloarthropathies). These complications can follow and depend on the activity of IBD or can be independent of the degree of intestinal inflammation [1, 2] (Table 5.1). Shared epitopes on skin, colon, and biliary epithelium and close HLA gene association may contribute to coexisting and overlapping clinical manifestations of IBD [3, 4].

Epidemiology

EIMs are reported to exist in up to 43% of patients with IBD [1, 5–7].

Having more than one EIM predisposes to the development of additional EIMs with over 25% of IBD patients having more than one EIM [8, 9]. Certain

Table 5.1 Organ system involvement, type of EIM, and correlation to disease activity

System	Type of EIM	Parallel disease activity
Dermatologic	Erythema nodosum	Yes
	Pyoderma gangrenosum	Unknown
	Sweet syndrome	Yes
	Anti-TNF skin lesions	No
	Oral lesions (aphthous stomatitis)	Yes
	Metastatic Crohn's disease	Yes
Ocular	Scleritis	Unknown/yes
	Episcleritis	Yes
	Uveitis	Unknown
Rheumatologic	Peripheral arthropathy	Yes
	Type 1 arthritis-pauciarticular (enthesitis, dactylitis)	No
	Type 2 arthritis-polyarticular	No
	Axial arthropathy	No
	Ankylosing spondylitis	No
	Isolated sacroiliitis	
	Inflammatory back pain	
Hepatobiliary	Primary sclerosing cholangitis	Unknown
	Cholelithiasis	Unknown
Other	Pulmonary complications (bronchiectasis, organizing pneumonia)	Unknown No
	Renal complications (glomerulopathy, amyloidosis, tubulointerstitial nephritis, nephrolithiasis)	Unknown Unknown
	Vascular complications (venous thromboembolism)	
	Joint complications (osteoporosis, osteopenia)	

manifestations that are more common in patients with IBD are joint manifestations, occurring in about 23–33%, which is closely followed by skin (up to 15%), ocular (up to 4–6%), and lastly hepatobiliary (1–4%) [1, 7, 8].

In addition to carrying a predominance in females, EIMs can also develop in about one-third of patients prior to a diagnosis of IBD.[2,8] If secondary effects of IBD and medications are taken into account, almost 100% of patients will have manifestations outside the gastrointestinal tract.

Pathogenesis

The pathogenesis of EIMs is not completely understood and is probably multifactorial, depending on the type of EIM. Some EIMs are directly related to IBD disease activity, while others are independent. Several proposed mechanisms leading to particular EIMs have been suggested, including autoimmunity, involvement of the tumor necrosis factor (TNF) pathway, and cross-reactivity of human epithelial colonic autoantigen in the skin, bile ducts, eyes, and joints supporting gut-synovial axis [10–12]. Upregulation of TNF at extraintestinal sites has been proposed to be the mechanism behind erythema nodosum (EN) and pyoderma gangrenosum (PG) [12].

Another proposed mechanism involves the concept of aberrant "lymphocyte homing". Gut-specific lymphocytes migrate to extraintestinal sites that have aberrant expression of gut-specific receptors such as MAdCAM1 and site-specific and non-site-specific ligands such as a4b7 integrin and VAP-1, respectively [12].

Environmental factors, type III and IV hypersensitivity reactions, and abnormal neutrophil function have all been proposed as possible causes of EIMs [10, 12].

Dermatologic Manifestations

The most common dermatologic manifestations are erythema nodosum (EN) and pyoderma gangrenosum (PG). Other rare dermatologic processes associated with IBD include Sweet syndrome, oral ulcers, and anti-TNF therapy-induced dermatologic complications (a secondary EIM).

Skin manifestations can be characterized as specific, reactive, associated, and treatment-induced complications.

Specific complications include metastatic CD, which is defined as noncaseating granulomas outside of the gastrointestinal (GI) tract and which has similar histopathologic features to the underlying disease process (i.e., granulomatous inflammation, as in the case of CD).

Reactive manifestations include PG and Sweet syndrome and are thought to share a causal relationship with common pathogenic mechanisms (i.e., abnormal neutrophil function). *Associated reactions* include EN and oral aphthous ulcers. These occur together with IBD but have not shown to exhibit a causal relationship.

Treatment-induced skin changes are side effects from immune-mediated mechanisms of therapy [10].

It may also be prudent to consider the strong association of IBD, especially CD, with classic psoriasis and biologic-independent melanoma [13], which do not parallel disease activity [14].

Erythema Nodosum

Epidemiology and Diagnosis

Erythema nodosum (EN) is the most common dermatologic manifestation in patients with IBD.

Prevalence of EN in IBD reaches 15% [10] and is more commonly seen in patients with CD [7, 8, 15]. Studies have also suggested higher female predominance and association with PG [15]. Believed to be a type IV hypersensitivity reaction, diagnosis is often clinical and rarely requires biopsy. It has a limited disease course [10, 16].

Clinical Presentation

EN is a type of panniculitis that affects subcutaneous fat in the skin and is defined clinically as raised, tender, symmetric, red-violet subcutaneous nodules with a diameter varying from 1 to 5 cm (Fig. 5.1) [16]. These lesions occur most commonly on extensor surfaces of the extremities and can particularly be seen over the anterior tibial area [16].

Onset is common in the setting of acute IBD flares, although it may also be present prior to IBD diagnosis. Since EN doesi not solely occur in IBD, it is important

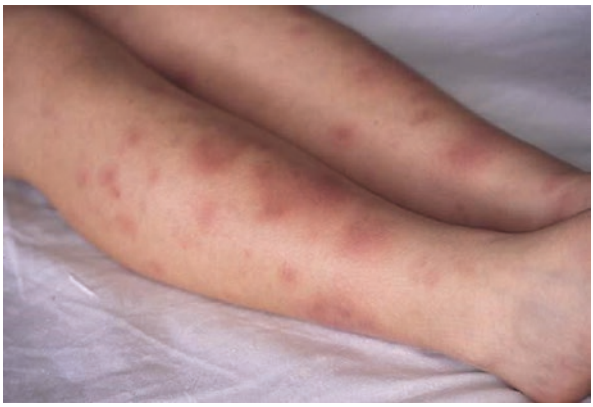

Fig. 5.1 Erythema nodosum presenting as raised, tender, red-violet subcutaneous nodules on bilateral shins. (Image obtained from: Kakourou et al. [17])

to consider other potential conditions associated with EN including infections (i.e., tuberculosis, *Yersinia*, *Streptococcus*), malignancy (i.e., lymphoma), other inflammatory conditions (i.e., Behçet's disease, sarcoidosis), medications (i.e., sulfonamides, oral contraceptives), and pregnancy [10].

Treatment is usually supportive, with focus on treatment of the underlying condition. However, in severe cases, systemic corticosteroids or immunosuppressive agents may be utilized.

Pyoderma Gangrenosum

Epidemiology

Although PG is the second most common dermatologic manifestation in IBD, prevalence in patients with IBD is low (up to 2%) [4, 7, 18]. However, PG does carry a high specificity for IBD, such that if a patient has PG, there is a 50% likelihood of them also having IBD. It is unclear if PG is associated more with CD or UC. Some studies suggest PG is more common in CD [8, 19], while others argue that there is an equal distribution of PG between UC and CD [7, 20]. PG is also more common in females and in African American/African patients [15, 19, 21] and is likely to be ANCA positive and ASCA negative in patients with coexisting CD [10].

Pathophysiology

The pathophysiology of PG is poorly understood. It is a neutrophilic dermatosis, and lesions are often preceded by local trauma, an entity known as "pathergy." A common site of prior injury is the stoma site after bowel resection.

It is unclear whether PG is associated with severity and disease activity of IBD or behaves independently from the degree of intestinal inflammation and thus remains an active area of investigation [10, 15, 20].

Clinical Presentation

PG lesions are characterized by painful, rapidly progressing, single or multiple erythematous ulcerative, or pustular lesions with poorly defined borders, ranging in size between 2 cm and 20 cm (Fig. 5.2). Lesions typically produce symptoms of pain, myalgias, fatigue, and/or fever [19] These lesions may progress to deeper ulcerating lesions that yield purulent or sterile exudate and occur mainly in the lower extremities [10, 19]. Peristomal pyoderma gangrenosum and other areas of the skin are potential, but rarer, sites of occurrence.

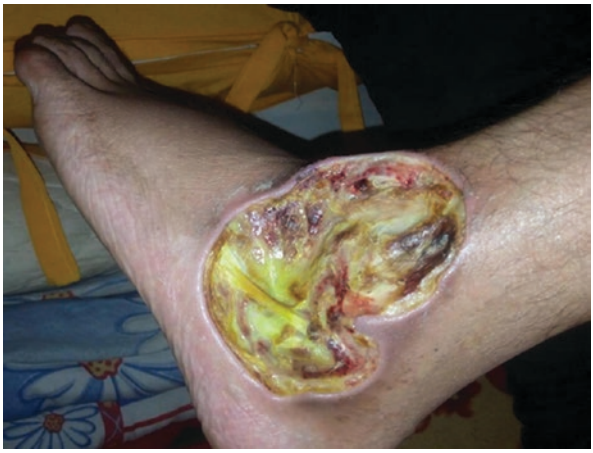

Fig. 5.2 Pyoderma gangrenosum presenting as painful, ulcerative lesions with poorly defined borders on the leg. (Image obtained from: Tharwat and Ahmed [22])

Diagnosis is based on the patient's clinical history and physical exam and is often challenging. Skin biopsy is recommended for diagnosis, as it can be helpful in excluding other potential causes, such as infection and other skin diseases. Histological findings vary depending on the site and age of the lesion but generally reveal neutrophilic infiltrate, neutrophilic pustules, and abscess formation [23].

Treatment

Disease course is unpredictable and treatment strategies are varied. In mild cases, local and topical therapy with intralesional corticosteroid injections, clobetasol propionate 0.05%, and topical tacrolimus are utilized. In more severe instances, a combination of systemic corticosteroids with maintenance immunosuppressive treatment is used. Immunosuppressants include calcineurin inhibitors (cyclosporine, tacrolimus), 6-mercaptopurine/azathioprine, methotrexate, mycophenolate mofetil, and TNF-α inhibitors [19, 24–27]. Recent studies have demonstrated early clinical remission after treatment with TNF-α inhibitors [28]. In a randomized, placebo-controlled study performed by Brooklyn et al., a higher remission rate was observed at 6 weeks after infliximab compared to placebo [29].

Symptom resolution occurs anywhere from a few weeks to over 14 months with a mean of around 5–12 months [19, 24].

Sweet Syndrome

Pathophysiology and Epidemiology

Sweet syndrome is a rare, systemic, and acute inflammatory dermatologic condition that is associated with both UC and CD. This condition may herald the onset of intestinal symptoms in one-fourth of patients and is associated with female gender

[30]. Although the exact pathogenesis is unclear, there is some suggestion that a type III hypersensitivity reaction may be involved. Biopsies reveal diffuse neutrophilic infiltrate involving the dermis and/or subcutaneous fat [31].

Clinical Presentation and Diagnosis

Sweet syndrome is characterized by the acute appearance of painful, tender edematous nodules, plaques, and papules involving the face, hands, trunk, arms, and legs [32, 33]. It is typically accompanied by systemic manifestations of fever, arthritis, and ocular symptoms, mainly conjunctivitis. Sweet syndrome may also be associated with malignancy, pregnancy, infections, and drugs [32, 33].

Treatment initially involves topical/systemic steroids, while second-line therapy includes infliximab [26, 34]. However, treatment of IBD remains the most important strategy as clinical disease runs parallel to IBD disease activity [35].

Oral Lesions

Epidemiology

Oral lesions are an associated finding of IBD, are more common in patients with CD, and carry a male predominance [7]. Oral lesions, which may be found in up to 10% of patients with IBD, include periodontitis and aphthous stomatitis and less commonly pyostomatitis vegetans. Other causes should also be explored including HSV, Behçet's disease, HIV/AIDs, and Reiter's syndrome.

Oral findings may be present years prior to the diagnosis of IBD and may occur in 10–25% of patients before the onset of gastrointestinal symptoms [36]. Oral lesions in the mouth are found primarily on the gingiva, labia, and buccal mucosa but may also exist on the tongue.

Diagnosis is primarily based on history and clinical symptoms; however, in uncertain instances, a biopsy may be performed. Biopsies might reveal lymphocytes, histiocytes, plasma cells, and neutrophils infiltrating into the submucosa and lamina propria [37].

Clinical Presentation and Pathophysiology

Aphthous stomatitis is characterized by painful, circular, or oval exudative lesions with erythematous borders that form on the tongue, soft palate, labia, and buccal mucosa (Fig. 5.3).

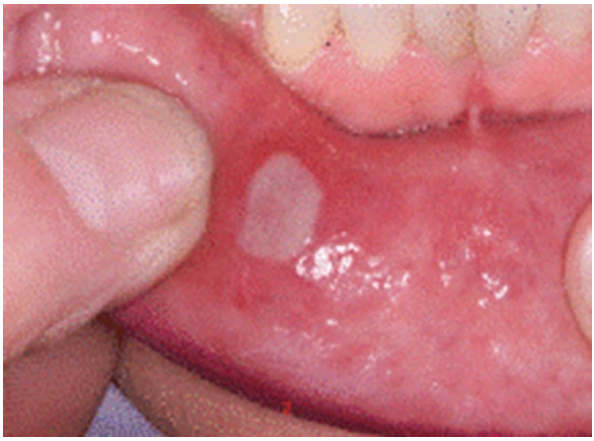

Fig. 5.3 Aphthous stomatitis presenting as painful oval exudative lesions with erythematous borders on the buccal mucosa. (Image obtained from Cui et al. [38])

Periodontitis is characterized by swelling, spontaneous bleeding, and gingival erythema. *Peristomatitis vegetans* is a severe, debilitating manifestation and includes ulceration and hemorrhagic erosions on the labia and buccal mucosa and, like aphthous stomatitis, responds to treatment of intestinal inflammation. It also may be associated with peripheral eosinophilia and sterile culture of exudative material [39].

Treatment includes antiseptic mouthwashes, topical corticosteroids, topical lidocaine, dexamethasone ointment, and treatment of underlying IBD. For refractory cases, systemic or corticosteroid injections and more recently anti-TNF therapy may be utilized with clinical success [27, 39–41].

Anti-TNF-Induced Skin Lesions

Epidemiology and Pathophysiology

Anti-TNF-induced skin lesions are well-documented and follow a separate course to IBD disease activity. Dermatological complications occur in approximately 20–30% of patients on anti-TNF therapy [42, 43]. A higher dose of treatment and younger age at the time of drug initiation yield a higher risk of skin manifestations [44].

Dermatologic side effects from anti-TNF agents include psoriasiform changes and spongiotic dermatitis, also referred to as eczematous skin eruptions.

Clinical Presentation and Diagnosis

Psoriasiform lesions might appear as scaly, erythematous plaques or pustules and present atypically on non-extensor surfaces such as the scalp or flexural surfaces. This particular dermatologic complication occurs in approximately 30% of patients who are treated with anti-TNF agents [44].

Eczematiform lesions are characterized by erythematous plaques, vesicles, and xerosis. These changes may occur in approximately 5–20% of patients on anti-TNF therapy [43].

Treatment

Dermatologic side effects from anti-TNF therapy are usually mild and reversible and usually remit after withdrawal of anti-TNF therapy [45]. Up to one-third of patients that suffer from this side effect may need a switch to a non-anti-TNF agent such as ustekinumab [42, 46].

Mild lesions may be treated with topical therapy (i.e., corticosteroids, vitamin D, emollients, and ultraviolet therapy) [10] while continuing the anti-TNF. Other anti-TNF-related non-dermatologic side effects are discussed in other sections.

Metastatic Crohn's Disease

Clinical Presentation and Diagnosis

Metastatic Crohn's disease is an entity defined as Crohn's-like lesions that are not continuous with the bowel.

It presents with similar features to CD including fistulas, ulcers, and nodules and can involve other parts of the body such as intertriginous areas, lower extremities, and facial and genital regions. Biopsies of lesions reveal similar histopathological findings to Crohn's disease [47].

Treatment

Treatment options are limited as disease is not related to intestinal disease activity and include topical or systemic corticosteroids, antibiotics, IL-12/23 inhibitors +/− immunomodulators, and anti-TNF therapy [10, 26, 47, 48].

Ocular Manifestations

Ocular manifestations including scleritis, episcleritis, and uveitis (anterior, intermediate, posterior, panuveitis) may occur in up to 13% of IBD patients with a mean occurrence of about 5–6% [1, 7, 8, 26]. There is a greater frequency of involvement in patients with CD and women with the exception of posterior uveitis having a predominance in UC patients [2, 5, 11]. Diagnosis is essential as it may affect

therapeutic options and management. It can be made through history taking and physical exam including a thorough ocular examination (i.e., slit lamp examination) and usually involves consultation of an ophthalmologist as distinguishing the subtypes of ocular manifestations is often challenging.

Episcleritis

Clinical Presentation

Episcleritis is characterized by acute onset of inflammation with resulting painless erythema of the layer beneath the conjunctiva. As it is the most common manifestation in patients with IBD especially in CD and occurring in up to 5% of patients, its presence usually correlates with increased intestinal inflammation [11]. Episcleritis does not lead to marked visual symptoms or impairment but can be complicated by scleritis, which in and of itself does cause visual symptoms.

Treatment

Management revolves around treatment of the underlying IBD flare and concomitant symptomatic control with cool compresses, lubricating eye drops, topical nonsteroidal anti-inflammatories, and topical corticosteroids [11].

Scleritis

Epidemiology

Scleritis is a much rarer complication occurring in approximately 1% of IBD patients, impacts the sclera, and can lead to visual impairment. Therefore, early diagnosis is imperative.

Clinical Presentation and Diagnosis

It presents with subacute development of severe ocular pain with radiation to the scalp and with tenderness to palpation over the eye. Anterior scleritis is more common than posterior scleritis and is associated with ocular hyperemia [11]. Early ophthalmological referral is important to prevent complications.

Treatment

In addition to management of patient's underlying intestinal inflammation, which can help to prevent recurrence, treatment of scleritis should be more aggressive with systemic steroids, non-steroidal anti-inflammatory drugs, and immunosuppressants [11, 49, 50]. Scleritis, if left untreated, can lead to complications such as optic nerve swelling, scleromalacia, and retinal detachment and loss of vision [49].

Uveitis

Epidemiology

Uveitis is a less common ocular complication, occurring in 0.5–5% of patients [4, 7]. This condition follows a more subacute to chronic presentation and can be subdivided into anterior uveitis (ciliary body and iris) and posterior uveitis (retina and choroid) [26]. Uveitis was discovered in up to 6% of IBD patients with a higher incidence in CD and women [7, 11, 50]. It follows an independent course from IBD activity [11, 49].

Clinical Presentation

Uveitis presents with severe pain, blurry vision, redness, and photophobia [11, 49] (Fig. 5.4).

Diagnosis is made via slit lamp examination, which reveals peri-limbic edema and inflammatory changes in the anterior chamber [26, 49].

Treatment of uveitis related to IBD should be undertaken promptly to avoid visual impairment.

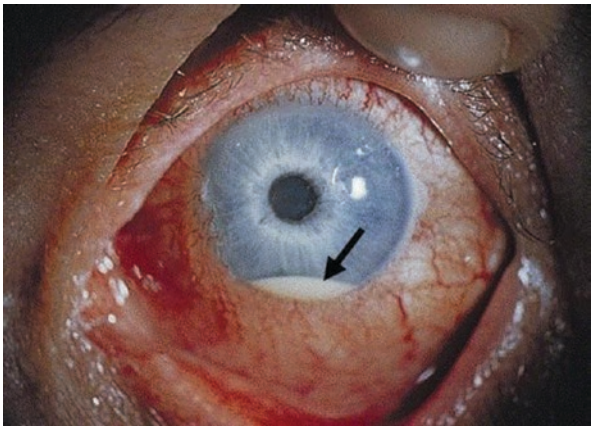

Fig. 5.4 Acute anterior uveitis presenting as pain, blurry vision, redness, and photophobia. (Image obtained from Muñoz-Fernández and Martín-Mola [51])

Treatment is centered on the use of topical steroids for anterior uveitis and cycloplegics, which help to prevent ciliary body and pupillary spasms causing ocular pain and adherence of iris to cornea [11]. Treatment of posterior uveitis may also include periocular steroids in addition to immunosuppressants such as infliximab, adalimumab, and golimumab [26, 27, 52] for more severe cases. Additional treatments may include systemic corticosteroids or immunosuppressives. Immunosuppressive therapy is usually preferable because steroids by themselves can lead to cataracts, open-angle glaucoma, and systemic side effects [50]. However, if there are other EIMs, systemic steroids may be the preferred choice [11].

Rheumatologic Manifestations

Joint symptoms are the most common EIM in patients with IBD, occurring in up to 40–50% of patients [1, 7, 53]. Joint manifestations carry no particular predominance in either UC or CD and may occur more frequently in females [10, 54]. Joint manifestations often precede or coexist with gastrointestinal manifestations and can even present several years before the onset of intestinal disease [55].

Joint EIMs are categorized into axial and peripheral (small and large) arthropathies.

Peripheral Arthropathy/Arthritis

Peripheral arthritis related to IBD can be divided into two types: type 1 arthritis (pauciarticular), which includes involvement of less than five large joints, and type 2 arthritis (polyarticular), which includes involvement of more than five small joints [54]. They are termed seronegative as patients are rheumatoid factor negative and are also hallmarked by their nonerosive, non-deforming pattern [50]. Enthesitis, dactylitis, and arthralgias are also included in this category.

Epidemiology

Pauciarticular arthritis most commonly affects large joints, with the knee being most commonly affected, and typically follows an asymmetric pattern. Polyarticular arthritis normally occurs in smaller joints such as the metacarpophalangeal joints, wrists, and ankles and follows a symmetric pattern of involvement. Prevalence of peripheral arthritis in IBD patients ranges from 7% to 16% (5–14% in UC and 10–20% in CD) [53].

Type 1 arthritis is associated with HLA-B27, HLA-B35, and DR-103, while type 2 is associated with HLA-B44 [49, 56]. However, HLA associations do not affect disease activity nor management in IBD patients.

Clinical Presentation

Pauciarticular arthritis presents acutely, has a shorter course of clinical symptoms (approximately 10 weeks), and correlates with IBD disease activity [57], whereas polyarticular arthritis may last up to 3 weeks and is generally independent of IBD disease activity [50]. Both type 1 and type 2 arthritis can be associated with uveitis, while type 1 can be associated with EN and other EIMs [58].

Enthesitis is defined as inflammation at the insertions of fascia and tendons into bones and has been known to lead to erosions.

Symptoms include pain, swelling, tenderness, and erythema. This entity appears more commonly than dactylitis.

Dactylitis may occur in IBD patients and includes diffuse inflammation of fingers or toes resulting in "sausage digits." Prevalence in IBD has been noted to be in 2% to 4% of patients [53].

Diagnosis of peripheral and axial arthropathies is mainly based on history and physical exam as noted in the clinical presentation above. Further tests including joint fluid analysis and imaging such as X-rays, magnetic resonance imaging (MRI), and computed tomography (CT) may be used to rule out other pathologies.

Treatment for peripheral arthritis includes treatment of the IBD flare for type 1. Other therapies include intra-articular/oral steroids, sulfasalazine, and COX-2 inhibitors. Second-line therapy includes infliximab, adalimumab, and vedolizumab and methotrexate [26, 27, 49].

Axial Arthropathy/Arthritis

Spondyloarthropathy (SpA) involves mainly the axial joints, but peripheral joint manifestations such as dactylitis and synovitis may coexist. Types of SpA include ankylosing spondylitis (AS), inflammatory back pain, and isolated sacroileitis.

All IBD patients with HLA-B27 are likely to develop AS, and HLA-B27 is found in up to 75% of patients with IBD-associated axial arthritis [50, 54]. However, HLA-B27 is not associated with sacroileitis in patients with CD.

Types, Epidemiology, and Clinical Presentation

Ankylosing spondylitis (AS) is the most common manifestation of axial involvement and generally follows an independent course from IBD activity. It occurs mainly in white males between the ages of 15 and 40 and coexists in up to 10% of patients with IBD [5, 57]. It presents as back or buttock pain, which is worse in the morning and relieved with exercise [50]. AS occurs more commonly in CD and may occur at any age when associated with IBD [5, 50, 54, 55, 59].

Diagnosis of AS involves clinical criteria with supporting radiographic evidence. Radiographic evidence may range from evidence of enthesitis, bone marrow edema, capsulitis, synovitis, to structural damage involving subchondral erosions, sclerosis, formation of syndesmophytes, and the classic "bamboo spine."

Isolated sacroiliitis involves bi- or unilateral inflammation of the sacroiliac (SI) joints. Although frequently asymptomatic, sacroileitis may present with buttock pain, pelvic pain, and decreased spinal mobility. Prevalence ranges from 2% to 32% in patients with IBD [53, 57].

Diagnosis of isolated sacroiliitis is based on clinical history and physical examination as well as imaging, which may reveal sclerosis, erosions, and/or ankylosis of the SI joint.

There is no correlation between the severity of sacroileitis and the duration of bowel disease, but it may be more prevalent with longer IBD duration [57].

Inflammatory back pain is defined as insidious back pain that improves with exercise, but not with rest. It is worse during the night and is also associated with morning stiffness. The age of onset is usually <40 years of age, with a duration of greater than or equal to 3 months. Prevalence may reach up to 30% of patients with IBD [60].

Treatment

Well-established treatment strategies for axial arthropathies include cautious use of short-term NSAIDs/COX-2 inhibitors, physical therapy, back exercises, steroid injections, and anti-TNF therapy [27, 49, 50, 60]. Sulfasalazine and methotrexate have not shown to be effective in the treatment of axial arthropathies [57].

When a patient has arthritis with concomitant gastrointestinal symptoms, it is important to consider other diseases that can involve both the joints and bowels including celiac disease, Whipple's disease, Behçet's syndrome, reactive arthritis, and parasitic infections.

Hepatobiliary Manifestations

Primary Sclerosing Cholangitis (PSC)

Epidemiology

PSC is a chronic inflammatory and fibrosing condition defined as multifocal stricturing and dilation of intrahepatic and extrahepatic bile ducts resulting in chronic cholestasis. This condition is more common in UC than in CD and occurs in up to 7% of patients with UC [5, 7, 8]. On the other hand, approximately 70% of patients with PSC have coexisting underlying IBD, UC predominant, with percentages

reaching up to 80% UC and 10% for both CD and indeterminate colitis [61]. Studies have additionally shown that IBD may precede the diagnosis of PSC by a median of 10 years [62] but may occur at any time in a patient's clinical course including after liver transplantation [61].

Clinical Presentation

Colitis presents at a younger age, tends to be more extensive with rectal sparing in patients with coexisting PSC, and may even initially appear endoscopically normal. Disease in both UC and CD, however, is less severe and has similar histopathological findings to patients without PSC [63]. In patients with PSC and CD, penetrating and fibro-stenotic disease is less common than only CD, and disease is less likely to be isolated to the ileum [62].

Pathogenesis

Proposed mechanisms behind the pathogenesis of IBD and PSC include autoantibody formation and the association of perinuclear antineutrophil cytoplasmic antibodies (pANCA) with both diseases, bile acid interactions with the gut microbiome, and "lymphocyte-homing" theory, where gut-specific lymphocytes migrate to aberrant receptors and molecules expressed in the liver resulting in inflammation. Other theories include the "leaky gut" model where increased gut inflammation results in increased permeability and bacterial translocation causing inflammation in the liver [62]. Lastly, alterations in the gut microbiome in PSC-IBD may have led to observed correlations between certain bacterial populations, namely, *Veillonella* and PSC severity [64].

Diagnosis

Because cholangitis in patients with IBD may be asymptomatic, screening with annual liver function tests is recommended [65–68]. Cholangiography is utilized to evaluate the biliary tree if elevations in alkaline phosphatase and/or bilirubin elevations are noted.

Magnetic resonance cholangiopancreatography (MRCP) is the recommended initial imaging tool over endoscopic retrograde cholangiopancreatography (ERCP) given its ability to provide similar information about the bile duct system without the risks of introducing infection into a static system of bile.

PSC is a risk factor for cholangiocarcinoma, which may occur in up to 15% of patients [49]. Given the high association of PSC with IBD, patients must be screened

for IBD at the initial diagnosis of PSC with a colonoscopy. There is also an increased risk of developing colorectal cancer or dysplasia in the colon in UC patients with PSC, and lesions tend to be more advanced at the time of diagnosis [69, 70]. In a study by Kornfeld et al., the 10-year cumulative risk of colorectal cancer in patients with initial diagnosis of PSC was approximately 16% [70]. Additionally, patients with known UC and PSC are five times more likely to develop dysplasia in the colon compared to those with UC alone [71]. In a meta-analysis by Zheng et al., patients with IBD and PSC were approximately three times more likely to develop colorectal cancer [72]. In patients with endoscopically invisible lesions and low-grade dysplasia, colectomy might be considered [73].

Recommendations suggest obtaining random biopsies with chromoendoscopy given the potential endoscopically normal appearing mucosa on colonoscopy. In patients with colitis, annual screening is recommended, and asymptomatic patients without colitis may be screened every 3–5 years [65–67]. Although it is unclear whether there is an increased risk of gallbladder carcinoma in patients with PSC and IBD, current guidelines for screening and cholecystectomy suggest a 6-month to 1-year screening with ultrasound and/or MRI and CA 19–9 and cholecystectomy for any mass < 1 cm [66] or gallbladder polyps larger than 8 mm [67].

PSC may lead to cirrhosis of the liver and its complications including variceal bleeding, development of ascites, and renal impairment and may ultimately require liver transplantation.

Small Duct PSC

There are a small proportion of patients who have macroscopically normal bile ducts with normal cholangiography but with elevated alkaline phosphatase. These patients may have small duct PSC, which requires a liver biopsy for diagnosis. These patients may ultimately go on to exhibit classic PSC [67].

Treatment

There are no validated treatments for PSC, and its course runs independent of IBD disease activity. Therefore, time from disease onset to requiring a transplant is also variable. Recent trials of vedolizumab, although revealing mild improvements in serum alkaline phosphatase, have not been shown to improve liver-related outcomes including cholangitis, cirrhosis, decompensation, or transplantation [74]. Ursodeoxycholic acid has been tried to improve liver enzymes with controversial results, and ERCP may be utilized to rule out malignancy and dilate dominant strictures [49, 62].

Liver transplant remains the treatment of choice for patients with end-stage liver disease, but recurrence of PSC after transplant is common (20% at 5 years). Most

patients are able to tolerate recurrence, but a proportion of patients may go on to severe disease again [67].

Other hepatobiliary pathologies in IBD patients include non-alcoholic fatty liver disease with steatohepatitis, concomitant autoimmune liver disease, pancreatitis (primary or medication related), and granulomatous hepatitis.

Other Organ Systems

Primary Manifestations

Primary manifestations include pulmonary and renal complications that are not classified as traditional extraintestinal manifestations but may occur in IBD.

Pulmonary manifestations include a wide range of findings including bronchiectasis, bronchiolitis, eosinophilic pneumonitis, and organizing pneumonia. Prevalence is unknown in the IBD population, but disease may parallel IBD intestinal activity. Diagnosis and thus treatment are centered around ruling out other etiologies such as medications and infections and treatment with steroids and/or TNF-α inhibitors [26].

Renal complications may present as a primary or secondary manifestation and include glomerulopathies, secondary amyloidosis, and tubulointerstitial nephritis, which does not parallel intestinal IBD activity. Treatment with withdrawal of potential offending medications (i.e., 5-ASA compounds) may be indicated.

Secondary Manifestations

Secondary manifestations are defined as consequences of IBD disease activity and medical or surgical treatments and mainly include joint and vascular complications, but other systems such as ocular, renal, and gallbladder may be affected.

Joint complications include osteoporosis and osteopenia due to chronic corticosteroid use, reduced physical activity, dietary malabsorption of vitamin D, and low serum albumin levels. The fracture risk is 40% higher in IBD patients than in the general population and is similar in females and males [50]. The American College of Gastroenterology (ACG) and the American Gastroenterological Association (AGA) recommend screening patients with IBD and steroid use of greater than 3 months with DEXA scans. Treatment is focused on calcium supplementation, vitamin D supplementation, and bisphosphonate therapy [75, 76].

Vascular complications include venous thromboembolism (VTE), which parallels IBD activity. Portal vein thrombosis can occur in this population. Anticoagulation and treatment of the underlying IBD may reduce the risk of developing further VTE.

Lastly, nephrolithiasis, cholelithiasis, glaucoma, and cataracts may also occur as potential secondary manifestations due to the disease or its treatment.

Overlapping Conditions

Dermatologic and rheumatologic conditions such as bowel-associated dermatosis-arthritis syndrome (BADAS) and cutaneous vasculitis/polyarteritis nodosa (CPAN) may occur in IBD. Another rare type of manifestation that has a coexisting dermatologic and solid organ manifestation is aseptic abscess syndrome.

Bowel-associated dermatosis-arthritis syndrome (BADAS) is characterized by erythematous macules, papules, and vesiculo-pustules secondary to recurrent and episodic neutrophilic dermatosis. This condition is typically seen in patients after jejunoileal bypass surgery but has also been reported in patients with underlying IBD. Although prevalence is unknown, BADAS presents clinically with fevers, chills, arthralgias, and myalgias [77, 78]. Treatments from small case series and case reports include corticosteroids, dapsone, and antibiotics [79].

Cutaneous polyarteritis nodosa (CPAN) is a small and medium vessel vasculitis, which may present similarly to PG or EN and/or with livedo reticularis. Histology reveals perivascular inflammation and immune complex deposition of IgM and C3 within the arterial wall. Other etiologies that may contribute to this entity include hepatitis B, hepatitis C, tuberculosis, parvovirus B19, and group A beta-hemolytic streptococcus [26]. Treatments include systemic glucocorticoids as monotherapy or with cyclophosphamide, methotrexate, or azathioprine.

Aseptic abscess syndrome is characterized by round, deep, and sterile lesions consisting of neutrophils on biopsy. These lesions can exist anywhere in the body including in the spleen, liver, lung, lymph nodes, brain, and pancreas and have a high association in patients with IBD. Patients experience weight loss, abdominal pain, and fever and can be treated with corticosteroids and anti-TNF therapy [80, 81].

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Chapter 6
Infectious Complications in Inflammatory Bowel Disease

Alexandra Garten Schmitt, Thomas Erwes, and Lisa M. Chirch

Introduction

The pathogenesis of inflammatory bowel disease (IBD), including onset, persistence, and recurrence, is intimately intertwined with infection. Much has been written and speculated about various infectious triggers of immune dysregulation, undoubtedly related to microbial imbalance [1]. Individuals diagnosed with ulcerative colitis (UC) or Crohn's disease (CD) are at increased risk of myriad infections by virtue of certain disease-related structural or anatomical abnormalities, such as abscess and fistula formation. Reactivation of certain viral infections such as herpes simplex or cytomegalovirus may predispose to other infectious complications, such as *Clostridium difficile* colitis (C. diff) [2]. C. diff has also been associated with relapse of IBD in several studies [3, 4]. The management and therapy of IBD have evolved considerably over the past decade, with significant associated improvement in the quality of life of affected individuals by virtue of manipulation of the immune system with biologic agents. However, with these benefits come tangible risks, most notably the increased risk of a variety of opportunistic infections [5]. This chapter will review state-of-the-art therapeutic approaches to IBD and associated risk of infectious complications and detail prevention strategies.

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R. Rajapakse (ed.), *Inflammatory Bowel Disease*, Clinical Gastroenterology,
https://doi.org/10.1007/978-3-030-81780-0_6

Therapy for IBD and Infection Risk

Each biologic agent targets different mechanisms in the inflammatory cascade of IBD. This immunosuppression varies, with some biologics acting upon innate host defense mechanisms and others tailored to a more "gut-specific" response. To fully understand the risk of opportunistic infection (OI) in IBD patients treated with biologics, it is first important to evaluate their mechanisms of action.

Specific Drugs and Drug Classes for the Treatment of IBD

Anti-TNF Agents

Tumor necrosis factor (TNF) is a cytokine produced by numerous immune cells, most often by macrophages and T lymphocytes [6]. TNF has several intracellular and extracellular roles, with a high propensity to promote inflammation. It recruits component cells essential to the formation of granulomas and aids in the proliferation of fibroblasts, which are responsible for creating the capsule around granulomas. TNF is therefore important in both the development and maintenance of granulomatous host defense.

Anti-TNF agents have been utilized in therapy of IBD for over 20 years, making the drug class one of the most thoroughly researched biologics in post-marketing [7]. Infliximab was approved by the Food and Drug Administration (FDA) to treat CD in 1998, followed by the approval of adalimumab and certolizumab in 2007 [8].

While there is still some debate on the nuanced mechanisms of anti-TNF agents, it is generally well accepted that anti-TNF agents work to treat IBD primarily through (a) neutralization of TNF-α, which is responsible for signaling pro-inflammatory molecules to the gastrointestinal tissue; (b) initiation of reverse signaling, which suppresses cytokine activity; and (c) promotion of apoptosis of T lymphocytes in the lamina propria reducing T cell proliferation, thought to be the driving force behind inflammation in CD [6].

Anti-TNF treatment is not a targeted therapy, as evidenced by its ability to treat numerous autoimmune conditions such as rheumatoid arthritis, psoriasis, ankylosing spondylitis, as well as IBD. There are benefits to systemic immune suppression in management of IBD, specifically in certain manifestations of CD. Unlike UC, which is limited to colonic involvement, CD can affect any part of the gastrointestinal tract and, in some instances, requires a broader immunosuppressive agent in order to achieve disease remission. Additionally, providers may find themselves needing to select a biologic treatment that is effective for both IBD and another co-occurring autoimmune condition(s). While anti-TNF agents have well-documented successes in both mild and the most severe cases of IBD, treatment with these agents carries a greater risk of opportunistic bacterial, mycobacterial, viral, fungal, and parasitic infections, many of which may not otherwise occur in the immune-competent host.

Vedolizumab

Vedolizumab is a selective leukocyte adhesion molecule inhibitor, approved for use in both CD and UC in 2014 [8]. Based on animal models, vedolizumab is thought to work as a gut-specific monoclonal antibody, which targets α4β7 integrin, inhibiting memory T lymphocytes from migrating to the inflamed gastrointestinal mucosa [9]. Recent human research suggests the mechanism of action of vedolizumab may not be solely associated with intestinal T-cell trafficking but also works to suppress intestinal inflammation by acting on the innate immune system via boosting intestinal macrophages and changing the expression of innate effector molecules, chemokines, and recognition receptors [9]. Safety data from six vedolizumab trials over 4 years involving nearly 3000 patients showed no increased risk of any infection associated with vedolizumab treatment compared to placebo, which is thought to be due to the gut-specific targeting of immune suppression [10]. While the safety profile of vedolizumab is promising from clinical trials, more long-term safety trials are needed to fully establish vedolizumab's safety profile.

Ustekinumab

Ustekinumab was approved for use in CD by the FDA in 2016 [11] and for use in UC in October 2019 [12]. Ustekinumab is a monoclonal antibody that works by binding to the p40 subunit of both IL-12 and IL-23 [13]. This creates a blockade of the IL-12 and IL-23 cytokines, preventing them from binding with their respective receptors and thus effectively preventing inflammation signaling to the immune cells.

The pathogenesis of Crohn's disease is thought to largely involve overexpression of T cells in the intestinal lamina propria, which release large quantities of interleukin-12 [13], while interleukin-23 receptor appears to play a critical role in the genomics of IBD.

Ustekinumab has an anti-inflammatory effect that is systemic, leading to its use not only in IBD but also in psoriasis and psoriatic arthritis [13]. Despite its systemic effects, it appears to have low incidence of opportunistic infections (OIs) among IBD patients, with only three documented case reports (*Listeria* meningitis, esophageal candidiasis, and disseminated cutaneous herpes zoster) [14].

In the PSOLAR registry for psoriasis, of all the biologics, ustekinumab had the lowest rate of serious infection per 100 patient years [13]. Although this registry is primarily for psoriasis patients, 1% of participants (approximately 200 patients) have concurrent CD. While ustekinumab's long-term real-life safety profile is not yet fully established for UC, existing data for CD patients appears to bolster the reputation of low OI risk.

Janus Kinase (JAK) Inhibitor

In May 2018, a Janus kinase (JAK) inhibitor called tofacitinib was approved for treatment of moderate to severe UC [11]. Tofacitinib is not approved for use in CD as of the date of this publication. Unlike previous biologic treatments for IBD, which rely on intramuscular injection or IV infusion, tofacitinib is the first oral tablet biologic treatment for IBD.

Tofacitinib's biologic mechanism is not fully understood [15]. It is thought to play a role in the blockade of inflammatory cytokines, specifically IL-12 and interferon (IFN)-γ, which in theory may increase the risk of intracellular infections by similar processes of anti-TNF agents (e.g., interfering with the genesis of macrophages and diminishing the maintenance of existing macrophages).

To understand the proposed mechanism of tofacitinib, it is first important to review the function of the JAK-STAT pathway. Initially, cytokines phosphorylate JAKs, and then JAKs go on to phosphorylate STAT proteins. Once freed, these STAT proteins activate transcription of inflammatory cytokines [16]. Tofacitinib works by inhibiting all four JAKs, effectively stopping the inflammation cascade before it has a chance to begin. This blocking of the JAK-STAT pathway prevents the creation of numerous inflammatory cytokines, many of which play central roles in the pathogenesis of IBD but also appear to be essential in the function of our primary immune response and ongoing maintenance of the host defenses.

Similar to anti-TNF agents, JAK inhibitors induce systemic immune suppression, leading to a wide array of OI risks for the patient. Tofacitinib is a relatively novel therapy in its application for treatment of UC [11]. As such, the majority of the safety data for tofacitinib is derived from rheumatoid arthritis (RA) randomized controlled trials. Until post-marketing data is accumulated for tofacitinib with long-term safety trials for its use in IBD, we will be reliant upon extrapolating safety risks from the RA groups who have been more extensively studied.

Infection Risk Based on Organism and Organism Type

Bacterial

Mycobacterium tuberculosis

Tuberculosis (TB) remains one of the most lethal infectious diseases worldwide [17]. Approximately 25% of the world's population is infected with *Mycobacterium tuberculosis*. In 2018, an estimated ten million people developed active TB infection, with an associated 1.2 million deaths in the HIV-negative population. While the incidence of TB deaths has declined by 27% globally since 2000, TB remains the number one cause of infectious death from a single pathogen and remains in the top ten leading causes of death overall [17]. Regionally, TB is most common in

Southeast Asia (44%), Africa (24%), and the Southern Pacific (8%). India (27%) together with China (9%), Indonesia (8%), Pakistan (6%), and the Philippines (6%) accounts for 60% of the world's TB population. While TB is common worldwide, US rates have declined over the last 25 years [18]. In 2018, there were an estimated three per 100,000 cases of TB in the United States compared to 316 per 100,000 in Indonesia, 199 cases per 100,000 in India, and 61 per 100,000 in China. Data collected by the Center for Disease Control and Prevention (CDC) from tuberculin skin tests collected from 2011 to 2012 found that incidence of latent TB in the United States was more prevalent in non-US-born persons (20.5%) as well as non-Hispanic Asians (22.2%) and Hispanics (12.3%) [18].

M. tuberculosis most commonly affects the lungs, known as pulmonary TB. Airborne transmission of *M. tuberculosis* begins with inhalation of the bacilli that are deposited in alveoli, setting off an innate immune response to neutralize and destroy the pathogen [19]. Extra-pulmonary TB accounts for 15–20% of cases and occurs when the infection spreads from the alveoli to the lymph nodes and solid organs [20]. Both in pulmonary and extra-pulmonary TB, the host defenses respond to the bacilli by production of T lymphocytes and macrophages, which work together in creating granulomas to wall off and contain the infection [19]. If this initial containment is successful, the host does not develop active TB following exposure but instead carries the encapsulated bacilli in necrotic form, known as latent TB [21]. As long as the host immune system is competent, the granulomas go on to successfully contain the infection in an inactivated state.

TNF plays a critical role in both the formation and maintenance of the host defenses [6]. When TNF is suppressed, it leads the host to be susceptible to reactivation of TB through the disintegration of the existing infected granuloma, allowing the once inactivated bacilli to become reactivated into an incompetent defensive cellular response. The incidence of TB among patients treated with anti-TNF agents was found to be 0.28 per 100 patient years [22], with those on anti-TNF agents five to ten times more likely to have reactivation of *M. tuberculosis* compared to the general population. It appears patients on anti-TNF agents are at increased risk of TB even if they have a negative TB screening test prior to treatment induction, which demonstrates the need for ongoing surveillance for these patients [23].

The incidence of *M. tuberculosis* infection during tofacitinib treatment is similar to that which occurs on anti-TNF treatment (0.21 per 100 patient years [16] vs. 0.28 per 100 patient years [22], respectively). The blockade of JAK inflammatory cytokines prevents intracellular signaling of IL-12 and interferon (IFN)-γ, which are essential in the creation and function of macrophages [15]. Thus, similar to anti-TNF agents, JAK inhibitors interrupt the genesis of macrophages and interfere with the production of components required to maintain the function of the macrophage, allowing the once encapsulated and inactivated *M. tuberculosis* infection to become reactivated.

Clinical trial data do not suggest that vedolizumab increases patients' risk of TB; incidence rates among participants were congruent with the population incidence rates of the country of origin [23]. Additionally, in post-marketing data, patients who did develop TB while on vedolizumab were able to resume vedolizumab after finishing TB treatment.

In theory, there is a risk of TB reactivation for patients on ustekinumab, and although the degree of risk is uncertain, it appears to be low [14]. The incidence of TB in patients on ustekinumab was 0.02 per 100 patient years [22].

Nontuberculous Mycobacteria (NTM)

Nontuberculous mycobacteria (NTM) represent a group of numerous organisms, most of which do not pose a threat to immunocompetent persons [24]. NTM are found in soil, water, and animal vectors. NTM infections among patients with IBD have been less extensively studied in comparison to *M. tuberculosis*. Within the existing research, there are a few NTM infections identified specifically in IBD patients receiving biologics: *M. avium*, *M. marinum*, and *M. abscessus*.

M. avium is the most common NTM in the United States [22] and one of the most common NTM infections in severely immunocompromised persons [24]. *M. avium* is not thought to pose a risk to immune-competent persons [25]. It is found in water and collected rainwater is a common source. Infection with *M. avium* occurs with inhalation of aerosolized particles, such as water spray from an outdoor shower or mist from a water hose. Even point-of-use water filtration devices can become colonized.

M. avium complex (MAC) refers to both *M. avium* and *M. intracellulare* and is a thoroughly researched OI among AIDS patients, in part due to its incidence (3% among patients with CD4 counts between 100 and 199 cells/uL) [26], but mostly due to its reputation as clinical complex to treat with its multidrug-resistant strains [27]. Disseminated MAC occurs nearly exclusively in those with CD4 counts below 50 cells/uL [26].

M. abscessus is the second most common NTM infection in the United States and usually affects soft tissues, skin, and lungs (although it can affect any organ). *M. abscessus* is often multidrug resistant, which can pose a significant threat to the immunocompromised. It is found both in soil and water. There are case reports of *M. abscessus* transmission from gardening, acupuncture, and cosmetic mesotherapy involving the injection of various substances under the skin to produce a tightening effect. *M. abscessus* affects not only the skin and soft tissues but also causes serious lung infection, especially for those with preexisting lung diseases such as chronic obstructive pulmonary disease (COPD) or cystic fibrosis (CF) [28].

There are case reports of *M. marinum* among IBD patients, commonly acquired by aquarium owners or fishermen [29]. *M. marinum* infections are usually limited to the skin; seventy-five percent of cases present as a solitary lesion on the hand or digit [30]. Among those on anti-TNF treatment, the clinical presentation more often takes a sporotrichoid form whereby the infection extends beyond the lesion, producing several nodules along the lymphatic vessels, and spreads to regional lymph nodes. *M. marinum* can invade deeper tissues in 20–40% of cases (tenosynovitis, osteomyelitis, arthritis, and bursitis).

Among the research examining OIs in biologic therapy, NTMs are often examined as a category of OI [31]; less often the individual NTM infection is parsed out in the data. Furthermore, the data that is available on NTM incidence in biologic therapy frequently does not focus on the IBD population exclusively, which limits its salience for application in this population.

Data on NTM infections among IBD patients receiving anti-TNF treatment is limited; most research on the topic reports the total incidence of NTM infection among those receiving anti-TNF treatment for any indication (e.g., infection rates for those with RA, psoriasis, ankylosing spondylitis, and IBD are reported together). As such, this data should be interpreted with caution and may not accurately reflect the risk of opportunistic NTM infection among IBD patients on anti-TNF agents.

According to Shim et al. [22], overall NTM infection for those receiving anti-TNF has been estimated at a rate of 230.7 per 100,000 patient years, similar to numbers reported by Yoo et al.: 238.2 per 100,000 person-years [31]. One analysis of OIs among 1165 patients on anti-TNF treatment found that the most common NTM infections were *M. intracellulare* ($n = 3$) and *M. avium* ($n = 2$) [31]. In this same cohort, 83% of patients who developed NTM infection were receiving anti-TNF treatment for RA and not for IBD. Of the 422 IBD patients, only one was reported to have NTM infection, though the specific NTM infection was not reported. There are 30 case reports of *M. marinum* in those receiving anti-TNFs, with at least one case of disseminated disease [30].

There is limited data on NTM infection risk with tofacitinib use, but the risk appears to be low, with only two cases of pulmonary NTM infection documented among the 5671 patients enrolled in tofacitinib trials [15]. Only one case report of *M. abscessus* while on ustekinumab treatment [22] was identified.

Listeria monocytogenes

Listeria monocytogenes causes a foodborne illness that often results in self-limiting diarrhea, but in the immunosuppressed, it can lead to bacteremia, bacterial meningitis, and rhombencephalitis [32, 33].

L. monocytogenes is an intracellular pathogen; the growth of intracellular pathogens is inhibited by TNF-α; thus, when TNF-α is suppressed, the intracellular growth proceeds unchecked [32]. Studies examining *L. monocytogenes* risk specifically in the IBD population are limited, but listeriosis was found to be 20 times more common in RA patients treated with infliximab compared to the general US population (incidence of 61 per 1,000,000 person-years) [32].

Estimates of incidence of high-risk complications from *L. monocytogenes* are limited to case reports, such as 69-year-old male with CD on anti-TNF treatment who presented to the Emergency Department (ED) with acute central nervous system (CNS) changes and was diagnosed with Listeria rhombencephalitis [33].

Due to the gut-selective nature of vedolizumab, it is plausible that patients on treatment could be at increased risk for OIs of the gut such as *Listeria* [10]. In an

analysis of the 2830 patients across six safety trials, one patient developed *Listeria* meningitis, though this patient was also taking corticosteroids and azathioprine at the time of infection.

Streptococcus pneumoniae

Streptococcus pneumoniae is an opportunistic gram-positive extracellular pathogen that colonizes the mucosal surfaces of the nasal epithelium [34]. It is the causative bacterial agent of numerous infections ranging from mild (e.g., otitis media), moderate (community-acquired pneumonia) to severe (sepsis and meningitis). It is spread through both contact and airborne transmission. It is estimated that anywhere from 25% to 65% of children carry *S. pneumoniae* whereas less than 10% of adults are carriers [34]. If the carrier's immune system is compromised, it allows for dissemination of the bacterium into the lungs via aspiration, which can then lead to bacteremia, as well as spreading through the sinuses and inner ear.

TNF-α is essential to the host defense against extracellular bacteria, leaving those who are treated with anti-TNF agents inherently at increased risk for extracellular bacterial infections such as *S. pneumoniae* [32].

In an analysis of the 2830 patients across six safety trials for vedolizumab, 36 patients were documented as having infection with *S. pneumoniae*, which equates to an incidence of 0.8 per 100 patient-years [10].

Viral

Herpes Zoster (HZ)

Initial exposure to varicella zoster virus (VZV) causes primary varicella, commonly referred to as chicken pox [11]. Reactivation of VZV leads to herpes zoster (HZ), commonly referred to as shingles. Anyone with prior VZV exposure is at risk for developing HZ [35]. After initial exposure to VZV, varicella remains dormant in the dorsal root ganglia or cranial nerves [11]; reactivation causes a painful rash with hallmark distribution across dermatomes.

The risk of HZ infection among the general population is greatest in women, and incidence increases with age [36]. Analysis of nearly 40,000 IBD patient charts between 1996 and 2015 found HZ infection follows a similar pattern of increased incidence with age and among women, but not surprisingly authors found HZ affects the IBD population at a higher rate than the general population, especially in young persons [36]. Incidence of HZ among the general IBD population was found to be 0.7 per 100 patient-years.

Congruently, analysis of disease incidence among health insurance beneficiaries (specifically those with United Healthcare, Medicare, and Medicaid coverage

between 2007 and 2010) found that those with IBD under the age of 60 were twice as likely to be diagnosed with HZ compared to those without IBD over the age of 60 [35]. Some have proposed that the higher observed HZ incidence among younger patients with IBD is due to the use of biologic treatments [36]. Reoccurring HZ infection is higher in the IBD population compared to the general population, with more than half of the reoccurrence rates observed in patients over the age of 60 [36].

TNF is central to the TNFR1-mediated apoptotic death of cells infected with viruses [32]. In post-marketing research of anti-TNF safety in the French RATIO registry, most documented OIs were viral. While it is presumed that patients receiving anti-TNF treatment for IBD are at increased risk for HZ, the evidence has been contradictory, with some multi-institutional studies showing no increased risk of HZ on anti-TNF treatment and other country-specific databases in Europe showing statistically significant increased risks. There are several proposed reasons for this conflicting data, namely, the varying regional practices of using corticosteroids during the induction phase of anti-TNF treatment and perhaps the varying inclusion criteria of participants between the retrospective analyses interferes with the ability to draw direct comparisons. More research is needed in order to understand whether anti-TNF treatment alone in IBD is associated with increased risk of HZ infection.

Tofacitinib is thought to affect antiviral immune response in a more dismantling fashion compared to other biologic agents due to its action upon JAK1 [16]. Theoretically, tofacitinib diminishes type 1 (IFN-α and IFN-β) and type 2 (IFN-γ) viral responses, leaving the JAK1 receptor inactivated, rendering the host response to viral infection as inept [15]. HZ infection poses arguably the greatest risk for patients treated with tofacitinib. Those on JAK inhibitors are more than six times as likely to have HZ infection as compared to the general population [36].

UC patients treated with tofacitinib appear to have much higher incidence of HZ compared to the general population, with some studies demonstrating incidence of four per 100 patient-years [11] up to 7.6 per 100 patient-years [37].

Disseminated Herpes Zoster (DHZ)

In most cases, HZ is controlled quickly and succinctly by the immune system, but in certain instances, the HZ infection spreads and is termed disseminated disease when more than 20 vesicles appear beyond the initial dermatome and/or more than two dermatomes are affected, signaling the presence of persistent viremia [38]. Unlike HZ, the incidence of DHZ appears to be the same between males and females. The relative risk of DHZ while on anti-TNF treatment for IBD is not reported.

In the UC clinical trials of tofacitinib, there was a documented increased risk of HZ compared to placebo, but none of the participants had more than one or two dermatomes affected, and the participants did not need to discontinue tofacitinib as a result of the infection [37].

It has been observed that of those on tofacitinib who develop HZ, the risk of complications from HZ was highest among those older than 65, Asians, or those with a history of prior anti-TNF treatment failure [39]. It is not clear why the Asian population may be disproportionally at increased risk for complications from HZ while on tofacitinib treatment, but it may be a result of regional variance. For example, population studies have found HZ incidence in China and Taiwan to be much higher (51% and 66%, respectively) compared to relatively lower rates in Western Europe (7–26%) [40].

Chronic Hepatitis B Virus (HBV)

It is estimated that 240 million people have chronic HBV worldwide, with close to 700,000 deaths annually due to HBV complications [41]. North America and Western Europe are relatively low-endemic regions with estimated prevalence of chronic HBV between 0.5% and 2%, compared to the high-endemic regions of China, Indonesia, Southeast Asia, and sub-Saharan Africa, which all report greater than 8% incidence rates. In recent years, there has been a documented increase in HBV infection among European populations, thought to be a result in part to the migration of refugees from endemic areas into Europe [42]. Epidemiologists anticipate rates of HBV infection may rise over the next few years as a result of this migration. Refugees with chronic HBV are younger, more likely to have coinfection with HIV, and are more vulnerable to suffering long-term complications from HBV due to limited access healthcare.

HBV can cause both acute and chronic diseases [41]. The infectivity of HBV is more than 100 times that of HIV, with those most at risk including IV drug users, those who practice unprotected intercourse with multiple partners, healthcare workers with needle-stick injuries, and the incarcerated [43]. Transmission of HBV occurs through blood, sexual, or vertical route [41]. Acute infection is characterized by a positive HB surface antigen (sAg) and a viral load (HBV DNA level) over 2000 IU/mL. If the HBsAg is detectable for greater than 6 months, the person is considered to be chronically infected. Patients who have no detectable HBsAg after 6 months are considered to have “cleared” the infection and are categorized as potential or occult carriers. Antibodies against surface antibody (HBsAb) sometimes develop in potential carriers, but not always.

In 2008, the CDC recommended all persons who are receiving immunosuppressive treatments should be screened for HBV prior to starting treatment [44]. This recommendation for screening was due to concerns for increased rates of reactivation of HBV in immunosuppressed persons. The term “reactivation” in reference to HBV generally means either (a) patients with chronic HBV experience increased viral replication and activity of once controlled disease; (b) patients who had been exposed to HBV and cleared the infection test positive for HBV sAg, suggesting they have reverse-seroconverted to chronic infection; or (c) patients who had been exposed to HBV and cleared the infection now have detectable HBV DNA levels on quantitative testing but remain sAg negative [41]. There is a general consensus that

HBV reactivation is significantly higher in patients receiving combination immunosuppressive therapies than single agents alone [23].

Patients on anti-TNF treatment are thought to be at greater risk of reactivation of chronic HBV [32], though there is conflicting data on the validity of this statement [44]. Some studies show no significant increased risk of reactivation of HBV for patients receiving anti-TNF therapy, while other studies show up to 25% of patients with a positive hepatitis B surface antigen (HBsAg) prior to treatment went on to experience reactivation. Screening for HBV prior to initiating treatment with anti-TNF agents for IBD has increased over time [44], and this variance in pre-screening of patients may in part account for the conflicting data on risk of HBV reactivation in this patient population. In 2008, the same year the CDC recommended HBV screening for immunosuppressed persons, IBD practice guidelines also included this recommendation.

In an analysis of over 3000 IBD patients from the Veterans Health Administration datasets between 2003 and 2011, Shah and Ho et al. found that only 8.9% of IBD patients were screened for HBV prior to anti-TNF initiation, compared to 43.2% who were screened in 2011 [44]. Additionally, they did not find any documented cases of clinically significant HBV reactivation among this group, which was the first study to specifically examine the risk of HBV reactivation among IBD patients receiving anti-TNF.

Although vedolizumab is not thought to increase the risk of opportunistic infections [10], clinical trials for vedolizumab excluded patients with chronic HBV [23]. In the Global Safety Database examining patients who received vedolizumab, 14 patients out of 114,971 patient years were identified as having a history of HBV infection, and three of these had confirmed chronic HBV. There were no liver-related adverse events reported in these 14 patients, and more than half had prior or current use of anti-TNF agents. It is generally accepted among gastroenterologists that single-agent immunosuppression with vedolizumab is unlikely to increase the risk of HBV reactivation, but further safety trials are needed in order to strengthen the validity of this observation.

There is limited data on the risk of HBV reactivation with the use of tofacitinib, and even less is known about how this possible risk affects the IBD population specifically [40]. Data gleaned from the rheumatoid arthritis trials suggest the risk of HBV reactivation on tofacitinib is real, although the incidence is low [40]. These findings may be in part due to the geographical variances of HBV, with low incidence in the United States. Further longitudinal analysis will be needed to fully establish the degree of risk.

Chronic Hepatitis C (HCV)

It is estimated that four million people in the United States have chronic HCV [43]. As with HBV, transmission of HCV occurs through blood, sexual, and perinatal routes. Unlike HBV, there is no vaccine active against HCV. Prior to 1992, blood

products for transfusion were not screened for HCV in the United States. Acute infection with HCV can be cleared or go on to develop into chronic infection [43]. Treatment for HCV in the last decade has made tremendous progress to the extent that the overwhelming majority of patients with chronic HCV can be cured.

Anti-TNFs may allow for proliferation of viral replication in HCV, but the available data is limited and often based on short-term observations [45]. The blockade of TNF-α may actually benefit patients with HCV since TNF-α contributes to the development of liver fibrosis through recruitment of pro-inflammatory molecules [45], although it is not known to what extent (if any) that this mechanism is protective. Overall, limited data exists on the risk of worsening HCV infection on anti-TNF therapy, but it appears the risk is low [32]. Whether this low apparent risk is due to under-reporting or due to actual low incidence is not known. Since eradication of HCV is now widely accessible and successful and the duration of treatment is relatively short (8–12 weeks depending on the agent), it is possible there is under-reporting of HCV incidence among patients receiving anti-TNF.

Clinical trials for vedolizumab excluded patients with HCV [23]. In the Global Safety database, 15 patients out of 114,971 patient years were identified as having a history of HCV infection. There were two liver-related events reported: one liver neoplasm categorized as "serious" and one liver mass categorized as "not serious." Similar to the limitations with research on HBV, the use of tofacitinib in the IBD population and the subsequent risk of HCV have not yet been fully examined.

Fungal

In a large retrospective analysis of IBD hospitalizations between 2002 and 2014 from the National Inpatient Sample (NIS) database, the prevalence of opportunistic fungal infections among IBD patients was around 2% [46]. As with all OIs, the combined use of biologics plus corticosteroids increases the risk of fungal infections and associated mortality among the IBD population [47]. Anti-TNF agents are the most often noted biologic agents associated with fungal infections, likely a function of their systemic immunosuppressive effects, although the long history of their use in IBD does render them the most well studied in post-marketing [48]. Histoplasmosis and candidiasis are the most frequent opportunistic fungal infections for patients on anti-TNF agents [32, 46]. The risk of opportunistic fungal infection with vedolizumab was not higher compared to placebo in trials [46].

Candidiasis

Candida albicans is an extremely common commensal microorganism [49]. *C. albicans* is responsible for mucosal infections such as vulvovaginal candidiasis and esophageal candidiasis as well as systemic infections including sepsis [49]. Among

the IBD population, candida most frequently affects the respiratory and gastrointestinal tracts, but it can lead to bloodstream infection as well [48]. In a systematic review of fungal infections in the IBD population, approximately 10% of candida infections lead to sepsis. The mortality from candidiasis-induced sepsis is estimated to be approximately 40%, and it is the fourth leading cause of sepsis overall [49].

Invasive fungal infections can occur in patients on anti-TNF therapy, though the vast majority of the literature notes that concurrent use of corticosteroids and anti-TNF agents poses the greatest risk [50]. Systemic candidiasis is theoretically more likely in those with suppression of TNF levels, specifically due to the subsequent reduced production of IFN, increased apoptosis of monocytes, and reduced granuloma maintenance; these three mechanisms render the host defenses unable to contain the spread of the infection and allow for fungal proliferation in several organs [50].

Histoplasmosis

Histoplasma capsulatum is found most often in bird and bat droppings, and while cats can develop histoplasmosis, cats cannot infect humans [51]. It is the second most common fungal infection among the IBD population in the United States where it is considered endemic. There are regional variances of incidence within the United States, with histoplasmosis more commonly found in IBD patients hospitalized in the Midwest [46]. Those who keep chicken coops or frequent caves for recreation or occupation are at greatest risk [51]. Symptoms of histoplasmosis include fever, chills, extreme fatigue, cough, headache, chest pains, and body aches [52]. Onset of symptoms can occur 3 days after inhalation of the spores up to 17 days later. It is usually a short-lived illness, although it is possible the lung infection can be long term in the immunocompromised or spread to the CNS.

Coccidioidomycosis

Coccidioides immitis and *C. posadasii* are organisms that cause coccidioidomycosis, more commonly known as valley fever [53]. It is common in the southwest United States, as well as Mexico and South America. The spores of *Coccidioides species* reside in dust and soil, although there have been rare cases of valley fever occurring after exposure to a wound infected with *Coccidioides* and from exposure to shoes and rocks contaminated with spores.

Among patients hospitalized with IBD, the incidence of coccidioidomycosis was most common in the western United States, which follows the same pattern of its regional prevalence [46]. Like other fungal infections, anti-TNF increases the risk of reactivation of coccidioidomycosis, although the incidence is limited to case reports [32]. Symptoms of valley fever include rash (erythema nodosum) on upper

body or legs, cough, shortness of breath, fever, fatigue, night sweats, muscle aches, joint pain, and headaches [54]. Onset of symptoms occurs anywhere from 7 to 21 days after exposure and will last a few weeks to a few months. Five to 10% of those with valley fever develop chronic lung disease as a result of infection.

Blastomycosis

Blastomyces are fungi that live in moist decomposing organic matter such as leaves and woods and can be found most commonly in forest soil in the areas of the United States that surround the Great Lakes and the Ohio, Mississippi, and Saint Lawrence River [55]. Infection with blastomycosis occurs after inhaling the spores from disrupted soil. Activities that can result in exposure include hiking, camping, and hunting in wooded areas of the Midwest. In a review of the NIS database, it was found that blastomycosis was more common in IBD patients hospitalized in the Midwest [46]. Symptoms of blastomycosis are similar to the flu, including fever, cough, night sweats, muscle aches, joint pain, weight loss, chest pain, and extreme fatigue [56]. Symptoms start 21–90 days after inhalation of the spores, and disseminated infection can occur.

Aspergillosis

Aspergillus is a mold, transmitted through airborne inhalation of conidia [57]. Most immune-competent individuals do not develop illness as a result of *Aspergillus* exposure; however, those that are immunosuppressed are at risk of developing invasive infection. In the immunocompromised, *Aspergillus* is the leading cause of fatal pneumonia [47]. Invasive pulmonary aspergillosis can then lead to disseminated disease involving the brain, skin, and bones [57]. Exposure to high quantities of *Aspergillus* is thought to occur during building construction or renovations, but it is also found throughout the indoor and outdoor environment as household dust and decomposing plant matter.

Estimates of the incidence of aspergillosis among the IBD population are limited to case reports and appear to occur in the setting of simultaneous corticosteroid use with biologics [47, 48].

Cryptococcosis

Cryptococcosis is an invasive fungal infection, acquired through inhalation of airborne propagules, which deposit into pulmonary alveoli [58]. Cryptococcosis poses significant risk among the severely immunocompromised, with reports of nearly

one million annual cryptococcal meningitis infections worldwide. Around 95% of all cryptococcosis infections derive from *C. neoformans*, which is found in the excrement of pigeons and other birds, amoebas, and sow bugs and lives within hollows of trees. Regionally, cryptococcosis is more common among IBD patients in the South [46].

Cryptococcosis infection is contained through granulomas, making TNF, interferon-y, and interleukin-2 critical in the host defense against cryptococcocal infection [58]. As such, those on anti-TNF treatment are at increased risk of developing the infection.

Parasitic

Leishmaniasis

Leishmaniasis is a parasitic infection caused by many different species of *Leishmania* [59]. It is widely endemic throughout both hemispheres, including in the Mediterranean, India, Africa, and across South and Central America. *Leishmania* species are associated with cutaneous, mucosal, and visceral disease most often in immune incompetent hosts. In the cutaneous presentation, leishmaniasis causes large treatment-resistant skin lesions which can be mistaken for other diverse cutaneous presentations of CD. While most persons exposed do not go on to develop infection, it is thought that the parasite can remain dormant and pose a threat for reactivation [59]. Although the risk of reactivation among IBD patients on biologics is largely unknown, it is a growing area of research and may be included in future screening guidelines prior to biologic initiation.

Strongyloides

Strongyloides stercoralis is an intestinal nematode found in tropical and subtropical areas. It most commonly results in a mild or subclinical gastrointestinal infection with skin manifestations in immunocompetent individuals but can result in severe disease in the immunocompromised [60]. Hyperinfection is most commonly identified in patients receiving chronic corticosteroid therapy but is theoretically possible in other forms of immunosuppression and has been rarely reported [61, 62]. In this type of presentation, patients are gravely ill and may develop gram-negative bacteremia and meningitis with multiorgan failure in the most severe cases. As such, many experts recommend consideration of screening individuals with a history of residence in or travel to endemic areas [63].

Preventing Infections in IBD

Taking a History from an Infectious Disease (ID) Perspective

Prior to starting immunosuppressive therapy for IBD, a complete history should be performed. Review of the indications for treatment as well as the mode of action of the drug used will lead to a better understanding of infectious risks for the patient. Firstly, any current or recent infections should be ruled out by reviewing signs and symptoms that the patient may be experiencing. A thorough travel, social, and exposure history may provide clues as to a potential causative agent. Once active infection is ruled out and immunosuppressive therapy is considered, future risks of infection can be identified by a complete exposure history. A history of past infection, in childhood or in household members, should be elicited as well. History of prior blood transfusions or organ transplants is also important as it can increase the risk of infections such as hepatitis B and C.

Travel History and Future Plans

An effective ID history always includes a detailed travel history. As noted above, treatment with immunosuppressive therapy may increase the risk of infection acquired in certain endemic areas. It is therefore important to obtain information about patients' recent travel as well as areas of prolonged residence. Plans for future travel should be discussed as well to determine if the patient will be at risk for exposure to additional infectious agents.

Occupation

Certain occupations may place the patient at risk for particular infections. An example would be dimorphic fungi present in soil where activities such as farming, soil excavation, and construction/demolition may place the patient at increased risk in the setting of immunosuppressive therapy [64, 65].

Patients working in healthcare may be at increased risk through interaction with patients harboring communicable diseases, such as tuberculosis. They are also more likely to be exposed to blood-borne pathogens in the setting of needle-stick injuries, with concern for hepatitis B and C, as well as HIV. In one retrospective study, though healthcare workers on immunosuppressive therapy were found to have a high number of *Clostridium difficile* and Epstein-Barr virus (EBV) or cytomegalovirus (CMV)-related infections, no significant risk was found compared to the control group without IBD [66]. Similar to healthcare workers, patients that were recently hospitalized or residents of nursing homes may be at increased of *C. difficile* infection [67]. Another occupational infection to be aware of is *Legionella*, acquired through exposure to aerosolized water sources. Exposure to air

conditioners, water fountains, or cooling towers may place the patient at an increased risk while on immunosuppressive therapy [68].

Hobbies and Activities

Like occupational activities, some hobbies may increase the exposure to specific pathogens though the route of exposure may differ. For example, histoplasmosis can be associated with spelunking through contact with soil that has been contaminated with bird or bat droppings [64]. Farming, as mentioned above, can also increase the risk of fungal infection by disturbing the soil. Farming as well as gardening can be associated with sporotrichosis, a fungal infection caused by *Sporothrix schenckii*, which can cause lymphangitis or pneumonitis [69].

Diet

Patients' dietary habits may also represent a source of infection, for example, the consumption of undercooked meat or unpasteurized dairy products. Immunosuppressed patients who ingest these types of foods can develop listeriosis, caused by the gram-positive bacterium *Listeria monocytogenes*, which can eventually lead to CNS disease [70]. Nondairy foods, such as cantaloupe, have been also known to cause sporadic listeriosis outbreaks [71]. Consumption of poultry, meats, and dairy products has been known to be associated with salmonellosis, caused by the gram-negative rod, *Salmonella* species. In immunocompetent patients, it can be associated with gastroenteritis but can lead to bacteremia, osteomyelitis, and endovascular infections in the immunocompromised [72].

Animal Exposures

In patients starting immunosuppressive therapy, it is important to gather information about any animal exposure, including house pets, farm animals, as well as any possible indirect contact, such as with rodents or bats in the home. Infections can be transferred from animal to human (zoonoses), or the pathogen may reside in the animal's environment. Immunosuppressed patients can be at risk for *H. capsulatum* infection, which is a dimorphic fungus found in soil that has been contaminated with bird or bat droppings. Patients owning birds or chickens, as well as spending time near chicken coops, may be at increased risk for histoplasmosis. Another agent associated with bird droppings is the fungus *Cryptococcus neoformans*, which can cause CNS, pulmonary, and disseminated infections in immunocompromised patients [73]. Patients receiving immunosuppressive therapy appear to be at increased risk of nontuberculous mycobacteria such as *Mycobacterium marinum* [74]. This acid-fast nontuberculous mycobacterial species is usually seen in aquatic environment and can cause skin lesions after breaks in skin are exposed to ocean, salt, or fresh

aquarium water, causing so-called "fish-tank granulomas." Immunosuppression particularly increases the risk of disseminated infection [75, 76]. Toxoplasmosis, which is caused by the protozoan *Toxoplasma gondii*, is associated with hand-to-mouth contamination with cat feces or consumption of raw meat. Exposure may cause a subclinical or mild influenza-like or mononucleosis-like illness from which healthy hosts recover with no complications. In immunocompromised hosts, the parasite may reactivate and may be disseminated to the CNS, eyes, heart, liver, or lungs [77]. Patients with pet reptiles, such as lizards, snakes, and turtles, as well as amphibians, such as frogs, are at increased risk of S*almonella* infection [78].

Sexual History

A comprehensive sexual history is necessary to identify possible sexually transmitted infections and to address any risk factors. The risk of HIV, HCV, and HBV is increased in men who have sex with men and in patients with multiple sexual partners. As noted above, reactivation of hepatitis B is a concern in IBD patients receiving certain therapies. Human papillomavirus (HPV) is the most common sexually transmitted infection (STI), and incidence may also be affected by immune status. The virus can cause infection of the skin and mucous membranes, leading to formation of warts and anogenital condylomas. Certain strains of HPV can be associated with malignancies of the cervix, vulva, penis, anus, or oropharynx. Though immune suppression may increase the risk of anogenital warts, there is currently no evidence that risk of malignancy is increased as well [79]. Herpes Simplex Virus (HSV) is also known to cause oral and genital lesions and, in some cases, can cause CNS infections. Patients undergoing immunosuppressive therapy may be at increased risk of developing herpes encephalitis [80].

Substance Use and Other Practices

Substance use, particularly intravenous drug use, is known to be associated with increased infection risk. As discussed above, HIV and viral hepatitis may be transmitted through sharing of needles, and IBD patients receiving biologic agents may carry an increased risk of progression and complications. Skin and soft tissue infections can also occur in the setting of IV drug use with the most typical organisms being *Staphylococcus aureus* and *Streptococcus pyogenes*. Similarly, patients who have tattoos placed using contaminated equipment are at risk for acquiring HBV and HCV, as well as skin and systemic bacterial infections [81–83]. Cigarette smoking is known to increase susceptibility to a variety of respiratory tract infections, including bacterial pneumonia caused by *Streptococcus pneumoniae* [84]. Infection with this organism can lead to meningitis in severe cases, particularly in immunocompromised patients. Proper vaccination as discussed below may prevent infection. Cigarette smoking can also increase the risk of pulmonary tuberculosis [85].

Table 6.1 represents an example of a complete history sheet to elicit important information prior to starting immunosuppressive therapy.

Table 6.1 Example of items to assess during a visit with an IBD patient planning to start immunosuppressive therapy

Exposure	Yes	No	Comments
Medical history Do you have any history of prior infections, including hepatitis and tuberculosis? Anyone in your household with a history of prior infections? Have you been recently hospitalized? Any history of organ transplant? Any history of blood transfusion? Any history of malignancy and prior cancer screenings?			
Travel and residence Have you traveled or lived outside the United States? Where? When? Have you traveled or lived outside your state of residence? Do you have future domestic or international travel plans? Does your home have known mold problems? Do you have well water?			
Occupation What do you do for a living? Do you work outdoors? Are you involved in farming, soil excavation, or construction/demolition? Do you work in health care? Are you a caretaker for the very young or elderly?			
Hobbies and activities Do you spend a lot of time outdoors? Where? Do you spend time in caves? Are you exposed to a lot of freshwater or saltwater? Do you do a lot of gardening? Do you wear gloves?			
Diet Do you consume raw/undercooked meat or fish? Do you consume processed meats? Do you consume unpasteurized dairy products? Do you consume soft cheeses?			
Animals and pets Do you have any pets in your home? Have you been in contact with farm animals? Any other recent animal contact, including wild animals or birds?			
Sexual history Are you sexually active? Do you use barrier protection? Do you have multiple sexual partners? Men, women, or both? Do you have any history of sexually transmitted infections (examples are herpes, syphilis, gonorrhea, and chlamydia)? Have you ever been tested for HIV or hepatitis? Have you ever had an abnormal pap smear?			
Substance use and other Do you smoke? Tobacco? Vaping? Other? Do you or have you ever used drugs? Intravenous? Shared needles? Do you have any tattoos? Sterilized equipment?			

Screening Methods for Specific Infections

A detailed discussion about any past or current infections is essential prior to starting any patient on immunosuppressive therapy. Additionally, there are several screening methods available that should be offered during the initial evaluation under appropriate clinical circumstances.

Tuberculosis

All patients with IBD should be screened for latent tuberculosis infection (LTBI) prior to starting immunosuppressive therapy. Reactivation of LTBI is a risk for patients starting on immunomodulatory agents, and early screening may prevent development of active TB with appropriate treatment. Though recommendations for treatment are consistent, there are no clear guidelines as to the gold standard for diagnosing LTBI. Recommended tests include the tuberculin skin/Mantoux test or Quantiferon-TB Gold/interferon gamma release assay (IGRA), followed by a screening chest radiograph if positive. In the setting of immunosuppression, a positive result for either of these tests is considered diagnostic of LTBI, although immunosuppression may significantly reduce their sensitivity. Once patients are started on immunosuppressive therapy, while most authors agree screening should be based on the individual patient and his or her level of risk, in general, patients should be screened annually at a minimum [86]. Several equivalent regimens are available for the treatment of LTBI and include the medications isoniazid, rifapentine, and rifampin used individually or in combination. Both the CDC and National Tuberculosis Controllers Association (NTCA) now recommend rifamycin-based treatment, which is shorter in course compared to the 6- or 9-month isoniazid monotherapy (6H and 9H). The three different short-course regimens include a 3-month period of once-weekly isoniazid plus rifapentine (3HP), a 4-month period of daily rifampin, and a 3-month period of daily isoniazid plus rifampin (3HR). The shorter-course treatments have been shown to be effective and safe as well as exhibit higher completion rates compared to the longer isoniazid-based regimens [87]. The longer 6H and 9H regimens have also been associated with higher risks of hepatotoxicity. Once LTBI is diagnosed and therapy is initiated, it is recommended to wait at least a month prior to starting immunosuppressive therapy for the patient with IBD [88].

Histoplasmosis and Coccidioidomycosis

Patients on TNF inhibitors are thought to be particularly susceptible to histoplasmosis and coccidiodomycosis because of TNF-α's role in the host's defense against fungal organisms [89]. While there are no clear screening recommendations for endemic mycoses prior to starting therapy, patients who have lived or are currently

living in endemic areas could be at risk. A high degree of suspicion is required when a patient from an endemic area participating in high-risk activities presents with consistent symptoms; a chest radiograph can be pursued to look for active or old disease, and certain serologic studies may prove valuable, such as a urine histoplasma antigen [90]. At this time, antifungal prophylaxis is not recommended for asymptomatic patients in endemic areas, but prompt therapy for suspected active infection in the context of an appropriate clinical presentation in an immunosuppressed individual is critical.

Hepatitis B

Immunosuppression poses a significant risk for reactivation of hepatitis B virus (HBV) and flare of HBV disease, leading in some cases to severe liver failure and death if left untreated [91]. A recent review from the Royal College of Physicians by Apostolos et al. [92] summarizes screening recommendations as well as appropriate antiviral prophylaxis if required. All patients starting immunosuppressive therapy should be tested for evidence of HBV infection with serologic testing, including HBV core antibody (anti-HBc) and HBV surface antigen and surface antibody (HBsAg and HBsAb). As a reminder, HBsAg is a marker of infection with anti-HBs representing either recovery from infection or immunity following vaccination. Anti-HBc is expected to be positive in acute (IgM) or chronic (IgG) infection and may be positive during viral reactivation. Patients with a positive HBsAg or anti-HBc should then have their HBV DNA measured as well as HBV e antigen and antibody (HBeAg and anti-HBe) to evaluate for a high replicative state and e antigen seroconversion, respectively. Serologic studies will help determine, along with the type of immunosuppressive therapy, the level of reactivation risk, with positive HBsAg conferring a higher risk [92]. Reactivation of HBV is eventually diagnosed by noting an increase in the HBV DNA level. Antiviral therapy is recommended for all patients with HBV reactivation, with first line being treatment with nucleos(t)ide therapy such as tenofovir and entecavir. Careful case-by-case review is recommended when there are questions regarding the necessity to interrupt immunosuppressive therapy once HBV reactivation is diagnosed. Patients deemed to be at moderate-to-severe risk of flare may need to temporarily hold or reduce therapy while being treated for HBV reactivation. A similar nucleos(t)ide regimen is recommended for prophylactic treatment for HBsAg-positive patients planning to start immunosuppressive therapy. Some patients may have a negative HBsAg but a positive anti-HBc suggestive of past exposure though lacking protective immunity. These individuals are, in theory, at risk for reactivation. Though the reactivation risk is relatively low for those patients when starting immunosuppressive therapy, many experts recommend antiviral prophylaxis, depending on the immunosuppressive regimen planned [90]. For patients with no evidence of past HBV infection or immunity, vaccination prior to initiation of immunosuppressive therapy is strongly recommended, as discussed below.

Strongyloides

Strongyloides infection, if left untreated, can be severe and, in the case of disseminated strongyloidiasis or hyperinfection syndrome, can be fatal [93]. Patients starting immunosuppressive therapy are at increased risk of infection, and screening for latent infection in endemic areas may be beneficial to prevent progression of disease. Though the gold standard diagnostic test for *Strongyloides* infection is serial stool examination, sensitivity is low in asymptomatic individuals, and serologic tests have become more widely available. Serologic tests have a high sensitivity but a low specificity as the tests can cross-react with other parasitic infections. If diagnosed, patients with chronic asymptomatic infections should receive prophylaxis to prevent disseminated disease, most often with ivermectin [60].

Vaccines

As discussed above, most treatments for IBD place the patient at increased risk of infection secondary to drug-induced immunosuppression. Several studies suggest that IBD itself increases the risk for various vaccine-preventable infections such as pneumococcal pneumonia, influenza, and hepatitis B, and immunosuppressive treatment exacerbates that risk [94]. It is important to note that immune dysregulation is present in IBD patients on immunosuppressive therapy as well as in treatment-naive patients. As such, these patients may have a diminished immune response to vaccinations compared to the general population [95]. Gastroenterologists are therefore strongly encouraged to discuss and, if able, provide vaccination during outpatient visits at IBD centers. Here, we review recommended vaccinations in patients with IBD as well as the notable contraindications. Due to the nature of the immunosuppressive drugs used in IBD, live vaccines can only be administered prior to initiating treatment.

Inactivated Vaccines

Inactivated vaccines contain viral or bacterial components that cannot replicate. As such, they are generally well tolerated and safe for patients with IBD who are on immunosuppressive therapy. There are also no contraindications for household members or other close contacts to receive such vaccines. Inactivated vaccines will typically produce a weaker immune response compared to live vaccines and will often require a booster administration.

Tetanus, Diphtheria, and Pertussis Vaccination

The recommendations for the DTaP vaccine are similar to the general population. The recommended timeline of administration starts between the age of 6 weeks and 6 years old with a series of five doses. This is followed at the age of 11 by a single booster of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) and then the tetanus and diphtheria toxoid booster (Td) every 10 years, as per the Advisory Committee on Immunization Practices (ACIP). There is currently inconclusive data regarding whether IBD patients' response to the vaccine is appropriate [96, 97].

Influenza

Patients with IBD are at increased risk for influenza infection, particularly when immunocompromised [98]. The vaccine is available as an inactivated intramuscular or intradermal form as well as a live intranasal form. As recommended by the ACIP, annual vaccination is recommended for all patients 6 months and older. Unfortunately, several studies have shown that patient with IBD tend to mount a weaker response to the influenza vaccine [95, 99]. A booster vaccination did not increase antibody concentrations. Although the inactivated form is safe to administer in patients with IBD on immunosuppressive therapy, it is recommended to vaccinate the patients prior to starting therapy. The live intranasal vaccine, on the other hand, should be avoided in immunosuppressed patients. Additionally, household and close contacts of immunosuppressed IBD patients should only receive the inactivated vaccine as well. If there is suspicion for contact with infected individuals, chemoprophylaxis with antivirals can be considered [100].

Streptococcus pneumoniae

IBD patients are at increased risk of pneumococcal pneumonia compared to the general population, with an even higher risk once started on immunosuppressive therapy [101, 102]. Per ACIP guidelines, the pneumococcal vaccine is recommended in patients with IBD with patients requiring both the 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23). One dose of the PCV13 vaccine should be administered to all IBD patients followed by a dose of the PPSV23 at least 8 weeks later in immunosuppressed patients or at least 12 months in immunocompetent patients. A booster dose of PPSV23 should then be administered 5 years after the first dose as well as an additional dose after the age of 65 [103]. If an IBD patient was previously vaccinated with PPSV23, then PCV13 should follow at least 12 months after. Immunocompetent IBD patients appear to have an intact response to the PPSV23 vaccine, though response can be diminished when treated with immunosuppressive therapy [104].

Hepatitis A

Hepatitis A vaccine is recommended in all children aged 12–23 months as well as older children that have not received the vaccination. Adults at risk of hepatitis A are injection drug users, men who have sex with men, those with chronic liver disease, or anyone traveling to endemic regions. The vaccination series consists of two doses separated by a period of 6–18 months. An adequate response to the vaccine has been shown in IBD patients, though seroconversion rates were overall decreased in patients on immunosuppressive therapy [86, 105].

Hepatitis B

All patients with IBD should receive the hepatitis B vaccine series regardless of immune status. Several studies have shown that patients starting anti-TNF therapy are at risk of reactivation of hepatitis B infection with some reports of fatal cases [87, 88, 106]. It is therefore important to obtain hepatitis B antibody levels before initiation of anti-TNF or any other immune-suppressive therapy. The vaccination schedule in patients with IBD, regardless of their immune status, is the same as the general population as advised by ACIP guidelines. It consists of a series of three doses at 0, 1, and 6 months for the Engerix-B or Recombivax vaccines versus two doses 4 weeks apart for the newer Heplisav-B vaccine. Titers should ideally be checked 1–2 months after the final dose to confirm seroprotection. A titer of the hepatitis B surface antibody equal or greater than 10 mIU/mL is considered adequate for protection against the virus [93]. In the case that titer levels are found to be too low, patients may require a double dose of the vaccine series. Alternatively, a combination vaccine for both hepatitis A and B (such as Twinrix) may provide higher immunogenicity than the hepatitis B vaccine alone [103]. Several studies have looked at the efficacy of the hepatitis B vaccine in patients with IBD compared to a healthy population, with one showing significantly lower hepatitis B surface antibodies in patients with IBD [99]. A meta-analysis by Jiang et al. revealed that older age and immunosuppressive treatment were the two biggest determinants of a poor response to the vaccine [102]. The type of immune-suppressive regimen is also associated with the response, with infliximab showing a lower seroprotective response compared to other drugs like vedolizumab, which was not shown to significantly affect the response to the vaccine [86, 104].

Herpes Zoster

Regardless of immune status, patients with IBD are at an increased risk of developing herpes zoster infection compared to the general population [107]. Those on immune-suppressive therapy are at an even higher risk, with most of the manifestations being

limited to cutaneous findings, although some cases of disseminated zoster have been reported [108]. Until 2017, only a live attenuated vaccine for herpes zoster was available (Zostavax), which was not recommended for patients on immunosuppressive therapy. An inactivated adjuvanted recombinant vaccine (Shingrix) is now available and recommended for immunocompromised patients. It consists of two doses, to be given 8 weeks apart. As in the general population, the vaccine is recommended in adults aged 50 and older.

Human Papillomavirus

Female patients with IBD, particularly on immunosuppressive therapy, have been found to be at an increased risk of developing cervical dysplasia and are therefore strongly advised to undergo annual cervical cancer screening [109, 110]. In patients with CD, there is an additional risk for anal neoplasia, and patient should be appropriately monitored as well [111]. The recommendations for the HPV vaccine are the same in patients with IBD as the general population, regardless of immune status. The HPV vaccine (Gardasil or Cervarix) is recommended for both males and females between the ages of 11 and 26, though vaccination can be started at age 9, per the CDC. If given between the ages of 9 and 14, the patients receive two doses at 0 and 6 months. If started after the age of 15, then the patients receive three doses at 0, 2, and 6 months. No difference in immunogenicity was noted in patients on immunosuppressive therapy [112].

Meningococcal Disease

There is currently no evidence that patients with IBD are at increased risk for *Neisseria meningitidis* infection, which can lead to meningococcal meningitis. There are two available vaccines in the United States, the meningococcal conjugate or MenACWY vaccines (Menactra or Menveo) as well as the serogroup B meningococcal or MenB vaccines (Bexsero and Trumenba). The vaccine recommendations are the same as the general population per ACIP guidelines. Preteens aged 11–12 are advised to obtain the meningococcal conjugate vaccine with a booster at 16 years old. The conjugate vaccine is also recommended for high-risk patients such as asplenic individuals, patients with complement deficiencies, those living in close proximity (college dormitories or military housing), and those traveling to endemic areas. The serogroup B meningococcal vaccine is also recommended in those aged 10 years and older who are at increased risk [113].

Table 6.2 summarizes recommendations for inactivated vaccines in patients with IBD.

Table 6.2 Recommended inactivated vaccines in patients with IBD

Vaccine	Check titers before immunization	OK for immunosuppressed	Vaccination recommendations
Tetanus, diphtheria, and pertussis	No	Yes	All patients with IBD with a Td booster every 10 years, one-time dose of Tdap
Influenza	No	Only inactivated vaccine	Recommended yearly in all patients with IBD during flu season
Pneumococcal pneumonia	No	Yes	If no prior vaccination, one-time dose of PCV13 followed by PPSV23 after 8 weeks if immunocompromised or 12 months if immunocompetent; another dose after 5 years and at the age of 65 (with at least 5 years elapsed since the last dose). If one dose of PPSV23 was already received, wait at least 1 year before administering PCV13
Hepatitis A	No	Yes	2 doses separated by at least 6 months
Hepatitis B	Yes	Yes	3 doses at 0, 1, and 6 months. Recheck titers 1–2 months after final dose. If nonimmune, booster with double dose or combination hep A/B vaccine
Herpes zoster	No	Only inactivated (Shingrix)	2 doses 8 weeks apart in adults aged 50 years and older. Live vaccine *not* recommended
Human papillomavirus	No	Yes	Males and females. 2 doses at 0 and 6 months if given between ages 9 and 14; 3 doses at 0, 2, and 6 months if age >15
Meningococcal disease	No	Yes	Meningococcal conjugate vaccine in high-risk individuals or preteens aged 11–12 with booster at age 16. Serogroup B meningococcal vaccine in high-risk individuals over the age of 10
Typhoid fever	No	Only inactivated injectable vaccine	Recommended in patients 2 years and older at least 2 weeks before travel to endemic areas

Adapted from https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html

Live Vaccines

Live vaccines are developed using an attenuated form of the infectious organism and tend to induce a stronger and longer-lasting immune response. These are generally not recommended in patients with IBD who are immunosuppressed due to the risk of disseminated infection.

Measles, Mumps and Rubella (MMR)

The ACIP guidelines recommend the measles, mumps, and rubella vaccine series for the general population, which consists of an initial dose starting at the age of 12–15 months followed by a second dose between the ages of 4 and 6. If there is no documentation of prior vaccination, MMR titers should be tested during initial office visits. If patients are found to lack immunity to any of the three viruses, they can be vaccinated if they are not on any current immunosuppressive therapy or plan to start in the next 6 weeks. Immunosuppressive therapy in the past 3 months is a contraindication as well [103]. Nonimmune patients should receive two doses 4 weeks apart. Additionally, the MMR vaccine series is safe for all household contacts of immunocompromised patients.

Varicella

In the general population, the varicella vaccination series consists of two doses starting at the age of 12–15 months with a subsequent dose between 4 and 6 years old [114]. Similar to MMR, if there is no documented history of varicella zoster vaccination, titers should initially be obtained. In nonimmune adults not on immune-suppressive therapy, the two doses should be given 4–8 weeks apart [115]. For those planning on starting immune-suppressive therapy, the vaccine series should be given at least 4–6 weeks prior to starting therapy. Vaccination should be delayed for 3 months if immunosuppressive therapy is discontinued [116]. It is safe for household contacts to receive the vaccine series though in the case of a vaccine-related rash, the affected individual should avoid contact with the immunocompromised patient [114]. The varicella vaccination is particularly important in IBD patients. Several studies have shown that patients with IBD are at an increased risk of primary varicella infection, leading occasionally to severe and sometimes fatal cases [115, 117], with an even higher risk in immunocompromised patients [118].

Herpes Zoster

Compared to the general population, patients with IBD, particularly when immunocompromised, are at an increased risk of herpes zoster infection secondary to reactivation of the varicella zoster virus [107]. As discussed above, there is now an inactivated vaccine for herpes zoster that is the preferred regimen for patient on immune-suppressive therapy. The ACIP recommends routine zoster vaccination for patients over the age of 50 for the inactivated vaccine (Shingrix) as opposed to over the age of 60 for the live attenuated vaccine (Zostavax). This live attenuated vaccine is still available, and though it is contraindicated in patients on high-level immunosuppressive therapy, those on low-level immunosuppression can safely receive this live vaccine. Patients should not receive the live vaccine if they received high-level immunosuppressive therapy in the past 3 months or are planning to start in the next

Table 6.3 Recommended live vaccines in patients with IBD

Vaccine	Check titers before immunization	OK for immunosuppressed	Vaccination recommendations
MMR	Yes	No	2 doses given at age 12–15 months and 4–6 years old, or in immunocompetent adults at least 4 weeks apart. Wait 6 weeks prior to starting immunosuppressive therapy
Varicella	Yes	No	2 doses at age 12–15 months and 4–6 years old, or in immunocompetent adults at least 4–8 weeks apart. Wait 4–6 weeks prior to starting immunosuppressive therapy
Herpes zoster	No	Live vaccine OK on low-dose immunosuppression, contraindicated on high-dose Inactivated vaccine recommended and safe	Live vaccine recommended in immunocompetent patients over the age of 60, or inactivated vaccine in all patients over the age of 50
Yellow fever	No	No	Recommended in immunocompetent patients 9 months and older travelling to endemic regions of South America and Africa
Typhoid fever	No	No. inactivated vaccine recommended and safe	Live oral vaccine only in immunocompetent patients 6 years and older who are travelling to endemic areas, particularly Southeast Asia. One capsule taken every other day, a total of 4 capsules, last dose at least a week before travel

Adapted from https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html

6 weeks. For household contacts, the live vaccine is safe for administration, but like varicella, household members who develop a vaccine-related rash should avoid contact with the immunocompromised patient.

Table 6.3 summarizes recommendations for live vaccinations in patients with IBD.

Conclusions

Biologic agents targeting various inflammatory cytokines have emerged as a standard of care for managing IBD and have drastically improved quality of life in many patients. With the widespread use of these agents, however, comes the need for awareness of risks and mechanisms to prevent them, most notably a myriad of

infections. A general understanding of infectious risks is warranted, including the spectrum of organisms that have the potential to cause disease, the circumstances that predispose patients to, and protect them from such infections. Involvement of infectious diseases specialists during the planning phases, prior to initiating these highly effective, yet high-risk therapies, may result in comprehensive and longitudinal assessment and abatement of infectious risks.

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Chapter 7
Healthcare Maintenance in the Patient with Inflammatory Bowel Disease: High-Yield Interventions

Isabel Roitman, Anjali Mone, and Arun Swaminath

Introduction

Inflammatory bowel disease (IBD) and the immune suppressive medications used to treat moderate to severe disease are associated with treatment-related complications including increased risks of infection and malignancy. Ensuring appropriate vaccinations and healthcare screenings can help to minimize the complications associated with this disease.

Healthcare providers managing IBD patients must familiarize themselves with the complexities of healthcare maintenance (HCM) in this population. Most IBD patients receive care from a gastrointestinal specialist, but primary care providers or general gastroenterologists may solely care for these patients as well [1]. In Bilal et al.'s analysis comparing implementation of IBD health maintenance quality measures among IBD specialists (those whose practice is at an IBD center) vs. non-IBD gastroenterologists, IBD specialists were more likely to deliver these indices (Fig. 7.1) [2]. Merging both specialty IBD care and preventive care can bridge the healthcare maintenance delivery gaps in IBD management.

Immunizations

Medications such as corticosteroids, immunomodulators, and biologics used in the management of IBD can increase susceptibility to infection. Despite this increased risk and the clear value of mitigating this risk through the use of vaccinations, the vaccination rates in the IBD population is lower than the general population [3]. It

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R. Rajapakse (ed.), *Inflammatory Bowel Disease*, Clinical Gastroenterology,
https://doi.org/10.1007/978-3-030-81780-0_7

Quality measures	IBD physicians n=216	Non-IBD physicians n=109	P-value
Corticosteriod-sparing therapies	43.9%	20.3%	0.001
Type, anatomic location and activity assesed	100%	100%	-
Bone loss assessment	65.7%	35.5%	0.001
Influenza immunization	61.4%	45.9%	0.008
Pneumococcal immunization	57.7%	34.3%	0.001
Testing for latent tuberculosis before initiating anti-TNF therapy	72.1%	100%	0.004
Assessment of hepatitis B virus before initiating anti-TNF therapy	79.1%	95.7%	0.06
Tobacco screening/cessation counseling	96.8%	89.0%	0.15
Adherence (percentage of core measures completed)	71.8%	58.8%	0.001
Average score out of 100 (Based on AGA BTE 100 point score)	73.9	66.3	0.001

AGA, American Gastroenterology Association; BTE, bridges to excellence; IBD, inflammatory bowel disease; TNF, tumor necrosis factor

Fig. 7.1 Compliance with bridges to excellence quality indicators among IBD and non-IBD gastroenterologist

is uncertain as to whether this is due to concerns about safety, efficacy, or just a lack of knowledge. The Crohn's and Colitis Foundation and Cornerstone Health have created a checklist to address this hesitancy and promote immunizations [4]. This checklist can be a practical reference and is easily accessible on the CCF web site. The importance of vaccinating IBD patients against influenza, pneumococcal pneumonia, hepatitis A and B; varicella, herpes zoster, human papillomavirus, tetanus, diphtheria, and pertussis; measles, mumps, and rubella; and meningococcal meningitis will be discussed in this chapter.

Education around this topic requires a longitudinal discussion because newly approved IBD medications may pose unique infection risks; the new vaccines may become available. Staying up to date on immunization guidelines for the general population and the immunocompromised population is advised, as providers are currently the most trusted advisors when it comes to vaccines. Keeping an open dialogue with patients and counseling them on the utility of vaccine implementation is a known predictor for vaccine acceptance [5]. The earlier this conversation occurs with the patient, the more time there will be available for the patient to make informed decisions, especially given the current climate of vaccine hesitancy [6].

Several strategies exist to optimize vaccine rates. Vaccination reviews and using checklists or the electronic health record can be done routinely by both the gastroenterologist and the primary care provider (PCP) [7]. Communication between gastroenterologist and PCP is advised via note sharing and/or direct communication to increase awareness of required vaccines. Educating and involving additional clinical staff, such as nurses, pharmacists, and advanced care providers, can promote IBD health maintenance beyond solely the doctor's encounters.

Timing of vaccine administration is critical. Vaccines should be administered prior to planned immunosuppressive treatments, although necessary IBD treatment should never be delayed in order to immunize. Waiting at least 2 weeks after administration of an inactivated vaccine to start immunosuppression may optimize immunogenicity of the vaccine [8]. According to the Infectious Diseases Society of

America, the ideal window to administer a live vaccine is at least 4–6 weeks prior to starting any immunosuppression in order to ensure safety [8].

Studies have shown that IBD patients on immunosuppressive treatments, especially anti-TNF agents, have reduced humoral response to the trivalent Influenza vaccine, the polysaccharide pneumococcal vaccine, and the hepatitis B vaccine [9]. Monitoring vaccine titers 4–8 weeks after immunization of hepatitis A and B to confirm seroconversion may be beneficial; however there is no universal consensus on result interpretation and management [10].

Live vaccines should be avoided in patients on immunosuppressive therapy due to the risk of disseminated infection; however a case by case decision may be considered when necessary [3]. According to the Crohn's and Colitis Foundation Professional Education Sub-Committee, systemic immunosuppression is defined as prednisone >20 mg/day for more than 14 days, azathioprine >2.5 mg/kg/day, mercaptopurine >1.5 mg/kg/day, methotrexate >0.4 mg/kg/week), cyclosporine, tacrolimus, infliximab, adalimumab, golimumab, certolizumab, ustekinumab, or tofacitinib [11]. Live adult vaccines include the intranasal flu vaccine (FluMist); the measles, mumps, and rubella (MMR); oral polio; chicken pox (varicella, Varivax), herpes zoster (Zostavax), or the yellow fever vaccine [12].

Immunizations: Influenza

Influenza is one of the most common vaccine-preventable illnesses in adults. Inflammatory bowel disease patients have a higher risk of influenza as well as its sequelae, including pneumonia and hospitalization, when compared to control populations [13]. More than 5% of IBD patients who develop symptoms from influenza infection require hospitalization (Fig. 7.2) [13]. Corticosteroids are an independent risk factor for acquiring influenza in the IBD population [13].

The influenza vaccine decreases hospitalization rates as well as morbidity and mortality associated with the flu [14]. Therefore, it is recommended annually for all IBD patients. The two available forms of the influenza vaccine are the live attenuated vaccine administered intranasally and the inactivated vaccine administered via injection. Although no studies have proven the risk of live vaccine transmission in the IBD population, it is advised that IBD patients on immunosuppressive therapies *and their household contacts* should receive the inactivated flu vaccine [15]. This vaccine is well tolerated among IBD patients and generally induces the appropriate immune response [15]. Given the ubiquitous availability of the influenza vaccine in pharmacies, clinics, and workplaces, modifiable barriers to patients receiving the vaccine are common misconceptions and fears. Providing vaccine counseling and Vaccine Information Sheets (VIS) to patients may help dispel these myths. Several studies have demonstrated that the provider role is vital in achieving successful influenza vaccine rates, and many patients attribute their physicians as the reason for getting vaccinated [16].

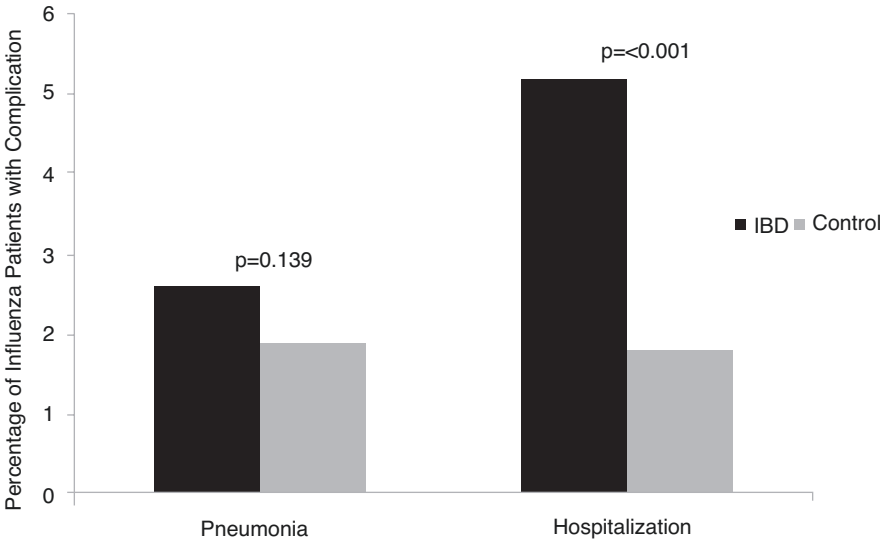

Fig. 7.2 Complications within 30 days of influenza diagnosis

Immunizations: Pneumococcal Pneumonia

Patients with IBD, particularly those treated with immunosuppressive medication, are at a higher risk for pneumococcal pneumonia [17]. According to CDC guidelines, immunization against pneumococcal pneumonia is advised for adults above age 65 and those younger with immunocompromising conditions including iatrogenic immunosuppression, which includes all biologic and immunomodulator therapies [18]. All adult IBD patients above the age of 19 planning to receive or are currently on immunosuppression should receive the pneumococcal vaccine [19]. This is different to the conventional recommendations for those age 65 and older and may contribute to vaccine hesitancy as potential insurance coverage may not be universal. This generally requires contacting the insurance company to verify coverage.

There are two pneumococcal vaccines: Prevnar 13 (PCV 13) and Pneumovax 23 (PPSV 23). For adult IBD patients, administration of *both* vaccines is recommended in order to provide immunity to all 24 serotypes of pneumonia [20]. Up until 2019, both vaccines were advised for the general population aged 65 and older; however, due to lower incidence of PCV 13 due to universal pediatric immunization for PCV 13, currently only PPSV 23 is recommended [21]. For IBD patients on immunosuppressive therapy however, PCV 13 is still advised, in order to improve overall immune response [19]. The order in which these vaccines are given is important: PCV 13 first, then PPSV 23 at least 8 weeks later, as this enhances immune response to the vaccines [19]. Subsequently, a PPSV 23 booster is advised every 5 years. If PPSV is given first, PCV13 should be administered 1 year later [22]. For IBD

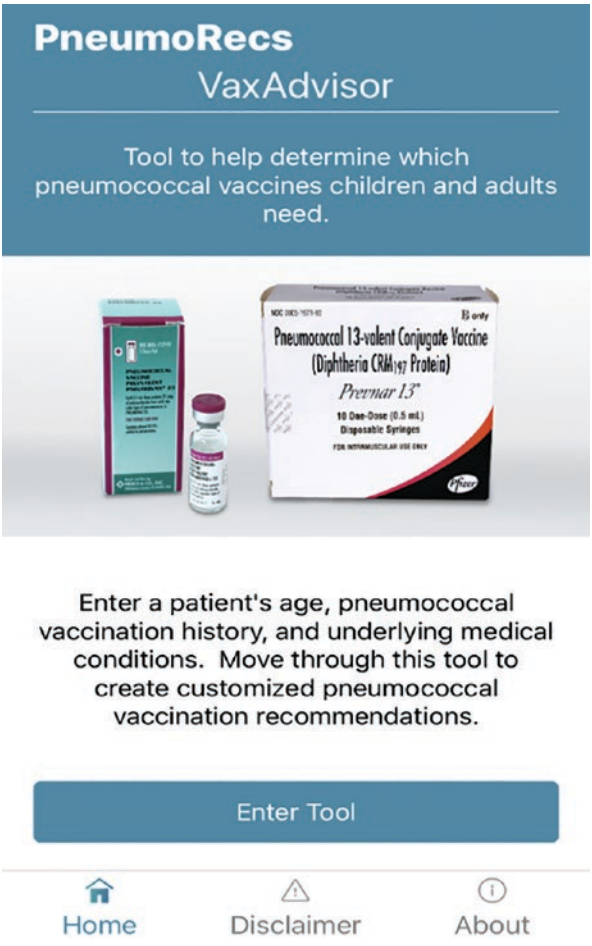

Fig. 7.3 CDC PneumoRecs VaxAdvisor App

patients under age 65 not on immunosuppressive therapy but with other risk factors, like smoking or asthma, PPSV 23 only is advised due to indirect effects of pediatric immunization of PCV 13 [21]. A helpful tool that can aid in identifying which pneumococcal vaccine is indicated is the PneumoRecs VaxAdvisor app (Fig. 7.3) [23]. This application factors in age, risk profile, and prior vaccination history and can be a practical guide for providers.

Immunizations: Varicella and Herpes Zoster

Herpes zoster (HZ) reactivation, also known as shingles, can be an agonizing condition that causes blistering of the skin and pain along involved dermatomes. Complications from herpes zoster include postherpetic neuralgia, bacterial skin

infection, ocular injury (if V1 involvement of the trigeminal nerve), and meningitis [24]. According to Long et al.'s study comparing the prevalence of HZ in an IBD cohort with non-IBD individuals, IBD patients are at a higher risk of herpes zoster, especially those on combination anti-TNF and thiopurine therapy, with an odds ratio of 3.29 [24]. Tofacitinib (Xeljanz) was released for the treatment of ulcerative colitis in 2018. Higher rates of herpes zoster have been detected in patients treated with tofacitinib, greatly emphasizing the need for immunization. The risk of HZ infection is observed to be a dose-related effect, with IR of 3.45 and 4.25 per 100 py at 5 mg and 10 mg twice daily dosing, respectively [25]. When appropriate, considering a decreased dose can mitigate this infection risk [26].

When prescribing tofacitinib, prior varicella exposure and immunity should be verified through history taking and serologic titers if the history is unknown. If the patient has no history of varicella exposure, the live varicella vaccine should be considered prior to starting therapy. If positive varicella titers are detected, with no record of previous dose of varicella vaccine, the recombinant HZ vaccine, Shingrix, should be given [8]. It is important to note that standard immunoassays are not as reliable in detecting prior varicella vaccination because the vaccine leads to lower antigen-antibody concentrations compared to active immunity from past infection [22]. Therefore, obtaining vaccine records and a patient's history can help identify those previously vaccinated [22].

Two HZ vaccines are currently FDA approved in the United States: live zoster vaccine (Zostavax) and the non-live recombinant zoster vaccine (Shingrix). The latter is recommended for use in the IBD population because of higher immunogenicity and better overall safety data in this population [25]. The Shingrix vaccine is currently recommended for patients aged 50 and older, but any adult with acquired immunity from past varicella infection is advised to obtain the HZ vaccine regardless of age prior to initiation of tofacitinib [25]. This may create an insurance hurdle given the strict reimbursement coverage for the vaccine. The cost for patients paying out of pocket can range from $101–$190 per injection, which may be an alternative option [25, 27]. To determine coverage and out of pocket expenses, the prescription can be sent to the patient's pharmacy for benefit and cost analysis [25].

The HZ series includes two injections with the second following 2–6 months after the first. Patients should be counseled on the adverse reaction of pain at the injection site with Shingrix, which occurred in up to 78% of patients in clinical trials [28]. IBD patients experience a similar rate of a local adverse reaction (74.6%) and a low risk of flares (1.5%) after immunization [25]. Despite this unpleasant though short-lived experience, Shingrix should be recommended due to its high efficacy rates. Among non-immunosuppressed populations, Shingrix is greater than 90% effective in preventing shingles, a significant improvement from the earlier live zoster vaccine, Zostavax, which is at most 51% effective [25]. For those patients who have previously received Zostavax, Shingrix should still be considered based on the improved efficacy rates [24]. Immunogenicity trials in IBD are lacking, but four phase 3 studies have demonstrated that the recombinant zoster vaccine produces persistent humoral response for at least 12 months after vaccination in immunocompromised adults [25].

Immunizations: Hepatitis A, B, and C

Screening for viral hepatitis prior to initiation of immunosuppressive therapy is one of the most important healthcare maintenance indices. Although hepatitis A is often short-lived and self-limiting, hepatitis B and C can be reactivated by common IBD treatments that alter immunity. Hepatitis B can reactivate in up to 50% of patients receiving immunosuppressive therapy, but reactivation of HCV is quite uncommon and has been only rarely reported in the IBD literature [29]. Reactivation of viral hepatitis can result in hepatic decompensation, a fate best avoided by identifying all patients at risk.

The hepatitis A virus (HAV) is a GI illness that is transmitted through the fecal-oral route. The HAV vaccine is routinely advised for all children aged 1–2 and to anyone older who has not been previously vaccinated [30]. All IBD patients are advised to receive the HAV vaccine, in alignment with CDC recommendations for the general population, especially if there is no previous history of vaccination or there are undetectable titers. Serologic testing prior to hepatitis A vaccination is not necessary but can be cost-effective by detecting patients who are already immune. Vaccination should not be postponed if titers or records cannot be obtained as there is no harm associated with re-vaccination [31]. Post-vaccination antibody confirmation 4–8 weeks after immunization can be considered to ensure seroconversion, given the lower rates in immunosuppressed patients [10]. Higher-risk individuals who should be monitored for vaccination completion include those traveling to endemic areas, males who have sex with males, people with HIV, or anyone with chronic liver disease [31]. The hepatitis A vaccine can be given as two injections over 6 months or in combination with the hepatitis B vaccine, in a three-part series over the same time span. Although two doses are recommended over a span of 6 months, if a delay in the second dose is unavoidable, the series does not need to be restarted [31]. The immunogenicity of a single dose of hepatitis A can last up to 10 years, with a second dose lasting up to 20 years in immunocompetent patients [30].

Hepatitis B is an infectious disease transmitted through body fluids with a prevalence of 2–8% in the global population [10]. All IBD patients should be screened for a prior history and immunization for hepatitis B virus (HBV), particularly those anticipating biologic, steroid, or immunomodulator therapy given the potential risk of reactivation. Therefore checking hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and hepatitis B core antibody (anti-HBc) *at the time of IBD diagnosis* is advised. If there is evidence of chronic hepatitis B (positive HBsAg and anti-HBc IgG) with or without detectable HBV DNA, antiviral prophylaxis should be started at least 7 days prior to initiation of immunomodulator and continued throughout and after treatment to reduce the risk of reactivation [10]. If HBsAg is negative, with positive anti-HBc IgG and undetectable HBV DNA, prophylactic antiviral treatment is not supported in those on monotherapy biologics, but close monitoring of ALT and HBV DNA is advised. Reactivation of hepatitis B can occur in up to 40% of immunocompromised patients [10]. Collaboration with a

hepatologist to co-manage these patients is strongly advised in order to adhere to the best practices of management.

Screening for hepatitis C virus (HCV) is advised for all IBD patients given the rising prevalence of hepatitis C in the aging population, as well as the unique challenges treating both HCV and IBD simultaneously can introduce. Timing and monitoring of biologic and hepatitis C antiviral therapy are important strategies during treatment. Although there is theoretical risk for biologics decreasing the efficacy of antiviral hepatitis C therapy, there are encouraging studies that dual IBD and hepatitis C therapy is safe and effective [32]. Given the possibility of cure for most patients, HCV should be treated prior to initiation of immunosuppressive treatment if possible. Withholding necessary IBD treatment is never advised. Therefore if immunosuppressive treatment is started prior to antivirals, close monitoring of concomitant therapy with serial liver function tests is advised, even though the risk of HCV reactivation is infrequent [29]. Collaborating with a hepatologist is essential in preventing progression of liver disease in those IBD patients with hepatitis C.

Immunizations: MMR, HPV, Meningococcal, and Tdap

Children aged 12 months to 12 years old are routinely advised to receive the measles, mumps, and rubella (MMR) vaccine. If there is no previous evidence of MMR immunity, vaccination is recommended for teens and adults, given as two doses 28 days apart [33]. MMR should be avoided in patients on immunosuppressive treatment because this is a live vaccine, but household contacts can be safely given the vaccine [22].

The human papillomavirus (HPV) vaccine, Gardasil 9, is recommended for all males and females aged 9–26. For those inadequately vaccinated, the HPV vaccine can be considered up until the age of 45 for IBD patients as a “catch-up” vaccine [34]. Studies indicate complete immunogenicity from Gardasil 9 in IBD patients even on immunosuppressive treatments with no increased adverse events when compared to healthy controls [35].

The inactivated meningococcal vaccine is advised in standard guidelines for children and young adults living in college dormitories. As patients with IBD are not at higher risk for meningitis, vaccination using routine recommendations is advised [36].

Tetanus and diphtheria (Td), although uncommon in developed countries, is still routinely advised for the general population [22]. All IBD patients should be given the Td vaccine every 10 years, with at least one series containing pertussis (Tdap) [22]. Pregnant women are advised to receive the Tdap vaccine in the third trimester regardless of previous vaccination [22].

Screenings

Patients with Inflammatory bowel disease should undergo heightened cancer surveillance due to the higher risks of skin, colon, and cervical cancer in this population. Some increases in risk are related to underlying disease and others due to the treatment strategies employed. Bone and eye health should be monitored as well, given the high frequency of related issues encountered in this patient group. Screening for mental health disorders and tobacco use is advised given its associations to worsening disease severity. Although not addressed in routine IBD guidelines, our practice screens for fatigue after noticing a high prevalence of this complaint in our patients [37].

Screenings: Bone Health

Metabolic bone disease (MBD) is one of the most common invisible systemic complications of IBD, ranging anywhere in prevalence from 10 to 60% [38]. Low bone density can lead to osteopenia or osteoporosis, putting patients at higher risk for bone fractures. For IBD patients, the biggest cause of MBD is corticosteroid use, but chronic inflammation causing impaired intestinal absorption of calcium and vitamin D; malabsorption due to extensive small bowel surgery; recurrent flares leading to low appetite or food avoidance, low BMI, and poor nutritional state; diminished overall energy and physical activity; and dairy avoidance in those who are sensitive or intolerant can all contribute to MBD [39] [40]. In order to manage bone health, a baseline axial bone density scan via dual energy x-ray absorptiometry (DXA) is advised for patients with at least one of the above risk factors. A DXA will provide an in depth understanding of the presence of osteopenia (T score between −1 and – 2.5 SD) or osteoporosis (T score of −2.5 or lower), which is associated with increased risk of bone fracture [40, 41]. If the DXA scan is normal, the Crohn's and Colitis Foundation recommends a repeat scan in 5 years. However more conventional guidelines recommend repeating only if the patient develops new risk factors including recurrent corticosteroid exposure for greater than 3 months [11]. If osteopenia is detected, bone density scans can be repeated at least every 2 years while also undergoing appropriate treatment [11].

Therapeutic management of osteopenia includes weight-bearing exercises, tobacco cessation, avoiding excessive alcohol intake, and increased dietary and supplemental calcium and vitamin D [42]. Adequate dosages of elemental calcium for those between the ages of 19 and 50 are 1000 mg/day and 1200 mg/day for women 51–70 years of age [43]. Many multivitamin formulations do not contain calcium citrate, the recommended form of supplemental calcium, as it can affect absorption of iron, zinc, and magnesium [44]. As a result, additional calcium supplementation with or without vitamin D can be purchased when indicated.

Vitamin D, most commonly vitamin D3 or cholecalciferol, 400 to 800 IU/day is advised for patients with osteopenia [42]. If deficiencies exist, higher doses with close monitoring of levels may be required (see Sect. 7.3) [42]. Once osteoporosis is detected, treatment by an endocrinologist and primary care provider is recommended. Avoiding high-dose corticosteroids in patients with MBD is preferred. For patients on steroid therapy, supplementation with 1 g calcium and 400 IU of vitamin D has shown to slow, but not prevent, bone loss [45].

Screenings: Eye Health

About 2–3% of IBD patients develop an eye manifestation of their inflammatory bowel disease [46]. Having regular, annual eye exams are advised for all IBD patients regardless of treatment modality to assess and monitor any irregular findings.

The two most common eye manifestations seen in IBD patients are scleritis and episcleritis [47]. These conditions can be unpredictable; therefore any sudden complaint of eye redness, pain, or visual changes requires prompt ophthalmologic evaluation. A more uncommon manifestation in IBD is uveitis, which does not reflect IBD activity and can sometimes precede IBD diagnosis [47]. Uveitis often presents in patients with other known EIMs such as joint or skin manifestations. Distinguishing between uveitis and other eye ailments requires ophthalmologic evaluation with slit lamp testing [47]. More subtle changes from corticosteroid use, like cataracts or glaucoma, are best identified by routine scheduled evaluations [39, 48].

Screenings: Colon Cancer

Colon cancer tends to occur 2–6 times more in patients with Inflammatory bowel disease compared to the general population [49]. A chronic inflammatory state, as well as genetic and environmental risk factors, likely leads to this increase [49]. Independent risk factors include inflammation involving more than one-third of the colon, increased severity of inflammation (as assessed by endoscopic and histologic scoring using 0–5 grading) and disease duration of at least 8 years (cumulative risk increases as duration increases) [50]. Colonoscopy is the gold standard for colon cancer detection; therefore IBD patients with colonic disease beyond proctosigmoiditis for 8 years or more should undergo surveillance colonoscopies [49]. American society recommendations differ, ranging between 1 and 3 years for colon cancer surveillance, although annual and biennial surveillance are most adopted [51]. For IBD patients with primary sclerosing cholangitis (PSC), annual screening starts at diagnosis given the higher rates of colon cancer among patients with PSC [52]. For patients with PSC and ulcerative colitis (UC), the odds ratio of developing CRC is 4.8, compared to IBD patients without PSC [53]. The higher cumulative risk

of developing colorectal cancer in PSC patients with IBD has been postulated at 2% in 5 years, 7–9% at 10 years, and 15% at 15 years, developing at an average age of 49.5 years old [52].

Managing colonic inflammation may help lower the risk of colon cancer, although there is no therapy that is proven to have specific chemopreventive effects on lowering cancer risk [49]. Epidemiologic studies have identified a lower incidence of colon cancer in the IBD population that has been attributed to better control of inflammation with the use of biologics [50]. Additional modifiable risk factors include avoiding tobacco, eating a high-fiber diet of fruits and vegetables, and limiting intake of processed foods and red meat [49]. In our practice, patients with excellent colon preparations, adherence to therapy and in endoscopic remission without a personal history of dysplasia, are offered less intensive biennial screening. Surveillance intervals should always be determined and discussed on a case by case basis based on history and risks.

Screenings: Skin Cancer

IBD patients have an increased risk of skin cancer, particularly nonmelanoma skin cancer (NMSC). In Long et al.'s review looking at NMSC incidence in IBD, the overall annual incidence rate of NMSC was 733 per 100,000 in the IBD sample, compared to 447 for controls [54]. This is likely due to the use of immunosuppressive medications, although the underlying immune dysfunction that occurs as part of the disease itself may also contribute through the decreased ability to repair damaged DNA [55]. The use of immunosuppressive treatments in IBD, like cyclosporine, mercaptopurine, azathioprine, and anti-TNF therapies, is the key driver of a higher cancer risk. As a result, screening for skin cancer with routine dermatologic exams is essential in this group. At a minimum, annual full body skin examinations are recommended to identify early abnormal skin changes [56]. In order to reduce skin cancer risk, patients should be counseled to wear SPF 30 or higher in the sun and minimize UV light exposure by avoiding tanning beds and excessive sunbathing (which varies depending on skin type, geographic location, and UV index) [54].

Screenings: Cervical Cancer

Screening for cervical cancer in immunocompromised IBD patients is advised annually due to the higher rates of cervical cancer and high-grade cervical dysplasia when compared to the general population [57]. The HPV vaccine is the best way to minimize this risk, and it is recommended for all IBD patients. Males and females can receive the vaccine as early as 9 years of age and up until age 45. In addition to the vaccine, yearly cervical exams with a pap smear are advised for all women with IBD. Female IBD patients should be encouraged to establish care and follow regularly with a gynecologist.

Screenings: Depression

Depression and anxiety rates are higher in IBD patients when compared to the general population. It is not clear which comes first, i.e., if IBD or depression and anxiety precede the other. Both mental states are situational to active disease, but baseline levels are also increased in patients with IBD [58].

Depression is linked to a lower quality of life, poor medication adherence, and worsened disease activity [58]. Routine mental health screenings should be implemented in this population to detect depression or anxiety. Objective screening tests, most often the Patient Health Questionnaire-2 and 9 (PHQ-2 and PHQ-9) or the Generalized Anxiety Disorder-7 (GAD-7), are brief, highly sensitive questionnaires that can be used [59]. Specific screening intervals have not been established; however screening at diagnosis, and when clinical or medication status changes, is reasonable [60]. If either depression or anxiety is detected, facilitating a referral for appropriate treatment, such as psychological counseling, is advised. In our practice, we have incorporated cognitive behavioral therapy (CBT) delivered by a licensed medical social worker (LMSW), because CBT has shown to improve quality of life and decrease anxiety and depression in IBD patients [61, 62]. Unfortunately, not all patients will have access to psychotherapy due to insurance coverage, so Support groups, through organizations like the Crohn's and Colitis Foundation or community health centers, should be offered, as a supplementary strategy.

Screenings: Fatigue

Fatigue is one of the most common complaints among IBD patients, affecting more than half of the IBD population [63]. Considered another extraintestinal manifestation of IBD, fatigue is observed in patients during both active and quiescent states of the disease. Although screening for fatigue is not part of standard healthcare maintenance recommendations, addressing fatigue may improve quality of life. The etiology of fatigue is multifactorial, stemming from the disease itself or the complications, medications, mood, and sleep disorders associated with it. Given the complex nature of fatigue, we focus on getting the disease into a deep remission. If the fatigue persists, we evaluate for non-IBD-related etiologies. We developed an algorithmic approach to screening for non-IBD etiologies of fatigue with attention to correcting anemia, nutritional deficiencies, mood disorders, and sleep disorders and identifying culprit medications. Often, these investigations occur in parallel. Our algorithm is presented in Fig. 7.4 [63].

Screenings: Tobacco

Tobacco cessation is strongly advised in Crohn's disease patients given the associations with worsened disease severity, flare-ups requiring hospitalization, and higher incidence of surgical complications [64]. The cessation of tobacco is associated

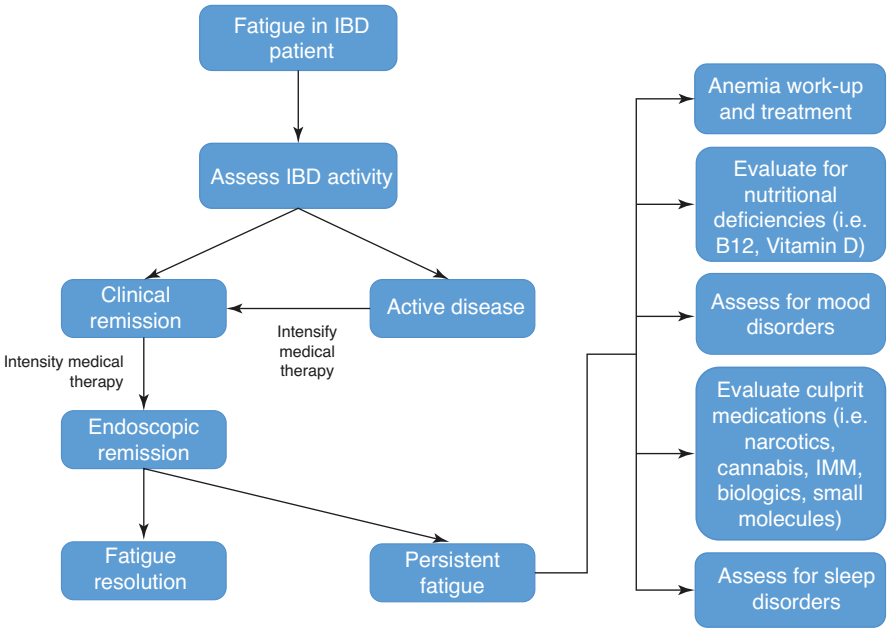

Fig. 7.4 Fatigue algorithm

with significant benefits that should be emphasized to patients including decreasing extraintestinal manifestations and lowering risk of surgical recurrence [65]. Patients' motivation to quit should be assessed at each visit [66]. Higher rates of depression and anxiety in Crohn's disease may contribute to a lower motivation to quit [64]. An interdisciplinary approach to tobacco cessation, including smoking cessation programs, pharmacotherapy, and psychological counseling, has been shown to be effective in the general population [64].

Several pharmaceutical options for tobacco cessation exist, including nicotine replacement (NRT), bupropion (Zyban), and varenicline (Chantix) [67]. Nicotine replacement is available in several forms including patch, gum, lozenge, nasal spray, and inhaler. NRT is available over the counter and is relatively inexpensive [67]. Bupropion (Zyban) and varenicline (Chantix) require a prescription and must be monitored carefully.

Bupropion is an attractive option to some patients as it can prevent weight gain and relapses [67]. It may also be combined with nicotine replacement for higher efficacy [66]. Treatment should begin 1–2 weeks before quit date, and dosing starts at 150 mg (sustained release) each morning for 3 days, then 150 mg twice daily for 3–6 months [68]. Some notable side effects include insomnia, dry mouth, and increased suicidal ideation in patients with a history of depression [68]. Contraindications to therapy include use of monoamine oxidase inhibitors within 14 days, history of eating disorder, and seizures [68].

Varenicline (Chantix) should also be started 1 week prior to quit date and continued for a total of 12 weeks. Dosing can be gradually increased from 0.5 mg per day on days 1 to 3, 0.5 mg twice daily on days 4 to 7, and then 1 mg daily after that [68]. If smoking cessation is not achieved, another 12 weeks can be added. Unlike bupropion, varenicline should not be given with nicotine replacement therapies [68]. Some common side effects like abnormal dreams, headache, and nausea are usually tolerable; however more severe adverse side effects that usually require cessation of treatment include behavior changes, aggression, and suicidal thoughts and actions [68].

Given the potential for serious adverse events from smoking cessation drugs, partnering with a primary care provider is advised for close monitoring [15]. Proposed complementary therapies include hypnotherapy, exercise, and acupuncture, although more studies need to be conducted to prove efficacy [64].

Nutrition

Comprehensive nutritional counseling is universally sought after by IBD patients and providers. Given the risk for nutritional deficiencies and malnutrition in the IBD population, close monitoring of lab values, weight, and appetite should be implemented routinely. Guidance from a dietician can be beneficial as supplemental nutrition and diet plans are highly individualized. Despite heavy interest in nutritional research within the IBD community, a "one-size-fits-all" diet has yet to be established.

Nutrition: Diet Counseling

Diet is perceived as a vital aspect of disease management for a majority of IBD patients. In a questionnaire sent to almost 300 Dutch IBD patients, more than half of participants reported diet as either more or equally as important as their medication for the treatment and outcomes of their disease [69]. In that same survey, 81% of patients stated their main source of nutritional knowledge was from their own experience. Providing accurate information to patients seeking dietary counseling is an integral part of healthcare maintenance. Dietary guidance can serve as a useful tool to promote healthy habits and prevent nutrient deficiencies. The addition of a dietician to discuss personalized diet plans with patients may provide extra insight and motivation. Diet is not a replacement for conventional therapy, especially in those with moderate to severe disease activity.

Exclusive enteral nutrition (EEN) has been studied and proven to induce clinical remission and even endoscopic remission in pediatric Crohn's patients [70], 2017. The same success has yet to be replicated in adult patients [71]. EEN has limitations

such as unpalatability, high cost, and difficulty with administration since some children require nasogastric tube placement [72]. Dietary studies in IBD are relatively inconclusive, and therefore there is no definitive diet that can be recommended for IBD patients [73]. There are limited animal studies that suggest eating food emulsifiers as well as red meat may induce a flare [73]. Recommending a diet rich in fruits and vegetables (may not be possible in those with symptomatic small bowel strictures) and low in red meat and processed foods may be advised [73]. A Mediterranean diet has shown some overall health benefits and seems to be in line with these recommendations [73]. The only randomized trial of diet compared Mediterranean diet with specific carbohydrate diet in Crohn's disease, DINE-CD, and we eagerly await the analysis of those results [74]. Monitoring for response with clinical and objective markers, evaluating for vitamin deficiencies, and ensuring adequate caloric intake should be part of routine dietary assessments.

Nutrition: Vitamin B12

Folate and vitamin B12 deficiencies are more prevalent in IBD patients as a result of malabsorption, history of ileal resections, and medication side effects [75]. Ileal involvement with Crohn's disease is an independent risk factor for folate deficiency, and ileal resection is an independent risk factor for vitamin B12 deficiency [76]. Medications, including sulfasalazine and methotrexate, additionally put patients at risk for folate malabsorption. Patients taking either medication should be supplementing with 1 mg folic acid daily. Particular attention should be given to IBD patients who follow a vegetarian diet as B12 is derived primarily from animal products.

Vitamin B12 and folate should be monitored frequently in Inflammatory bowel disease especially when deficiencies are detected [79]. Recognizing and treating abnormal values are vital given the debilitating outcomes that can occur. Clinical features of B12 and folate micronutrient deficiencies are often subtle, such as fatigue, paresthesia, and mouth ulcers; however more severe manifestations can involve neuropsychiatric complications [77].

Vitamin B12 deficiency is diagnosed when B12 levels are less than 150 pg per mL. Vitamin B12 can be supplemented either intramuscularly by mouth or via nasal spray. Given the controversy over efficacy of oral and nasal solutions, intramuscular cyanocobalamin is the standard recommended treatment [77]. Dose replacement can vary, as limitations to self-injection can prevent patients from obtaining appropriate dosing. The *American Family Physician* guidelines recommend B12 injections of 1 mg three times per week for 2 weeks, in those without neurologic complications [78]. In our practice, patients who are not willing to self-inject come in for weekly office injections for 4 weeks. These injections are often ongoing; therefore transitioning to oral replacement can bridge injection treatments. Some nutritional sources of vitamin B12 include shellfish, fatty seafood, and fortified cereals [79].

Nutrition: Iron

Iron deficiency anemia (IDA) is a common manifestation in inflammatory bowel disease due to chronic blood loss and malabsorption. Common symptoms of IDA include fatigue, pallor, and tachycardia, but this condition can often go unnoticed leading to delayed diagnosis. Since IDA leads to an overall lower quality of life in the IBD patient, prompt detection and treatment are important [80].

An iron panel, which includes ferritin, transferrin, transferrin saturation, and hemoglobin, should be checked every 3 months in patients with active disease and every 6–12 months in patients in remission [80]. When assessing for response during supplementation, monitoring levels 4 weeks after initiation of treatment is advised [81]. The type of repletion, oral or IV, depends on the severity of anemia, tolerance to the chosen medication formulation, and current disease activity. In patients with hemoglobin above 10 g/dL and quiescent disease, with no prior intolerance to oral formulations, oral iron may be initiated. Oral iron should be avoided during an active flare because of the risk of worsening IBD activity, which has been seen in animal studies from the rise in pro-inflammatory effects of oxidative stress [82]. Side effects to oral iron may be mitigated by using slow release iron formulations and daily doses less than 100 mg of elemental iron [81]. If intolerable side effects such as abdominal pain, constipation, or nausea develop or there is a known history of intolerance, then IV iron should be initiated [80]. The role of the gastroenterologist in treating IDA depends on availability of resources and comfort with infusion replacement protocols.

New formulations of IV iron are well tolerated and safe in the IBD population. Previous formulations of high molecular weight iron dextran, no longer in use, caused serious infusion reactions, causing many of the current misconceptions surrounding IV iron [82]. Anaphylactic risk was evaluated between four common forms of IV iron in a study by Wang et al. [83]. Between iron dextran, ferumoxytol (FXT), gluconate, and sucrose, iron sucrose had the least risk, while iron dextran had the highest risk [83]. In our practice, our preferred IV iron formulation is ferric carboxymaltose (FCM) because it has the most clinical evidence and is also well tolerated. Dosing for FCM is 1000 mg or 20 mg/kg once weekly, infused over 15 minutes. Iron levels should be re-evaluated 4 weeks after treatment. Referral to a hematologist should be considered to manage anemia, especially when deficiencies persist despite standard treatment approaches. It is crucial to note that treatment of the underlying disease should be the first aim in treating patients with IBD, as the most common cause of IDA in this population is blood loss through active disease state [82].

Nutrition: Vitamin D

The association between low vitamin D and inflammatory bowel disease is unclear, but some studies indicate that vitamin D plays a vital role in keeping inflammation at bay through regulation of inflammatory cytokines and inhibition

of proinflammatory cell proliferation [84]. Vitamin D deficiency has not yet been established as a cause or an outcome of IBD. Patients who are at a higher risk of vitamin D deficiency are those with impaired nutritional absorption, food restriction, or who avoid the sun (through skin coverings due to cultural reasons or to avoid sun damage) [85].

The cutoff values for treating vitamin D deficiency vary across several societies, ranging between 20 and 30 ng/mL of 25(OH)D [85]. The optimal vitamin D concentration in IBD patients has yet to be determined, although 30–50 ng/mL is considered a safe and potentially beneficial target [86]. Preferred treatment includes supplementation with vitamin D3, as this is the most potent form of vitamin D and should be used over alternative formulations, such as vitamin D and D2. Society guidelines vary in suggestions for what is adequate dosing. IBD patients may even require higher dosing than what is recommended for the general population [86]. The recommended range of dosing for IBD patients is between 1800 and 10,000 IU of cholecalciferol [86]. Although sun exposure increases vitamin D synthesis, there is no harmless threshold to recommend to patients that will not increase the risk of skin cancer. Dietary sources of vitamin D include egg yolks, oily fish, liver, and fortified foods such as some brands of yogurt, plant milks, and orange juice [85].

Special Considerations

Special Considerations: Healthcare Maintenance in the Older Adult

Older IBD patients, aged 65 and older, are a vulnerable group that requires special attention, because they received even less patient-directed preventive services. Only 50% of older adults receive the recommended vaccines and cancer screenings despite the higher risk of infection and malignancy [87]. Establishing routine healthcare maintenance visits with the older patient is imperative in order to prevent disease, monitor comorbidities, and manage polypharmacy.

Infection risks are higher in the older patient, and many of these risk factors, such as malnutrition, surgery, vaccination, hospital readmission, and immunosuppressive therapy, are modifiable [88]. Special care regarding monitoring disease response should be taken to avoid relapse and hospital admission. The older IBD population engages in higher healthcare utilization and costs with longer lengths of stays, higher hospitalization rates, and hospital mortality rates [89].

Age-specific vaccinations are advised for the older IBD patient. The high-dose influenza vaccine and the pneumococcal vaccine (PPSV 23) are recommended at the age of 65. Ensuring patients have received their shingles vaccine, as well as all other routine vaccinations, is recommended.

Nutritional screening and correction for at risk vitamin deficiencies including thiamine, riboflavin, vitamin D, calcium, magnesium, selenium, and zinc are important.

Treating anemia may prevent cognitive impairment, falls, fractures, and mortality [90]. Dietician counseling can be offered in order to maximize nutritional intake. For patients with comorbidities like diabetes and chronic kidney disease, improved insurance coverage may be obtained, and there is dual benefit to dietary counseling.

Screening for depression, which can often be accelerated in aging, should be performed routinely. If any signs of depression or mood changes are detected, resources for community services and mental health counseling should be offered. For patients with any cognitive decline, medication adherence may be a challenge. Creating a collaborative healthcare team, with the primary care provider, pharmacist, nurse, and family member can help keep older patients on track.

Special Considerations: Medication Adherence

Pharmacotherapy for IBD management is the backbone of therapeutic intervention. Medication adherence is associated with better disease outcomes and decreased hospitalization burden. Despite this, medication adherence rates in the IBD population are poor [91]. Nonadherence rates greatly vary in the IBD population, ranging anywhere from 2 to 93% [91]. Nonadherence, which can be defined as taking medications less than 80–95% as prescribed, can lead to disease relapse, loss of response to biologic therapy, worse quality of life, and increased morbidity and mortality [91]. Monitoring adherence and identifying risk factors for nonadherence should be at the forefront of HCM encounters. Providing supportive modalities to promote treatment adherence can be implemented in order to optimize patient outcomes. Providers should address patient's medication concerns before beginning treatment and periodically throughout maintenance therapy.

Monitoring for adherence can be performed using objective and subjective measurements. Serum drug levels for biologic and immunomodulator treatment can be obtained. Low drug levels may indicate missed doses, and undetectable levels may suggest self-discontinuation of treatment [91]. Patient confirmation should verify any speculation as other issues may be driving behavior. We have seen drug affordability result in pill splitting. Self-reporting with diary entries, interviews, and questionnaires can provide useful insights into adherence rates and reasons for avoidance [91]. Asking open-ended questions that are nonjudgmental can prevent biased responses and provide clinical insight [91].

Provider interventions to promote medication adherence should consist of patient engagement and encouragement. Direct observation of patients undergoing infusion or injection therapy may endorse compliance. Maintenance therapy in the form of subcutaneous injections can be offered to be administered in the provider's office if nonadherence is predicted. Office injections may be especially beneficial to those patients with a history of nonadherence or needle phobia. If patients plan to self-inject at home, virtual visits can be offered as an additional means of ensuring good technique, while also monitoring compliance.

Visual and auditory reminders, such as alarms and pill boxes, can aid in medication adherence. Cognitive behavioral therapy can be offered to patients who are not

motivated or have negative thoughts associated with treatment [91]. Medication counseling from an IBD pharmacist has been shown to decrease nonadherence rates in the IBD population [92]. Combination of several patient-centered methods to help motivate medication adherence may lead to improved patient outcomes.

Special Considerations: Complementary Medicine

Complementary medicine includes a variety of treatment options that are used in conjunction with conventional therapies. IBD patients are known to have high levels of fatigue, anxiety, and depression, all complex conditions that require a multidisciplinary, integrative approach [93, 94]. Some studies have shown that complementary medicine can help with symptom and pain control, improve quality of life, and improve overall mood and attitude toward health and well-being. There are a variety of emerging complementary medicine options in the literature including medical cannabis, various diets, acupuncture, vitamin and minerals supplements, probiotics, and mind-body therapies. Patients are increasingly turning to alternative and complementary options, and it is estimated that up to half of IBD patients use these at some point [95]. However, appropriate evidence is often lacking**.** In fact, patients are willing to spend large amounts of money for complementary and alternative therapies. A recent national health survey estimated that 38% of adults in the United States use alternative therapies and spend over $30 billion dollars [96]. There is a perceived favorable side effect profile for alternative therapies because traditional medicine is associated with complications including, but not limited to, infection, myelosuppression, and malignancy [97]. It is important to note that this is a dynamic and evolving field and more rigorous testing is needed to understand the risks and benefits of complementary medicine in IBD. Although these therapies can have positive benefits, complementary medicine should not replace conventional therapies. Considering the popularity of these therapies among IBD patients, it is important for both patients and practitioners to be informed about the safety and efficacy of these treatments to allow for evidence-based practices. While a review of all complementary interventions is beyond the scope of this chapter, we have included a section on cannabis since this product will become increasingly available, and adopting a strategy to discuss this in a nonjudgmental and transparent manner will be useful to both the practitioner and the patient. We have incorporated this topic into our healthcare maintenance visits, which is less disease and drug focused, since patients are sometimes curious and have questions that lead to a more detailed discussion.

Cannabis

Cannabis sativa, best known as marijuana, has earned significant interest from patients and investigators for its perceived benefit to manage bowel-related symptoms. In fact up to a third of IBD patients have reported trying marijuana [98].

Although cannabis has gained its popularity for its psychogenic effects, there are endogenous cannabinoid receptors in the enteric nervous system, which have an influence on gut motility [99]. Cannabinoids are involved with activating the endocannabinoid system, which helps to regulate gastrointestinal functions including pain, motility, and inflammation. Activating the endocannabinoid system can help in IBD [100]. The two most studied and active chemicals in the *C. sativa* plant are tetrahydrocannabinol (THC) and cannabidiol (CBD). While THC is responsible for psychoactive effects, both THC and CBD have roles in modulating pain, motility, and inflammation in the gut [101].

Cannabis seems to have a therapeutic role for IBD patients, but research is still in nascent stages and is still evolving. Furthermore, the variability of available cannabis preparations and modes of consumption make studying cannabis in a randomized, controlled trial setting extremely challenging. In the United States, cannabis is considered a Schedule I substance at the federal level and is considered illegal for recreational use and medicinal use and cannot be given for research purposes [102]. However as of 2020, at the individual state level, marijuana is legal for recreational use in 15 states and Washington DC and decriminalized in 16 others, and medical marijuana is legal in 35 states and Washington DC.

Initial interest came from studies in mice showing possible anti-inflammatory effects which prompted studies in humans [103]. Although less robust in humans, early trials showed improvement in clinical symptoms for patients with Crohn's disease [104, 105]. While there are several observational studies showing improvement in pain, diarrhea, and mood symptoms with patients using cannabis, at the moment, there are only three small randomized placebo-controlled trials investigating cannabis in active Crohn's disease. The early randomized trials were comparing smoked cannabis cigarettes to placebo, and over 90% of the cannabis group reported positive response. In a placebo-controlled trial, patients were given 230 mg THC in the form of cigarettes for 8 weeks, and the treatment group had a statistically significant improvement in CDAI scores, but the benefit was lost within 2 weeks after stopping the drug suggesting the absence of a more definitive interruption of inflammation [104]. In a follow-up study, patients with active Crohn's disease, many of whom had failed immunomodulators and biologics, were given 10 mg CBD oil twice a day for 8 weeks vs. placebo. The treatment group reported improved symptoms, but there was no difference in CDAI reduction between the groups [106]. In a similar study presented at UEG week, Naftali et al. recruited 46 patients with moderately severe Crohn's disease and randomized them to 8 weeks of cannabis oil containing 15% cannabidiol and 4% tetrahydrocannabinol versus placebo. Patients report significant improvement in symptom severity and quality of life but no statistically significant difference in endoscopic scores or inflammatory markers [107]. It is interesting to postulate whether cannabis temporarily relieves symptoms but has no effect on the biological activity of the underlying disease. These later studies used a different administration method of cannabis than previous studies, oral cannabis compared to the previous smoked cannabis. This oral mode of administration method allowed the ability for proper blinding, which was challenging with smoked preparations since smoked cannabis can give a sense of euphoria. In light of these

findings, it is essential to emphasize to patients the importance of staying on their conventional therapies and that cannabis has a supplementary role in treating patients with IBD. Interestingly there is some data showing statistically significant improvement in Mayo scores in UC patients using THC cannabis cigarettes. Unfortunately objective disease activity markers including C-reactive protein (CRP) and fecal calprotectin (FC) and endoscopic disease activity did not show any statistical differences [98].

Aside from a lack of data showing that cannabis decreases inflammation in IBD, there are legal and psychosocial ramifications with cannabis use, particularly in the young and adolescent population. Access remains restricted in certain states with concerns about the link between marijuana and dependency and addiction. Additionally, there is no standardization in the quality and dose of cannabis product that patients are getting. Cannabis and, in particular, higher cannabis doses, chronic marijuana use, and synthetic marijuana preparations are associated with cognitive impairments including amotivational syndrome, psychosis, learning deficits, as well as nausea, vomiting, cyclic vomiting syndrome, motor vehicle accidents, and fertility issues [95, 108, 109]. Chronic cannabis use in CD patients was also a strong predictor for needing surgery [110]. Patients should also be counseled about the risk of e-cigarette, or vaping, product use-associated lung injury (EVALI). Vitamin E acetate is an additive in THC-containing e-cigarettes and is now known to be strongly linked to EVALI, a severe pulmonary illness [111]. At our clinic, we advise our patients to avoid vaping and use alternative methods for ingestion.

Questions surrounding the safety profile and side effects of cannabis, particularly regarding the dosing and mode of administration, highlight the need for additional research. The European Crohn's and Colitis Organization has recently published a review with recommendations for complementary medicine and psychotherapy in IBD. They do not recommend cannabis and suggest there is limited evidence to suggest any positive effect on disease course [112]. The Crohn's and Colitis Foundation similarly notes that more research is needed regarding cannabis and IBD and that currently there is not enough evidence to suggest that medical cannabis reduces IBD inflammation or improves disease activity [113]. Prior to cannabis being recommended as an adjunct to address specific symptoms, more trials establishing safety and efficacy of cannabis are needed, and patients should be counseled about potential adverse effects.

Conclusion

IBD specialists must have a comprehensive understanding of the unique needs of IBD patients and take a proactive role in the assessment and screening of healthcare needs in order to improve the quality and rates of preventive care administered to IBD patients. Many of these patients are on immunosuppressive agents, so the benefit of interventions to mitigate treatment-related adverse effects is especially critical. To effectively co-manage these patients, IBD teams must advise primary care

physicians regarding the wide range of issues that IBD patients need assessed including vaccinations, osteoporosis screening, cancer and dysplasia surveillance (colorectal cancer, skin cancer, cervical cancer screening), depression and anxiety, and smoking. We have found that a multidisciplinary approach with the gastroenterologist "quarterbacking" the team is the most effective strategy to guide the IBD patient through a complex care pathway.

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Chapter 8
The Woman with Inflammatory Bowel Disease: Fertility, Pregnancy, and beyond

Sanket Patel and Haleh Vaziri

Overview

IBD is a chronic inflammatory condition that affects roughly 1.6 million people or 0.5% of the US population [1]. Patients are typically diagnosed in the second and third decades of life, with more than half of affected cases being women, many of whom are of childbearing age [2, 3]. These women often present with concerns about fertility, the immediate and long-term effects of the disease and its treatment on the fetus, and the impact of pregnancy on disease course and vice versa. There are also special considerations regarding babies who have been born to mothers with IBD, especially in the era of biologic therapy. The complexity of the disease and its treatment require a multidisciplinary tactic with the primary goal being to have the disease under control while keeping the mother and child safe. Providers should guide their patients by using evidence-based medicine while incorporating a shared decision-making approach.

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R. Rajapakse (ed.), *Inflammatory Bowel Disease*, Clinical Gastroenterology,
https://doi.org/10.1007/978-3-030-81780-0_8

Fertility

Many women with IBD have fertility concerns. There is also evidence showing that more women with IBD choose to remain childless, compared to the general population, due to misconceptions about pregnancy and IBD [4, 5, 6]. While the fertility rates in women with ulcerative colitis (UC) or Crohn's disease (CD) in remission are comparable to the general population, the rates may decrease in women with active IBD or prior pelvic surgeries like ileal pouch-anal anastomosis (IPAA) and proctectomy [7, 8]. This is probably related to inflammation and scarring of the fallopian tubes or ovaries. Dyspareunia may also play a role in patients who have perianal disease.

Women with IBD should be referred to a fertility specialist if they are unable to conceive after 6 months of timed intercourse. While assisted reproductive technology (ART) may not be as effective in these patients as in infertile women without IBD, especially if they have had prior surgeries, it is reassuring to know that chances of live birth are comparable to the general population when pregnancy does occur [9]. It is also important to remember that currently available medical therapies for IBD do not decrease fertility in women [10, 11].

Male fertility may also be affected, especially if they have impotence secondary to prior proctocolectomy or if they are being treated with medications such as methotrexate (MTX) and sulfasalazine. These drugs may cause reversible oligospermia. MTX can theoretically lead to mutation in sperm [12]. It is advisable to hold MTX therapy for 3 months and transition sulfasalazine to mesalamine 4 months before conception, because spermatogenesis takes 3–4 months [13, 14, 15, 16, 17, 18]. Mesalamine is not associated with oligospermia [13, 14]

Preconception

All women with IBD should receive preconception counseling and family planning as part of their routine care with their gastroenterologist and obstetrician/gynecologist. Colorectal surgeons and maternal-fetal medicine specialists should also be involved in their care when appropriate. Preconception counseling provides an opportunity to review contraception, discuss healthcare maintenance, address patient's concerns regarding heritability to offspring, and optimize nutrition status. This is also an important time to emphasize smoking cessation and disease control while examining the safety of different IBD therapies during pregnancy and lactation. Preconception care reduces the risk of having an infant with low-birth-weight (LBW) and prevents IBD relapse in pregnant women by promoting smoking cessation and medication adherence [19].

Contraception

Education regarding contraception should occur at preconception visits. Patients should be encouraged to use the safest and most effective option for reversible,

long-acting birth control. Options include an intrauterine device or an implant which can be hormonal or nonhormonal. Since IBD patients are at higher risk for venous thromboembolism (VTE), estrogen-containing contraception should be avoided if possible, especially in smokers and those with personal or family history of thromboembolic events.

Healthcare Maintenance

Healthcare maintenance should be part of the routine IBD visits. Women are recommended to undergo regular Papanicolaou smears, stay up to date with recommended vaccinations, and avoid alcohol, tobacco use, narcotics, and recreational drugs. Cannabis is sometimes used in IBD patients to alleviate pain. However, its use should be discouraged in patients who are trying to conceive, pregnant, or breastfeeding due to its potential role in neurodevelopmental impairment in a growing fetus and infants, based on the recommendation by obstetric practice guidance [20]. Alcohol and smoking cessation improve parturition outcomes such as fetal alcohol spectrum disorder and smoking-associated LBW [21, 22].

Genetics

CD and UC are observed to cluster within families; however, they do not obey the traditional Mendelian pattern of disease. Their pathogenesis is multifactorial and due to the dysregulated immune response to the gut microbiota in genetically susceptible hosts with possible environmental triggers such as antibiotics, infections, stress, and diet. Genome-wide association studies (GWAS) have led to the discovery of more than 200 genetic loci, which may play a role in IBD pathogenesis, with some genes implicated in both diseases while others being more specific to CD or UC [23]. Compared to the general population, the familial risk of IBD is about 8–12% when looking at first-, second-, and third-degree relatives with IBD [24, 25]. The chance of having IBD has been reported to be about 36% when both parents are affected [26]. Genetic influences are more substantial with CD compared to UC [27]. Disease concordance is higher in monozygotic (MZ) than dizygotic (DZ) twins implicating the role of genetics. The concordance rates for CD are about 20–56% in MZ and 0–7% in DZ twins. These rates for UC are about 6–19% and 0–5%, respectively [25]. These numbers indicate the importance of epigenetic and environmental factors in the pathogenesis of IBD in addition to genetics.

There is limited epidemiological data regarding other ethnic and racial groups because most data is based on Caucasians with an insufficient sample size of different ethnic and racial populations. While the highest incidence of IBD is in Caucasians, especially Ashkenazi Jews, IBD-associated hospitalization and mortality are more prevalent among non-Hispanic blacks [28, 29].

Nutrition and Supplements

Nutrition should be optimized to achieve ideal body weight preferably before conception. Patients should be encouraged to eat a healthy, well-balanced diet. While nutrition consultation may be beneficial for all IBD patients before a planned pregnancy, it is highly recommended in patients with additional risk factors such as those with active disease, prior small bowel surgeries that influence the absorption of nutrients, and obese or underweight patients [30]. Inadequate gestational weight gain (GWG) is often a concern for women with IBD, especially when their disease is not well controlled. These patients have a twofold increased risk of infants with small-for-gestational-age and a 2.5-fold higher risk of preterm births [31].

Essential nutrients to address at preconception visits include folate, vitamin B12, vitamin D, and iron. These vitamins and minerals are often present in prenatal vitamins, which are routinely recommended in the general obstetric population, but a higher dose may be needed in some IBD patients. Folic acid deficiency during pregnancy can lead to neural tube defects in the fetus. Low levels may arise in patients on a low residue diet, small bowel involvement, or those being treated with sulfasalazine; therefore, supplementation with at least 2 mg/day is recommended [32]. Patients with CD who have undergone ileal resection or suffer from terminal ileum disease may be deficient in vitamin B12. Therefore, levels should be checked and replacement therapy initiated if needed. Similarly, vitamin D levels are often low in IBD patients, particularly during pregnancy, and they should be checked during preconception visits and supplemented accordingly [33]. Additionally, iron requirements are increased during pregnancy, making this a vital micronutrient. Iron replacement can be done via an oral or an intravenous route. Constipation may accompany oral iron supplementation, which may cause abdominal pain. If abdominal pain with constipation occurs after starting oral iron supplementation, patients can be treated with stool softeners and laxatives safely during pregnancy.

Women should limit their caffeine intake to 250 mg per day during preconception and conception phases. A growing number of herbal supplements are available over the counter for the treatment of IBD patients. Given the lack of robust data regarding the safety and efficacy of herbal remedies and the presence of significant methodological barriers in studies evaluating them, the use of these supplements should be discouraged in pregnant patients.

Disease Control

In general, being in remission for at least 3 to 6 months, preconception significantly reduces the risk of an IBD flare intra- and postpartum. Quiescent disease at conception dramatically increases the chances of having a healthy pregnancy and delivering a healthy full-term baby. Pregnant patients with UC experience disease flare more commonly compared to CD, which mostly occurs during first and second

trimesters. In UC patients who become pregnant, it is estimated that one-third will remain in remission, one-third will improve, and one-third will worsen. While the exact etiology of this remains unclear, possible explanations include a shift from T-helper 1 (Th-1) to T-helper 2 (Th-2) cells which occurs to protect the fetus, smoking cessation, or undertreatment of UC at preconception [34].

Medications

Most medical therapies for IBD are considered safe for women planning a pregnancy with few exceptions. As a general rule, most treatments should be continued during the preconception phase to optimize fertility while maintaining remission. Aminosalicylates or 5-aminosalicylic acid (5-ASA) derivatives are generally safe during this period. Women on Asacol HD should be changed to an equivalent dose of an alternative mesalamine due to concerns over dibutyl phthalate in the enteric coating and its effect over reproductive biology in animal models [35]. Patients who are being treated with sulfasalazine should maintain folic acid supplementation at a dose of 2 mg per day.

Glucocorticoids, in general, should never be used as maintenance therapy, and patients who are planning to get pregnant should aim to achieve steroid-free remission for at least 3 months before conception using a steroid-sparing agent.

Thiopurines, 6-mercaptopurine (6-MP) or its prodrug azathioprine (AZA), should be continued if the patient has been in remission on these medications as monotherapy. In patients on dual therapy with thiopurines, the risk and benefits of stopping concomitant thiopurines should be considered given a higher risk of infections with combination therapy.

MTX is teratogenic and is an abortifacient. Therefore, effective contraception methods should be employed for all women of childbearing age while using this drug and the patient should receive adequate counseling regarding its teratogenicity in order to prevent unplanned pregnancy. For women planning to conceive, MTX must be stopped at least 3 months before conception. When alternative therapy is needed in the interim, remission should be maintained on the new drug for at least 3 months before conception.

There is a significant amount of evidence regarding the safety of anti-TNFs during pregnancy based on registry data. Although similar data is still not available for the other biologics such as vedolizumab and ustekinumab, the consensus appears to be that they are safe during pregnancy. Therefore biologic therapy with anti-TNFs [infliximab (IFX), adalimumab (ADA), golimumab (GOL), and certolizumab pegol (CZP)], integrin inhibitors [vedolizumab (VDZ)], and interleukin 12/23 inhibitor [ustekinumab (UST)] should be continued in patients already on them, due to the importance of maintaining remission during pregnancy. In patients who are on dual therapy, particularly with anti-TNFs and immunomodulators, one should consider checking the drug levels before conception, especially when planning to stop the immunomodulators.

Small molecule Janus kinase inhibitor, tofacitinib, is a relatively new drug, with limited safety data in pregnancy. Due to its short half-life, it is recommended that tofacitinib be discontinued for at least 1 week prior to planned conception to allow this drug to wash out [3].

In men, the majority of IBD medications are safe to continue during the preconception period, with only a few exceptions. Sulfasalazine should be switched to one of the 5-ASAs about 4 months before conception due to reversible oligospermia [36]. MTX, which has a theoretical mutagenic effect on sperm, should be held 3 months before conception [12].

Conception

Disease in Remission

About one-third of patients who have been in remission at conception may flare during pregnancy [37]. Flares occur at a similar rate in nonpregnant IBD patients over 9 months [38]. Disease flares should be managed aggressively to avoid complications such as preterm delivery and LBW. Patients who are in remission should be monitored with laboratory workup every semester. These include a complete blood count, a liver profile, and any other necessary labs which may be indicated due to their specific therapies. At the same time, maternal-fetal monitoring should include routine antepartum care with fetal growth ultrasound in the third trimester and checking the perineal area for any active disease [3]. Laboratory values must be carefully analyzed in pregnancy as hemoglobin and albumin values often decrease while erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are often elevated. Trends of ESR and CRP help for disease monitoring; however, fecal calprotectin is a more reliable marker for this purpose.

Active Disease

Patients are more likely to experience a flare of disease during pregnancy if the disease is active at conception; this is especially so for patients with CD [39]. Women with IBD, especially non-Caucasian race and those with a history of IBD related surgery, are at a higher risk of adverse pregnancy outcomes such as venous thromboembolism (VTE), malnutrition, and the requirement for blood transfusion, compared to non-IBD patients [40, 41, 42]. Women with active CD, especially active perianal disease, have higher rates of fourth-degree perineal lacerations and cesarean deliveries [43]. Patients with active disease should have their medications adjusted to obtain remission, while being monitored more frequently with blood work, fecal calprotectin, and follow-up visits every 2 weeks through office visits,

electronic messaging, and telehealth encounters [3]. Maternal-fetal monitoring in these patients includes a nutrition consult, early screening for gestational diabetes in those being treated with steroids, cervical length screening (ultrasound at 18–22 weeks with obstetrics follow-up if length <25 mm), fetal growth surveillance every month (starting at 24 weeks), and third-trimester antepartum fetal surveillance (routine nonstress test and biophysical profile) [3].

Disease assessment with either imaging or endoscopy should only be undertaken in pregnancy when anticipated results may change patient management. Imaging modalities include X-ray, ultrasound, CT scan, and MRI. Diagnostic accuracy is comparable for both MRI and CT scans. If imaging study is needed, ultrasound and MRI without gadolinium (lack of safety data) are considered safe modalities, especially during the first trimester, while radiation exposure with X-ray and CT scans may be problematic and should be avoided whenever possible. Regarding endoscopic evaluation, unsedated flexible sigmoidoscopy is preferable and safe to perform during all trimesters but best avoided if possible in the first and third trimesters. If colonoscopy is necessary, it should be performed under obstetric anesthesiology monitoring [11]. When procedural sedation is needed, propofol is considered safe; however, benzodiazepines should be avoided. Patients should be placed in the left lateral decubitus position to avoid aorto-caval compression, and fetal monitoring should occur before, during, and after endoscopy.

Medications

The goal of IBD therapy during pregnancy is to maintain remission in order to improve maternal-fetal outcomes. Table 8.1 provides a summary for specific dosing recommendations and safety of IBD drugs during pregnancy and lactation using the LactMed database and the new US Food and Drug Administration's (FDA) Pregnancy and Lactation Labeling Rules, keeping in mind that pregnancy categories (i.e., A, B, C, D, X) are no longer used [44, 45]. One should remember that the long-term effects of the newer medications on the offspring of women treated during pregnancy are lacking, and some recommendations regarding the newer therapies are based on limited data.

Medications that are typically safe to continue during pregnancy are aminosalicylates, thiopurines, and biologic therapies. MTX should never be used, and tofacitinib should be avoided if possible. Mesalamines are considered safe during pregnancy. Animal models have raised concern over mesalamine teratogenicity with phthalate-containing compounds (e.g., coating of Asacol HD); however, human studies have not been able to demonstrate this [35]. In light of this, a switch to an alternative mesalamine of an equivalent dosage should be made. Mesalamines are overall safe and preferred over sulfasalazine, but if sulfasalazine is chosen, then 2 mg of folic acid should be supplemented.

Glucocorticoids are often necessary for the treatment of active disease states; however, maintenance use should be avoided in all IBD patients, particularly during

Table 8.1 Pregnancy and lactation safety of commonly used drugs in IBD [3, 11, 44, 45]

Drug class	Pregnancy safety	Preconception recommendation	Conception recommendation	Breast milk transfer	Breastfeeding safety
Aminosalicylates	Low risk	Switch Asacol HD to alternate mesalamine due to the presence of DBP (teratogenic in animals) in its enteric coating. If using sulfasalazine, add 2 mg per day of folic acid supplementation (mesalamine formulations are preferred)	Same as preconception recommendations	Poor excretion into breast milk (metabolites do appear in breast milk)	Acceptable (monitor breastfed infant for diarrhea)
Budesonide	Low risk	Short course for flare	Short course for flare	Detected in small concentration	Acceptable
Prednisone	Moderate risk (increased risk of gestational diabetes, PROM, preterm birth, and congenital defect)	Short course for flare	Short course for flare	Dose-dependent levels detected in breast milk (for high-dose therapy, prednisolone is preferred)	Acceptable (delay breastfeeding 1–2 hours after a dose)
Thiopurines	Low risk (monotherapy is preferred if possible)	Monotherapy is preferred (increased infection risk with dual therapy)	Monotherapy preferred (increased risk with dual therapy) Avoid introduction during pregnancy, given the delayed onset of action and the risk of pancreatitis	Detected in small concentration	Acceptable (delay breastfeeding 4 hours after a dose)
Methotrexate	Contraindicated (teratogenic and abortifacient)	Avoid 3–6 months prior to conception	Contraindicated	Detected in small concentration	Contraindicated

Cyclosporine	Limited data (risk of preeclampsia, maternal hypertension, gestational diabetes, preterm birth, and LBW)	Standard dose when used for salvage therapy	Standard dose when used for salvage therapy	Detected with variable levels	Acceptable (monitor infant levels)
Infliximab	Low risk (monotherapy)	Standard dose	Last dose 6–10 weeks before EDD or 4–5 weeks if monthly dosing (resume 48 hours postpartum)	Detected in small concentration	Acceptable
Adalimumab	Low risk (monotherapy)	Standard dose	Last dose 2–3 weeks before EDD or 1–2 weeks if weekly dosing (resume 48 hours postpartum)	Detected in small concentration	Acceptable
Certolizumab pegol	Very low risk (monotherapy; not actively transported through the placenta)	Standard dose	No need to change the dosing schedule No placental transfer	Detected in small concentrations in some women	Safe (absorption from infant GI tract unlikely)
Golimumab	Low risk (monotherapy)	Standard dose	Time last dose 4–6 weeks before EDD (resume 48 hours postpartum)	Detected in small concentration	Acceptable
Natalizumab	Low risk	Standard dose	Time last infusion 4–6 weeks prior to EDD (resume 48 hours postpartum)	Detected in small concentration	Acceptable
Vedolizumab	Low risk	Standard dose	Time last dose 6–10 weeks prior to EDD or 4–5 weeks if monthly dosing (resume 48 hours postpartum)	Detected in small concentration	Acceptable

(continued)

Table 8.1 (continued)

Drug class	Pregnancy safety	Preconception recommendation	Conception recommendation	Breast milk transfer	Breastfeeding safety
Ustekinumab	Limited data (probably low risk)	Standard dose	Time last dose 6–10 weeks prior to EDD or 4–5 weeks if monthly dosing (resume 48 hours postpartum)	Detected in small concentration	Acceptable
Tofacitinib	Limited data	Discontinue at least 1 week prior to conception	Avoid if possible (especially during first trimester)	Unknown	Unknown
Amoxicillin/ clavulanic acid	Low risk	Standard dose	Preferred over other antibiotics during pregnancy Avoid as maintenance therapy	Detected in breast milk	Acceptable
Ciprofloxacin	Low risk (arthropathy in animals)	Standard dose	Avoid as maintenance therapy	Detected in small concentration (short course likely safe)	Acceptable (delay breastfeeding 3–4 hours after dose; monitor infant for diarrhea and/or candidiasis)
Metronidazole	Low risk (risk of cleft lip)	Standard dose	Short courses. Avoid in the first trimester if possible. Avoid as maintenance therapy	Detected in breast milk (mutagenic)	Contraindicated
Rifaximin	Limited data (teratogenic in animal studies)	Avoid if possible	Avoid if possible (malformation in animal models)	Poorly absorbed orally and unlikely to reach breast milk	Unknown (alternative agent is preferred)

**EDD* estimated date of delivery

pregnancy due to higher rates of adverse maternal-fetal outcomes. These adverse outcomes may include preterm delivery, higher cesarean section rates, LWB, and an increased risk of gestational diabetes [46].

Evidence for the safety of thiopurines during pregnancy is somewhat confusing. Although robust data are lacking regarding their risk during pregnancy, routine discontinuation is not recommended [47]. Thiopurines disrupt DNA replication and block the purine synthesis pathway, which is teratogenic to animals when given intravenously and intraperitoneal [48]. Some studies have demonstrated that thiopurine use during pregnancy for active disease or maintenance therapy may carry a higher risk of preterm birth and an increased risk of congenital malformations like atrial/ventricular septal defect and intrauterine growth restriction (IUGR) [49, 50]. However, more reliable data to date support their safety with no increased risk in maternal-fetal complications [51, 52, 53]. Since having active disease in pregnancy leads to poorer outcomes, the risks of stopping thiopurine treatment may be much higher compared to the possible adverse effects. Therefore, it is reasonable to continue the maintenance monotherapy. The overall safety of thiopurines is possibly attributable to the human placenta acting as a barrier to 6-MP and AZA and their metabolites [54]. During pregnancy, there is a shift in the metabolism of thiopurines resulting in lower concentrations of 6-thioguanine (6-TGN) level and higher levels of 6-methylmercaptopurine (6-MMP); however, toxicity does not result from this shift, and the postpartum levels revert to baseline [55]. Therapy with thiopurines should not be started during pregnancy to treat active disease because of the slow onset of action, risk of pancreatitis, and bone marrow suppression.

MTX, as discussed earlier, is contraindicated in pregnancy due to its teratogenic effects. It can lead to MTX embryopathy or fetal MTX syndrome, a combination of craniofacial defects, congenital limb anomalies, and developmental delays [12, 56].

There is limited data on the use of T-cell inhibitors like cyclosporine and tacrolimus in pregnant IBD patients, with most data derived from transplant patients. Cyclosporine may be needed as salvage therapy in severe acute steroid-refractory ulcerative colitis to avoid colectomy [57]. In comparison, cyclosporine use may not increase the risk of congenital malformation [58], but there may be an association with an increased prematurity rate. However, it is unknown if this is an effect of this medication or the woman's underlying condition [59]. Other reported adverse maternal-fetal outcomes include preeclampsia, maternal hypertension, gestational diabetes, preterm birth, and LBW; however, it has been safely used in the treatment of fulminant, steroid-refractory UC [60, 61]. Tacrolimus carries a lower risk of maternal hypertension but a higher incidence of neonatal hyperglycemia, hyperkalemia, renal injury, and approximately 4% rate of congenital malformations [62, 63, 64]. Placental transfer of calcineurin inhibitors to the fetus does occur, with levels in a newborn detected days after birth [65].

Despite the risk of placental transfer of IFX and ADA to the infant, anti-TNF therapy is considered safe and does not lead to adverse maternal-fetal outcomes. During pregnancy, IFX levels increase, while ADA levels remain stable after accounting for changes in albumin, body mass index (BMI), and CRP [66]. CZP is a pegylated anti-TNF agent that does not cross the placenta. Dosing and timing of

biologics should be adjusted, so that drug trough levels occur at the time of delivery without interruption of therapy if possible. Biologic therapy in utero does not confer an increased risk of severe infections in the short or long term [67]. Monotherapy is typically preferred due to a threefold increased risk of infections to infants on combination therapy with thiopurines [52, 68]. When using dual therapy before pregnancy with immunomodulators, the decision to switch to monotherapy rests upon disease severity and should be decided case by case.

Integrin inhibitors (NTZ and VDZ) should overall be continued during pregnancy. There is limited data regarding the use of NTZ, an IgG4 anti-integrin, during pregnancy in IBD patients. NTZ safety profile from multiple sclerosis (MS) data supports continuation during pregnancy, with no worrisome adverse events in newborns except for anemia [69, 70]. Given the risk of IBD relapse when stopping the therapy and its associated detrimental effect on maternal-fetal outcomes, it is recommended to continue NTZ during pregnancy. This approach is supported by favorable results in MS literature and the PIANO registry for Crohn's disease pregnancy outcomes while on NTZ [71, 72, 52]. VDZ is a gut-selective a4b7 integrin inhibitor with much better safety data. Animal models have not demonstrated teratogenicity secondary to VDZ [73]. Trial data and post-marketing surveillance reports for VDZ were limited by sample size and follow-up; however, no safety concerns for pregnancy outcomes were identified from VDZ exposure [74]. In a case-control observational, multicenter study of 186 pregnancies in 164 women, no new safety signal was detected when VDZ was used during pregnancy [75]. Patients treated with VDZ have live birth and miscarriage rates similar to the non-IBD population. At the same time, infants reach typical developmental milestones with no significant infection rates and have only a slightly higher rate of congenital anomaly unrelated to VDZ use [76].

There is insufficient safety data for UST in pregnancy, with one case series demonstrating similar rates of live birth compared to the general population [77, 78]. Animal studies have not shown teratogenicity, and human data from dermatology literature have not implicated any fertility issues or congenital malformations [79, 80]. Based on the available data, it is recommended that UST should be continued during pregnancy, given the deleterious effects of a flare off therapy.

Tofacitinib may cross the placental barrier and lead to teratogenicity, as demonstrated in animal models at supratherapeutic doses [81]. Although data in human pregnancy are limited, maternal-fetal outcomes appear to mirror those of the general population [82]. Until more human data is available, tofacitinib should be avoided if possible, especially during the first trimester. Due to its short half-life, it has been recommended to discontinue tofacitinib for at least 1 week before conception to allow this drug to clear from the body. In patients who wish to continue this treatment due to their limited therapeutic options, providers should inform them regarding possible risks, benefits, and alternatives. Efforts should be made to avoid its use during the first trimester when possible because the organogenesis of the developing fetus occurs during this time.

Antibiotics are commonly being used in the treatment of abscesses, fistulizing CD, and pouchitis. Ciprofloxacin, metronidazole, amoxicillin/clavulanate, or

rifaximin is commonly used in managing these patients. Ciprofloxacin in high doses has been associated with bone and cartilage damage in animals and infrequently in humans; however, therapeutic doses are unlikely to pose a teratogenic risk [83, 84]. Metronidazole is carcinogenic in animals, but this has not been demonstrated in humans [85, 86]. Short-term use of metronidazole is probably safe during pregnancy due to the absence of reported significant teratogenicity in pregnant women [87, 88]. Amoxicillin/clavulanate can be used during pregnancy and is the preferred antibiotic as it does not lead to an elevated risk of congenital abnormalities in infants [89]. Rifaximin lacks adequate data in pregnant women but has been associated with malformations in animal studies when administered to pregnant rats and rabbits at supratherapeutic doses [90].

Surgery

Surgical intervention may be required in patients with severe acute refractory ulcerative colitis, bowel perforation, severe gastrointestinal hemorrhage, abscess, or bowel obstruction. Increased parity has an inverse relationship with surgical interventions and clinical activity [34]. If surgery becomes necessary in patients with fulminant UC, a subtotal colectomy and Brooke ileostomy can be safely performed with low maternal-fetal morbidity and mortality [91]. Rarely, iatrogenic uterine manipulation may lead to spontaneous abortions or preterm labor. This type of surgical care is best accomplished by an experienced surgeon with a multidisciplinary team-based approach. Unless urgent, the ideal time to perform surgery is postpartum or second trimester if surgery cannot wait until delivery.

Delivery and Postpartum Care

Mode of Delivery

Most IBD patients can proceed with vaginal delivery unless there is a specific obstetric indication for cesarean delivery. If perianal disease (abscess, rectovaginal or anorectal fistula, anal fissure, or stenosis) is present or there was prior rectovaginal fistula, then cesarean delivery is recommended [92, 93]. When the estimated date of delivery (EDD) approaches, serial perineal inspections should be performed. Obtaining GBS cultures around 35 weeks of pregnancy presents an opportunity to check for active perianal disease [3].

In patients with IPAA, there may be a temporary alteration in the pouch during the third trimester. While only a few cases may experience long-term problems, in most women, the functional status of the pouch returns to prepregnancy levels after pregnancy is over. The mode of delivery does not affect the outcome of the pouch function [94]. The risk of injury to the anal sphincter is higher with vaginal delivery

compared to cesarean section [95]. The decision to perform cesarean versus vaginal delivery in these patients should be made in a multidisciplinary team approach with a shared decision-making process to allow the patient's desire to be an integral part of the process and consider the potential risk of injury to the sphincter. All patients who undergo cesarean delivery should be on both mechanical (early ambulation and sequential compression devices) and pharmacologic (low molecular weight heparin) VTE prophylaxis, while mechanical alone is appropriate in patients after vaginal delivery [96]. The postpartum period carries the highest risk of VTE in pregnant patients, and extended thromboprophylaxis should be considered up to 3–6 weeks after birth [97, 3].

Breastfeeding

Breastfeeding is generally recommended to all mothers, with few exceptions. Recommendations from the American Academy of Pediatrics should be followed, including exclusive breastfeeding for 6 months, which may be continued as complementary foods are added to the infant's diet [98]. Key exceptions on this list include women who are being treated with MTX, tofacitinib, rifaximin, and metronidazole with the former three options lacking robust pregnancy data and the latter being a potential mutagen with significant break milk concentration [45].

Along with standards for infant feeding, mothers should maintain optimal nutritional status by increasing daily caloric intake to 2300 to 2500 kilocalories (kcal) per day, which is 450 to 500 kcal above the average recommendation for nonpregnant women [99]. Breastfeeding mothers should eat a healthy, well-balanced diet. Omega-3 fatty acids, essential nutrients for infant development, should be supplemented by adding at least 200 mg per day because breast milk levels are dependent on maternal blood levels [100]. Nutritional consultation should be provided during this period for women who have an active flare or an ostomy to optimize nutritional status. Herbal galactagogue, particularly fenugreek, should be avoided in IBD patients due to the risk of bleeding and diarrhea [101]. Although many IBD medications can be detectable in breast milk, the overall safety profile is acceptable for most of them, given the low concentrations of less than 1% of maternal serum concentrations in breast milk. Specific considerations for lactation safety of commonly used IBD drugs according to the US National Library of Medicine LactMed database are detailed in Table 8.1.

Infant Monitoring

Although the lack of significant congenital malformations is reassuring, pediatricians should be informed about biologics in utero when applicable. Fetal Fc receptor actively uptakes maternal IgG across the placenta as early as week 13 [102]. This

uptake rapidly increases during the third trimester and until delivery. The most efficiently transported subclass of immunoglobulin is IgG1, including IFX, ADA, GOL, VDZ, and UST, followed by IgG4, which includes NTZ [103]. Due to this active transportation, the drug level of medications such as IFX and ADA increases up to fourfold in the infant at birth compared to maternal levels and remains detectable for up to a year [68, 104]. This placental transfer does not occur with CZP, as this medication lacks the Fc portion. Because of detectable levels up to a year, infants who are exposed to biologics in utero, except for CZP, should not receive live vaccines for a minimum of 9 months or after drug level becomes undetectable in the infant. There are no contraindications to other recommended non-live vaccines for the newborns.

Summary

The advent of new therapies has led to an exciting time in the management of women with IBD who wish to get pregnant and have a normal pregnancy course and a healthy baby. A favorable maternal-fetal outcome is achievable in most patients, but this can only be accomplished by addressing the misconceptions and misinformation among healthcare providers and patients. This goal can be reached by providing evidence-based data, emphasizing the importance of maintaining healthy nutrition, and having the disease in remission during preconception, conception, and postpartum phases. We hope this chapter offers guidance for healthcare providers to confidently formulate a successful standardized plan to achieve optimal pregnancy results using a multidisciplinary team-based approach.

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Chapter 9
Unique Challenges in the Diagnosis and Management of the Pediatric IBD Patient

Jeffrey A. Morganstern and Alexander Schosheim

Overview

While inflammatory bowel disease (IBD) occurs across all ages, pediatric IBD (PIBD) has its own unique characteristics including subtypes of disease and other challenges that come with a diagnosis at a young age. IBD is divided into Crohn's disease (CD), ulcerative colitis (UC), and inflammatory bowel disease unclassified (IBDU). In pediatrics, there is another entity known as very early-onset IBD (VEO-IBD). These disorders have distinct pathologic and clinical characteristics, but their pathogenesis remains poorly understood.

CD is typically characterized by transmural, granulomatous inflammation which can occur anywhere from the mouth to the anus, often discontinuously. UC on the other hand is limited to the colon and consists of superficial ulceration of the bowel mucosa. IBDU is typically in patients with colitis but without distinguishing features of either UC or CD [1]. While UC is more common in adults, CD is diagnosed more frequently in the pediatric years.

Most IBD can develop at any age, but those diagnosed in childhood tend to have a more complicated course than their adult counterparts as they have been noted to have more significant disease with extensive anatomic involvement and rapid progression soon after the time of diagnosis [2]. There have been significant advances in the understanding and management of PIBD, but it continues to be a disease that is treatable, not yet curable.

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R. Rajapakse (ed.), *Inflammatory Bowel Disease*, Clinical Gastroenterology,
https://doi.org/10.1007/978-3-030-81780-0_9

Clinical Manifestations

Patients with PIBD typically present in late childhood or early adolescence, but they may present at any time. The presentation of PIBD may be similar to that seen in adults, but they have some unique clinical manifestations as well.

Like adults, pediatric patients with a new diagnosis of IBD may have gastrointestinal symptoms, such as loose stool, bloody diarrhea, abdominal pain, or tenesmus, or systemic symptoms such as fever and fatigue. On physical exam these patients can have abdominal tenderness and/or mass, perianal disease, or occult blood in the stool. Other extraintestinal manifestations include arthritis, uveitis, aphthous stomatitis, clubbing, and rash (i.e., erythema nodosum or pyoderma gangrenosum).

Unique to pediatric patients, growth failure is a common presenting sign of IBD. Patients with IBD may have suboptimal gains in weight or height or may lose weight. The earliest and most subtle form of growth failure is a decrease in height velocity. Up to 50 percent of patients with CD have a decrease in height velocity before the onset of any other intestinal symptoms [3]. Delayed puberty can also be seen in the pediatric population. While growth failure is commonly seen, a considerable number of pediatric patients are also overweight when they present with IBD, as obesity is prevalent in many populations.

Differential Diagnosis

Since the concern for IBD can be due to various symptoms and signs, considerations in the differential diagnosis depend on the clinical features of the individual patient.

Rectal bleeding in pediatric patients with no additional signs or symptoms can be seen with anal fissures, hemorrhoids, polyps, Meckel's diverticulum, and milk protein proctocolitis (infants). If a patient has rectal bleed with other symptoms such as abdominal pain, the differential may include infectious colitis with enteric pathogens, intussusception, Henoch-Schonlein purpura (HSP), or familial Mediterranean fever (FMF).

If presenting with growth failure and diarrhea, celiac disease would be included in the differential. The differential diagnosis for diffuse or poorly located abdominal pain is extensive and can include functional abdominal pain disorders such as irritable bowel syndrome. Focal abdominal pain, specifically in the right lower quadrant, can be seen with appendicitis and very rarely tuberculosis or lymphoma [4]. In female patients, gynecologic disease must be considered as well with lower abdominal pain.

Diagnosis

Diagnosis of Crohn's disease, ulcerative colitis, and IBDU is based on clinical signs and symptoms, endoscopy, histology, and radiology. Any child with signs and

symptoms suspicious for IBD should undergo a complete diagnostic workup including infectious workup, upper endoscopy, colonoscopy with ileal intubation, and in most cases, small bowel imaging. Biopsies must be taken from all segments of the gastrointestinal tract that are needed for a complete evaluation.

In addition to the typical IBD workup, in patients under 6 years of age, diagnostic evaluation for primary immunodeficiencies is essential and includes family history and clinical features of infections, autoimmunity, or complications. Pathology should be reviewed to identify atypical features. In addition, dihydrorhodamine (DHR) test for CGD and flow cytometry to assess T/B-cell subsets and maturation should be obtained. Workup of natural killer cell function and use of an IL-10 suppression assay (identifies only IL-10 receptor defects) may be helpful. It is also noteworthy that in VEO-IBD, calprotectin may not be elevated [5].

While there are no specific consensus diagnostic criteria for IBD, there have been multiple classification schemes to differentiate the different subtypes of IBD. The Montreal classification of IBD was developed in 2005, but it had limitations with respect to PIBD. The dynamic nature of PIBD with changing disease location along with growth failure was not well encapsulated in the Montreal classification, so an international group of experts in PIBD created the Paris classification of PIBD which was published in 2011(see Fig. 9.1).

The Paris classification included important modifications such as classifying age at diagnosis (either 0 to <10 years (A1a) or 10 to <17 years (A1b)). It also included distinguishing the disease location and allowing patients with stenosing and penetrating CD to be classified in the same patient. Lastly, growth failure was added to the classification criteria. The Paris classification was designed to seamlessly transition into the Montreal framework for the adult population.

Later, the "Porto criteria" were developed as a consensus-based clinical guideline for the diagnosis of PIBD. They were created by an international group of experts in PIBD using the Paris classification as a major reference point [6]. More recently, that same group of experts from the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), in continuation with the Porto criteria, aimed to create and validate criteria called "PIBD-classes" to standardize the classification of the different IBD subtypes [7].

Growth Failure and Poor Weight Gain in IBD

Pathogenesis of Growth Failure

Normal pediatric growth begins with extremely rapid growth in infancy. From age 3 to puberty, growth is steady at about 6 cm/year. Attaining adult height depends on a pubertal growth spurt of up to 12 cm/year which occurs for boys at ages 10–15 and for girls at ages 8–13. Within 2 years after the growth spurt, growth plates close and no further growth is possible. Due to this limited timeframe for linear growth, it is important to intervene and treat pediatric IBD before growth failure becomes permanent adult short stature.

	Montreal	Paris
Age at Diagnosis	A1: <16 yo A2: 17-40 yo A3: >40 yo	A1a: 0-10 yo A1b: 10-17 yo
Location	L1: Terminal ileal +/- limited cecal L2: Colonic L3: Ileocolonic L4: Isolated upper disease	L1: Distal 1/3 ileum +/- limited cecal L2: Colonic L3: Ileocolonic L4a: Upper disease proximal to Ligament of Treitz L4b: Upper disease distal to Ligament of Treitz and proximal to distal 1/3 of ileum
Behavior	B1: Non-stricturing, non-penetrating B2: Stricturing B3: Penetrating P: Perianal	B1: Non-stricturing, non-penetrating B2: Stricturing B3: Penetrating B2B3: Penetrating and stricturing P: Perianal
Growth		G_0: No growth delay G_1: Growth delay

Fig. 9.1 Comparison of Montreal and Paris classifications [6]

Growth failure may be defined as a decrease in height velocity, decrease in height percentile (crossing growth curves or plateau), or simply failure to reach predicted adult height. Growth failure frequently occurs in IBD, more so in Crohn's disease than ulcerative colitis. It is typically the stunted type, meaning that patients are normal height for weight but low height for age. Alternatively, malnutrition can present as wasted, in which height is normal for age but the child is significantly underweight for height [8]. A mixed picture can also be seen. IBD-related growth failure often becomes more striking as the child's peers go through their growth spurts.

Given that growth impairment can occur prior to the onset of gastrointestinal symptoms and diagnosis is typically made up to a year after onset of symptoms, there can be considerable delay in treatment from the onset of growth failure.

Chronic malnutrition is a major cause of growth failure. Malnutrition in IBD may be due to a combination of reduced intake (to avoid symptoms), intestinal malabsorption, and increased energy expenditure due to chronic inflammatory state.

When Crohn's disease is diagnosed in the prepubertal years, up to 85% of patients can have growth failure. In ulcerative colitis, it is far less common (up to 10%) [9]. Why? The simple answer is that Crohn's disease causes inflammation at the absorptive site (small intestine) and resulting malabsorption, whereas UC is limited to the colon and therefore not associated with malabsorption. However, the explanation is more complex.

Growth hormone (GH), or somatotropin, is secreted by the pituitary gland in a pulsatile manner. It binds to GH receptor at end organs including the liver and bone. Insulin-like growth factor 1 (IGF-1) or somatomedin C is produced by the liver and bone in response to GH. IGF-1 is a direct mediator of growth, promoting it by stimulating cell growth and proliferation and inhibiting apoptosis [10]. Deficiencies of either GH or IGF-1 result in suboptimal growth.

Several studies have demonstrated normal urinary growth hormone levels in IBD patients [10]. Thus, growth hormone deficiency does not appear to play a major role in growth failure in IBD. However, it does play a significant role in corticosteroid-induced growth failure. In fact, pediatric patients who received growth hormone in addition to corticosteroids had improved rates of clinical remission compared to those who received corticosteroids alone. They also had improved height velocity and improved bone ages, suggesting that adult height potential would more likely be reached [11].

Crohn's disease and ulcerative colitis have different cytokine profiles. Crohn's disease is associated with higher levels of interleukin-6 (IL-6) and TNF-alpha which are produced by inflamed small bowel. These cytokines are known to play an important role in growth failure.

Interleukin-6 is a pro-inflammatory cytokine which is markedly elevated in conditions such as Crohn's disease and juvenile idiopathic arthritis. Transgenic mice engineered to overexpress IL-6 exhibit poor growth and low levels of IGF-1, despite food intake similar to their wild-type counterparts [12]. Treatment of these transgenic mice with a monoclonal antibody against IL-6 receptor restored normal growth.

In human children, a homozygous IL-6 promoter mutation has been associated with significantly lower height and higher CRP levels at the time of Crohn's disease diagnosis [13].

Although TNF-alpha is a major target for biologic therapy, there is less evidence for its direct involvement in growth failure. Rats with experimental colitis given anti-TNF medications did not increase their IGF-1 levels but did show improved growth. This suggests a non-IGF-1-mediated role of TNF-alpha in growth failure [14]. In a longer-term cohort study of pediatric Crohn's patients, treatment with infliximab over 32 months showed significant improvement in height Z-score [15].

Corticosteroids inhibit growth via several mechanisms. They inhibit growth hormone release as well as cause decreased pulsatility of GH release [10]. They also

inhibit production of GH receptor in the liver and thus IGF-1 production [10]. These effects can both be overcome by administration of exogenous GH.

Vitamin and Mineral Deficiencies

Children with IBD are at risk for developing nutritional deficiencies due to a combination of reduced intake, restrictive diets, malabsorption, nutrient loss, and medication side effects. A recent retrospective study examined the laboratory results from 359 children with IBD for prevalence of nutritional deficiencies at diagnosis and at follow-up [16]. Median follow-up time was 7 years. The most common deficiencies were in iron, zinc, vitamin D, and folic acid. Magnesium and vitamin B12 deficiencies were relatively rare. Their findings are summarized in the following table (Fig. 9.2):

Nutritional Assessment

In our practice we recommend every IBD patient to meet with a dietician on a regular basis. At that time a full nutritional assessment is done including height, weight, and body mass index. BMI Z-score is calculated and all measures are plotted on growth charts. A diet record is completed and analyzed for total energy intake, as well as protein, fat, and carbohydrate intake. This is consistent with recommendations from ESPGHAN which suggest twice a year diet records for younger children and once a year for adolescents [17]. Micronutrient levels are checked and supplemented as necessary.

While underweight is the most common presentation, up to 30% of IBD patients may present with obesity at the time of diagnosis [18]. Because delayed puberty can be a significant manifestation of IBD, ESPGHAN recommends that pubertal stage be assessed regularly from diagnosis until completion of puberty in children with

	Crohn's disease		Ulcerative colitis	
	Diagnosis	Followup	Diagnosis	Followup
Iron	88	39.5	77	40
Zinc	53	11.5	31	10
Vitamin D	39	36	49	33
Folic acid	10	13	3.8	9.7

Fig. 9.2 Comparison of Montreal and Paris classifications [16]

IBD 10 years and older [18]. Intervention in the early stages of delayed puberty is more effective than when treatment is delayed.

Although bone mineral loss is a significant concern in patients with IBD and especially those who have taken corticosteroids, there is insufficient evidence to support routine bone densitometry (DEXA) testing in pediatric IBD patients, other than those at high risk for osteoporosis [18].

Treatment

While there is a lot of overlap in the management and treatment of patients with the different subtypes of PIBD, there are some unique differences. In general, the treatment of IBD is in two phases: induction of remission and maintenance of remission. The treatment goals in PIBD are maintaining remission and avoiding complications, optimizing current treatments before switching, not persevering if current treatment is clearly not working, optimizing growth and pubertal development, returning to a normal lifestyle, promoting mucosal healing, and preventing intestinal damage. Induction of remission involves treatment with either a nutritional approach (i.e., EEN), corticosteroids, or an anti-TNF agent.

Medical

Selection of medical therapy for each patient must be tailored to their disease severity and location. For patients with mild disease limited to the terminal ileum and/or colon with no other complications, an initial approach may include the use of aminosalicylates, with or without antibiotics. If there is active ileitis, the choice of aminosalicylate should be a timed-release or pH-sensitive release form of mesalamine. For moderate or severe disease, patients may use glucocorticoids or anti-TNFs. For patients with complicated CD (extensive small bowel disease, severe ulcerating colonic disease, growth failure during puberty, severe perianal disease, or steroid-unresponsive disease), induction with an anti-TNF is preferred rather than induction therapy with glucocorticoids followed by an immunomodulator as these patients have an increased risk of poor disease outcome [18].

Maintenance of remission begins with immunosuppression. This may be accomplished in the form of thiopurines, methotrexate, or biologics. Methotrexate may be chosen as first-line treatment in the presence of coexisting juvenile inflammatory arthritis (JIA) or severe arthralgia, but biologic therapy (predominantly anti-TNF agents) is being used more commonly and earlier in the disease course for children who do not respond to initial induction treatment and/or where maintenance immunosuppression fails or when the duration of time to effectiveness appears too lengthy to achieve important short-term treatment goals. Aminosalicylates and antibiotics can be a mainstay of treatment in mild cases, but when dealing with moderate to

severe disease, they are used in selected cases only usually as adjuncts to other therapies rather than stand-alone therapeutic options.

Most medical treatments, although initially studied in one disease, have been shown to be efficacious in both CD and UC. One exception is aminosalicylates, which have much stronger data to support their use in UC than in CD.

The recognition of intestinal dysbiosis in UC has led to interest in the use of fecal microbial transplantation (FMT) as a treatment for UC. Theoretically, healthy donor feces should "normalize" the patient's fecal microbial composition to induce and support intestinal homeostasis. FMT has become more commonplace in the treatment of refractory *Clostridium difficile* infection. In a single-center pilot study, 10 children (7–21 years) with mild to moderate UC received FMT from healthy donors by fecal retention enema daily for 5 days [19]. Seven of nine subjects showed clinical response by Pediatric Ulcerative Colitis Activity Index (PUCAI) score within 1 week. Six of nine maintained the improvement at 1 month. A more recent study aimed to assess the effectiveness of a 2-week FMT course in children with IBD (eight with UC and two with CD) [19]. Ten patients, 10–17 years of age with moderate to severe IBD (all with pancolitis), received a course of eight doses of FMT via a nasoduodenal tube or gastroscopy. PUCAI and PCDAI were recorded in addition to C-reactive protein (CRP) and fecal calprotectin on the day before the first FMT and then on the day before the next course. Clinical response was noted in 9/10 patients (seven UC and two CD). Clinical remission (PCDAI and PUCAI <10) was noted in 3/8 UC patients and 2/2 CD patients.

Nutritional

Nutritional approaches to IBD are becoming more commonplace, specifically in PIBD as growth, weight gain, and nutrition while avoiding the side effects of corticosteroids are essential in the pediatric population.

To induce remission, exclusive enteral nutrition (EEN) is the most common choice for active Crohn's disease in much of the world, but it is less popular in North America [20]. In 2014, the European Crohn's and Colitis Organization (ECCO) released consensus guidelines that recommended EEN as the first-line treatment for inducing remission in patients with luminal CD [21]. Interestingly, while treatment with EEN is effective in achieving remission in children, the results have not been as favorable in adults [22].

Multiple pediatric studies give strong support to the role of EEN in Crohn's disease including two previous meta-analyses and a systematic review with remission/response rates of 70–80% in most published studies [23–25]. EEN, while having efficacy similar to corticosteroids, provides better growth and mucosal healing.

Enteral nutrition has also been explored for maintenance therapy. Enteral feeding is often used as an adjunctive therapy for maintenance of remission in CD, particularly in Japan. In a 2006 randomized control trial, subjects were provided half of the nutrition requirements by an elemental formula with the remaining 50% of the

nutrition requirements met by consuming an unrestricted diet. The relapse rates in the half elemental diet group were significantly lower (34.6% vs. 64.0%) than the control group [26]. The primary limiting factor to the success of EEN is patient adherence, with noncompliance having reported as 5–20% in various studies [27].

With the difficult nature of EEN in the pediatric population, other diets have been explored as well including a low-residue diet, semi-vegetarian diet, the Mediterranean diet, and FODMAPs diet. Of the diets that have been investigated, few have shown promise beyond EEN. Some that have shown promise include the specific carbohydrate diet (SCD), the inflammatory bowel disease-anti-inflammatory diet (IBD-AID), and the Crohn's disease exclusion diet (CDED) (Figs. 9.3 and 9.4).

	EEN	SCD	IBD-AID	CDED
Induction	Y	N	N	N
Maintenance	N	Y	Y	Y
Clinical Improvement	Y	Y	Y (limited data)	Y (limited data)
Mucosal Healing	Y	N	N	N

Fig. 9.3 Comparison of dietary treatments in PIBD

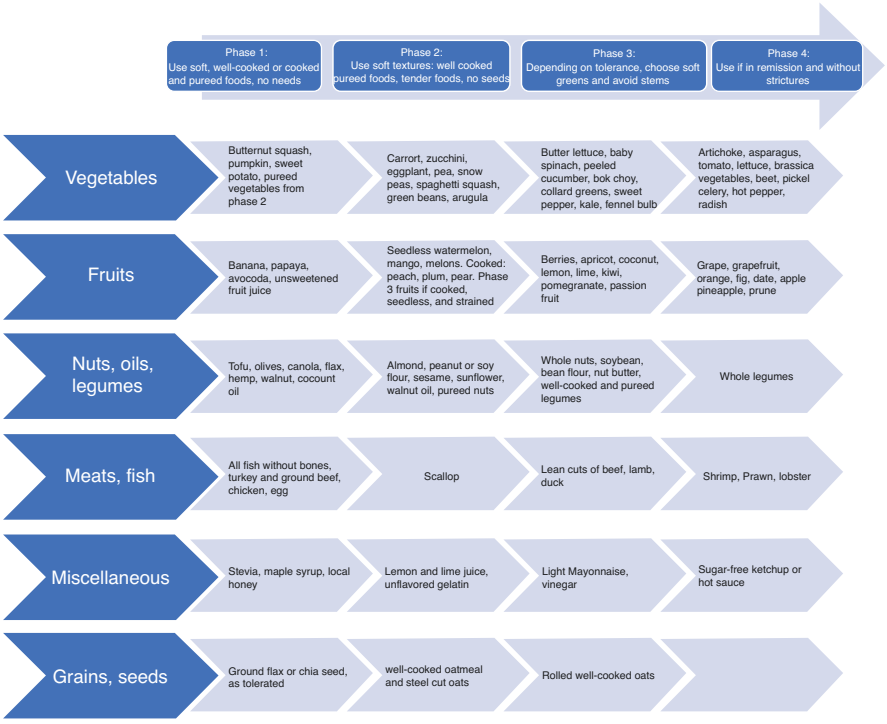

Fig. 9.4 Phases of IBD-AID [32]

The SCD was originally introduced as a way to manage celiac disease, but in the early 1990s, the diet became better known for its use in IBD patients. The diet claims to restore bacterial balance in the bowel leading to decreased intestinal inflammation. The diet limits carbohydrates to monosaccharides found in fruits, nuts, honey, and fully fermented yogurt and excludes disaccharides (sucrose, maltose, isomaltose, and lactose) and most polysaccharides. Also excluded are all grains and starches, including wheat, barley, corn, rice, yams, and potatoes. In addition, highly processed foods with emulsifiers and preservatives are excluded [29]. Unfortunately, there is a lack of evidence-based published data on the SCD, with only retrospective surveys and case reports/series at this time [28, 30, 31]. Although SCD shows promise in improving clinical symptoms in pediatric IBD patients, lack of serologic and histologic improvement of disease indicates more studies are needed.

The development of the IBD-AID is similar in concept to the SCD in that it is based on the theory that dysbiosis is caused by certain carbohydrates acting as substrates to pathogenic bacteria in the lumen of the gut [32]. The IBD-AID restricts intake of lactose and refined and processed complex carbohydrates and includes the ingestion of pre- and probiotic foods. It also modifies dietary fatty acid intake. The diet is in four phases (Fig. 9.4) [33]. A retrospective case series using IBD-AID found that among subjects who attempted the diet ($n = 27$), 100% reported reduced symptoms and were able to come off of at least one of their prior medications [34]. Similar to SCD, evidence is based primarily on symptoms with no data from biomarkers of inflammation or histologic changes on biopsy, so future studies are needed.

The CDED involves elimination of processed foods, including gluten, dairy products, gluten-free baked goods and breads, soy products, and processed foods including foods with emulsifiers (Fig. 9.5). It was created as an option for partial enteral nutrition (PEN) as the most significant issue with EEN is compliance. A 12-week prospective trial of children with mild to moderate CD was performed in Israel in which pediatric patients were randomly assigned to a group that received CDED plus 50% of calories from formula for 6 weeks (stage 1) followed by CDED with 25% PEN from weeks 7 to 12 (stage 2) ($n = 40$, group 1) or a group that received EEN for 6 weeks followed by a free diet with 25% PEN from weeks 7 to 12 ($n = 38$, group 2). At week 6, 30 (75%) of 40 children given CDED plus PEN were in corticosteroid-free remission vs. 20 (59%) of 34 children given EEN ($P = 0.38$). At week 12, 28 (75.6%) of 37 children given CDED plus PEN were in corticosteroid-free remission compared with 14 (45.1%) of 31 children given EEN and then PEN ($P = 0.01$; odds ratio for remission in children given CDED and PEN, 3.77; CI 1.34–10.59). In children given CDED plus PEN, corticosteroid-free remission was associated with sustained reductions in inflammation (based on serum level of C-reactive protein and fecal level of calprotectin) [34].

Overall, UC is less amenable to nutritional interventions as compared with CD. Elimination diets rarely result in significant improvement in symptoms in UC patients, and as growth failure is far more common and problematic in CD as opposed to UC, the nutritional therapy of growth failure becomes more essential for CD over UC.

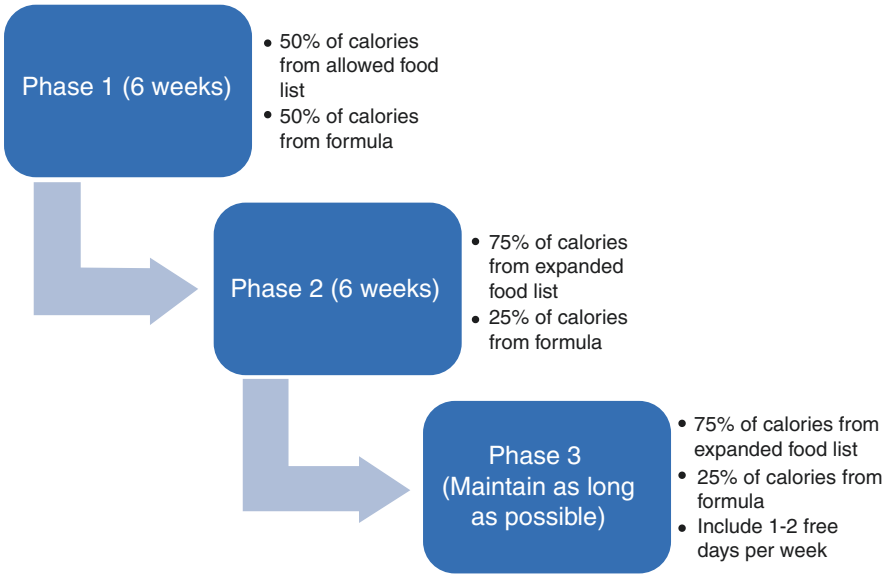

Fig. 9.5 Phases of CDED [34]

Surgical

Surgery in CD is predominantly for patients who do not respond to medications or for those who develop complications (abscess, fistula, perforation, hemorrhage, obstruction, or stricture) that can only be treated surgically.

A postoperative review in pediatric patients with CD revealed that an estimated 3.4–7.9% will undergo surgery within 1 year of diagnosis, 13.8–47.2% by 5 years, and 28–34.5% by 10 years, [35] so while CD treatment is primarily medical, many patients will require surgery at some point. The highest risk factors for initial surgery include patients with stricturing and penetrating disease, anti-*Saccharomyces cerevisiae* antibody (ASCA) positivity, hypoalbuminemia, leukocytosis at diagnosis, and poor growth [36]. In addition to rapid improvement in an ill patient, in pediatric patients, catchup of growth and puberty is a major benefit [37].

When managed medically, approximately 5–20% of children with ulcerative colitis undergo colectomy within 1 year of diagnosis with outcomes only partially predicted by disease severity at baseline [38]. Colectomy may be indicated for various reasons. In an emergent situation, it is indicated for patients with acute severe colitis with uncontrolled hemorrhage or complications such as a perforation or toxic megacolon. Those who fail to respond to aggressive medical management within 2 weeks or after failure of a second-line therapy may also be a candidate for urgent surgery. Patients who are unresponsive to or cannot be weaned from glucocorticoids, who experience unwanted side effects, or who have surveillance biopsies that suggest a risk for developing cancer may electively undergo colectomy. In addition,

some patients proactively elect to have colectomy [39]. While colectomy should be essentially curative in UC, CD may still be diagnosed at a later time. In 5–25% of patients, CD is later diagnosed, in which case, surgery is not curative [40].

Health Maintenance Issues

Immunizations

In 2013, the Infectious Diseases Society of America published a "Clinical Practice Guideline for Vaccination of the Immunocompromised Host." [41] They recommended vaccination of children with IBD following the same schedule as healthy children. However, live attenuated vaccines should be avoided during immunosuppressive therapy, in the 4–6 weeks preceding the start of treatment, and up to 3 months following discontinuation of treatment. This can be problematic when a child requires immunosuppressive therapy soon after diagnosis which is often the case. For this reason, it is recommended to check vaccine titers at the time of diagnosis and to take advantage of any time period allowing catchup in vaccinations before immunosuppressive therapy begins. Fortunately, most pediatric patients have already completed their live vaccines (measles, mumps, rubella, varicella) at the time of diagnosis. However, it is not uncommon in our practice to find patients with suboptimal vaccine titers despite adhering to the recommended vaccine schedule. Despite good reasons to check titers early, a survey of pediatric gastroenterologists has demonstrated that only about half of them ascertain their patients' immunization status at the time of diagnosis [42].

Non-replicating vaccinations can and should be given regardless of immunosuppressive therapy. This includes the annual influenza vaccine. Both non-replicating and live attenuated vaccines may be given to household contacts.

While non-replicating vaccines are permitted during immunosuppressive therapy, their ability to generate an immune response has been shown to be diminished, especially in those taking anti-TNF therapy. A prospective study of 100 pediatric IBD patients on infliximab found that only 56% of those previously vaccinated had actual immunity to hepatitis B [43]. Of those that were not immune, 76% did develop immunity after receiving a booster dose, bringing the total immunity to 86% of previously immunized patients. Further research is warranted to determine the utility of vaccine booster doses in immunosuppressed patients such as those being treated for IBD.

Psychological Support

Psychosocial well-being and mental health are important components to overall health, particularly in children with a chronic disease. In fact, addressing psychosocial needs can improve health outcomes such as treatment adherence and quality of

life [44]. Older children and adolescents are particularly vulnerable to psychosocial adjustment problems, as they are going through a time of emotional, cognitive, and social transition [45]. In adolescents, self-identity is in flux, and teens have a harder time incorporating their chronic disease into their self-image compared to their younger counterparts [45].

Despite the importance of addressing psychosocial well-being, the evidence shows that we as providers are coming up short. A large cross-sectional anonymous survey of pediatric IBD patients at a single children's hospital aimed to determine whether gaps in overall care were present, as well as any deficiencies in addressing particular aspects of care including psychological care [45]. Of note, more than 40% of those surveyed reported that their child had not discussed family relationships, peer relationships, academic performance, extracurricular activities, or mood with a medical provider in the previous year (including both gastroenterologists and primary care providers). Among adolescents, >60% reported that no one had discussed body image with them. More than 40% had not discussed family or peer relationships, sex and sexuality, or drug and alcohol use. The authors speculate that these deficiencies may be due to several reasons, including lack of "ownership" of each aspect of care by either the PCP or subspecialist, as well as inadequate communication between PCP and subspecialist. A lack of resources and time to address these topics at the visit is also likely a contributor (Fig. 9.6).

In addition to the normal changes that adolescents undergo, psychopathology is also a significant concern for which patients should be screened. Depression is common among teens, and studies have shown higher rates of depression among adolescents with IBD than the general population and higher than in youth with other chronic diseases such as diabetes and tension headaches [46]. In addition, the IBD patients had more behavioral problems and were less likely to communicate with a parent, tending to internalize their problems. Simple tools to quickly screen for suicidal ideation and depression are now available such as the Patient Health

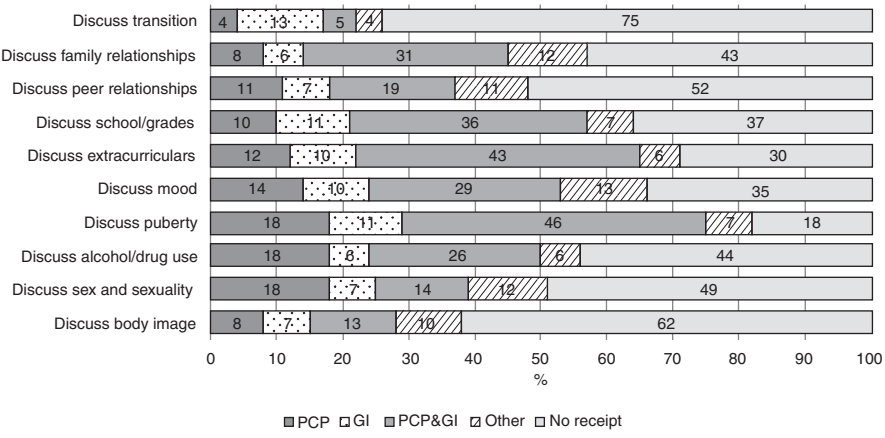

Fig. 9.6 Services received last 12 months per adolescent report (total $n = 84$) [44]. (Permission to reprint obtained)

Questionnaire (PHQ-9) [47]. The PHQ-9 has been shown to correlate highly to more sophisticated tools. A recent study utilized this questionnaire and determined that 15% of patients with IBD, diabetes, or cystic fibrosis tested positive. Perhaps equally important, the survey took only 3 minutes to administer, making it easily adaptable into any clinician's office routine [48]. Other studies have found rates of depression as high as 25% among adolescents with IBD and an association between depression and relapses of IBD [49, 50]. It is plausible that pro-inflammatory cytokines could have a direct effect on mood [45].

Anxiety has also been associated with IBD, but the evidence is not as strong as the connection with depression. Depression with visceral hyperalgesia is also common even when IBD is inactive [51]. Rectal sensory threshold for pain (RSTP) has been shown to be decreased in children even with quiescent IBD compared to healthy controls [52]. Sleep disturbance is commonly seen in our practice and has been shown to be present in up to 65% of children and adolescents with IBD [53].

School functioning comprises academic performance, attendance, educational attainment, and psychosocial functioning [45]. There is some evidence that individuals with IBD have higher rates of school absence; one study estimated the mean lifetime school absence to be 13 weeks, significantly higher than the study's comparison group [54]. However, those with IBD do not differ from healthy individuals in terms of percentage of classes failed or in final educational level attained [55].

Transitioning to Adult Care

Transition to an adult provider is an inevitable occurrence for any pediatric patient with a chronic disease. However, there are many questions surrounding it. At what age should transition occur? Over how long a period of time? What should the involvement of the parents be? What are the roles of the two providers involved? How should the adolescent/young adult demonstrate readiness to make the final transition?

In 1972, the American Academy of Pediatrics Section on Child Health redefined pediatric care to include birth through age 21 years [56]. This set the standard for years to come for general pediatricians as well as subspecialists including adolescent medicine physicians. In our practice we make the final transition at age 22–23 when the patient is typically finishing college and/or settling in one geographic location. This helps avoid changing providers more than once.

Despite the importance of the transition process, one study found that 75% of adolescents and 76% of parents surveyed reported that no medical provider had discussed the transition process with them [46]. Another study found that less than half of adolescents report time alone with their clinicians, an important step toward becoming an adult patient [57].

While age is an important factor, readiness to transition depends on general maturity and ability to take on self-care. It also requires specific skills and

knowledge such as how to make appointments with one's provider, understanding one's medications and their purposes. Questionnaires have been created to assess readiness to transition. One of them which is widely used across disciplines is the Transition Readiness Assessment Questionnaire (TRAQ) [58]. It gauges comfort levels in five broad categories: managing medications, appointment keeping, tracking health issues, talking with providers, and managing daily activities. Each category includes several questions, and each question is given a score from 1 to 5.

Transition clinics are a multidisciplinary approach to facilitating adolescents' transition into adult-oriented care. They typically involve meeting with a pediatric gastroenterologist, adult gastroenterologist, nurse, and mental health professional all in the same setting. IBD-yourself is another questionnaire designed to assess self-efficacy specifically for IBD patients attending transition clinics [59]. In addition to assessing general transition readiness, it assesses knowledge related to IBD and diagnostic tests.

An IBD transition clinic in Tel Aviv, Israel, invites all IBD patients to attend 3–4 sessions, starting at age 17 [60]. Patients meet with a pediatric and adult gastroenterologist, IBD nurse, and a psychologist. A 3-year study of all patients enrolled in their transition clinic was completed, with administration of the IBD-yourself questionnaire before and after transition. The authors report that self-efficacy scores were significantly higher in all domains after completing the transition. Studies like these do support the utility of transition clinics; however they present many difficulties including coordinating the schedules of all involved (including the patient) and the inability of multiple providers to bill for the same visit.

In lieu of a transition clinic, many practices have taken the approach of having the patient establish care with the adult gastroenterologist and then returning to the pediatric gastroenterologist one last time to discuss the proposed plan with a familiar face.

Very Early-Onset Inflammatory Bowel Disease (VEO-IBD)

Overview

VEO-IBD is defined as IBD that occurs in children before the age of 6, while infantile IBD is a subset of VEO-IBD that develops in children less than 2 years of age [61]. Approximately 6–15% of the pediatric IBD population presents at <6 years of age [62]. This group of patients is more likely to have monogenic defects that alter immune function or disturb epithelial barrier function. Although this typically leads to a more severe and refractory disease course, these genetic findings have led to effective targeted therapies [63]. While IBD in young children has always been uncommon, this patient demographic is now experiencing the greatest rise in incidence [64].

Clinical Features

Patients with VEO-IBD have more severe disease with more years of disease burden whether or not they have a monogenic variant of IBD. They have higher rates of surgical interventions, extraintestinal manifestations, and failure of TNF inhibitors. Compared with older IBD patients, VEO-IBD most commonly presents as colonic disease with 40% of VEO-IBD patients having pancolitis at presentation [65]. Although patients may present with colonic disease, the extent and location of disease can change and advance, making it difficult to differentiate UC from CD. In addition to the young presentation, other features that raise suspicion of monogenic IBD include family history of IBD and/or immunodeficiencies in multiple family members; recurrent infections or fevers; associated features of autoimmunity; very severe presentation and/or resistance to conventional therapies; symptoms or signs of hemophagocytic lymphohistiocytosis (HLH) (hepatomegaly, fever, cytopenias, high ferritin); lesions of the skin, nails, or hair; or history of cancer in the patient [63].

Genetics

New genetic discoveries are continuously occurring, but monogenic defects have been detected in only approximately 15–20%, of patients with VEO-IBD [5]. Many of the defects have been specifically identified in the youngest patients with infantile IBD. As of March 2020, more than 50 implicated genes have been discovered, of which, many involve primary immunodeficiency genes [63]. When a genetic etiology is clinically suspected, every effort to detect these defects must be made, as the finding may radically affect therapy. Whole exome sequencing (WES) and targeted genetic panels are key factors in the diagnostic approach and, in combination with the clinical history, can be powerful tools to identify monogenic disease. Currently, there are multiple panels that are publicly available including through EGL Genetics, the Children's Hospital of Philadelphia, Invitae, and the Mayo Clinic.

Genetic defects that have been identified in VEO-IBD are associated with intestinal epithelial barrier function, phagocyte bacterial killing, hyper- or autoimmune inflammatory pathways, and development and function of the adaptive immune system [63].

A break in the intestinal barrier can lead to chronic intestinal inflammation [66].

Loss-of-function mutations in *ADAM17* resulting in ADAM17 deficiency, *IKBKG* resulting in X-linked ectodermal dysplasia and immunodeficiency, *COL7A1* resulting in dystrophic epidermolysis bullosa, *FERMT1* resulting in Kindler syndrome, and TTC7A resulting in multiple intestinal atresias as well as severe combined immunodeficiency syndrome (SCID) all result in neonatal inflammatory skin and bowel lesions. Familial diarrhea may occur with gain-of-function mutations in *GUCY2*. Other gain-of-function mutations include *EGFR* which leads to skin

lesions and IBD and *TGFBR1* and *2*, which are associated with Loeys-Dietz syndrome and connective tissue disorders in addition to IBD [63].

Several genetic variants can alter the development or function of adaptive immune cells in a cell intrinsic or extrinsic manner. 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 or T-cell receptor. 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 including agammaglobulinemia, X-linked agammaglobulinemia (XLA), common variable immune deficiency (CVID), and IgA deficiency [67, 68]. Wiskott-Aldrich syndrome results from a loss-of-function mutation in the Wiskott-Aldrich syndrome protein (*WASP*) and includes clinical manifestations of thrombocytopenia, eczema, immune deficiencies, and intestinal inflammation. In VEO-IBD patients with this genetic defect, they typically have pancolitis in addition to other autoimmune processes [69].

Defects in regulatory T cells can clinically present as colonic disease as well as an enteropathy. Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome is most often secondary to mutations of the forkhead box protein 3 (*FOXP3*) gene. These patients frequently present with neonatal severe secretory diarrhea, failure to thrive, infection, skin rash, insulin-dependent diabetes, thyroiditis, cytopenias, and other autoimmune disorders [63]. Some other genetic defects that have been found to cause IPEX-like disease include loss-of-function mutations impacting IL-2/IL-2R interactions, STAT5b (signal transducer and activator of transcription 5b), and ITCH (itchy E3 ubiquitin protein ligase) or gain-of-function mutations in STAT1 [70]. A novel loss-of-function mutation in CTLA4 (cytotoxic T lymphocyte-associated protein 4), a surface molecule of regulatory T cells that directly suppresses effector T-cell populations, was also identified in VEO-IBD [71].

Homozygous loss-of-function mutations in *IL10* ligand and receptors *IL10RA* and *IL10RB* are associated with significant intestinal inflammation, particularly in infantile VEO-IBD, and were the first genes to be identified as causative for VEO-IBD [72]. Since IL-10 is an anti-inflammatory cytokine that maintains homeostasis through suppression of an excessive pro-inflammatory response, in addition to intestinal inflammation, IL-10 defects are associated with arthritis, folliculitis, and a predisposition to lymphoma as well [73].

There are several genetic variants that influence bacterial recognition and clearance. Mutations in any part of the complex molecules (CYBB, CYBA, NCF1, NCF2, NCF4) can result in loss of superoxide production and CGD which can present as intestinal inflammation as well as autoimmune disease. Some other genes including *ITGB2*, leukocyte adhesion deficiency type 1 (LAD1), *SLC35C1* (LAD2), and *RAC2* (ras-related C3 botulinum toxin substrate 2) (RAC 2 deficiency) are involved in bacterial recognition and clearance but also are related to defects in motility [63].

Several hyper- and autoimmune diseases have been linked with intestinal inflammation in children with VEO-IBD. While each disease has a different mechanism and phenotype, mevalonate kinase deficiency (hyper IgD) (loss-of-function

mutations in an enzyme critical for metabolism), familial Mediterranean fever (FMF) (loss-of-function of cytoskeletal proteins), Hermansky-Pudlak syndrome (loss-of-function of proteins involved in organelle fusion or biogenesis), and X-linked lymphoproliferative syndrome (loss-of-function of proteins involved in cell signaling or apoptosis) all have intestinal inflammation. These patients are of great concern as they are prone to fatal HLH in the setting of infection, most typically EBV, and they typically present with severe colonic and perianal fistulizing disease [74].

Treatment

The treatment of VEO-IBD with time has become a more personalized precision medicine approach. With the higher rate of monogenic defects, it makes VEO-IBD ideal for individualized treatment. Currently, the treatment for VEO-IBD patients is dependent on an individual patient's history and diagnostic evaluation. When one of the identified defective pathways is identified, it may require treatments not typically used for IBD in older children and/or adults. In cases in which there are no genetic or immunologic defects identified, therapy is often in line with that of older IBD patients.

While genetic testing is a major part of the workup in VEO-IBD, many patients remain without an identified genetic defect [63]. Some children may have a mild disease course and respond to minimal therapy, but often, patients with VEO-IBD will have an inadequate response to conventional therapies and may require extraordinary approaches to treatment including aggressive dosing and completely alternative treatment approaches.

In certain circumstances, detection of a disease-causing genetic variant may allow for the appropriate therapy to be chosen. In VEO-IBD patients with a defect in IL-10 and IL-10 receptor (IL-10R), use of allogeneic hematopoietic stem cell transplantation (HSCT) for induction of remission has been shown to be lifesaving [73]. HSCT has also been proven to be curative in IPEX, WAS, and *XIAP* deficiency. Some T-cell and T-regulatory cell defects, B-cell defects, and combined defects have also been successfully treated with HSCT including FOXP3 deficiency, IL2RB defects, DOCK8 immunodeficiency, RAG1 and RAG2 defects, STAT1, PIK3CD, and SCID [63].

Some targeted gene therapies have been used for maintenance or as a bridge to HSCT. These therapies are used as maintenance therapy and, in some cases, as a bridge to HSCT. Abatacept, a *CTLA4* agonist, can be used in patients with CTLA4 or LRBA defects by inhibiting the hyperactive T-cell signaling [75]. Rapamycin has also been successful in these patients. As a bridge, these medications have been used for patients with defects in *FOXP3* and *PIK3CD* mutations [63]. Not only is identification of genetic defects important for treatment but also to avoid therapy that is potentially harmful. In CGD, because of further immunosuppression risks,

anti-TNFα therapy is contraindicated with association with adverse outcomes and risk of mortality [76].

Immunomodulatory therapy can be used as monotherapy in some patients with VEO-IBD or in conjunction with a biologic therapy, although azathioprine/6-mercaptopurine (AZA/6-MP) has been utilized less with the link to hepatosplenic T-cell lymphoma (HSTC). When used as therapy in patients with VEO-IBD, higher thiopurine dosing is often required to obtain therapeutic levels. If thiopurines are used for treatment, close monitoring of thiopurine metabolites is important especially as pediatric patients grow and change the formulation of the medication from suspension to pill form [63].

While biologic medications have become a mainstay overall in IBD, patients with VEO-IBD tend to have a less robust response to biologic medications. A review of 33 children with VEO-IBD showed maintenance of infliximab (IFX) therapy at 1, 2, and 3 years of 36%, 18%, and 12%, respectively, which is far below the levels of infliximab therapy maintenance seen in the older patients [77, 78]. More aggressive dosing regimens including starting infliximab at 10 mg/kg, more frequent infusions, and proactive drug monitoring may improve long-term durability of the treatment [63].

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Chapter 10
Colon Cancer Screening and Surveillance in the IBD Patient

Osama Siddique, Haleh Vaziri, and Joseph C. Anderson

Epidemiology and Risk Factors

Common Considerations for Ulcerative Colitis (UC) and Crohn's Disease (CD)

The association between inflammation (colitis) and cancer was first described in 1863. Since then, the link between cancer and inflammation has been strengthened by a large number of studies examining this association. The risk of colorectal cancer (CRC) in patients with IBD is higher than that for those without the disease [1]. Many risk factors have been identified including a family history of CRC, gender, age, and extent of inflammation among others.

A registry-based follow-up of familial CRC and IBD was done on nearly 20,000 patients to assess for risk of CRC. A family history of CRC was associated with a more than twofold increase in CRC, with the risk of a CRC diagnosis increasing up

The contents of this work do not represent the views of the Department of Veterans Affairs or the United States Government

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R. Rajapakse (ed.), *Inflammatory Bowel Disease*, Clinical Gastroenterology,
https://doi.org/10.1007/978-3-030-81780-0_10

to 29% in patients with first-degree relatives diagnosed with CRC before the age of 50 [2]. In an average risk population, men have a 40% higher risk of sporadic CRC as compared to women [3]. This increased risk is also observed in the IBD population, as demonstrated in a large population-based cohort study which found the risk of CRC was 60% (RR, 1.6) higher in men compared to women [4].

Patients with IBD are more likely to be diagnosed with CRC at an earlier age as compared to the general population. In a population-based study from Hungary, the average age of diagnosis of CRC in IBD was 51 years, which was almost 15 years younger than the average sporadic CRC [5]. This may in part be due to the presence of long-standing inflammation, which may increase the risk of CRC in patients with IBD [6, 7].

In the age of integrative medicine, it is important to consider the role of diet and physical activity on increasing risk of CRC in the IBD population. For example, it has been shown that reduced activity in patients with severe IBD may increase CRC risk. One study on participants who were enrolled in a 12-week exercise regimen showed reduced levels of trimethylamine N-oxide (TMAO) with higher physical activity levels [8]. TMAO, whose precursor molecule is produced by gut bacteria, has recently been linked with carcinogenesis [9]. The same study also reported lower TMAO levels in patients on a hypocaloric diet. This emphasizes the effect diet may have on the risk of CRC. A murine study investigated the effect of dietary fat on microbiota [10]. Mice were fed with a diet of which 37% of its energy was from fat, similar to the western diet. Mice fed with milk fat showed higher production of sulfite-reducing bacterium called *Bilophila wadsworthia*. In a genetically susceptible mouse model which lacked interleukin-10, an anti-inflammatory signaling molecule, the presence of *B. wadsworthia* promoted colitis. The possibility that chronic inflammatory changes in part induced by diet in a genetically susceptible IBD patient may promote carcinogenesis can be a focus for future research.

Epidemiology and Risk Factors for Colorectal Cancer in Crohn's Disease

Over the past two decades, the incidence of CRC in patients with CD has been declining. Possible explanations include more aggressive disease management with the advent of newer therapies, stronger surveillance strategies, better colonoscopic equipment, and dye technology utilization. This declining trend in the incidence of CRC has been observed in the US population. The annual standardized incident rate of CRC in the CD population versus the general population was 87.9 vs 43.9 per 100,000 person-years in 1998 and has dropped to 73.9 vs 53.1 per 100,000 person-years in 2010 [11].

The absolute risk of CRC in patients with Crohn's disease (CD) has been a subject of debate over the past few years. The wide variation in the relative risk from 2.5 to 5.6 is likely due to differences in the extent of inflammation in the colon [12, 13]. The lower rate of reported CRC in CD is probably related to the fact that

patients with limited colonic disease or isolated small bowel involvement were included. A meta-analysis has subsequently reported that the involvement of any extent of colonic mucosa inferred a higher risk of CRC in comparison to ileocecal disease and isolated ileal disease. The relative CRC risk in the latter group was reported as low as 1.1 (95% CI, 0.8–1.5) which was not statistically significantly greater than the general population ($p = 0.7$) [13]. Thus, colonic involvement of Crohn's disease is a major factor in predicting CRC risk.

In contrast to ulcerative colitis (UC), smoking is an independent risk factor for more severe CD [14]. While current smokers have a complicated phenotype with more severe perianal disease, they are less likely to have colonic disease [14]. There are currently no studies assessing the risk of CRC in smokers with CD. Patients with Crohn's disease have a higher likelihood of early colonic intervention in the form of colonoscopic stricture dilation and surgical intervention, which may reduce the CRC risk through incidental detection of precancerous lesions, but more data are needed to clarify this hypothesis [15].

Epidemiology and Risk Factors for Colorectal Cancer in Ulcerative Colitis

The overall incidence of CRC in UC is around 1.6% [16]. Varying incidence of CRC in UC has been reported which may, in part, be due to different patient characteristics including disease extent and duration. While there is a higher risk of CRC in UC patients with extensive and pancolitis compared to the general population, some data suggest that this risk may not be higher in patients with limited disease [16]. One study has observed that patients with proctosigmoiditis and proctitis may have minimal or no increased risk of CRC [17].

While proctocolectomy eliminates the risk of CRC, patients who have undergone ileal pouch-anal anastomosis (IPAA) may have an increased risk of pouch dysplasia and cancer [18]. Unfortunately, there is no universally accepted recommendation regarding pouch surveillance. High-risk features that have been identified include having the colectomy done for the presence of CRC, concurrent diagnosis of PSC, family history of colon cancer, and severe pouchitis with ileal villous atrophy [19].

In addition to the disease extent, the severity of disease on endoscopic and histological involvement in long-standing UC has also shown to be significantly correlated with the risk of CRC [20]. The presence of pseudopolyps resulting from severe inflammation and regeneration of tissue reduces the capability of the endoscopist to adequately discern between a premalignant and malignant lesion. A case-control study highlighted the odds of diagnosis of CRC in UC with pseudopolyps to be as high as twofold in comparison to the controls [21]. Even after adjusting for surveillance colonoscopies and anti-inflammatory therapy, pseudopolyps remained a significant risk for CRC.

Although PSC has been linked to both UC and CD, it is more common in patients with the former. Around 2% of patients with IBD have PSC, while 80% of patients with PSC have IBD [22]. It is well recognized that patients with IBD-PSC have a higher risk of CRC as well as cholangiocarcinoma. Recent studies have found the risk of CRC to be as high as fivefold as compared to those UC patients without PSC [22, 23]. These data suggest that a more rigorous surveillance protocol should be followed in these patients.

Carcinogenesis in IBD

Role of Inflammation

Carcinogenesis in IBD seems to be multifactorial, with colonic inflammation playing a major role in increasing the risk. A retrospective study which assessed more than 10,000 biopsies from patients undergoing surveillance colonoscopies showed that patients with more severe histologically (not endoscopic) active inflammation had higher rates of CRC [24]. Suppressor of cytokine signaling 1 (SOCS1) blocks excessive signaling from inflammatory cytokines such as interferons and interleukins and has been shown to possess strong antitumor properties. Suppressors of SOSC1 have been shown to be amplified in CRC [25].

Genetic Alteration

Neoplastic progression in IBD has been linked to genetic abnormalities including an early loss in heterozygosity of p53 (Fig. 10.1). This loss in heterozygosity is correlated with progression of dysplasia in UC, with loss of at least 33% of p53 allele in low-grade dysplasia, 63% in high-grade dysplasia, and 85% in carcinoma [26].

Based on the whole-exome sequencing analysis, the most common mutation in IBD-associated CRC was in*TP53* gene, which codes for the tumor suppressor P53 [25]. Mutations in other unique genes such as *SOX9* and *EP300*, which drive the WNT/β-catenin pathway, have been reported in IBD population [25]. *APC* is a rare and late mutation in IBD-associated CRC in comparison to sporadic CRC, where it is an early mutation. Thus, the presence of the WNT/β-catenin pathway activation without precursor *APC* mutation in CRC is likely contributing to the higher risk of colon cancer [27].

Defective hypermethylated MMR genes, which manifest as microsatellite instability (MSI), are present in 12–15% of sporadic CRCs [28]. The hypermethylation of a promoter region called hMLH1 within the MMR gene is specifically and strongly associated with sporadic CRC through the serrated pathway. Though not unique to the sporadic CRC, the hypermethylated hMLH1 segment is also found in

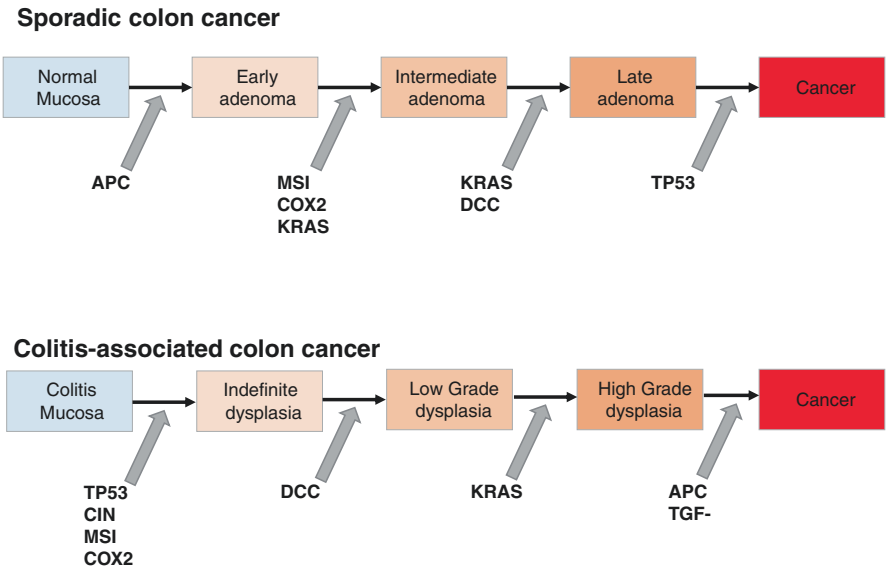

Fig. 10.1 Molecular pathogenesis of sporadic and colitis-associated cancer

colitis-associated CRC. In a study which used methylation-specific PCR, methylated hMLH1 was identified in 46% of the high-frequency MSI in IBD-associated cancers [29].

Mice with a defect in *MSH2* mismatch repair gene, which do not develop sporadic CRC with microsatellite instability (MSI), were studied for frequency and grade of dysplasia and CRC when exposed to external triggers of inflammation. Twenty-eight of the 30 mice induced with inflammation developed dysplasia or cancer with MSI [30]. Thus, mismatch repair defects play a major role in IBD-related CRC.

Free Radical and Immune-Mediated

Nitric oxide synthase (NOS2), a free radical enzyme, facilitates the deamination of 5-methylcytosine for induction of G:C and A:T transitions at the CpG sites in the p53 tumor suppressor gene. Higher (NOS2) activity has been positively linked with the deamination of the p53 gene in colon cancer [31]. Higher NOS2 activity was also observed in patients with UC compared to controls ($p = 0.02$) [32].

Complex immunological interactions between innate and adaptive immunity play an important role in immune regulation, primarily through cytokine production driving the inflammatory response. Th17 cells which are a subset of T-helper cells have been recognized as pro-inflammatory cells when mediating mucosal immune response [33]. Blocking the Th17 activation in mice has shown reduced inflammation and subsequent colon cancer [34].

Mouse models have shown interleukin-6 (IL-6) induces signal transducers and activators of transcription (STAT3) and may promote progression of intestinal epithelial cells toward cancer. Biopsy specimens from patients with UC, UC with high-grade dysplasia (HGD), UC with CRC, and sporadic CRC were included in a study. Researchers concluded that patients with active UC, high-grade dysplasia, and UC with CRC had significantly higher IL-6 and STAT3-positive epithelial cells than the control [35].

Tumor necrosis factor-α (TNF-α) has also been shown to have increased expression in mice treated with dysplastic agents. TNF-α binds to p55 receptor (TNF-Rp55) which promotes angiogenesis and tumor growth. Mice deficient in TNF-Rp55 have reduced risk of having mucosal inflammation and colonic tumor formation [36].

Microbiome

In addition to the role of genetic and immune-mediated factors in IBD carcinogenesis, there is a new interest in how an individual's microbiome may alter inflammatory cascades, contributing to barrier dysfunction, development of colitis, dysplasia, and cancer.

Compared to healthy controls, *Fusobacterium*, *Enterococcus faecalis*, *and Enterobacteriaceae* family are significantly higher in the stool samples of patients with IBD [37, 38]. Tumors from mice exposed to *Fusobacterium nucleatum* show a pro-inflammatory microenvironment which is similar to the *fusobacteria-positive* CRC in humans [39]. *E. faecalis* has also shown to be pro-inflammatory in a study of germ-free, IL-10-deficient mice. These mice were exposed to multiple pure bacterial cultures, yet only the mice exposed to *E. faecalis* developed not only IBD but also rectal dysplasia and cancer [40].

Butyrate-producing bacteria and bifidobacterium are lower in patients with active IBD compared to patients in remission [41]. Sources of metabolic stress including medications, infections, and mucosal inflammation decrease the transepithelial resistance in IBD patients which results in increased translocation of bacteria and inflammation. Butyrate-producing bacteria can significantly reduce transepithelial permeability and packaged as prebiotics could serve as valuable prophylaxis against IBD relapse [42]. More studies are needed but it appears that the microbiome plays a role in IBD-related CRC.

Surveillance and Intervals

Goals and Considerations of Surveillance

Current American and European guidelines recommend initiation of colonoscopic screening 8 years after diagnosis of CD colitis involving more than one-third of the colon and UC involving more than the rectum [43, 44]. The goal of initiating

screening and surveillance protocol is to detect dysplasia as early as possible to prevent progression into CRC. The intervals between surveillance colonoscopies should be based on previous colonoscopies and histology, extent of inflammation, PSC, and FH of colon cancer in first-degree relatives.

A delay of even a few years from the initial recommended exam has been associated with an increased risk for CRC [45]. In addition to earlier detection of cancer, patients, who undergo colonoscopy within 6 to 36 months of the diagnosis of CRC, have a lower mortality rate (14% vs 34% [$p = 0.012$]). Recent colonoscopy has been associated with a reduced all-cause mortality even after adjusting for comorbidities, age, and gender (OR, 0.34) [45].

IBD patients are at higher risk for having interval CRC (iCRC), and they are therefore recommended to have frequent colonoscopic evaluations. In a study by Burke et al., compared to non-IBD patients, IBD patients experienced a shorter interval between index colonoscopy and CRC diagnosis (20.7 v 35.1 months) [46]. Rutter et al. reported that 50% of the CRCs diagnosed in UC population over a period of 30 years were iCRC [47]. A multicenter retrospective analysis from the Netherlands showed an incidence of 30% for iCRC in both UC and CD population after adjusting for possible contributing factors such as inadequate bowel preparation, inadequate surveillance intervals, and management of dysplasia [48].

Endoscopic and Histological Considerations Dictating Intervals of Surveillance

Endo-histological progression of CRC in IBD follows an inflammation-dysplasia-cancer sequence with nonlinear progression between indefinite dysplasia (IND), low-grade dysplasia (LGD), and high-grade dysplasia (HGD) (Fig. 10.2) [49]. While most dysplastic lesions were previously considered invisible, newer techniques and better image resolution on colonoscopies have shown that most of these lesions may be macroscopically visible [50].

A true invisible or flat lesion may contribute to a higher iCRC [51]. In comparison, visible and polypoid lesions which are amenable to endoscopic resection have a low CRC incidence rate of 0.5% annually, which supports the current recommendation for resection and surveillance strategy for these lesions [52].

There is significant interobserver variability among pathologists in grading dysplasia in IBD patients, especially when reporting IND and LGD [53]. The interobserver variability which can contribute to reporting lower dysplasia level may partly be responsible for the high rate of progression from IND to advanced neoplasia [54, 55]. Progression to advance neoplasia was reported at 1.5 cases per 100 person-years in patients with IND compared to 0.7 in control [54]. These limitations in adequately discerning different grades of dysplasia and its concerning progression to CRC have led to recommendation of a second expert gastrointestinal pathologist to review these slides [44].

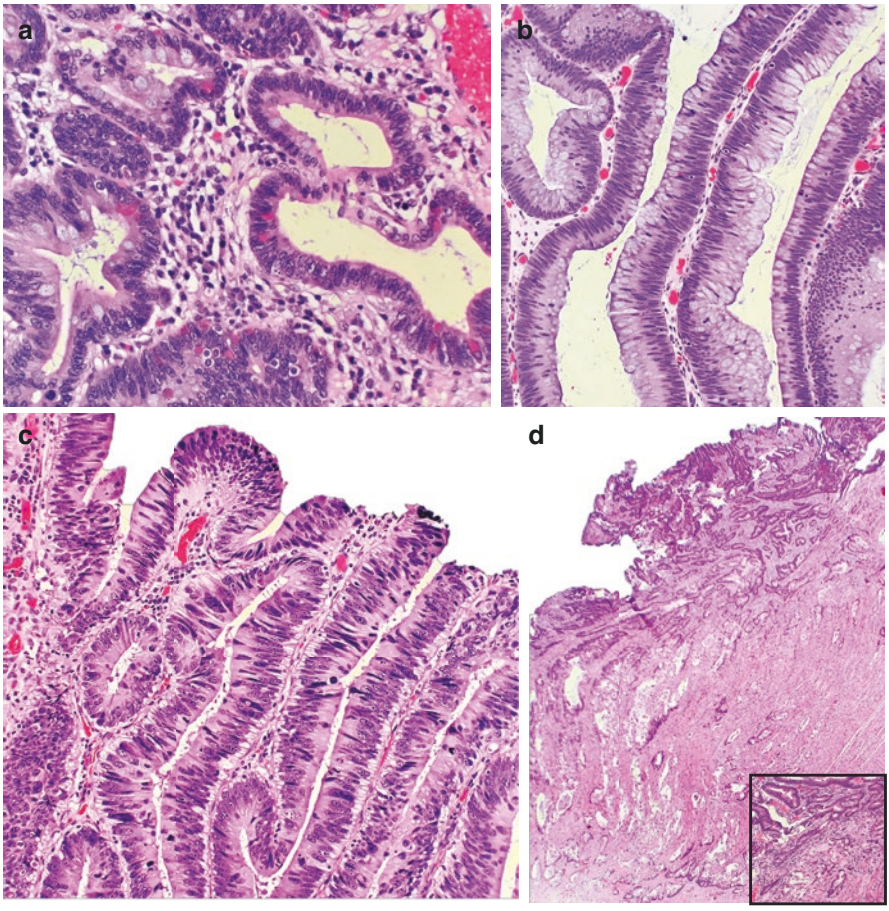

Fig. 10.2 (**a**): Indefinite dysplasia: focus of atypical nuclei in a patient with Crohn's colitis (x400). (**b**) Low-grade dysplasia: stratified nuclei with polarization to the basement membrane (x200). (**c**) High-grade dysplasia: high nuclear to cytoplasmic ratio, loss of polarity of nuclei (x200). (**d**) Invasive carcinoma (x20) inset x200

A study found that 10% of IBD-related CRCs were low-grade tubuloglandular adenocarcinoma which arises directly from LGD [56]. Identification of patients with LGD at higher risk of progression may be beneficial to prevent CRC. The presence of aneuploidy in a flat LGD may identify patients at high risk of progression into HGD and CRC (HR, 5.3) [57]. Thus, patients with LGD and aneuploidy may require more intensive management than those without this finding.

Contrary to the above data, a study by Marion et al. followed 44 dysplastic lesions in 24 patients for an average of 27.8 months and observed no dysplasia-associated adverse effects such as surgery or CRC [58]. While a close follow-up at an IBD center may have contributed to lower cancer risk, the use of newer technologies including high-definition (HD) colonoscopy and chromoendoscopy (CE) may

have highlighted mucosa with dysplasia that could have been missed in older studies, leading to artificially reported high progression rate from dysplasia to CRC. In addition to confirming the diagnosis of invisible dysplasia by a second GI pathologist who is experienced in IBD, patients should be referred to IBD specialists with expertise in chromoendoscopy for identification and removal of the dysplastic lesion. There are no current comparison trials on surveillance vs colectomy for non-polypoid dysplastic lesions; thus current American consensus continues to emphasize of close follow-up [59].

Method of Surveillance

Dysplasia can be visible or invisible, focal or multifocal. Newer colonoscopic imaging techniques including utilization of HD imaging, CE, and narrowband imaging (NBI) may improve the yield of surveillance.

The quality of endoscopic imaging depends upon resolution and magnification. Resolution is the ability to distinguish two approximated points and is a function of pixel density. A higher pixel density of an image improves the ability to discriminate detail [60]. Older standard definition (SD) imaging on average had around 367,000 pixels compared to up to 1.25 million pixels in the newer generation colonoscopes [60]. In a recent meta-analysis, the adenoma detection rate of HD vs SD was 40% vs 30% (RR 1.13; 95% CI, 1.05–1.22; $P = 0.001$) [61]. HD exams in IBD patients increase the detection of dysplastic lesions from targeted biopsies in comparison to the exams with SD scopes [62].

While the American Gastroenterology Association (AGA) and European Crohn's and Colitis Organization (ECCO) suggest the use of at least 32 random biopsies throughout the colon if CE is not available [44, 49, 63], this recommendation is based on old pre-high-definition endoscopy literatures and may not be relevant to current practice due to the advent of newer endoscopic imaging techniques [59]. This approach of obtaining random biopsies is undermined by recent literature which shows that recommended number of random biopsies only sample 1% of the colonic mucosa and has a subpar detection rate for dysplasia of less than 2 per 1000 biopsies taken [64]. In a randomized controlled trial, targeted biopsies were non-inferior to random biopsies, while being more cost-effective and less time-consuming [65].

CE can be used to further enhance dysplasia detection rate in IBD. CE utilizes indigo carmine or methylene blue to help differentiate normal and pathological mucosa [66]. Methylene blue is absorbed by normal epithelial cells, while dysplastic cells remain unstained providing the contrast needed to delineate dysplastic lesions (Fig. 10.3). Indigo carmine, on the other hand, stains mucosal structure by pooling in the mucosal grooves and pits which may be challenging to rectify since washing will remove the dye. Although this may lead to uneven staining, some endoscopists prefer the use of indigo carmine due to its non-absorbing nature. In a prospective study of IBD patients on surveillance protocol, each colonic segment

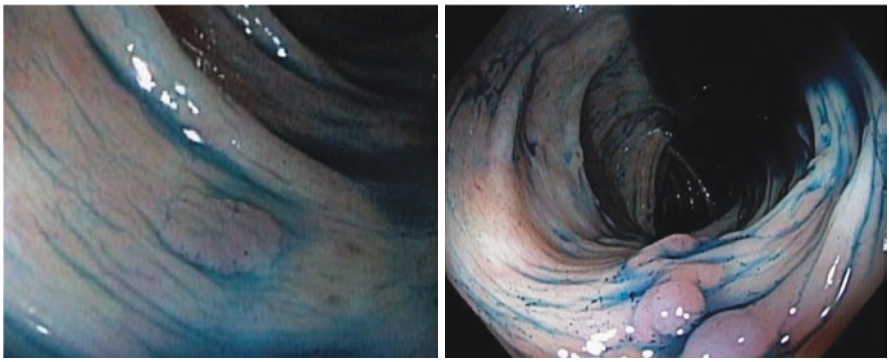

Fig. 10.3 Flat lesions highlighted by chromoendoscopy

was initially surveyed with white light endoscopy (WLE) followed by CE and had an incremental dysplasia yield of 54% in patients surveyed with CE [67]. When colonoscopies were performed with SD (41.5%) and HD (58.5%), use of CE lead to a comparable incremental increase in dysplasia detection between SD and HD colonoscopes [67]. CE with targeted biopsies is also more cost-effective than WLE with random biopsies [68]. Though the average duration of colonoscopy increases by 9 minutes, a meta-analysis revealed a greater proportion of patients with dysplasia were identified by CE compared to SD-WLE [59, 69]. While targeted biopsies resulted in better dysplasia detection compared to random biopsies, the exam utilizing CE trended toward a higher yield (*p*, 0.057) [69].

Data on the superiority of HD imaging in combination with CE (HD-CE) versus HD-WLE for detection of dysplasia is inconclusive. In a prospective study by Alexandersson and colleagues, a higher number of lesions with dysplasia were detected in patients with HD-CE with random biopsies versus HD-WLE with random biopsies (*p*, 032) [70]. In contrast in a randomized controlled trial, there was no significant difference in dysplasia detection rate between HD-CE-targeted biopsies versus HD-WLE random biopsies (3.9% vs 5.6%; *p*, 0.749) [71]. In contrast to the national guidelines, the above data may support the use of HD-CE with random biopsies but not targeted biopsies.

Optical image filtering or virtual chromoendoscopy (NBI, FICE, i-scan) are interesting alternatives to the current modalities. NBI can filter out red and green light bands providing more blue light bands at 415 nm wavelength. Just like NBI, FICE and i-scan are fully reversible and available with just a click of a button on the scope. These techniques may also be less time-consuming compared to dye spray CE. There are discrepant findings regarding the utility of NBI in CRC prevention in IBD patients. One randomized trial showed no difference in detection of dysplasia between NBI and conventional HD imaging [72]. Conversely, another study demonstrated a higher percentage of missed lesions compared to dye spray CE [73]. Yet, NBI has been suggested as an acceptable method in UC surveillance when using HD colonoscopies [43]. Even though a couple of recent meta-analyses observed no

difference in dysplasia detection between dye spray and virtual CE, robust data are still lacking, and virtual CE is still not recommended [59, 74, 75].

Based on the above data, the 2015 US national consensus statement recommended that endoscopists perform a high-definition colonoscopic exam, while using chromoendoscopy for surveillance of dysplasia [59]. Though the national consensus statement does not comment on use of targeted versus random biopsies while using CE, the European guidelines recommend CE in general and with targeted biopsies where expertise is available [44]. In certain cases such as concomitant PSC, personal history of neoplasia, and tubular colon, random biopsies are still beneficial regardless of the method of surveillance [76].

Intervals

Recommended intervals between surveillance exams vary between different GI societies (Table 10.1). However, the timing of the first screening which is 8 years after the initial diagnosis of IBD remains as a consensus recommendation. There is also a consensus of performing annual surveillance exams for patients with PSC [19, 43, 44, 49, 59].

AGA published their recommendations a decade ago with surveillance colonoscopies every 1 to 2 years [49]. This interval can be increased to every 1 to 3 years in patients who had two negative exams. AGA also endorsed a more rigorous surveillance protocol in patients with a family history of CRC and personal anatomical abnormalities such as stricturing disease [49]. BSG, on the other hand, recommended 5-year surveillance plans for patients with no endoscopic evidence of colitis and to proceed with 3-year surveillance in patients with mild colitis, family history of CRC at age ≥50 years, and post-inflammatory polyps. They did recommend a more rigorous yearly colonoscopy for moderate to severe biopsy-proven colitis and personal history of stricturing disease [19].

AGA updated its position in a consensus statement with the American Society of Gastrointestinal Endoscopy (ASGE) in 2015 [59]. The SCENIC consensus statement recommends a 3- or more year follow-up surveillance of low-risk individuals without any colitis on at least two or more surveillance endoscopies. The statement did emphasize an annual colonoscopic exam in patients with pseudopolyps, strictures, or first-degree family history of CRC.

The ECCO presented their consensus guidelines in 2017 recommending a 2–3 year surveillance interval in patients with extensive mild to moderate active colitis or family history of CRC at age ≥50 years. For patients who are at high risk with severe active inflammation, personal history of strictures, or a family history of first-degree relative with CRC age ≤ 50 years, annual surveillance was recommended. All other patients can follow surveillance intervals of every 5 years [44].

The American College of Gastroenterology (ACG) published guidelines on the management of Crohn's in 2018 and UC in 2019. The guidelines on Crohn's disease

Table 10.1 Colorectal surveillance recommendations by different societies

Society	Beginning of surveillance interval	Surveillance schedule	Surveillance method
AGA (2010)	1. Patients with UC proctosigmoiditis to be screened as per age-specific guidelines 2. Patients with less than a 1/3 involvement of colon in CD should undergo age-specific screening as per guidelines 3. Patients with PSC to start screening at time of diagnosis 4. UC patients screening to begin 8–10 years after diagnosis 5. CD patients screening to beginning 8–10 years after diagnosis	1. PSC patients should undergo yearly surveillance 2. UC patients should undergo surveillance every 1–2 years 3. CD patients should undergo surveillance every 1–2 years	Random biopsies CE was endorsed as well
ECCO (2017)	1. 8 years after IBD symptoms 2. UC disease limited to rectum should undergo age-specific screening per guidelines 3. Start screening at time of PSC diagnosis	1. Low risk: 5 years. 2. Intermediate risk: 3 years 3. High risk: 1 year	HD-CE with targeted biopsies. Alternatively, random biopsies every 10 cms
ACG – Crohn's (2018)	1. 8 years after diagnosis of Crohn's disease involving ≥30% of colon 2. Crohn's limited to ileum should undergo age-specific screening per guidelines		HD-WLE, patients with history of dysplasia or PSC can undergo CE
ACG – UC (2019)	1. 8 years after diagnosis of IBD 2. UC disease limited to rectum should undergo age-specific screening per guidelines 3. Start screening at time of PSC diagnosis	Every 1 to 3 years, based on previous colonoscopies and risk factors	When using SD utilize CE When using HD can use WLE with NBI or CE
BSG (2019)	1. 8 years after IBD symptoms 2. Start screening at time of PSC diagnosis	1. Low risk: 5 years 2. Intermediate risk: 3 years 3. High risk: 1 years	HD-CE. Targeted biopsies are recommended

Society recommendation on screening and surveillance for CRC in IBD

CRC colorectal cancer, *IBD* inflammatory bowel disease, *AGA* American Gastroenterology Association, *UC* ulcerative colitis, *CD* Crohn's disease, *BSG* British Society of Gastroenterology, *ECCO* European Crohn's and Colitis Organization, *ACG* American College of Gastroenterology, *HD* high definition, *SD* standard definition, *CE* chromoendoscopy

ECCO low risk, no endo-histological inflammation; intermediate risk, mild/moderate activity on endoscopic or histological examination, presence of pseudopolyps, family history of first-degree relative with CRC ≥50 years; high risk, severe activity on endoscopy or histology, PSC, family history of CRC ≤ 50 years of age, or stricture/dysplasia in the last 5 years

BSG low risk, no endo-histological inflammation and Crohn's disease with ≤50% of colon involved; intermediate risk, mild activity on endoscopic or histological examination, presence of pseudopolyps, family history of first-degree relative with CRC ≥50 years; high risk, moderate/severe activity on endoscopy or histology, PSC, family history of CRC ≤ 50 years of age, or stricture/dysplasia in the last 5 years

did not clarify surveillance intervals but did recommend screening of patients with involvement of >30% of the colon after 8 years of initial diagnosis [77]. ACG guidelines on UC recommended a 1- to 3-year interval in patients with UC of any extent beyond the rectum. Stricter surveillance protocols should be considered in high-risk patients, such as those with a family history of CRC, personal history of stricture, and extensive inflammation [43].

Future Trends in Surveillance

Compliance with the 1- to 3-year surveillance recommendation of high-risk patients in clinical settings remains suboptimal. A study found that only 25% of eligible patients underwent at least one surveillance colonoscopy in a 2-year period, even among high-risk individuals [78]. Thus, especially in light of high rates of interval CRC in IBD, there remains a need for an accurate, patient-centric surveillance test in patients with IBD. To address this issue, a group from Mayo Clinic used stool samples to detect specific loci methylation to target IBD patients at risk for HGD and CRC. Methylation levels at specific promoter regions of these genes identified CRC and HGD with 92% sensitivity (95% CI, 60%–100%) and 90% specificity (95% CI, 86%–93%) [79].

Another potential future screening tool is confocal laser endomicroscopy (CLE), which is a catheter-based microscope, passed through the colonoscope. Using a low-powered laser through the microscope, the physician can obtain high-magnification images of the mucosal layer of the GI tract, potentially diagnosing abnormal histology during the procedure in targeted high-yield biopsies. CLE is able to distinguish neoplastic and nonneoplastic tissue with very high accuracy and is comparable to conventional colonoscopic histopathology [80]. The effectiveness of CE, which at this time is the most recommended method of surveillance, in combination with CLE showed 4.75-fold more neoplasias detected ($P = 0.005$) compared to conventional colonoscopy, and 50% fewer biopsy specimens ($P = 0.008$) were required [81].

Though not currently being studied specifically for IBD-related CRC, artificial intelligence (AI) systems are allowing for real-time computer-aided detection (CADe) of polyps. CADe uses an artificial intelligence device, which in real time processes images and superimposes green boxes on high-risk lesions. A recent multicenter randomized trial using CADe showed a significantly higher adenoma detection rate (ADR) (RR, 1.30; 95% [CI], 1.14–1.45) and a higher diminutive adenoma detection rate compared to conventional colonoscopy (RR, 1.26; 95% CI, 1.01–1.52) [82]. Neural network-based AI was recently studied in a meta-analysis and observed to have a higher ADR compared to conventional colonoscopy (32.9% vs 20.8%; RR, 1.58; 95% CI 1.39–1.80; $P = <0.001$) [83]. Utilizing this technology for flat, invisible lesions in IBD patients may have its benefits, though its applicability in the IBD population is yet to be investigated.

Chemoprevention

There has been some interest in preventing CRC in IBD using the medications we currently use to treat colitis. Studies on 5-aminosalicylic acid resulted in mixed results. In the non-referral population, the pooled adjusted odds ratio of CRC risk with use of 5-ASA was 0.95 (95% (CI), 0.66–1.38). The clinic-based studies' meta-analysis yielded a pooled OR of 0.58 (95% CI, 0.45–0.75) [84]. With overall underwhelming data on its protective role, mesalamine usage for chemoprevention is not currently indicated.

Thiopurines have also been studied, albeit retrospectively, for any protective effect against CRC. A retrospective chart review study of 315 patients who underwent surveillance colonoscopy with an average follow-up of 8 years did not show a protective effect of thiopurine use in the prevention of CRC [85]. A couple of follow-up meta-analyses have yielded mixed results with Jess and colleagues showing no overall protective role of thiopurines (OR = 0.87; 95% CI, 0.71–1.06), while the study by Gong et al. showing significant protective effects (RR = 0.71; 95% CI, 0.54–0.94) [86, 87]. Thiopurines may have some benefit in reducing inflammation and consequently may have some protective role in the prevention of CRC.

There is a lack of data on the role of biologic therapies for chemoprevention. There was initial concern regarding anti-TNF therapy promoting malignancy, but multiple studies, including a national database study out of the Netherlands and data from the TREAT registry, showed no signals indicating an increased risk of malignancy including CRC [88, 89]. One can postulate that reduction in colonic inflammation with these effective therapies may play a role in prevention of dysplasia and progression to CRC, though prospective studies need to be performed to assess this hypothesis.

Conclusion

IBD-related CRC is a multimodal disease, and its screening and surveillance require a multidisciplinary effort. Healthcare providers should familiarize themselves with the ever-changing risk factors and guidelines for surveillance of these high-risk populations. Complex yet swift progression of dysplasia to malignancy in a visible or invisible lesion should be on every gastroenterologist's radar when following these patients through the initial screening or subsequent surveillance exams. With the advent of new technologies, different methods of screening and surveillance, close follow-up, and earlier referral to IBD specialists, the high CRC risk in IBD patients will hopefully decrease.

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Chapter 11
The Utility of Endoscopy in Inflammatory Bowel Disease

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Introduction

This chapter will review the endoscopic diagnosis and treatment of inflammatory bowel disease. We will discuss screening guidelines, typical endoscopic findings in IBD, and postoperative endoscopic evaluation guidelines in IBD. Additionally, we will discuss clinical uses of alternative imaging technologies like capsule endoscopy, endoscopic retrograde cholangiopancreatography (ERCP) in primary sclerosing cholangitis (PSC), confocal laser endomicroscopy (CLE), and balloon enteroscopy in IBD. Finally, we will discuss therapeutic applications of endoscopy in IBD.

Screening Guidelines

The aim of endoscopic screening in inflammatory bowel diseases is the early detection of colorectal cancer. The hazard ratios for colorectal carcinoma in patients with IBD versus those without IBD ranged between 1.24 and 1.36 [1, 2]. The remission

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R. Rajapakse (ed.), *Inflammatory Bowel Disease*, Clinical Gastroenterology,
https://doi.org/10.1007/978-3-030-81780-0_11

phase is usually seen as an optimal time to get screened. The first screening colonoscopy should be offered 8 years after a diagnosis of Crohn's disease or ulcerative colitis. Differences among various recommendations of scientific societies do exist and are covered more extensively in another chapter. Although authors recommend endoscopic follow-up after screening in all IBD patients, specific intervals are to be decided with patient risk in mind. Patients with low risk include ulcerative proctitis and Crohn's disease with involvement of less than 1/3 of the colon. High-risk patients are those with primary sclerosing cholangitis (PSC), extensive colonic involvement, moderate-severe active inflammation sustained over time, first-degree relative with colorectal carcinoma at age less than 50, stenosis, or dysplasia detected during the previous 5 years. Colonoscopies for CRC screening must be performed annually after ileal-anal pouch construction in a patient with high-risk factors (dysplasia or previous colorectal carcinoma). Many authors suggest using the Paris classification when dealing with dysplastic lesions and confirmation by a second pathologist on occurrence of dysplasia [3]. Narrowband imaging uses filters that only allow certain wavelengths of light to pass through it. This helps highlight the mucosal and vascular architecture. A study done by Goran et al. compared the rates of dysplastic lesion detection between narrowband imaging and white light endoscopy. The study found that although there was no significant difference between targeted and random biopsies, the cost of targeted biopsies was lower. A lower withdrawal time was also cited as an advantage of using narrowband imaging. There was no improvement in the recognition of dysplasia when using narrowband imaging (compared to white light endoscopy). Although narrowband imaging with targeted biopsies resulted in a higher rate of dysplasia detection compared to white light endoscopy, the difference was not statistically significant. Narrowband imaging could offer the advantage of needing fewer biopsies to diagnose neoplastic lesions. Narrowband imaging was also found to detect more adenoma-like lesions. The author believes that combining narrowband imaging and white light endoscopy leads to improved rates of dysplasia detection and recommends this combination to target biopsies in all IBD patients [4]. Chromoendoscopy uses indigo carmine dyes or methylene blue staining to potentially delineate pathologic foci of interest. The concept of targeted biopsies (highlighted by chromoendoscopy) to detect carcinoma seems enticing. Some studies have shown chromoendoscopy to be superior to random biopsies in detecting colorectal carcinomas. It is also very useful in IBD-primary sclerosing cholangitis subtype where the risk of colorectal carcinoma is very high [5].

Typical Endoscopic Findings

Typical endoscopic findings often give rise to scoring systems. These scoring systems help grade severity of the disease and provide a means to communicate endoscopic findings between observers in a uniform manner.

Crohn's Disease

Visualized Findings

Endoscopic findings in conjunction with histology help distinguish Crohn's disease from other inflammatory colonic entities like ulcerative colitis, infectious colitis, and ischemia. Some endoscopic findings that favor Crohn's disease are the presence of aphthous ulcers, cobblestoning, noncontinuous involvement/skip lesions, fistulae, strictures, and ileal involvement [6, 7]. Upper GI findings are similar to lower GI findings [6, 7]. Some areas of particular interest are the rectum and anus (see Fig. 11.1).

Rectal and anal Findings

Rectal sparing is seen in 40% of patients with Crohn's colitis on endoscopy [8]. The rectum should be examined initially by digital rectal exam to feel/look for strictures or internal fistulas [9]. Anal findings in Crohn's disease include skin tags, perianal fistulae, fissures, abscesses, stenosis, hemorrhoids, etc. Skin tags and hemorrhoids may be operated upon if needed and abscesses drained if required. Abscesses may lead to fistula formation. The Parks classification sorts fistulas into superficial, intersphincteric, trans-sphincteric, extra-sphincteric, and supra-sphincteric [10]. The American Gastroenterological Association (AGA) classifies fistulas into simple

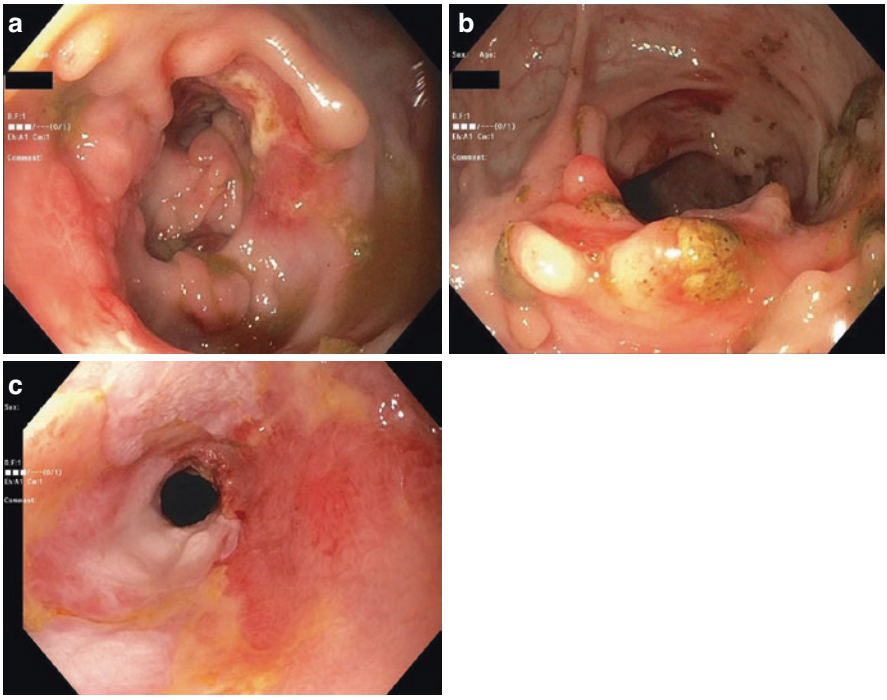

Fig. 11.1 (**a**, **b**) Colonic lesions in Crohn's disease. (**c**) Colonic stricture

(low, single, external opening, no abscesses, no strictures, and absence of rectovaginal fistulas) and complex (high, involving a significant part of the external anal sphincter, multiple external openings, pain, evidence of abscesses, presence of rectovaginal fistulas, and active rectal luminal disease) [10, 11]. Fistulas can be further diagnosed with EUA (examination under anesthesia), endoscopic ultrasound (EUS), or magnetic resonance imaging (MRI). A combination of these tests improves diagnostic precision [10].

Scoring Systems

In order to be more objective and possibly guide therapy, Crohn's disease activity scoring systems have been developed. Three commonly used systems are the Montreal classification, Crohn's Disease Endoscopic Index of Severity (CDEIS), and the Simple Endoscopic Score for Crohn's Disease (SES-CD).

Montreal Classification

The Montreal classification for Crohn's disease considers the age at diagnosis, location of disease activity, and behavior of the disease to demonstrate different disease states [12] (see Table 11.1). The Montreal classification can also help in guiding therapy. A retrospective cohort study by Grass et al. assessed the risk for ileocecal resection at 6 months and 1 year in patients with terminal ileal Crohn's disease. The authors sought to develop an objective algorithm for providers to definitively choose between surgery and escalation in medical management. The study used CT/MR enterography to detect terminal ileal inflammation and associated features of perienteric inflammation, presence of strictures, stricture length, upstream bowel dilatation, and other associated penetrating complications. These findings were then classified according to the Montreal disease classification. The study concluded that patients who were classified as B2 or B3 on the Montreal classification scale had a significantly higher likelihood of undergoing ileocecal resection (using B1 as reference, hazard ratios for B2 and B3 were 2.73 and 6.80, respectively, both $p < 0.0001$). The study also found that being younger significantly increased the likelihood of undergoing ileocecal resection [using 19–29 years as reference, hazard ratios for the

Table 11.1 The Montreal classification for Crohn's disease

Age at diagnosis	A1	Less than 16 years of age
	A2	17 to 40 years old
	A3	Above 40 years old
Location	L1	Ileal
	L2	Colonic
	L3	Ileocolonic
	L4	Isolated upper GI disease (added to L1-L3 when present)
Behavior	B1	Non-stricturing, non-penetrating
	B2	Stricturing
	B3	Penetrating
	p	Perianal disease (added to B1-B3 when present)

30–44 year age group was 0.83 (p = 0.4), the 45–54 year age group was 0.58 (p = 0.04), and the 60+ age group was 0.45 (p = 0.01)] [13, 14].

Crohn's Disease Endoscopic Index of Severity (CDEIS)
The CDEIS is a complex endoscopic scoring system. It takes into account the depth, extent, and location of the ulcers to calculate a score. It needs experience/training and is difficult for beginners.

Simple Endoscopic Score for Crohn's Disease (SES-CD)
The SES-CD score was developed out of a need to simplify endoscopic activity scoring. The score grades the size of ulcers, percentage of ulcerated surface, percentage of affected surface, and the presence of narrowing on a four-point scale (0–3) [15].

Ulcerative Colitis

Visualized Findings
Endoscopic features seen in ulcerative colitis are erythema, edema, ulcerations, loss of mucosal vascularity, mucosal granularity and friability, pseudopolyps, and continuous colonic inflammation [6, 7]. Backwash ileitis (terminal ileum inflammation sometimes confused as Crohn's disease) and a cecal patch (inflammation around the appendicular opening that is sometimes mistaken for a Crohn's skip lesion) must be kept in mind during the endoscopy. Just like in Crohn's disease, ulcerative colitis must be distinguished from other causes of colitis like infectious colitis, ischemic colitis, clostridium difficile colitis, drug-induced colitis, ischemic colitis, and segmental colitis associated with diverticulosis (SCAD) (see Fig. 11.2) [6, 7].

Scoring Systems
As in Crohn's disease, scoring systems have been developed for UC.

Three common ones are the Montreal classification, Mayo score, and the modified Mayo score.

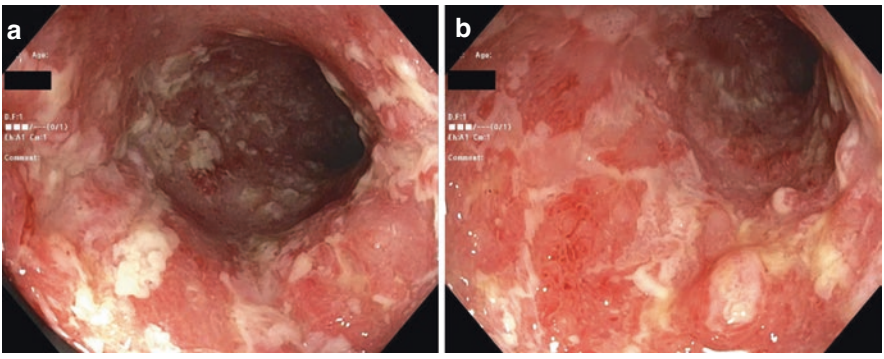

Fig. 11.2 (**a**) Ulcerative colitis of the rectum; (**b**) ulcerative colitis of the sigmoid colon

Montreal Classification

The Montreal classification for ulcerative colitis divides cases based on the extent of the disease (ulcerative proctitis, left-sided UC, and extensive UC or pancolitis) (see Table 11.2) [12].

Mayo Scoring System

The Mayo score takes invasive (endoscopic) and noninvasive parameters of ulcerative colitis to formulate a 12-point score. The four parameters are rectal bleeding, stool frequency, physician assessment, and endoscopic appearance [16, 17] (see Table 11.3, Mayo UC score) [16]. The modified Mayo scoring uses the endoscopic Mayo subscores (mucosal appearance on endoscopy) for five colonic segments (ascending colon, transverse colon, descending colon, sigmoid colon, and rectum) then summates the scores to get a modified score. This modified score is then multiplied by the disease extent (measured in decimeters during withdrawal) and divided by the number of segments with active inflammation to give the final modified Mayo score (see Table 11.4) [18].

Table 11.2 The Montreal classification for ulcerative colitis

Extent	
E1 (ulcerative proctitis)	Inflammation distal to the rectosigmoid junction
E2 (left-sided UC)	Inflammation of the colorectum distal to the splenic flexure
E3 (pancolitis)	Inflammation of the colorectum proximal to the splenic flexure

Table 11.3 The Mayo score

Rectal findings	
0	Normal
1	1–2 stools per day more than normal
2	3–4 stools per day more than normal
3	>4 stools per day more than normal
Rectal bleeding	
0	None
1	Visible blood with stool less than half the time
2	Visible blood with stool half of the time or more
3	Passing blood alone
Mucosal appearance on endoscopy	
0	Normal or inactive disease
1	Mild disease (erythema, decreased vascular pattern, mild friability)
2	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3	Severe disease (spontaneous bleeding, ulcerations)
Physician rating of disease activity	
0	Normal
1	Mild
2	Moderate
3	Severe

Table 11.4 Modified Mayo score example

Segment of colon examined	Inflammation	Mayo endoscopic subscore
Rectum	Yes	3
Sigmoid	Yes	3
Descending colon	Yes	2
Transverse colon	Yes	2
Ascending colon	No	0
	4	10

Extent of inflammation (calculated during withdrawal): 6.
Modified Mayo score: 10 × 6/4 = 15.

Table 11.5 Rutgeerts score table

Score	Definition
i0	No lesions
i1	Less than five aphthous lesions
i2	More than five aphthous lesions with normal mucosa between the lesions or skip areas of larger lesions or lesions confined to the ileocolonic anastomosis
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse inflammation with already larger ulcers, nodules and/or narrowing

Post-op Endoscopic Evaluation in Crohn's Disease and Ulcerative Colitis

In postoperative Crohn's disease, ileocolonoscopy is considered to be the gold standard in the confirming diagnosis and monitoring of postoperative Crohn's disease recurrence. Patients with Crohn's disease get surgery due to medical therapy failure or due to complications like bowel obstruction, fistula, or abscess formation. Early detection of postoperative endoscope recurrence has been shown to prevent recurrent complications and further morbidity. Rutgeerts et al. conducted a prospective cohort study for postoperative lesions in Crohn's disease. Seventy-three percent of patients in the study had endoscopic lesions at the end of 1 year. Only 20% a patient had clinical symptoms at the end of 1 year. Endoscopic recurrence was found in 85%, and symptomatic recurrence was found in 34% of the patients at the end of 3 years. The study found that patients with endoscopic recurrence at the end of 1 year developed early clinical recurrence compared to patients without endoscopic recurrence at the end of 1 year [19]. Furthermore, Rutgeerts and colleagues found that lesions at the neo-terminal ileum can foresee Crohn's disease recurrence when done 6 to 12 months postoperatively depending on their severity. This landmark study by Rutgeerts et al. led to the formulation of the Rutgeerts score (see Table 11.5) [20]. The Rutgeerts score assesses the severity of postoperative recurrence and prognosis in Crohn's disease patients after ileocecal resection [19, 20].

Another scoring system was developed to assess endoscopic recurrence in Crohn's disease. The postoperative endoscopic index of severity (POCER index) uses the size, depth, and circumferential extent of anastomotic ulcers to formulate a

score [20]. POCER index seems to be infrequently used. Currently, there is no consensus as to when to start postoperative screening in patients after an ileocecal resection. Yamamoto recommends that screening colonoscopies should be done 6 to 12 months after ileocolonic resection mainly to detect early neo-terminal ileum lesions. Vaughn et al. recommend that patients who have undergone an ileocecal resection get a screening colonoscopy within the first 12 months. Some of the risk factors for postoperative recurrence which should be taken into consideration for postoperative screening include active smoking, history of previous surgical resection, penetrating disease, resection histology, and myenteric plexitis in resection specimens. Decreased recurrence rates with the use of mesalamine, thiopurines (6-mercaptopurine and azathioprine), antitumor necrosis factor antibodies (infliximab and adalimumab), and antibiotics (nitroimidazoles) have all been reported. Probiotics however were not shown to decrease the recurrence of postoperative Crohn's disease. Many authors recommend specifically that patients who were considered to be at a higher risk of postoperative Crohn's disease recurrence should be considered for medical prophylaxis with anti-TNF antibodies very early on after surgery and before the recurrence colonoscopy [19, 20, 21]. Different post-op anastomotic configurations such as end to end, side to side, and end to side can be seen on endoscopy and also have significance. It sometimes can be used to decide screening intervals and therapy for recurrence. End-to-end anastomosis is the preferred surgical anatomy as it results in a continuous linear passage for bowel contents that mimics normal bowel. This has been shown to result in lower complication and hospitalization rates [20]. Side-to-side anastomosis, although easier to perform, can lead to pooling of contents with potential for fecalization, chronic distention, sooner recurrence, and other complications.

In ulcerative colitis, total proctocolectomy and ileal pouch-anal anastomosis is the surgery of choice. However, the surgery comes with its own set of postoperative complications. First, the pre-pouch ileum should be looked at during the pre-op colonoscopy for inflammation which should be treated pre-op. Once the pouch has been created, careful surveillance needs to be undertaken. Some of the common causes of pouch dysfunction are pouch breakdown with leakage, pouchitis, cuffitis, mistaken diagnosis of Crohn's disease, and underlying neoplasia [22]. Pouchitis is the most common complication post total proctocolectomy + ileal pouch-anal anastomosis. Its occurrence is reported to be between 18 to 27% [22]. Post-op, the pouch mucosa should be examined to look for inflammation, ulceration, and polyps on endoscopy [23]. Endoscopic surveillance of the pouch must include four quadrant biopsies from the upper and lower pouch and four more from just below the anastomosis. One must be careful to avoid biopsies from the suture lines as these may demonstrate signs of histologic inflammation, which may incorrectly suggest pouchitis [23]. Strictures at the neo-terminal ileum-pouch junction or inflammation, strictures, and fistula in the pre-pouch ileum should be carefully looked for while performing the exam. Any of these findings are suggestive of Crohn's disease. Normal pouch mucosa with inflammation just below the anastomosis may point to cuffitis, especially if the anastomosis was made using staples. Pouchitis and cuffitis can occur concomitantly [23]. Within the pouch ileo-ileal anastomosis breakdown

with leakage can also occur. In patients with severe fulminant colitis, a subtotal colectomy instead of a total proctocolectomy is done as part of a three-stage procedure. The procedure involves a subtotal colectomy, end ileostomy, and Hartmann's pouch (diverted rectum), followed by closure of the end ileostomy and construction of the ileal pouch-anal anastomosis [24]. Proctoscopy of the Hartmann pouch and ileoscopy via the end ileostomy are important prior to the final operative-stage situation. The Hartmann pouch end must be examined for stump leaks, possible fistula, intrapelvic abscesses, and diversion proctitis (inflammation due to lack of nutrients to the rectal mucosa from luminal bacteria). Ileoscopy of the end ileostomy must be carefully done to look for Crohn's disease of the small bowel and post-colectomy enteritis syndrome [24].

Specialized Endoscopic Evaluations

Small bowel balloon enteroscopy is usually indicated in patients with suspected small bowel Crohn's disease (who have already undergone CT enterography, magnetic resonance enteroclysis, or wireless capsule enteroscopy). It includes procedures such as push enteroscopy, single balloon enteroscopy, double balloon enteroscopy, and spiral enteroscopy. This section will discuss the role of balloon enteroscopy (single and double) in diagnosis. Some of the advantages of enteroscopy over small bowel capsule endoscopy are the ability to get a biopsy, no risk of capsule retention, and potential for stricture dilation if needed. The diagnostic yield of finding small bowel pathology using balloon enteroscopy is between 50 and 60% (compared to magnetic resonance enteroclysis) [25, 26].

The double balloon enteroscope has two balloons: one is attached to the tip of the scope, and the other one is on the overtube. The scope is inserted as far as possible, and then the overtube balloon is extended to the furthest point of enteroscope and inflated to anchor it in place. The scope is then advanced again as far as possible into the bowel. The balloon at the tip of the scope is then inflated to anchor the scope in place. The overtube balloon is then deflated and the overtube is then advanced over the scope. This process is then repeated. The enteroscope can be inserted orally or caudally.

Complications of double balloon enteroscopy are perforation, pancreatitis, and bleeding. In a large series reported by Tharia, the risk of pancreatitis was 0.3%, bleeding 0.2%, and perforation 2% [25].

The technique used in single balloon enteroscopy is the same as double balloon enteroscopy, except that the tip is used to anchor the scope in place instead of a balloon. Single balloon enteroscopy has a shorter preparation and procedure time, when compared with double balloon enteroscopy, but lower success rate for traversing the entire small bowel. Prabhu et al. reported in a review article that a complete small bowel evaluation was achievable between 16 and 86% for double balloon enteroscopy and between 0 and 22% for single balloon enteroscopy [27].

Small bowel capsule endoscopy (SBCE) was introduced in 2001. It has made complete small bowel visualization possible. In one study it was found to be superior to small bowel radiography, colonoscopy with ileoscopy, CT enterography, enteroclysis, and push enteroscopy for detecting non-stricturing small bowel Crohn's disease [28]. Studies vary but overall the sensitivity for suspected Crohn's disease is about 75% [29]. Currently three SBCEs are available in the USA: PillCam SB (Given Imaging Yokneam, Israel), EndoCapsule (Olympus, Allentown PA), and MiroCam IntroMedic Co. (Seoul, South Korea). The capsule contains a camera, battery, and an ultrahigh-frequency image transmitter. The camera has a resolution of about 0.2 mm. It captures 2–6 frames per second and has a field of view ranging from 145 to 170 degrees. The battery life is about 8–10 hours. SBCE can be used to detect obscure small bowel Crohn's disease, identify active Crohn's disease, monitor disease activity in established small bowel Crohn's disease, detect complications of IBD like bleeding and neoplasms, and can assess mucosal healing while on biological agents [30, 31]. The Lewis score is the most common scoring system for SBCE evaluation of Crohn's disease. The small bowel is divided into three tertiles based on transit times. Each tertile is then scored based on the presence or absence of signs of Crohn's disease (strictures, ulcers, fistulas). A score of less than 135 is normal, a score between 135 and 790 indicates mild or low degree of mucosal inflammation, and a score above 790 represents moderate to severe inflammation [31]. The Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) is another scoring system that uses proximal and distal small bowel segment signs like inflammation, disease extent, and strictures to generate a score [31]. Complications of SBCE do occur. The most concerning is capsule retention. In patients with active Crohn's disease or suspected strictures, a dissolvable patency capsule can be administered to test the patency of the gut – the Agile patency system pill (Given Imaging, Yokneam, Israel). The patency capsule is the same size as the small bowel capsule endoscope and is radiopaque. If patients successfully pass the patency capsule, then they are given the capsule endoscope. The patency capsule slowly dissolves over time if it does not pass. Whenever a retention occurs with a standard capsule (non-passage for more than 2 weeks), then corticosteroid treatments (for inflammatory strictures), double balloon endoscopic retrieval, or surgical removal can be attempted [31, 32].

Endoscopic retrograde cholangiopancreatography (ERCP) also has a role in the care of IBD patients. IBD patients with cholestasis symptoms accompanied by altered liver biochemistry tests (increased transaminases, increase in GGT and alkaline phosphatase) require imaging of the bile ducts to be ruled out for primary sclerosing cholangitis (PSC). The presence of PSC in patients with IBD is associated with a 55-fold increase in the risk of cholangiocarcinoma acquisition [35]. Although other noninvasive methods such as MRI or CT can evaluate for bile duct abnormalities, endoscopic retrograde cholangiopancreatography (ERCP) can best visualize strictures of the biliary tree. At ERCP, tissue can be acquired to evaluate for cholangiocarcinoma and strictures can be treated. During ERCP, brush cytology, direct bile duct tissue biopsies (transpapillary intraductal biopsy), and cholangioscopy-directed miniature forceps biopsy can all obtain tissue for carcinoma evaluation.

Combining the three biopsy collection techniques has a higher sensitivity in detecting cholangiocarcinoma when compared to brush cytology alone. Conversely, patients diagnosed with PSC should have a colonoscopy with multiple biopsies to evaluate for the presence of concomitant IBD [33–38]. PSC increases the risk of colon cancer in IBD patients with a history of colitis. Therefore yearly surveillance is recommended for these patients. Therapeutic biliary interventions for PSC by ERCP are a well-established treatment. Biliary strictures can be treated by balloon dilation or stenting. However, this is mainly in the setting of a dominant duct stricture and symptoms like cholangitis, jaundice, pruritus, and worsening liver biochemistries. Balloon biliary dilation alone may be sufficient to relieve obstructive symptoms in some cases with success rates ranging from 89 to 97% [27]. Stents (metal or plastic) can be placed in cases where balloon dilation alone has failed to keep the stricture dilated [35, 36]. ERCP-related complications which include pancreatitis (the most common at 5–7%), cholangitis, perforation, and hemorrhage can all occur. Oral antibiotics for 5 days after a biliary dilation to prevent cholangitis are advised. The presence of Crohn's disease, cirrhosis, sphincterotomy, and biliary dilation all increase risk of post-ERCP complications [35, 36].

Confocal laser endomicroscopy (CLE) can be useful in the diagnosis and determining disease activity in IBD. A systematic review done by Rasmussen et al. reported that CLE can help with in vivo assessment of inflammation and barrier function, surveillance, and molecular imaging of the gut mucosa. His study found that patients with quiescent CD had an increased number of crypts and goblet cells when compared to patients with active disease. Increased cellular infiltrates, vascular alterations, and micro-erosions were all found in active disease patients. The study found that crypt changes on CLE were strongly correlated with inflammation on histology [39]. Rasmussen's study also found features on CLE that can predict relapse. The number of epithelial gaps was found to forecast future hospitalizations or surgeries in patients with IBD. An increase in gap density was found to increase the hazard ratio 1.1-fold (CI, 1.01 to 1.20) for hospitalization or surgery [39]. The study found mixed results for dysplasia surveillance using CLE. In another study CLE was compared to the Crohn's Disease Endoscopic Index of Severity (CDEIS) in patients with CD. A high CDEIS score was found to correlate with increased crypt tortuosity and an increase in the number of dilated crypt lumens. An increase in vascularity and the number of goblet cells was also seen in this group. This study was also able to differentiate between quiescent and active Crohn's disease on endomicroscopy even when the mucosa was endoscopically normal [40]. CLE can also be used to assess pouchitis in patients with a proctocolectomy. Scoring systems have been developed. The Crohn's Disease Endomicroscopic Activity Score (CDEAS) is a score to assess Crohn's disease activity using confocal laser endomicroscopy. The scoring included features seen on endomicroscopy, such as crypt number, crypt tortuosity, crypt lumen, the presence of micro-erosions, vascularity within the lamina propria, the number of goblet cells, and cellular infiltrate within the lamina propria. One point was given to each feature, with scores ranging from 0 to 8 [40]. Another system, the Watson score, assesses epithelial barrier dysfunction in inflammatory bowel disease using confocal laser endomicroscopy. The amount of

cell shedding and intensity of fluorescein signal (a marker for local barrier dysfunction) are used to describe the score. The score is divided into three grades that characterize the defects, viz., normal, functional defect, and structural defect. Normally, cell shedding is confined to single cells per shedding site without fluorescein leakage. A functional defect is characterized by cell shedding confined to single cells per shedding site and visible fluorescein in the intestinal lumen. The intensity of fluorescein in the intestinal lumen is the same or brighter than that in the epithelium. Fluorescein plumes may be present in the lumen, outside the epithelium. Structural defects are characterized by micro-erosions. A micro-erosion occurs when lamina propria is exposed to the lumen with multiple cells shed per site. Fluorescein is visible in the intestinal lumen at an intensity that is the same or brighter than epithelial fluorescein [41].

Therapeutic Endoscopy in IBD

Some major considerations for therapeutic endoscopy in IBD are dysplastic lesion removal, stricture dilation, drug delivery, stent placement, and fecal microbiota transplant. Just as drug therapy continues to evolve in treating IBD we continue to see therapeutic endoscopy evolve in IBD therapy.

Endoscopic removal of dysplastic lesions has become a standard in the management of dysplastic IBD lesions. Multiple factors guide the lesion's treatment such as endoscopic and histologic findings and patient characteristics such as age, general condition of the patient, and patient preference. Endoscopically unresectable visible dysplastic lesions and dysplasia in flat mucosa are an indication for colectomy. Features like ill-defined margins, submucosal invasion, asymmetrical lift during an endoscopic mucosal resection (EMR) attempt, ulcerations or large depressions, and flat neoplastic changes with distorted pit patterns adjacent to the lesion render a dysplastic lesion unresectable. Known dysplastic lesions that are amenable to endoscopic resection can be removed by endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) [42]. EMR is performed by first using a submucosal lifting solution such as Orise™ (Boston Scientific, Marlborough, MA) and then a snare that captures the target tissue. The grasped tissue is then transected using an electrosurgical current. Lesions larger than 10–15 mm are usually removed in a piecemeal fashion. Dysplastic lesions >10 mm are usually removed using EMR. ESD is performed by also injecting a lifting solution into the submucosa and then creating an incision around the perimeter of the lesion. Then a specialized instrument is used to dissect the lesion from the deeper wall layers. ESD is generally indicated in lesions that have a higher likelihood of cancer invading the superficial submucosa and for lesions that cannot be removed using EMR due to submucosal fibrosis or post-EMR recurrences. EMR is relatively simple to perform, uses only a few devices, and has been used successfully for a long time. Recurrence rate is the major shortcoming of EMR. Risk factors for recurrence include piecemeal resection and lesions larger than 10 mm; with these factors, the recurrence rate is about

15–20%. ESD however has the advantage of allowing en bloc resection of any type of lesion regardless of size. Interestingly, ESD has not clearly been reported as having a higher complication rate than EMR. Nevertheless, ESD is more technically demanding than EMR and requires advanced endoscopy tools and skills. It is also a longer procedure than EMR. Common complications of both EMR and ESD are perforation and significant bleeding (>2gms Hb) reported in the range of 1.5% and 2.5%, respectively [43, 44].

Endoscopic stricture dilation is a much-used therapeutic modality in the management of IBD. More than one-third of Crohn's disease patients develop strictures within 10 years of onset. Strictures can be inflammatory, fibrotic, or mixed. Some risk factors for developing fibrostenotic strictures in Crohn's are diagnosis under the age of 40, presence of perianal disease smoking, and the need for steroids during the first flare. Stricture symptoms include postprandial abdominal pain, bloating, nausea, vomiting, and weight loss. Options to treat fibrostenotic strictures are endoscopy and surgery (all surgical techniques are included here). Endoscopic balloon dilation helps with the management of short fibrotic strictures, often delaying surgery. However, endoscopic stricture dilatation has not been shown to prevent surgery [45]. The most common location is at the distal ileum or ileocolic junction. Short, straight strictures that are non-ulcerated without adjacent abscesses have the most success with endoscopic balloon dilation. Balloon dilation has a high initial success of about 80% [45]. However, the long-term success (2–5 years) ranges from 25 to 75% [45]. Factors associated with dilatation success are native strictures, strictures less than 5 cm, straight strictures, and mainly fibrotic strictures. When a stricture is out of reach while using a standard upper endoscope or colonoscope, a double balloon enteroscope can be used for therapeutic intervention. The dilatation technique is a bit of an art. One study done by Koltun found that insufflation using a through the scope (TTS) balloon should be held for 1 to 4 minutes and repeated until the lumen is adequately appreciated visually. His successful dilation was defined by ability to pass the endoscope through the stricture. Another study done by Coelho-Prabhu recommended an insufflation time of 30 to 120 seconds, and success was defined as dilating the stricture until mucosal tearing occurred. Others state strictures can be dilated to 18–20 mm [46]. IBD stricture dilatation is generally safe with about a 3% overall complication rate. The most common complications are perforation and bleeding [27, 45, 47]. Stricture biopsy and careful evaluation for cancer before any stricture dilatation should be performed.

Drug delivery of intralesional injection of triamcinolone has been used along with (TTS) balloon dilation for improved stricture management. It is usually administered after the last largest size dilation session. The local anti-inflammatory effect of triamcinolone has been proposed to decrease scarring of strictures post-dilatation [27]. Some suggest that it prolongs the interval between dilations or need for surgery. However, steroid injection is not a generally accepted therapy for IBD strictures. Intralesional infliximab injection has also been tried. An open-label study done by Swaminath et al. tested the effect of intralesional infliximab injection (via a sclerotherapy needle) in three patients with Crohn's colitis and strictures. All three patients were refractory to systemic infliximab, had colorectal strictures and

obstructive symptoms, and were free of malignancy (excluded by biopsy). All three patients had stricture injected with infliximab during the first endoscopy. This was done in a radial pattern with 10 milligrams per injection for a total of 9 to 12 doses. Healing was assessed 2 weeks later by a follow-up endoscopy. All three patients had normal mucosa on endoscopy with stricture resolution at 2 weeks. One patient was symptom free for 7 months and then for 5 months after repeat injection. Another patient was symptom free for 8 months. The third patient was symptom free for 8 months after receiving a total of five injections every 4 months [48]. Biological injections into IBD strictures will need more studies before they can be adopted as a standard therapy.

Stents can be used to treat fibrotic strictures both with and without endoscopic dilatation. The use of stents aims to avoid the common shortcoming of stricture dilatation, i.e., recurrence. Their use is also appealing since the alternatives, surgical strictureplasty or surgical stricture resection, have significant post-op complications and can lead to the development of short bowel syndrome. Self-expanding metallic stents (SEMS) can achieve endoscopic strictureplasty, reducing the need for repeat procedures by increasing the duration of radial force dilatation. A prospective study done by Attar et al. on 11 patients looked at stent dilation for strictures. Nine patients had an ileocecal/ileocolic resection and two patients were surgery naive. Stent placement was found to be successful in 10 out of 11 patients (the unsuccessful procedure was complicated by angulations impeding cannulation by the fluoroscope guidewire). On follow-up, one patient went to surgery due to recurrence of obstructive symptoms at day 34. Although the stent was in position on CT scanning, endoscopy revealed that the stent was embedded in the stricture, could not be extracted, and had to be removed by surgery. Overall, out of the ten patients with successful stent placement, only five had successful extractions of their stents on day 28 as planned [27, 48, 49]. Stent migration was a significant issue with the other cases. At this time the use of stent placement in IBD is still being developed. Venezia et al. reviewed the use of self-expanding metallic stents (SEMS) in nonmalignant conditions of the lower gastrointestinal tract (like IBD, acute diverticulitis, radiation colitis, post-anastomotic leakages, and stenosis). They concluded that endoscopic balloon dilation is the current treatment of choice in Crohn's disease strictures and that information regarding the efficacy and safety of stent use in IBD strictures was too limited and inconclusive. In his review, the most common indication for the use of a stent in IBD strictures was as a bridge to surgery. Most studies used covered self-expanding metallic stents (cSEMS). The author recommends considering the use of cSEMS in patients with a long stricture, a fibrotic stricture, and when the anatomy makes balloon dilation too difficult. The use of fully covered stents prevents adherence to the bowel mucosa and thus facilitates stent removal but carries a high risk of stent migration. Partially covered stents have a lower likelihood of stent migration but a higher risk of adherence to the bowel mucosa and thus present difficulties at the time of stent removal. The author states that biodegradable stents offer a lot of promise in IBD since stent removal is not required and longer action is possible, although limited data on biodegradable stents prevents an accurate assessment of clinical outcomes currently. It is generally recommended that surgery be

performed for any colonic strictures in ulcerative colitis since such strictures should be treated as malignant [50].

Fecal microbiota transplant (FMT) has been evaluated for therapy in IBD. Gut bacteria have been proven to be important in the pathogenesis of many GI conditions. Dysbiosis appears to play a role in conditions like recurrent disease and clostridium difficile super infections in the IBD patient. The role of fecal microbial transplantation is to restore a harmonious balance of gut flora. Overall, studies regarding the efficacy of fecal microbiota transplant have been mixed. The use of fecal microbiota transplant for inflammatory bowel diseases is not FDA approved and needs an investigational new drug application officially but still is being performed as a compassionate use at some centers. The stool used for fecal microbiota transplant is first tested for infections, toxins, and parasites. The use of stool banks to obtain donors is preferred over a known donor. All antibiotics must be stopped 24 to 48 hours before the procedure. The transplant can be done usually by colonoscopy, but both nasogastric infusion and enemas have been used. Long-term data on fecal microbiota transplant is lacking. It is found to be safe in the short term. Increased stool frequency, borborygmus, small bowel perforation, and infection (CMV) were some of the adverse effects noted after fecal microbiota transplant. Some long-term effects like obesity, diabetes mellitus, and colon cancer due to alterations in microbiota have also been postulated [51].

Lopez et al. reviewed the role of fecal microbiota transplant (FMT) in inflammatory bowel disease. The study notes that when antibiotics are used in patients with ulcerative colitis or Crohn's disease, disease activity was subsequently worsened. Also, probiotics have been shown to have some efficacy in some colitis patients. The bacterial flora in the feces of IBD patients has been shown to differ from that of healthy individuals. Areas of active inflammation have reported to demonstrate a lower healthy bacterial load. Bacterial RNA sequencing has revealed an increase in *Escherichia coli*, *Campylobacter* species, and *Mycobacterium avium* and a decrease in *Bacteroidetes* and *Firmicutes* in the Crohn's disease gut. The author suggests this imbalance as a potential target for future management of IBD. CD T4 activation and anti-inflammatory cytokine production are other mechanisms through which commensal organisms contribute to the anti-inflammatory response. Lopez's systematic review of FMT as primary therapy in IBD found that patients with Crohn's disease were more likely to have a response to FMT as compared to patients with ulcerative colitis (61% remission rate in Crohn's disease versus a 22% remission rate in ulcerative colitis). However, two randomized controlled trials in the review showed conflicting results of FMT though with a caveat. The first trial showed higher rates of remission in those receiving FMT over those who only received placebo enemas (remission was defined as a Mayo score of less than 2). The second study found no significant differences (defined as at least a one-point decrease in the Mayo score) between patients who received FMT versus patients who received a placebo. However, this second study carried out the fecal transplant via a nasoduodenal tube. This difference led the authors to postulate that the route of FMT administration may have a significant impact on the success of FMT, with lower gastrointestinal administration being more effective than administering FMT via a nasoduodenal

tube to the upper GI tract. The safety profile of FMT has also been reviewed. Some reported adverse effects are transient fevers, abdominal tenderness, elevation of inflammatory biomarkers, and vomiting (seen after duodenal infusions). Serious adverse events, although rare, have been reported. IBD flares and infections have been seen in some reports. Larger clinical trials that focus on the efficacy (both short and long term) and safety of FMT need to be done. Pinpointing the most effective component (species of bacteria/bacterial metabolites/nonbacterial components) of FMT will be important before it can become an effective treatment for IBD. Additionally, microbiome profiling that leads to individualized microbial treatments is another avenue worth exploring in the future of FMT [52].

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Chapter 12
Changing Paradigms in the Management of the Elderly IBD Patient

Simon J. Hong and Seymour Katz

Introduction

Inflammatory bowel disease (IBD), a group of chronic diseases which include Crohn's disease (CD) and ulcerative colitis (UC), affects 6.8 million people worldwide [1]. The peak age onset of IBD is 30–40 years, but a bimodal distribution with a second peak at 60–70 years has been reported in numerous epidemiological studies [2–4]. Approximately 15% of cases are diagnosed after the age of 65, and currently 25–30% of the IBD population is estimated to be above age >60 [5, 6]. Furthermore the prevalence of IBD in the elderly is increasing, with 214 per 100,000 CD and 315 per 100,000 UC patients greater than age 60 in the USA [7]. Notably, 25% of IBD healthcare costs are accounted for by 15% of IBD patients diagnosed after age 60, reflecting a disproportionate use of resources in this group [8, 9]. Given the rising burden of illness in IBD in the elderly, it is becoming increasingly important to accurately characterize the unique traits of this population.

Elderly-Onset vs. Adult-Onset Elderly

There is increasing recognition of IBD diagnosed at an elderly age, or elderly-onset IBD, as a distinct entity from IBD in elderly patients with disease onset during adulthood [6].The distinction between these two groups is important because of differences in disease phenotypes, prognosis, and response to therapy [6].

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R. Rajapakse (ed.), *Inflammatory Bowel Disease*, Clinical Gastroenterology,
https://doi.org/10.1007/978-3-030-81780-0_12

Definition of older age in the IBD population varies in the medical literature from ages 55 to 70. However, in a recent topical review in IBD in the elderly, the European Crohn's and Colitis Organisation established 60 as the most widely accepted definition of elderly-onset IBD [10]. In recent years, large population-based epidemiologic studies have sought to better characterize the phenotypic differences of the elderly-onset IBD group.

Most published cohorts from various countries show a higher prevalence of UC than CD in the elderly-onset IBD population [9, 11]. In the large, multicenter Spanish Working Group (GETECCU) study of 1374 elderly patients, 62% had UC, and 38% had CD [12].

Differences in disease phenotype and behavior also exist in elderly-onset IBD patients. In a population-based study from Sweden, UC was more commonly left-sided in elderly-onset (age > 60) than the adult population (28% vs. 15%) and less commonly proctitis (14% vs. 23%) or extensive disease (28% vs. 34%) [13]. Similar findings of less extensive disease in elderly UC patients were found in a population-based study from Western Hungary and a large multicenter cohort from Italy [11, 14]. In the French-based EPIMAD registry, 45% of elderly-onset UC patients had left-sided UC compared with 29% with proctitis and 26% with extensive colitis [15]. Disease extension is rare and only occurs in 9–16% of patients [9, 11]. Younger UC patients tend to present with more severe symptoms including diarrhea and systemic involvement (fever, weight loss), whereas elderly patients present with more frequent constipation or tenesmus [14].

Key Point
Elderly-onset IBD patients have a different phenotype which is less extensive, more inflammatory, and with low rates of progression and extraintestinal manifestations compared with younger-onset patients.

Elderly-onset CD is characterized by a predominance of pure colonic disease (L2) and inflammatory behavior (B1). Similar to UC, disease extension is rare in CD with stable location reported in 92% of patients [9, 15]. Initial behavior is predominantly inflammatory (B1) in 78% of elderly-onset CD patients, followed by stricturing (B2) in 17%, and penetrating (B3) in 5%. Compared with adult-onset patients, elderly patients have higher rates of stricturing disease (24% vs. 13%) and lower rates of penetrating (12% vs. 19%) or perianal (17 vs. 23%) disease [12]. Elderly-onset CD disease behavior also remains stable over time, with only 9% of patients progressing from B1 to B2 or B3 [9].

Extraintestinal manifestations (EIMs) appear to be less common in elderly-onset IBD. The EPIMAD registry found an EIM rate of 3% in the elderly population compared with 5% in the adult population ($P < 0.05$), while the GETECCU study found a difference of 12% vs. 14% which did not reach statistical significance [9, 12, 15]. Arthritis is more common in adult-onset patients (8% vs. 6%, $P = 0.0001$), whereas there is no difference in dermatologic manifestations [12, 13].

Genetics and Pathophysiology

Genetic factors have been less well-studied in elderly patients, but some key differences have been identified. A family history of IBD is less frequent in elderly-onset IBD patients and is reported in only 7% of elderly-onset CD and 3% of elderly-onset UC patients, compared with 14% and 7% of patients with adult-onset CD and UC, respectively [9].

Several genetic mutations have been identified which are associated with pediatric-onset CD, including NOD2, POUF5F1, TNFSF15, and HLA DRB *501, indicating a relationship among susceptibility genes and age of onset [16]. However no genetic mutations have yet been identified which are correlated with elderly-onset IBD.

Aside from genetic susceptibility, there is now an increased understanding of the fundamental aging processes that result in pathophysiologic alterations to organ systems, causing a decline in function over time. These deteriorative mechanisms include cellular senescence, damaged molecules, progenitor cell dysfunction, and chronic inflammation [17]. Aging is associated with immunosenescence with impaired innate and adaptive immune systems due to a decrease in hematopoiesis, while conversely it is associated with a chronic state of low-grade inflammation from pro-inflammatory cytokine release from peripheral mononuclear cells [18, 19] (refer Table 12.1). With aging, there is a decrease in macrophages, Toll-like receptor function and phagocytic ability of polymorphonuclear cells, while there is an increase in TNF production [20]. In the gut, increasing age is associated with a decrease in microbial diversity and an increase in facultative and obligate anaerobes [21].

Key Point
The different "biology" of the elderly, with an overall decline in immune function, necessitates caution when prescribing immunosuppressive therapies for IBD.

Table 12.1 Factors specific to the care of the elderly IBD patient

The elderly IBD population is increasing such that by 2030 one in three IBD patients will be over 60 years of age
Confounding comorbidities such as ischemic colitis, segmental colitis associated with diverticulosis (SCAD), malignancy, and infectious colitis (e.g., C. *difficile*, *Giardia*, amebiasis) should always be considered
The elderly have a different biology with altered pharmacokinetics, drug metabolism, and volume of distribution of medications, all of which impact therapeutic options
Immunosenescence increases infection and malignancy susceptibility
Obstacles to therapeutic adherence include polypharmacy, drug-drug interactions, comorbid diseases, insurance, and social support
Fit versus frail status impacts therapeutic and surgical outcomes.
Surgery is not a failure but an acceptable therapeutic alternative in certain patients particularly at risk for long-term risks of medical therapy
Treatment goal is steroid-free symptom relief which trumps the need for proven mucosal healing in the elderly

Treatment Considerations

Overview

Important physiologic considerations in the elderly include a reduced glomerular filtration rate, increased body fat, decrease in lean muscle mass, and a decrease in total body water which may alter the pharmacokinetics and metabolism of drugs [19, 22]. An increased risk of polypharmacy and medication interactions among elderly patients with IBD combine to impact on the efficacy and increase the side effects of therapies for IBD [23] (refer Table 12.2).

5-ASA

According to current US society guidelines, aminosalicylates (5-ASA) are recommended as maintenance therapy in mild-to-moderate UC, with biologic therapy preferred in moderate-to-severe disease [24, 25]. In CD, 5-ASAs have not demonstrated effectiveness and are not recommended for long-term maintenance therapy [26].

Despite these society recommendations, 70–90% of elderly patients with UC and 36–77% of those with CD are taking 5-ASAs in population-based studies [13, 27, 28]. This indicates that a substantial proportion of elderly patients are treated with 5-ASA therapy, in contrast to evidence demonstrating a lack of effectiveness in CD and risk of suboptimal treatment in moderate-to-severe UC.

A major factor in the persistence of 5-ASA therapy is likely due to its relatively benign side effect profile. Ninety-two percent of patients on 5-ASAs tolerate therapy without adverse events necessitating drug discontinuation [29, 30]. 5-ASAs have been associated with renal disease with several case reports linking 5-ASA and interstitial nephritis. More recent studies have shown that chronic kidney disease in IBD patients is likely related to underlying inflammatory disease, not 5-ASA use [31, 32]. Given this safety profile, it is understandable that clinicians favor using these therapies as long-term maintenance. Yet there is currently insufficient

Table 12.2 Elderly IBD patient-specific strategies

Updated list of providers, diagnosis, and medications on a laminated card to be carried by the patient. Do not rely on iPhones, iPads, or phone apps
Update vaccinations, cancer screening, and dental and vision visits
Second listener should be present with office visits whenever possible, preferably a family member or other caregiver
Provide clear unambiguous instructions to be reviewed with office staff and patient's companion before leaving the office or clinic

evidence that 5-ASAs have a different (i.e., more effective) therapeutic impact in older IBD patients compared with younger patients.

Key Point
5-ASAs are effective for mild-to-moderate UC, but there is no basis for use in Crohn's disease; renal toxicity should be monitored but is less of a risk than previously thought.

Steroids

Corticosteroids play an important role in inducing remission, but their long-term use is limited by unfavorable side effects which include congestive heart failure, hypertension, osteoporosis, glaucoma, diabetes, psychosis, and infection [33]. Despite these known risks, elderly IBD patients are more likely to receive corticosteroids and less likely to receive immunomodulators or biologics than their younger counterparts [13, 34]. In the EPIMAD registry, the cumulative probability of receiving corticosteroids over 10 years was 40% and 47% for UC and CD, respectively, in the elderly, compared to a 15% and 27% probability of receiving immunomodulators or biologics for UC or CD in adult patients during that same time frame [9].

The adverse risks of corticosteroids in the elderly can be substantial. In the prospective TREAT registry, 55 of 6290 (0.9%) patients died over a mean follow-up of 5.2 years, and the predictors of mortality in multivariate logistic regression were prednisone use, narcotic use, and increasing age. Similarly, multivariate analysis of severe infections which occurred in 106 (1.7%) patients identified corticosteroid use and increasing age as significant predictors [35]. In a population-based study of 3552 elderly-onset IBD patients in Quebec, CA, corticosteroids given within 45 days were associated with a 2.8-fold increased risk of serious infections compared with nonsteroid users [36]. In addition to these serious outcomes, other significant adverse events associated with steroids in elderly IBD patients include risk of fractures, venous thromboembolism, depression, anxiety, and sleep disturbance [36, 37]. Given all of these risks, corticosteroids in the elderly should be used with an appropriate plan for alternative long-term maintenance therapy.

Key Point
When using corticosteroids, an "exit strategy" to an immunomodulator or biologic therapy should always be considered.

Immunomodulators

Current US society guidelines state that thiopurines (azathioprine or 6-mercaptopurine) can be used for maintenance of remission in UC or CD [26, 38], but there is a paucity of literature regarding efficacy of thiopurines specifically in the elderly population. One population-based study of 4107 elderly-onset IBD patients in the UK found that thiopurine use for more than 12 months was associated with a 70% reduction in risk of colectomy in UC patients, but not in those with CD [39]. Of note, the time period of this study was 1990–2010, when overall use of biologics in the studied population was extremely low compared to thiopurine use (1–3% vs. 12–16%, respectively).

Despite their potential therapeutic benefit, the real-world usage of thiopurines in the elderly IBD patient remains low. Data from the French population-based cohort EPIMAD reported a 2.6% probability of starting thiopurine within the first year of diagnosis, and over the course of their lifetimes, only 135 of 841 patients (16%) underwent immunomodulator therapy [9, 40].

These low rates of usage are in large part due to concerns about the substantial side effect profile of thiopurines. Elderly IBD patients at baseline have an increased risk of lympho- and myeloproliferative disorders compared with the general population [41]. Large prospective observational studies performed by the CESAME group demonstrated that exposure to thiopurines is associated with an increased risk of several malignancies, including non-melanoma skin cancer, myeloid leukemia, myelodysplastic syndromes, and lymphoproliferative disorders (both Hodgkin's and non-Hodgkin's lymphoma) [42–45]. The risk of pancreatic cancer appears to be elevated (SIR 7.29, 95% CI 1.82–29.16) in elderly IBD patients with thiopurine exposure [41].

Key Point
Thiopurines are limited to maintenance, never induction therapy. Long-term use is fraught with infection and malignancy risk.

In addition to malignancy, thiopurine use is associated with increased infections. In a French nationwide study, patients exposed to thiopurine monotherapy were at increased risk for serious infections, including shingles and opportunistic infections compared with those who were not exposed, and the absolute risk of infection was two- to threefold greater in patients 65 or older [46].

Several drug-drug interactions are important when considering use of thiopurines in the elderly. Azathioprine inhibits the effects of warfarin-necessitating dose uptitration [47, 48]. Several drugs interfere with the metabolism of thiopurines, including sulfasalazine and its metabolite 5-ASA, furosemide, and allopurinol, potentially leading to drug toxicities [49, 50].

Biologic Agents

Data regarding the efficacy and safety of biologics in the elderly with IBD are limited, given that the median age of patients in large registry randomized control trials is generally in the 40s. Based on population-based data, the use of biologics is lower in elderly patients, which may be a result of concerns about safety.

TNF-Alpha Antagonists

TNF-alpha (TNF-a) antagonists are currently recommended for moderate-to-severe UC and CD, yet data on effectiveness and safety in elderly patients are limited. Use of TNF-a therapies in the elderly IBD is mostly guided by retrospective studies. In a nested case-control from Leuven, Belgium noted that clinical response rates were lower at 10 weeks in patients age ≥60 (68% vs. 89%, $P < 0.001$) but were not significantly different at 6 months (80% vs. 83%, $P = 0.64$), suggesting a prolonged time for treatment effect [51]. A multicenter retrospective study by Adar et al. noted clinical remission rates of 50% and 58% at 3 months and 12 months, respectively, in IBD patients initiated on TNF-a after the age of 60 [52]. In this study the rate of clinical remission decreased with increasing age (OR 0.94 for each 1-year increase in age, [95% CI 0.89–0.99]).

While long-term remission rates appear to be similar in the elderly, rates of discontinuation are higher with 25% of patients older than 60 discontinuing TNF-a by 12 months compared with 7% of younger users [53]. Infection occurs in a larger proportion of elderly cessation of TNF-a than younger patients [53]. Studies have reported overall infection rates from 11% to 22% in elderly IBD patients on TNF-a, with rates of severe infections as high as 15% [51, 53, 54]. Furthermore, infection rates in elderly patients are consistently higher than those in younger patients with a two- to fourfold increase reported in studies [12, 53].

The risk of malignancy is of concern for elderly IBD patients on chronic immunosuppression. Advancing age is a risk factor for lymphoproliferative diseases in IBD patients compounded by thiopurine use [54, 55]. An initial meta-analysis on TNF-a therapy found a threefold increase in the risk of lymphoma over the general population [56]. However, it should be noted that the majority of these patients had prior immunomodulator exposure and more recent studies have not replicated these findings [57–59]. In the TREAT (Crohn's Therapy, Resource, Evaluation, and Assessment Tool) registry, the risk of lymphoma with TNF-a monotherapy was similar to those who are TNF-a naïve over a mean follow-up of 5 years [59]. Longer-term studies are required to establish the risk of lymphoproliferative disorders in the elderly IBD population on TNF-a therapy.

Vedolizumab

Vedolizumab, a monoclonal antibody directed against the integrin subunit α4β7, prevents migration of inflammatory cells into the intestinal lumen by interfering with mucosal cell adhesion molecule-1 (MAdCAM-1). This drug is approved for treatment of both moderate-to-severe CD and UC [60, 61]. Given its gut-selective nature, it is seen as a favorable option for elderly patients, and current evidence suggests that it is effective in this population. In a post hoc analysis of the GEMINI 1 and 2 registry trials by Yajnik et al., vedolizumab was similarly effective across three different age groups (≤35, 35–55, ≥55), with 33% vs. 27% vs. 29% of CD patients and 33% vs. 42% vs. 39% of UC patients, respectively, achieving corticosteroid-free remission at 52 weeks [62]. A multicenter retrospective cohort study of 284 patients by Cohen et al. found that both clinical and endoscopic response rates at week 52 were similar between elderly (age 60 or older) and younger (age 40 or younger) patients [63]. Lastly, in the aforementioned Adar et al. study, rates of remission were numerically higher for TNF-a than vedolizumab at 3 months (38% vs. 50%, $P = 0.07$) but were comparable at 6 months (45% vs. 54%, $P = 0.23$) and 12 months (54% vs. 58%, $P = 0.63$) [52]. These findings suggest a slower onset of action but an equivalent long-term effectiveness and durability of response of vedolizumab in elderly IBD patients.

The safety profile data for vedolizumab are somewhat conflicting. In Yajnik et al. trial, rates of malignancy and infection in the older patients (≥55) were similar to their younger counterparts [62]. In contrast, Cohen et al. reported an increased risk of infections in the elderly compared to younger patients (12% vs. 2%, $P = 0.002$). All were nonfatal infections, predominantly of the nasopharynx, urinary tract, skin, and vulva, or *Clostridioides difficile* [63]. In Adar et al., rates of significant infections were comparable between TNF-a and vedolizumab (20% vs. 17%), as were rates of *Clostridioides difficile* (21% vs. 18%) [52]. These data are from retrospective studies and large studies, but extensive follow-up is required to elucidate the potential safety benefit of vedolizumab over other biologic agents.

Ustekinumab

Ustekinumab is a monoclonal antibody that targets the p40 subunit of interleukin (IL)-12/23 which has demonstrated efficacy and safety in both UC and CD [64, 65]. However, in the UNITI/IM-UNITI and UNIFI registry trials, outcomes were not stratified by age, and the study population was relatively young with a mean age range of 37–42 years old in their treatment arms. No retrospective data exists yet for the elderly IBD population. In the psoriasis literature, two small retrospective studies (total 46 elderly patients) noted no serious infections over a follow-up of 1–2 years, although it is important to note that dosing for psoriasis is significantly lower than that for IBD [66, 67]. A recent meta-analysis of 30 ustekinumab randomized control trials noted no increase in any serious or mild/moderate adverse events compared with placebo [68]. Although this data suggests that ustekinumab has an

overall favorable safety profile, more studies are needed to determine its effectiveness and safety in elderly IBD patients specifically.

Key Point
Biologics should *not* be delayed in the elderly patient when indicated, particularly when replacing corticosteroids.

Tofacitinib

Tofacitinib, an oral small molecule which targets the Janus kinase pathway, has shown efficacy in UC, but not CD [69, 70]. The initial registry trials and subsequent post hoc analyses of IBD trials did not show an increase in venous thromboembolism (VTE) in the IBD population [71]. However, in the rheumatoid arthritis population, an increased risk of deep vein thrombosis, pulmonary embolism, and death has been identified with the higher 10 mg twice daily dosing in post-marketing studies [72]. This risk is generally higher in patients with baseline cardiovascular or VTE risk factors, including age ≥50, hypertension, diabetes, current smoking status, and coronary artery disease. Consequently the drug labeling for tofacitinib now includes a boxed warning recommending use of the lowest effective dose for the shortest duration possible [72]. Given the theoretically increased risk of VTE in the elderly IBD population, it is advised that tofacitinib should be used with caution in the elderly IBD population.

Surgery

Data regarding the risk of surgery among elderly-onset IBD patients are somewhat conflicting.

In the elderly population, overall surgery rates are higher in CD than UC patients. In Everhov et al., 22% of CD and 6% of UC with elderly-onset disease underwent surgery by 5 years [13]. Similarly, the cumulative probabilities of surgery at 10 years were 32% in CD patients compared with 8% in UC in another population-based study [9].

Data suggests that in patients with UC, elderly age is an independent risk factor for surgery, whereas in CD it is not. In a population-based study from Ontario, CA, of 21,218 incident cases of IBD, patients with elderly-onset UC (≥65 years) had higher rates of surgery compared with young adults (age 18–40) (adjusted HR 1.34, 95% CI 1.16–1.55) whereas in those with CD, no differences in surgical rates were seen among different age groups [73]. Similar results were reported in a systematic review and meta-analysis by Ananthakrishnan et al., which described an increased risk of surgery in patients with elderly-onset UC, defined as age ≥50 (OR 1.36, 95%

CI 1.18–1.57), but not CD (0.70, 95% CI 0.40–1.22) when compared with patients with onset of disease at age <50 [74].

In contrast, in a large Dutch population study, there were no differences in risk for surgery for UC (HR 0.88, 95% CI 0.53–1.46) or CD (HR 1.19, 95% CI 0.85–1.67) when comparing adult-onset with elderly-onset IBD patients [6]. Similarly, in a large cohort study of seven centers in the USA, no differences in rates of surgery were found among different age groups, including elderly-onset IBD, elderly adult-onset IBD, and younger IBD [75]. A meta-analysis comprising 9 studies with 14,765 patients by Rozich et al. found elderly-onset IBD patients had similar rates of surgery as those with adult-onset disease [76].

In summary, these findings suggest that elderly-onset IBD may not necessarily imply a more benign disease course, as overall colectomy rates are comparable in CD and are equal or higher in UC than in younger counterparts. This may be based on several factors. Elderly patients with IBD are less likely than younger patients to receive immunosuppression which may lead to more uncontrolled disease [74, 76]. Long-term thiopurine use of more than 12 months has been associated with a 70% reduction in risk of colectomy in elderly onset UC [39]. Conversely, earlier elective surgical intervention may be preferred to avoid the side effects of long-term medical therapy, which is supported by one retrospective medical analysis in which elective colectomy provided a survival benefit over medical therapy in UC patients older than 50 [77].

Key Point
Comparable rates of colectomy in elderly IBD patients refute the theory of a "less active" disease course in the elderly.

Frailty

Frailty is an emerging metric that is increasingly recognized as an important predictor of disease-related outcomes. Frailty is a state of increased vulnerability due to an erosion of homeostatic reserve. This often follows acute stressors which lead to a functional decline that is accelerated, rather than the gradual decline in physiologic reserve seen with normal aging [78]. Frailty is a disorder of multiple interrelated physiological systems including the brain, endocrine system, immune system, and skeletal muscle which leads to marked changes in functional ability, loss of adaptive capacity, and diminished resiliency [78, 79].

Key Point
"Fit vs. frail" status has a major impact on therapeutic decision-making and outcomes.

Studies have shown frailty is an often neglected part of the routine assessment of IBD patients and may be overlooked in a considerable proportion of elderly IBD patients [80]. One cohort study of 135 IBD patients aged ≥65 found that 23% had reduced hand grip strength and 44% had an abnormal Geriatric 8 (G8) questionnaire, which indicates higher vulnerability and increased impairment [81]. Underrecognition of this frailty has important consequences for IBD patients. This is associated with increased morbidity, septic complications, and cardiopulmonary complications in patients undergoing colectomy for UC [82]. In a recent study by Qian et al. using a nationwide claims database of 47,402 patients with IBD, frailty was independently associated with a 57% higher risk of mortality, 21% higher risk of all-cause readmission, and 22% higher risk of readmission for severe IBD [83]. Frailty is also associated with increased infections in elderly IBD patients on TNF-a (aOR 2.05, 95% CI 1.07–3.93) or immunomodulators (aOR 1.81, 95% CI 1.22–2.70), as well as increased mortality (OR 2.90, 95% CI 2.29–3.68) [84, 85].

Assessment of frailty is now recommended as part of preoperative evaluation of geriatric patients [86]. Once identified, interventions such as prehabilitation and interdisciplinary geriatric co-management may help to improve surgical outcomes in high-risk patients [79]. Structured multicomponent exercise programs can reverse frailty [87] and should be done for at least 4 weeks prior to surgery for optimal benefits [88]. In patients undergoing colorectal surgery, the use of prehabilitation is associated with improved walking distance and a significant improvement in physical fitness in 60% of patients, compared with 21% in patients who do not undergo prehabilitation [89].

Cancer and Mortality

Colitis-associated colorectal cancer (CRC) is a risk for all patients with long-standing UC and CD, with an increased risk associated with longer duration of disease [90]. One analysis of US health claims data showed that the incidence rate of CRC in elderly IBD patients was 0.27/100 person-years compared to 0.20/100 in similar age patients without IBD [91]. Furthermore, elderly patients with IBD have a threefold higher rate of early or missed CRCs after colonoscopy than those without IBD [92].

Data on malignancy in elderly-onset IBD patients was described in a French population-based cohort study of 844 patients aged >60 years by Cheddani et al. In this study, there did not appear to be an increased risk of CAC in elderly-onset IBD patients (SIR = 1.03, 95% CI 0.62–1.70), nor an increase in small bowel carcinoma compared with younger IBD patients [41]. There was an increased risk of malignant lymphoproliferative (SIR 2.49, 95% CI 1.25–4.99) and myeloproliferative diseases (SIR 2.18, 95% CI 1.09–4.35). Thiopurine exposure was not associated with an increased risk of cancer in elderly-onset IBD, but it is important to note that only 15% of patients had exposure to thiopurines [41].

Key Point
Cancer must be considered when all established IBD therapies fail in the elderly IBD patient.

Deaths are more frequent among elderly-onset IBD patients compared with patients age 18–40 years old, with a difference of 8% vs. 0.07%, respectively ($P < 0.0001$), as reported in one case-control study of 2748 patients [12]. In a population-based cohort of IBD cases in Ontario, CA, Nguyen et al. also reported a higher IBD-specific mortality in elderly-onset CD (33.1/10,000 person-year) compared with that in middle-age CD (5.6/10,000 person-year; *P*, 0.0001) and young adult CD (1.0/10,000 person-year) but was not different by age in UC. In elderly patients, solid malignancies were the leading cause of death accounting for 22.9% in UC and 26.4% in CD. IBD was the third most frequent cause of death accounting for 6.3% and 9.1% of deaths, respectively [73].

COVID-19 and the Elderly IBD Patient

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) is a novel virus which emerged in late 2019 in Wuhan, China, and quickly spread to become the deadly global pandemic known as COVID-19 (coronavirus disease 2019). The mortality of COVID-19 in older patients is remarkably high, with 80% of deaths in the USA occurring in patients age 65 or older [93]. An analysis of 72,314 cases in China revealed an overall case fatality rate of 2.3% for all adults, compared with 8% in patients aged 70–79 years and 14.5% in those older than age 80 [94]. It is now known that the mechanism of cell entry for SARS-CoV-2 is via angiotensin-converting enzyme-2 (ACE-2) receptors which are found throughout the body, notably in the lungs, endothelium, heart, kidneys, and GI tract [93, 95].

Due to the immunocompromised status of patients with IBD and the presence of ACE-2 receptors in the lower GI tract, there is concern about the susceptibility of elderly IBD patients to COVID-19. ACE-2 receptors are found in the absorptive enterocytes of the ileum and colon, and up to 41% of patients with COVID-19 have been found to have fecal shedding of SARS-CoV-2 with a median shedding duration of 22 days [96, 97]. Furthermore, ACE-2 receptor expression is increased in IBD patients compared with controls, suggesting the possibility that patients with IBD might be particularly susceptible to COVID-19 [98]. However, evidence thus far indicates IBD by itself does not appear to be an independent risk factor for severe COVID-19 outcomes when compared with the general non-IBD population [99].

Increasing age does not increase the risk of contracting COVID-19 in IBD patients, based on a nationwide VA cohort study of 37,857 patients [100]. However in IBD patients who do develop COVID-19, increasing age and increasing number of comorbidities are associated with an increased risk of severe outcomes, defined as ICU admission, ventilator use, and death in the international SECURE-IBD registry [101].

Key Point
IBD alone or with TNF-a therapy does *not* increase susceptibility to COVID-19. Conceivably, biologic therapy may be protective.

The use of immunosuppressants in IBD patients with COVID-19 is a concern due to their inhibition of intracellular signaling cascades needed to fight infections [98]. The use of corticosteroids in IBD patients was associated with worse outcomes [99, 101]. However, a recent meta-analysis of 249,095 patients showed that the average pooled incidence of COVID-19 in IBD patients on TNF-a (0.68 per 1000) is lower than that of all IBD patients (1.93 per 1000), suggesting the possibility that TNF-a use may be protective against COVID-19 [102]. Furthermore, in the SECURE-IBD registry, TNF-a use was not associated with severe outcomes, even when accounting for increasing age in multivariate regression modeling [101, 102]. In a study from the initial epicenter of the US pandemic, immunosuppression with biologics is not associated with poor COVID-19 outcomes [103]. While our understanding of this deadly pandemic is evolving rapidly, early data on IBD and COVID-19 are reassuring.

Conclusion

In conclusion, elderly-onset IBD is increasing in prevalence and will account for a substantial proportion of all IBD patients in the future. The phenotypic and physiologic differences between elderly- and adult-onset IBD have important impacts on therapeutic management and outcomes. Furthermore, an increasing understanding of frailty, surgical risk, and infectious and malignant complications will better inform care of these patients. Lastly, as new public health challenges such as COVID-19 emerge, it is important to be aware of their unique impact on the elderly IBD population.

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Chapter 13
Surgical Management of the Complex Crohn's and Ulcerative Colitis Patient: When to Redo a Pouch

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Role of the IBD Surgeon

Management of patients with inflammatory bowel disease (IBD) has become increasingly complex, but concurrently fascinating, as new advances and challenges have arisen in the era of modern medical therapy. Classically, surgery in IBD has been considered a last resort, but currently, involving a surgeon at an early stage of the disease is considered good clinical practice and is a part of most quality-control metrics.

Over the past two decades, surgeons have sub-specialized from general surgery to colorectal surgery and, now, even more specialized as IBD surgeons. Simultaneously, minimally invasive surgery with smaller incisions and the adoption of postoperative-enhanced recovery programs are responsible for a full recovery after only 2–4 weeks postoperatively [1]. Surgery is now also safer; complications from postoperative adhesions and incisional hernias have been greatly reduced. Concurrently, imaging has significantly improved, allowing better preoperative planning and follow-up.

Meanwhile, numerous new drugs (biologics) have emerged, which revolutionized the treatment of IBD. Unfortunately, these expensive new agents are not always prescribed by experienced gastroenterologists, drug levels are not always monitored, antibodies may develop, and medical therapy is occasionally futile. Expertise is especially important when biologics are used while complications are already

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R. Rajapakse (ed.), *Inflammatory Bowel Disease*, Clinical Gastroenterology,
https://doi.org/10.1007/978-3-030-81780-0_13

present, thus exposing patients to the side effects of the medications, without any clinical benefit. Furthermore, the long-term adverse effects of some biologics are yet to be fully described [2]. It has also become clear that prolonged medical therapy without the desired effect can also induce harm. For instance, in fistulizing Crohn's disease (CD), such a situation may increase the loss of healthy organs if the inflammatory process extends to innocent bystander structures, which might additionally need surgical resection. The durability of medical therapy to heal intra-abdominal fistulae is low, and before the complications become even more serious, surgery should be considered [3].

Medical therapy is indicated at opposite ends of the IBD spectrum: when there is minimal inflammation and, conversely, with complicated IBD which would require an extensive resection leading to a risk of short bowel and significant morbidity, medical therapy should be used preoperatively to decrease the gross amount of bowel resected. For the cases between the two poles, surgical resection is indicated when the morbidity caused by continued extensive medical therapy is more significant than the potential disability of the surgical alternative. For example, in a Crohn's patient that can undergo a limited, low-risk operation associated with an improved quality of life and no risk of short gut, a surgical intervention is justified [e.g., minimally invasive ileocolic resection for limited disease, instead of biologics].

Surgery as the first approach for complicated disease, or for those who have an apparent uncomplicated disease, is an important consideration; this enables gastroenterologists to have the intestinal disease extirpated with no gross disease in situ, allowing quick initiation of medical therapy to minimize recurrence. This not only avoids futile medical treatment but can return the patient's quality of life and is a cost-effective treatment strategy.

These considerations justify the early involvement of a surgeon in the multidisciplinary management of IBD patients as surgery should not be considered a failure but rather an integral part of the treatment. The conundrum is, *when* is the right time for surgical consultation? To succinctly generalize an answer in this process, we advocate that an IBD surgeon should be involved in these situations:

- When a second biologic is about to be started
- When a patient needs inpatient treatment for IBD
- In most ulcerative colitis (UC) patients for an early discussion about pouch surgery and outcomes

In this chapter, we will review the key topics in CD and UC surgical management.

Operative Management of Crohn's Disease

Surgical indications in CD:

- *Disease persistence/progression while on medical management* is the most frequent indication. We consider persistence/progression when no clinical improvement is achieved under optimal medical treatment or when moderate to severe side effects of therapy are consistently present over 6–12 months.

- *Bowel obstruction.* Inflammatory stricturing of the small or large bowel can lead to symptoms in up to 54% of CD cases [4]. Majority of the time, the acute episode can be managed with medical treatment alone, and with symptomatic improvement and nutritional optimization, long-term remission can be obtained. If there is recurrent obstruction, a short-interval elective resection without a temporary stoma can be performed. Cold symptomatic strictures, i.e., those without a significant inflammatory component, should not be treated with IBD medications but rather undergo upfront surgery. A minimally invasive procedure can be performed for a primary resection.
- *Fistulae and abscess.* Intra-abdominal abscesses occur in up to 28% of CD patients [5]. If the abscess is less than 4 cm in diameter, medical management with antibiotics might suffice. An abscess larger than 4 cm warrants drainage, best achieved with percutaneous drainage by interventional radiology or, if needed, surgery. Fistulae can develop from inflamed intestinal disease to nearby viscera, including adjacent loops of small or large bowel (e.g., ileosigmoid fistula, enteroenteric fistula), bladder (enterovesical), female reproductive organs (enterovaginal), psoas muscle, or skin (enterocutaneous).
- *Perforation.* A spontaneous perforation can occur within the dilated section of bowel proximal to a stenotic segment.
- *Ureteral obstruction* is rare complication (approximately 5% of CD cases) [6] that can be produced by inflammation, abscess compression, and secondary fibrosis. Removal of the offending bowel segment usually results in resolution of the ureteral obstruction; however consultation with a urologist can guide preoperative expectations and informed consent.
- *Major hemorrhage.* In the rare cases where endoscopy or angiography are unable to control bleeding, emergent surgery may be necessary. However, more frequently, the acute episode can be managed endoscopically or via angiography, and an elective operation can be planned.
- *Malignancy.* CD patients are at an increased risk for malignancy of any part of the intestinal tract, and that risk is dependent on the extent of disease, as well as disease duration. Although the overall incidence is low (0.2% at 10 years and 2.2 at 25 years), the cancers can be very aggressive [7]. Patients with CD are also at increased risk of lymphoma, independent of medication side effects.

The surgical approach in terminal ileal CD is resection of the diseased segment. There has been a shift in the attitude to intestinal resection margins from radical removal to one of conservation with only grossly diseased segments being removed. The bowel included in the anastomosis should be free from overt active disease and ulceration, but a few aphthous ulcers present at the anastomosis should not be a cause for further resection.

In terms of anastomosis type, we advocate for an end-to-side stapled anastomosis. With this technique, staple lines do not cross (staple line crossing in the setting of IBD can lead to anastomosis leakage), and in the case of a future recurrence at the anastomotic site, the resulting anatomy is more favorable for endoscopic dilatation. The widely popular side-to-side stapled anastomosis, although faster and resulting in a wider anastomotic surface, does not result in decreased recurrence

and leads to sacrifice of more bowel length with recurrent resections. This should be especially taken into consideration in patients who are at potential risk for short bowel syndrome. CD affecting the small bowel has to be treated with the same conservation mentality; strictureplasties are indicated in patients with prior small bowel resections of more than 100 cm, patients with known short bowel syndrome, and recurrences within the first year from resection. Strictureplasty is contraindicated in cases of local sepsis (phlegmon-abscess-peritonitis), suspicion of dysplasia or cancer, and when the strictured segment is in close proximity to a segment that will be resected. The presence of fistulae with chronic inflammation (not acute active inflammation) is a relative contraindication.

Traditionally, strictureplasties have been used in the jejunum and ileum; nevertheless, they can be safely used in the second, third, and fourth portion of the duodenum with increasing experience. On the other hand, colonic CD is not well addressed with strictureplasties; anecdotal results have been unsatisfactory due to the extensive inflammatory process commonly seen in colonic CD and a higher chance of underlying malignancy. This latter is addressed better with segmental resection, all the time maintaining the principles of bowel conservation.

A special situation is when patients present with toxic colitis. This is seen most frequently in UC patients and will be discussed in a separate section.

Surgical Management of UC: Restorative Proctocolectomy with Pelvic Pouch

A restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) has been the surgical procedure of choice in patients with ulcerative colitis (UC) since 1978, when it was first described by Parks and Nicholls [8]. Prior to that, total proctocolectomy with a permanent end ileostomy was the standard operation for patients with UC, and later, its indication was expanded to include select patients with Crohn's proctocolitis [9]. The first pelvic pouch shape was a handsewn S-pouch with the rectal muscular tube left in situ, while the distal rectal mucosa was stripped. It was created with a protective ileostomy which was then reversed a few months later, allowing for restoration of bowel continuity. Later, linear staplers were created, and their indications for use were expanded to pouch surgery because a series of improvements were made to make the technical aspects of pouch creation more facile. In addition, efforts to minimize future malignancy and improve pouch function led to the adoption of different stages and shapes of pouch creation [8, 10]. A J-shaped pouch with a double-stapled technique (first staple line transversely at the anorectal junction removing the rectum, second circular staple to create an end-to-end ileal pouch-anal anastomosis) offers the best functional results and is comparatively more straightforward to create than a handsewn S-pouch. The double-stapled technique also allows the anal transitional zone to remain in situ, which allows for better bowel control over a handsewn pouch-anal anastomosis after mucosectomy (stripping the anal transitional zone beginning at the dentate line and handsewing

the pouch to the dentate line) [11, 12]. Since the pouch's function and survival are most affected by postoperative pouch sepsis, the pouch should only be created under optimal conditions, such as without current immunosuppressive medications and after treatment of malnourishment. This often means performing a subtotal colectomy (STC) with end ileostomy as the first stage of eventual pouch creation as the patient can then be weaned off immunosuppressive medications before performing the proctectomy and pouch creation. The decision is then to protect the pouch with a diverting ileostomy (three-stage IPAA) or without (modified two-stage) [13]. A two-stage pouch is a total proctocolectomy with IPAA and diverting stoma and is most commonly used when patients require an IPAA in the setting of dysplasia (without malnourishment or in the setting of immunosuppressive medications/steroids). A one-stage operation is used for similar indications and is a total proctocolectomy with pouch creation without an ileostomy. Each stage needed to restore bowel continuity has its inherent risks, such as multiple exposures to anesthesia, repeated hospital stays, incisional pain, and stoma complications, but a three-stage IPAA has the best long-term functional results because it is associated with the lowest rate of postoperative pelvic sepsis [14]. Table 13.1 shows the most representative series comparing two vs. three-stage pouch surgery.

The stages (1, 2, modified-2, 3), shape (J-, S-, W-, H-pouch), and anastomosis (handsewn, double-stapled) remain debated in the surgical literature, while the indications for colectomy are agreed upon. Disease progression despite medical therapy, intolerance to medication side effects, and dysplasia/malignancy remain

Table 13.1 Most representative series comparing two-stage vs. three-stage pouch surgery in inflammatory bowel disease

Author	Year	*n*	3 stages (%)	Complications/sepsis	Evacuatory function
Nicholls [33]	1989	152	62%	No differences	*Better with 3S*
Galandiuk [34]	1991	871	11%	*3S: more septic complications, less obstruction*	Similar results
Penna [35]	1993	156	50%	*2S: more complications and reoperations*	*Better with 3S*
Heustchen [36]	2002	554	29%	No difference at 1- and 3-year follow-up	NR
Swenson [37]	2005	54	57%	No differences	Similar results
Lim [38]	2007	335	NR	No differences	NR
Hicks [39]	2013	144	19.4%	2S: more complications, same anastomotic leak rate	NR
Gu [40]	2013	588	69%	Sepsis: 2S: 18% vs. 3S: 8%	NR
Bikhchandani [41]	2015	2002	27.5%	No differences	NR
Kochar	2018	2395	34%	3S: less complications and reoperations	NR
Lee	2019	212	25.9%	No difference	Similar results

2S two-stage procedure, *3S* three-stage procedure, *NR* not reported

the main indications for surgery, and early collaboration with a surgeon always benefits the patients. Though rare, it is unfortunately too common that some patients with UC, who have progressed through multiple medications and have required multiple inpatient hospitalizations, were never informed of a surgical option to treat their disease. Despite advances in medical therapy, one-third of UC patients will require a restorative proctocolectomy, and timely referral to an IBD surgeon will allow a multidisciplinary approach to manage the disease and optimize outcomes. Worth mentioning is the fact that a small group of patients who have rectal-sparing UC do not need an IPAA and can instead undergo a subtotal colectomy with ileorectal anastomosis, thus avoiding any pelvic dissection associated with possible pelvic nerve damage.

Despite a trend toward major IBD centers of excellence and the era of biologic treatment, an extensive retrospective review of the New York State database has shown that there has been a significant increase in postoperative morbidity as well as an increase in staged procedures [15]. These results are hypothesized to be secondary to patients being sicker at the time of surgery because of ongoing trials of medical treatment, decreased involvement with IBD surgeons early on in the disease process from hesitation to consider surgery because of patient anxiety/fear, or the gastroenterologist's reluctance to abandon medical therapy to the finality of surgery [16]. Early involvement with a surgeon will allow a shared decision-making process that will empower the patient and medical team to make timely decisions, resulting in decreased morbidity.

The pouch is not without its complications. After an IPAA has been created, pouch dysfunction, including chronic pouchitis or ongoing septic events, is often deemed "Crohn's disease of the pouch" because many surgeons are unwilling to consider that a correctable mechanical pathology is responsible for the patient's condition. Ultimately, they blame Crohn's disease of the pouch as the underlying pathology. The patient is then referred back to their gastroenterologist to consider antibiotic treatment of chronic pouchitis or initiation of immunosuppressive medications to treat Crohn's disease of the pouch. As various medical therapies are tried with a failing pelvic pouch, patients become increasingly deconditioned with a low quality of life. This situation can be avoided by having a multidisciplinary team with experience in managing pouch dysfunction to determine the cause of the problem: i.e., primary Crohn's disease of the pouch versus a mechanical issue that should be addressed with a redo pouch or other interventions.

When a patient is referred for pouch surgery, the timing of surgery, nutritional status, medication use, malignancy, and clinical status determine the best operative technique to be used. Minimally invasive surgery (laparoscopy/robotic) has its role in pouch creation but must be practiced with care because minimally invasive pouch surgery has led to a trend of incomplete proctectomies and pouch twists [17, 18]. Patients with acute toxic colitis, chronic UC (CUC), indeterminate colitis, and Crohn's disease (CD) all have different operative needs, but there should be no confusion that the primary objective in the acute setting is always saving the life of the patient and not risking their life to save the colon and rectum. In addition, all

available efforts should be made to minimize postoperative morbidity and mortality, optimize pouch function, and increase the pouch's longevity.

We will briefly focus on the technical aspects of the pouch and redo pouch creation and emphasize the benefits and drawbacks of the various restorative procedures in order to facilitate multidisciplinary discussion between the medical and surgical services caring for IBD patients. It must be recognized that additional operations do add morbidity and hospital costs, but they also increase the pouch's longevity by decreasing postoperative pelvic sepsis.

Surgical Management of Acute Toxic Colitis and Chronic Ulcerative Colitis

The management of acute toxic colitis and chronic ulcerative colitis is vastly different. The paramount focus of a surgical emergency in toxic colitis is to control bleeding, control sepsis, and avoid squandering future surgical options to restore continuity. Conversely, the focus of elective operations is to complete the operation as precisely as possible in order to avoid morbidity and mortality and optimize pouch function. Toxic colitis mandates efficient extirpation of the colon to remove the bulk of the disease, fecal diversion of the rectum with an ileostomy, and avoiding a pelvic dissection with pouch creation in the acute setting. Surgical management of acute toxic colitis is indicated in patients with sepsis secondary to perforation, peritonitis, hemorrhage, and progression in spite of medical management [19]. A multidisciplinary team is best to manage these patients because distinguishing severe colitis that may respond to medical escalation versus toxic colitis requiring emergent surgery is often a challenging decision. When patients present with a flare, regardless of current immunosuppressive medications, surgical consultation should be obtained and the patient managed in collaboration with medicine and surgery. Parenteral steroids are typically started if the patient is admitted to a monitored care setting after ruling out infectious etiologies such as *Clostridium difficile* colitis, *Escherichia coli*, *Shigella*, cytomegalovirus (CMV), ova/parasite, and ischemic colitis [19]. On admission, the patient should have a thorough clinical exam to include a history of bowel habits, with attention to the possibility of abdominal peritonitis and examination for perianal disease suggestive of CD. Severe colitis and fulminant colitis are described according to Truelove and Witts or a more novel classification system. Severe colitis is defined as at least six bloody stools per day along with anemia, elevated erythrocyte sedimentation rate (ESR) >30 mm/h, fever, and tachycardia. Fulminant colitis is defined as more than ten bowel movements per day along with ongoing rectal bleeding, an ESR above 30 mm/h, the requirement of blood transfusions, fever (>37.5 C), tachycardia, abdominal pain, acute colonic dilation (>5.5 cm), loss of haustration, and an edematous colonic wall on cross-sectional imaging or plain radiographs [19] (Table 13.2).

Table 13.2 Truelove and Witts colitis severity index [42]

	Mild	Severe	Fulminant
Stools (#/day)	<4	>6	>10
Blood in stool	Intermittent	Frequent	Continuous
Temperature (C)	Normal	>37.5	>37.5
Pulse	Normal	>90	>90
Hemoglobin	Normal	>75% of normal	Transfusion required
ESR	<30	>30	>30

[a]*ESR* erythrocyte sedimentation rate

In the absence of peritonitis and without clinical deterioration from admission to hospital day 3, the patient may be bridged to long-term therapy with infliximab or cyclosporin. Patients who continue to have over 8 bloody stools per day, or 3–8 stools associated with a C-reactive protein (CRP) over 45 mg/L despite optimal medical treatment after hospital day 3 have a colectomy rate of 85% [20]. A flexible sigmoidoscopy can be performed to document the disease severity of the distal bowel and obtain biopsies to check for CMV. If a durable response is seen, a transition to a steroid taper with outpatient medical management can be formulated after the initiation of infliximab or cyclosporin as an inpatient. However, there must be multiple checkpoints during the hospital stay that mandates surgical consideration: admission, lack of improvement on intravenous (IV) steroids, and lastly, if there is no progress after rescue infliximab or cyclosporin initiation. With signs of clinical deterioration or lack of improvement, emergent surgery will be needed, and, in such a scenario, the patient will undergo an operation with minimal physical reserve while on high-dose steroids or additional immunosuppressive medications. Therefore a subtotal colectomy with end ileostomy is the procedure of choice; any consideration of a proctectomy with IPAA should be abandoned in the acute setting. The subtotal colectomy will result in an end ileostomy with the bulk of the disease (the colon) resected, allowing most patients to wean from all medications before pouch creation; the rectum will remain in situ for the emergent surgery. A proctectomy will follow the subtotal colectomy after 6 months of nutritional improvement and cessation of all medications. The proctectomy and ileal pouch creation can be diverted with ileostomy, and reversal 3 months later (three-stage procedure), or left undiverted (modified two-stage).

Furthermore, any doubt about the diagnosis, UC versus Crohn's proctocolitis, should result in a subtotal colectomy before any pouch creation, as the entire colonic specimen may allow for pathologic clarification of the disease. Furthermore, if the pathology results reveal Crohn's disease, the patient may still be a candidate for an IPAA, but their informed consent should make it clear that there is a lower chance of pouch survival than in UC patients. Additionally, a subtotal colectomy with end ileostomy will allow for a hypothesized passive elongation of the small bowel mesentery, allowing for a tension-free pouch anastomosis to the anal canal, a concern when patients undergo a one-stage or two-stage IPAA.

A subtotal colectomy can be performed with a minimally invasive platform, such as laparoscopic or robotic, as it has shown to be safe and results in equivalent outcomes compared to an open laparotomy except for prolonged operative time [17]. In extremis, a traditional laparotomy incision is more efficient for removing the diseased colon and stopping the ongoing sepsis because the additional time required for a minimally invasive surgery can be dangerous to the septic patient [21]. The ultimate decision regarding type of surgery is driven by patient safety and the surgeon's familiarity in completing the operation with their preferred platform. However, in an emergent setting, a subtotal colectomy with an end ileostomy should be the planned procedure regardless of modality. The only caveat is a unique circumstance of a historic procedure created before modern medications when the colon was too friable for manipulation: a "Turnbull-blowhole" colostomy and ileostomy [22]. This operation is rarely performed but has seen its indication in pregnant patients needing urgent surgical intervention, precluding eventual IPAA [23].

With the subtotal colectomy performed in an emergent setting, the technical point of consideration is the rectal stump. There are two options for the rectal stump in an emergent setting with a colorectum healthy enough to maintain an intact staple line at the rectosigmoid junction: leave the rectosigmoid in the pelvis or tack the staple line superficial to the fascia and close the skin over it (Fig. 13.1). The benefit of leaving the rectosigmoid in the pelvis is to allow a minimally invasive operation to be completed without an additional incision (made vertically or Pfannenstiel superior to the pubis) and to decrease the occurrence of staple line dehiscence secondary to a relative staple line ischemia that may result from tension as the colon is brought to the fascia level [24]. The benefit of tacking the staple line to the fascia is to prevent pelvis sepsis should the staple line dehisce. A dehisced staple line from a rectum left in the pelvis can result in pelvic sepsis, obscure the plans for the future proctectomy, and cause increase in morbidity. Conversely, a dehisced staple line

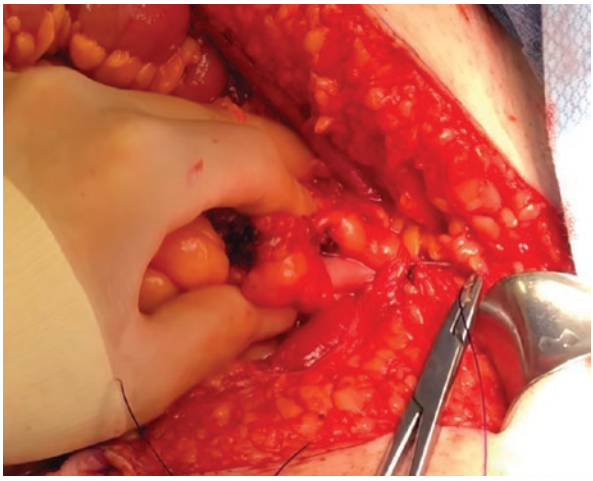

Fig. 13.1 Intraoperative photo of the stapled-off rectosigmoid colon being tacked superficial to the fascia to prevent a staple line dehiscence in the pelvis during a subtotal colectomy for ulcerative colitis. The skin is closed over the buried rectosigmoid and can be opened if a staple line dehiscence occurs

tacked to the fascia results in a wound infection that can easily be treated with incision, drainage, and antibiotic treatment, without causing any increased difficulty for the future proctectomy. Lastly, if the transverse staple line along the rectosigmoid falls apart during the operation because of a severely diseased colon, the rectosigmoid can be matured as a mucus fistula just above the pubic incision; this will hopefully avoid pelvic sepsis and can be pouched with a stoma appliance.

When to Redo a Pouch

Though the short-term success rate of an IPAA is around 95%, many patients suffer from mechanical and inflammatory problems leading to a failure rate of up to 15% [25, 26]. When an IPAA is successful, patients will no longer suffer from constant fecal urgency secondary to proctitis and typically have around six bowel movements per day and one at night. Consistently, the quality of life scores are high, and only a fraction of patients younger than 45 years old state that they have any social, work, or sexual restrictions [27]. Unfortunately, some patients suffer from acute postoperative complications and chronic pouch dysfunction and may not receive a clear answer about their underlying pathology or treatment options. These patients become so deconditioned before seeing a pouch specialist that the once dreaded thought of a diverting ileostomy is now accepted to improve their quality of life [28]. However, in 2–7% of patients after IPAA who present with a constellation of symptoms that mimic CD of the pouch, the diagnosis may be changed to CD, thus obscuring the diagnosis of a mechanical problem of the pouch. Mechanical complications include a chronic anastomotic leak with abscess, retained rectum causing proctitis, a pouch twist leading to obstructive defecation, efferent and afferent loop syndrome, small bowel obstructions, or chronic pouchitis [29]. Even symptoms highly suggestive of Crohn's disease of the pouch, such as multiple perianal fistulae requiring seton drainage, can be caused by an IPAA-anastomotic leak necessitating drainage via the perineum. This situation leads to a dilemma where patients are mislabeled as "Crohn's disease" rather than investigating the pouch for a possible underlying mechanical problem [30]. Moreover, patients may have a phenotype of CD that is amenable to a restorative proctocolectomy but has pouch failure, not because of CD but because of a mechanical problem associated with its construction. With rectification, their pouch may be salvaged, and they can avoid a permanent stoma even in the setting of CD [29].

Redo Pouch Workup

The most crucial element when considering a patient for redo IPAA is the history of the patient. Many patients who convert their diagnosis from UC to CD have years of normal pouch function without overt symptoms of CD before the onset of

symptoms. These patients typically state "everything was fine for [X]-number of years" before their current symptoms. Conversely, patients who present for consideration of redo IPAA who have an inherent mechanical issue with their pouch voice they "never felt right" after IPAA creation, typically within a year of the index IPAA. That is highly suggestive that an issue resulting from the onset of pouch creation may be amenable to redo pouch and CD is not the underlying factor. A caveat is a select group of patients who develop Crohn's disease of the pouch and are candidates for a redo pouch procedure. They must understand that their redo pouch may ultimately require a permanent ileostomy. Almost all redo pouch procedures are driven by the patient's desire to avoid a permanent stoma, and attempts to dissuade a patient from having a redo pouch or to undergo pouch excision should be avoided.

The workup for a redo pouch consists of a thorough history and physical, paying particular attention to the onset of symptoms. The pathology from the previous operations and operative reports is reviewed to look for evidence of non-caseating granulomas consistent with CD or mention of a total proctocolectomy with pouch creation during acute toxic colitis, which could predispose the patient to an incomplete proctectomy, anastomotic leak, stricture secondary to tension on the anastomosis, or other technical or anatomic abnormalities (Fig. 13.2). Previous cross-sectional images should be reviewed to assess for evidence of adhesive bowel obstructions and overt pathology that may present in parallel to pouch dysfunction, or new imaging should be performed. The standard workup consists of a contrast-enhanced magnetic resonance (MR) image of the pelvis to assess for pelvic sepsis (abscess or sinus tracts) and evidence of pouch twist by examining where the mesentery is positioned (Fig. 13.3). A gastrografin enema can be performed to assess for stricture, fistula, sinus tract, or afferent loop syndrome. An exam under anesthesia with flexible pouchoscopy can be performed to assess for retained rectum, length of the cuff, pouch twist, anastomotic leak, and pre-pouch bowel inflammation suggestive of CD. Select patients may need an MR enterography to assess for proximal small bowel inflammation consistent with CD. Other patients with presumed paradoxical defecation may need anal manometry to rule out dyssynergic defecation. Additional findings and their treatments are summarized in Table 13.3.

A formal redo IPAA involves an upfront diverting ileostomy for 6 months, followed by a full abdominopelvic pouch mobilization with any number of additional procedures, such as possible pouch untwisting, completion proctectomy, debridement and drainage of chronic granulation tissue, conversation from a double-stapled to a mucosectomy with handsewn anastomosis, and other intraoperative techniques. However, some pouch surgery is less invasive, and some can even be attempted endoscopically. For example, afferent loop syndrome (ALS) can be managed endoscopically or with minimally invasive pouch mobilization and pouch pexy. A chronic leak from the tip of the J may be managed with a limited laparotomy or minimally invasive surgery by transection with a linear stapler or oversewing the chronic leak site [31]. A multidisciplinary pouch team should manage these scenarios; their intervention may not require a formal redo pouch procedure.

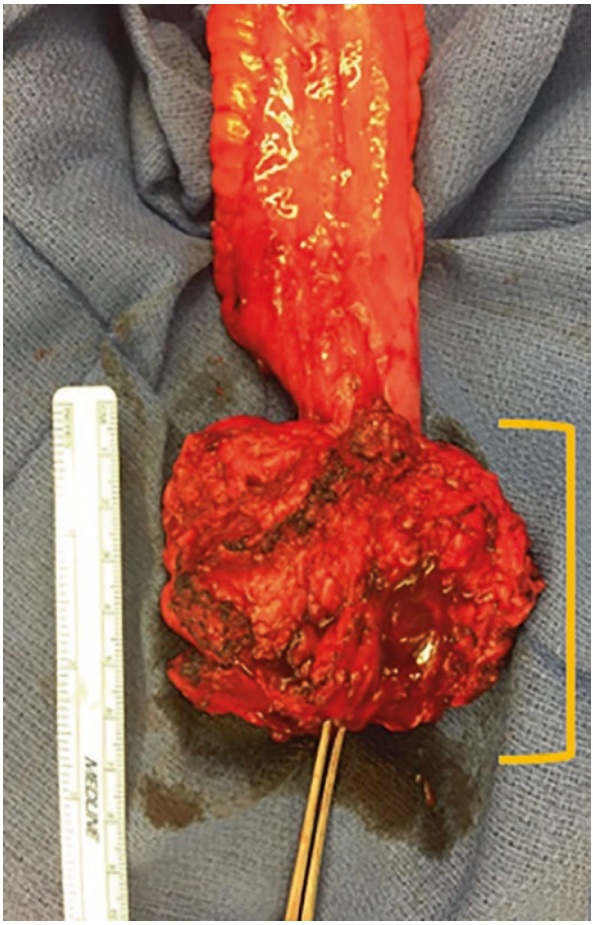

Fig. 13.2 Intraoperative photo of a J-pouch with approximately 6 cm of retained rectum (orange bracket) leading to chronic ulcerative proctitis causing chronic pouchitis and an anastomotic stricture

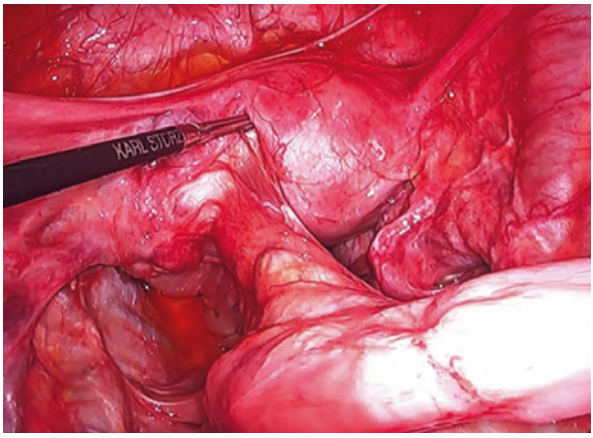

Fig. 13.3 Still image from a diagnostic laparoscopy showing a pouch twist after a laparoscopic IPAA leading to pouch dysfunction. The pouch is seen twisting around the mesentery as it lays in the pelvis

Table 13.3 Complications and management of pouch surgery [43]

Pouch dysfunction	Diagnosis	Treatment
Pouchitis	Pouchoscopy, biopsy	Oral antibiotics Chronic: Crohn's disease workup Absence of Crohn's disease: workup for mechanical complication, consider redo IPAA or pouch excision
Fistula	Exam under anesthesia, MRI	Drain sepsis, possible seton placement, advancement flap, LIFT procedure Complicated: workup for Crohn's disease, consider workup for mechanical complication
Anastomotic leak	Exam under anesthesia, MRI, pouchogram	Delay ileostomy closure Leak from pouch body: drainage sepsis, antibiotics. If refractory, consider redo IPAA or pouch excision Leak from tip of J: attempt to divide with linear stapler, redo pouch Leak from anastomosis: serial exams, place vacuum sponge or mushroom catheter drainage, lay open sinus tract, may need redo pouch prior to ileostomy reversal
Bowel obstructions	Cross-sectional imaging, pouchogram with post-evacuation images	Adhesive bowel obstruction: adhesiolysis Pouch twist: redo IPAA Afferent loop syndrome: endoscopic or surgical intervention
Anastomotic stricture	Physical exam, pouchoscopy, cross-sectional imaging	Anastomotic stricture: dilation (operative, self-dilation) Chronic: pouch advancement, redo IPAA/excision
Obstructive defecation	Anal manometry, pouchogram with post-evacuation images	Dyssynergic defecation: pelvic floor physiotherapy, biofeedback, lifestyle modification (refractory, consider ileostomy) Efferent limb syndrome: redo IPAA to correct long efferent limb of S-pouch
Cuffitis	Exam under anesthesia, pouchoscopy	Medical treatment with anti-inflammatory suppository or enemas Chronic: pouch advancement flap

MRI magnetic resonance imaging, *LIFT* ligation of internal fistula tract, *Pouchogram* gastrografin enema to evaluate a pelvic pouch

Redo IPAA

Redo IPAA should be performed at highly specialized referral centers with the experience and resources to perform such a complex operation. The redo operation consists of cystoscopy with ureteral stents, adequate intravenous access, arterial line placement, consideration of an epidural catheter, a midline incision, and an operative team with experience in performing redo pouch procedures. Prior to this, patients undergo a diverting loop ileostomy (laparoscopic if feasible) for 6 months to enable them to develop the physical and mental reserve for their redo procedure

because many patients present severely malnourished and deconditioned. The diverting loop ileostomy should be fashioned 20 cm proximal to the inlet of the pouch to allow for the new stoma site to be used as the ileal-anal anastomosis during the redo pouch, known as a "thoughtful ileostomy." The "thoughtful ileostomy" can be used as the anastomosis if required and, in doing so, does not contribute to any bowel loss [32]. The most extensive series on redo pouches was published from the Cleveland Clinic in 2015; the outcomes of over 500 patients who underwent a redo IPAA were reviewed [26]. In their study, the mean time to redo ileal pouch was 3 years, with a wide range from within a year of IPAA creation to almost 30 years later. The most common indications for redo pouch were leak/fistula, followed by dysfunction, pouchitis, stricture, incontinence, neoplasm, and bowel obstruction, in decreasing frequency. Patients with a minimally invasive pouch were more likely to have retained rectum leading to pouch failure. Though the "thoughtful ileostomy" should be created in all cases if new pouch construction is needed, over half of the patients could have their index pouch preserved during redo pouch surgery; the majority needed a handsewn neo-IPAA.

Postoperative complications occur in just over half of patients, with pelvic sepsis being the most common complication, followed by bowel obstruction/ileus, anastomotic leak, wound infection, and other common postoperative morbidities. The success rate of redo pouches is lower than the index pouch, as 20% of patients will have a failure of their redo IPAA. Though a minority of patients can have their redo pouch salvaged even after a failed redo IPAA, the index pouch survival is much higher, and every effort should be made to maximize its longevity, for example, by utilizing an initial three-stage IPAA focusing on a proper proctectomy without a pouch twist. The 1-year redo pouch survival is over 98% in high-volume centers, with an overall 5- and 10-year survival of 90% and 82%, respectively. Functional outcomes and quality of life after redo IPAA are worse than after index pouch surgery; however, patients would recommend the operation to others and undergo the operation again based on questionnaire results. Redo IPAA has a higher incontinence and seepage rate, with over half of patients needing to wear a pad overnight and an average of six bowel movements during the daytime, with two at night. Though the results may be worse than index pouch function, overall, patients are happy with their redo pouch function, especially compared to having to live with a permanent ileostomy.

In conclusion, redo IPAA is a safe procedure that provides patients with acceptable functional results and quality of life. Despite being performed in highly specialized centers, pouch survival is lower than the index pouches, and delays in diagnosis occur because of many surgeons' predisposition to blame pouch complications on Crohn's disease of the pouch. Redo procedures are motivated by the patient's desire to avoid a permanent ileostomy, and thorough communication on pouch survival and the multiple operations required to redo the pouch are needed. A "thoughtful ileostomy" should be performed before redoing a pouch that will require a full abdominopelvic pouch mobilization. Thought should also be exercised in deciding which patients may have an ileostomy omitted when their pouch

is created. Minimally invasive IPAA and omission of a protective stoma lead to mechanical failures, not Crohn's disease, and are responsible for many patients needing a redo pouch.

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Chapter 14
The Economics of IBD: Is There a Future for a Medical Home?

Ipek Sapci, Benjamin Click, and Scott R. Steele

Introduction

Inflammatory bowel diseases (IBD), consisting of ulcerative colitis and Crohn's disease, are chronic complex conditions that are associated with disability and impaired quality of life [1, 2]. IBD affects nearly seven million people globally, with a higher prevalence in locations with higher socioeconomic index [3]. Worldwide, North America has the highest age-standardized prevalence rate of 422 cases per 100,000 people [3]. In addition, it has previously been shown that the overall prevalence of IBD is increasing in countries that previously had a low prevalence, and it is increasingly being recognized that IBD is creating a growing burden on healthcare systems. This excessive burden inevitably impacts the global economy due to the high worldwide prevalence of IBD. As an example, the Crohn's and Colitis Foundation has estimated that the total annual direct cost of all US patients with IBD was between 11 and 28 billion US dollars [4, 5]. In addition, this cost was shown to have increased in the last two decades. Further, in the last 20 years, hospitalizations and associated charges for IBD have increased exponentially [6].

Cost drivers of IBD care include pharmacotherapy, hospital admissions, emergency department visits, and surgical treatment [7]. Not surprisingly, the high economic burden of IBD is thought to be tied to the complex nature of the disease because Crohn's disease (CD) and ulcerative colitis (UC) are a subset of diseases with varying presentations often necessitating a combination of medical and surgical therapy. Medical therapy often includes costly newer monoclonal antibodies

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R. Rajapakse (ed.), *Inflammatory Bowel Disease*, Clinical Gastroenterology,
https://doi.org/10.1007/978-3-030-81780-0_14

and small molecules that can be extremely expensive, some with no "generic" substitute. Due to the high prevalence and complex nature of the disease, IBD creates an economic issue both for the patient trying to cover the costs and for the provider who is trying to keep expenses to a minimum, while still providing state-of-the-art care. In addition to the aforementioned drivers of cost, unlike most chronic diseases, the IBD patient population consists mostly of young adults. Disease exacerbations frequently cause disruptions in patients' employment status, creating an additional financial burden for the patient. Reports show that patients with IBD not only experience higher healthcare costs but they also have higher wage-related opportunity loss [5]. Further, as IBD (especially CD) can be associated with lifelong recurrences or flares, the impact compounds over time.

More recently, the Crohn's and Colitis Foundation formed a task force to further investigate the cost of IBD. The cost of IBD task force used insurance data and looked at 52,782 IBD patients and compared them to non-IBD controls. They reported that patients with IBD had over three times higher costs compared to the non-IBD cohort. They also had twice the out-of-pocket costs per year [5]. Although it describes the high economic burden of IBD, this detailed cost analysis did not include the insurance premium paid by patients and as a result likely *underestimated* the real-life financial burden for these patients. It is also important to highlight that annual costs were considerably higher in the first year after diagnosis (~$25,000). Further, after the first year of diagnosis, the costs stabilized; however, 7–8 years after diagnosis, it increased once again to a similar point of $25,000 [5].

IBD is also unique from a healthcare cost perspective as a relatively small group of patients contribute to a large majority of economic burden, while the specific diagnosis of CD can drive the costs even higher [5]. Yu et al. found that, in the United States, total costs of CD patients in the top 25% averaged $60,582 per year and more than $300,000 per year for patients in the top 2% [8].

Clearly, patients with IBD include a diverse population of patients with different healthcare expenditures. In this chapter we will discuss drivers of cost in IBD in detail and describe the IBD specialty medical home (IBD SMH) model that has recently been described to decrease costs and improve the overall quality of care.

Healthcare Costs of Pharmacologic Treatment in IBD

Using pharmacologic agents is typically the first step in the management of patients with CD and UC [9]. These agents consist of anti-inflammatory drugs, immunomodulators, and biologics. Recent studies have reported that pharmacy expenses are one of the largest cost drivers and can consist of up to 35% of direct costs [7, 10]. Besides maintenance, pharmacological therapy is also initiated in most patients before escalation to surgery or during hospitalizations. Adding to this, treatment algorithms have recently emphasized earlier use of biologic agents to prevent disease progression and optimize outcomes. Thus, more patients are likely to receive these costly agents even compared to more recent data. When considering the total

costs, we need to take other factors into consideration. Aside from the therapy itself, potential adverse effects of the pharmaceutical agents and possible complications related to subsequent surgery further increase the risk of hospital admissions and consequently the economic burden [11].

Not all medications are associated with higher costs. Anti-inflammatory drugs are often the preferred agents for treating mild colonic and rectal disease and usually comprise the initial phase of the pharmacological therapy. Importantly, treatment with aminosalicylates can initially have lower costs, but when followed over time, an increase in cost was observed in these patients in later years. Antibiotic treatment may also be necessary and was associated with higher costs in the first year after diagnosis, but this was shown to decrease over time [12]. Opioids may be required when managing patients with IBD and pain or high ostomy outputs. Concurrent opioid use has been associated with higher ED and hospital admissions, which can potentially contribute to increased costs [5]. This could potentially be related to disease severity, but comorbidities such as chronic pain could also have driven healthcare utilization. Furthermore, medical service costs were found to be highest for corticosteroid use in CD and UC [12]. Patients who had corticosteroids included in their regimen were more likely to have IBD-related procedures and events, likely again a signal of disease activity or severity. This shows that medical management is closely tied to the chronicity of the disease and adverse events patients experienced with IBD, which in turn, affect the costs [12].

The use of biologic agents has been described as one of the major parameters that drives the cost of IBD treatment much higher than other disease processes. On the positive side, since these agents have been introduced, they have greatly influenced the management of IBD [13]. Although they are effective in putting patients into remission, their novelty and in many cases lack of a generic counterpart cause them to be associated with greater annual total medical costs [12, 14, 15]. Furthermore, some patients do not tolerate them and will have potential adverse effects that also contribute to the costs [12, 14, 15]. In comparison to other classes of medications, patients who are treated with biologic agents are reported to have higher costs, and this increases over time [5]. Kappelman et al. reported infliximab to be the most costly of these medications, with almost 10% of CD patients having two or more claims for infliximab infusion [10]. This is based on the number of patients on this medication and its use versus the individual dose cost. Coward and colleagues have demonstrated that biologic use (i.e., infliximab) when used in the hospital was also identified as an independent predictor of overall increased costs [16]. Again, these findings may likely simply reflect the fact that significant disease activity or severity is associated with consequently higher healthcare utilization.

It has also been suggested that high costs of biologic agents may be compensated by decreasing the healthcare utilization and surgery rates; however, despite the small decrease in healthcare utilization costs, median total costs were increased after initiation of antitumor necrosis factor (TNF) in a Canadian study [17]. While improving disease-related outcomes and quality of life for patients, further research is necessary to clearly define any cost benefits of biologic agents – especially given the hefty associated price tag. It is also important to note that an individual's

specific disease may influence total cost of care. Consistently, CD is associated with higher total costs compared to UC. This may relate to treatment algorithms for certain providers or within certain health systems. In an analysis of over 30,000 patients, CD patients were more likely to have had episodes of anti-TNF treatment, while UC patients were more likely to be managed with aminosalicylates predominantly [12]. In addition, oral corticosteroid monotherapy or combination of steroids with immunomodulators was a strong predictor of adverse events in Crohn's disease, which can contribute to increased costs. Patients who were having medical therapy with oral corticosteroid involving regimens were more likely to require ED visits and surgery compared to other therapies [12].

Hospitalizations and Surgical Costs

More than half of patients with IBD who are treated with pharmacologic options fail to achieve clinical remission at 1 year [18]. As stated, this frequently necessitates hospital admissions and surgical management in both CD and UC patients [19]. The risk of undergoing surgery 10 years after diagnosis of UC and CD was reported to be 15.6% and 46.6%, respectively [20]. Similarly, in a population-based study from Minnesota, the cumulative probability of requiring a colectomy from the time of diagnosis was 18.9% at 10 years in UC patients [21]. Of note, this rate may be decreasing, potentially tied to increasing biologic utilization [22]. Despite the trend in decreasing risk over the past 60 years, there is still a substantial surgery risk that may add to the associated healthcare costs [20].

Kappelman et al. looked at treatment costs for adults and children with IBD and found that 40% of hospitalization costs occurred during admissions due to surgery [23]. Another study by Coward et al. reported extensive costs for UC flares and colectomy ranging between $5,499 and $23,698. These costs were, not surprisingly, found to be higher for patients who underwent surgery compared with medically responsive patients [16]. Surgery, however, may be cost-effective in select populations, especially considering the length of time that patients may be required to receive high-cost immunotherapy. In the LIR!C trial, De Groof and colleagues compared the cost-effectiveness of laparoscopic ileocecal resections in CD patients with medical therapy and found that the total direct healthcare costs at 1 year were lower in the resection group compared with the infliximab group, with a mean difference of 8931 euros [24]. These results point to the fact that the cost of surgical treatment of IBD needs to be investigated further and may potentially have cost benefits compared to treatment with biologics in select circumstances.

Patients with CD and UC have increased rates of hospitalizations compared to non-IBD controls, with additional differences existing between CD and UC patients [23]. In fact, the mean total costs of patients with CD were almost five times that of a matched control [10]. Patients with IBD were also found to have higher per-patient inpatient costs when compared to patients with rheumatoid arthritis, suggesting that even compared to other chronic inflammatory conditions, IBD still

carries higher inpatient costs [7]. CD patients, in particular, had higher rates of hospitalization for both surgical admissions and medical hospitalizations. They were also more likely than UC patients to have had previous inpatient hospitalizations (25.3% vs. 14.8%). In order to contain these costs, it is important therefore to identify patients who are at higher risk for hospitalizations and surgical treatment. For CD patients, steroids were found to predict this risk, as yearly surgery rate was almost threefold for patients who were on steroids [12]. Another systematic review showed that 53–66% of the direct medical costs in IBD were related to hospitalizations, with an average hospitalization cost of $37,459 in the United States [8]. It is acknowledged that disease severity significantly affects costs. Patients with severe disease can have three- to ninefold higher costs compared to patients in remission [8].

Higher healthcare utilization by CD patients has been shown in other studies. It was also reported that direct average annual healthcare cost of CD is greater than UC [25]. A systematic review investigating economic and quality of life burden of CD found that the total economic burden of CD can reach 15.5 billion dollars in the United States [26]. For CD, close to one-third of the costs related to care were attributable to hospitalization, one-third to outpatient care, and over one-third to pharmacy-related costs [10]. Mean total costs for patients with CD were reported to be more than 10,000 USD and almost five times the cost of matched controls [10]. Disease remission was associated with increased quality of life in patients with CD and a decrease in hospitalizations and surgeries, which contributes to decreasing treatment cost on many fronts [27].

All these factors should be taken into consideration when evaluating the financial impact of treatment for IBD patients, as differences in management based on disease severity can greatly affect the costs.

Overall Cost of IBD

Total annual direct cost of all US patients with IBD was estimated to be between 11 and 28 billion dollars [4]. In addition to pharmacological and surgical management, there are multiple other factors that increase the cost of IBD treatment. These include outpatient visits, endoscopic procedures, and any imaging and laboratory tests performed. Additionally, workforce loss due to absenteeism or sick leave further contributes to indirect costs included in these estimates [28]. These indirect costs can be potentially modifiable and important to follow as they may lead to not only changes in costs but also outcomes as well.

In a nationwide healthcare utilization report, it was found that annual rates of emergency department visits were 11%, hospitalizations were 6.5%, and surgeries were 2.8% in IBD patients. In addition, the percentage of patients having at least an annual outpatient visit was 94%, with CD patients having higher rates when compared to other disease processes [29]. As an example, outpatient costs of IBD treatment were found to be 53% higher when compared to a similar population with

rheumatoid arthritis [7]. Outpatient utilization also includes procedures that are more common in IBD such as endoscopic procedures [23]. The reported annual colonoscopy rates were 25% and 34% for CD and UC, respectively [29]. More recently, Park et al. investigated 52,782 patients with IBD, and this group incurred a greater than threefold higher direct cost of care compared with non-IBD controls and more than twice the out-of-pocket costs, with all-cause IBD costs rising after 2013. Patients with IBD also experienced significantly higher costs associated with time spent on healthcare compared to controls. The burden of costs was most notable in the first year after initial IBD diagnosis. The study identified several key drivers of cost for IBD patients: treatment with specific therapeutics (biologics, opioids, or steroids), emergency department use, and healthcare services associated with anemia, relapsing disease, or mental health problems [5]. These recent detailed reports highlight the high healthcare utilization by IBD patients and shift the focus to strategies to optimize the management of IBD and to decrease the costs for patients, while improving their quality of life and alleviating the burden on the global economy.

IBD Specialty Medical Home

It is important to, again, reiterate the context in which all this data should be evaluated. IBD has the highest prevalence in the United States and is one of the most expensive gastrointestinal diseases to treat [30, 31]. It is estimated that up to three million Americans are affected by IBD [32]. As such, implementing ways to significantly improve this group of patients' care and to focus on doing it in a proactive manner can have a profound impact. Conversely, failure to do so not only can result in a significant economic burden but also can create lifelong challenges for both the patient and their healthcare providers [7, 15, 33]. Coordinating care among all providers is also critical to success. Optimal IBD care requires not only coordination between medical and surgical specialties but also integration of other disciplines, to provide a multifaceted evaluation, addressing problems with nutrition and psychosocial factors such as anxiety and depression. This creates unique financial challenges; as healthcare providers spend more time on the complex, high-utilizer patients and patients are, more often than not, billed for multiple services. In addition, IBD does not exclusively affect the gastrointestinal system, and patients also have increased risk of infections, vascular complications, certain malignancies, and higher rates of concomitant mental health disease [34, 35]. Due to its multifactorial nature, IBD patients frequently receive fragmented care that is not always well-coordinated. These issues resulted in the creation of several value-based healthcare models that were directed toward cost reduction and improvement of quality of care, by facilitating coordinated multidisciplinary care.

One of these is the IBD specialty medical home (IBD SMH). A medical home can be described as a smaller team of providers, with one provider acting as the patient's main point of contact who takes on the role of coordinating the individual

patient's acute and chronic care. The medical home model was initially established in primary care, and relative improvements in quality was reported with varied changes in cost [36, 37]. This model aims to manage the patient by an interdisciplinary team that provides the patient with integrated continuous care [38]. Its main focus is to increase patient surveillance and create individualized treatment plans. It also aims to overcome financial challenges and create better plans for patients and their providers. Another goal of the IBD SMH is to address psychosocial determinants of care and to use technology to decrease the number of visits, by using virtual healthcare and remote monitoring to survey and manage patients effectively [38].

Medical homes often aim to decrease cost and integrate care primarily for patients with complex disease who require frequent visits and high utilization of resources. A crucial point of the IBD SMH is that it aims to decrease cost for the patient, while optimizing management. One worry is that the higher cost of IBD treatment may cause increased stress for the patient and possibly decrease patient compliance. In this capacity, the IBD SMH aims to better understand patient needs and focus on patient benefit.

The first IBD SMH was conceptualized and launched at UPMC (University of Pittsburgh Medical Center) in collaboration with the UPMC Health Plan. In the UPMC model, the medical home had the gastroenterologist as the primary physician. The patient care multidisciplinary team consisted of a gastroenterologist, dietician, social worker, psychiatrist, advanced practice providers, nurse care coordinators, and when necessary, colorectal surgeons and chronic pain specialists [15, 38, 39]. UPMC's IBD SMH initially aimed to enroll high-utilizer IBD patients; however, it eventually extended to include all adult IBD patients covered with UPMC Health Plan. After implementation of the IBD SMH, UPMC witnessed a 47% reduction in ED visits and 36% reduction in hospitalizations. Patients who were enrolled in the IBD SMH also reported increased quality of life scores. It is notable to mention that this model reported the greatest improvement in patients in the most extreme quartiles, suggesting that the most severe patients can substantially benefit from care provided by the IBD SMH [39, 40].

Another important aspect of the IBD SMH is that it incorporates psychosocial well-being of the patient in its foundation. Besides the biological effects of the disease, psychosocial factors greatly affect patients' daily life, resulting in disrupted work attendance. Every patient enrolled was evaluated for behavioral health conditions or psychosocial barriers to care, and individualized treatment plans were implemented. These incorporated social support, stress reduction training, and behavioral skills. These strategies addressed the problems IBD patients had with pain, anxiety, depression, and stress. Behavioral health providers were integrated into creating management plans. Focusing on these issues in IBD patients has the potential to reduce outpatient visits and hospital admissions [38, 39]. It is also important to stratify care and individualize treatment based on disease complexity. A complexity score has been previously described that involves biologic, social, and psychological domains (Table 14.1) [15, 41]. This score further allows patients to be evaluated objectively and customized care plans to be developed based on

Table 14.1 Complexity risk score to individualize care in IBD specialty medical home

Domain	Complexity category	Score threshold
Biological	1. Current (patient-reported outcome)	IBD activity measures
	2. Current (objective)	Serological markers, endoscopy, radiographic
	3. History (lifetime)	IBD medication history, hospitalization, surgeries
Psychological	1. Current (past 6 months)	Anxiety and depression screening scores
		Psychiatric diagnoses
		Opioid use
	2. History (lifetime)	Psychiatric diagnoses and treatments
		Opioid use
Social	1. Current (past 3 months)	Relationships
		Environment
		Meaningful activity
	2. History (past year)	Relationships
		Environment
		Meaningful activity
Health system	1. Current(past 3 months)	Emergency department visits, hospitalization, medical relationships
	1. History (past year)	Emergency department visits, hospitalization, medical relationships
Motivation to change health behavior	1. Current (past 3 months)	Motivational interviewing

Each category scores on a scale from 0 (none) to 6 (severe) for a maximum total score of 60
Total score interpretation: 0–26 (minimal complexity); 27–35 (moderate complexity); 36–60 (high complexity)

Adapted from: Lobo et al. [41], Click and Regueiro [15]

both disease complexity and drivers of healthcare utilization. Based on this scoring, patient visits can be further individualized, thus increasing the efficacy of the IBD specialty medical home [15, 41].

One of the distinctive features of IBD management is the process of reaching a definitive diagnosis in the first instance. IBD can be challenging to diagnose in and of itself and requires not only detailed clinical factors but also diagnostic techniques such as colonoscopy and radiologic imaging that add to the overall healthcare costs even before the disease is diagnosed. IBD is also unique in that the treatment of disease is not focused on cure, as it currently has none, but on continuous control of disease activity in order to keep patients in remission. As such, multiple different avenues must be taken to achieve this goal. An IBD SMH, with the focus on a multidisciplinary proactive approach, is the ideal setting. Evaluating its impact financially is therefore more difficult because the economic burden that IBD creates is not limited to healthcare costs. Indirect costs in IBD, such as sick leave or early retirement, also greatly contribute to the economic burden. Keunzig et al. found that patients with IBD had higher indirect costs compared to non-IBD

patients and they were more likely to be absent from work and have a decrease in productivity. In a meta-analysis of studies between 1994 and 2014, the annual indirect cost of absenteeism for IBD patients ranged from $515.67 USD (USA) to $14.727 USD (Germany) per patient per year, even after adjusting for purchasing power disparity [42]. Another large US survey found that, on average, IBD patients required an extra 4.8 days off work and $783 USD in excess lost wages annually when compared to people without IBD [30]. In this regard, the IBD SMH has the potential to better guide patients in improving their daily life and subsequently reducing these costs.

It is vital to achieve longevity of coordinated care, which can at times be challenging in IBD patients. Scheduling regular meetings with the treating teams can help to review care plans, monitor implementation, and standardize care within the IBD SMH. Incorporating telemedicine to the practice can also potentially increase patient adherence and can help to address any problems without delays. In addition, many psychosocial problems can be addressed outside the clinic using telemedicine or smartphone-based applications. In the UPMC IBD SMH model, 35% of all behavioral visits were completed using telemedicine [38].

It is also important to note that the concept of an IBD SMH is fluid. Design and implementation can vary based on healthcare institution strengths, available resources, patient populations, and payer landscape with potential partners. Other centers have reported programs designed to address key components of the medical home including remote monitoring (Project Sonar by Illinois Gastroenterology Group in collaboration with Blue Cross Blue Shield) and value-based care initiatives at UCLA [43–45]. These two different models of integrated care have focused on improving chronic care delivery and have previously reported outcomes in both adults and pediatric patients [44–47]. The Illinois Gastroenterology Group (Project Sonar) and University of California Los Angeles (UCLA) both brought together multiple providers from different specialties, each focused on the major aspects that most IBD patients typically required (e.g., endoscopy, medicine, surgery, GI). Project Sonar reported a decrease in symptom intensity, ED visits, and hospital admissions through a combined approach. The UCLA model also reported comparable results with reduced ED visits, endoscopies, hospitalizations, and surgeries when compared to patients not involved in the integrated approach [43–45].

How to Start an IBD Specialty Medical Home?

Starting an IBD SMH can have variations, as there is no clear process. Preparations to start an IBD SMH should include in-depth discussions with the team members and health plan providers. Champions in each of these arenas are critical to success, because availability of the team members and accessibility of the medical home are both crucial aspects for patients. Another important aspect of the structure is telemedicine/virtual medicine, as previously noted [47]. Necessary technological infrastructure for the healthcare provider and patient alike should be planned in detail.

Before constructing an IBD SMH, it is important to investigate the individual center's data regarding drivers of cost and expenditures, as these may differ between institutions. Identifying these and the population that contributes highest to the cost will help create a suitable plan with the help of the insurance providers [38]. Data assembly and tracking is also important to consider and should not be omitted. In addition to regular clinical data, patient-reported outcomes should be collected during the course of surveillance, beginning with the initial visit. This will help better guide the care team and can also help stratify patients based on severity and individual needs [15].

Click et al. has recently reviewed the necessary components of an IBD SMH. These were single or few large payers with an interest in a specialty population, physician champions who are involved in a new healthcare delivery model, substantial IBD population to maximize value or at least 300 high-utilizer IBD patients, outcome measures with a defined goal of success, multidisciplinary team-based care model, and incorporating technology [15]. All the components are important in planning of an IBD SMH, and each should be discussed thoroughly during the development process.

From a patient's perspective, enrollment in a medical home starts with a referral and an intake visit by the primary provider gastroenterologist. Based on patient requirements, additional visits and follow-ups can be scheduled with team members other than the primary provider. It is vital to coordinate the schedulers to ease patients' scheduling needs. It is suggested that the schedulers address each patient's top three problems and their top three expectations from the visit. This step is very important in order to focus on the patient-centered approach. Furthermore, when applicable, synchronizing clinical visit days for gastroenterology and colorectal surgery providers who are part of the IBD SMH may help in enrolling and evaluating new patients. Team huddles can also be useful to better standardize care. In essence, huddles identify patients based on the severity of their disease, allowing standardized scheduling plans to be created. For instance, patients with well-controlled disease can be scheduled for yearly visits, and the focus can be to optimize work-life balance for this group. Patients with more severe disease may require monthly visits, and all attempts can be made to focus on a transition from controlling active disease to achieving and maintaining remission. Finally, including a pediatric gastroenterologist, when available, in the IBD SMH will expand IBD care to ease transition of management for pediatric patients as they reach adulthood.

Conclusion

Patients with IBD commonly receive lifelong care from a limited number of providers, each with potentially high costs of treatment. In this manner, healthcare utilization cost is concentrated in a small proportion of patients. This makes IBD a candidate for a specialty medical home that aims to provide patients with accessible, inclusive, and well-coordinated patient-centered care. Creating an integrated

patient care environment with an IBD SMH has the added potential benefit of decreasing both direct and indirect costs. This value-based model engages patients in learning how to manage their symptoms and in integrating behavioral and dietary health practices in their lives. This may, in turn, decrease absenteeism and early retirement and decrease indirect costs related to IBD. As more data regarding value-based care models become available, there will be better guidance for patient selection, development of highly integrative models that will include different aspects of disease management, and improved resource utilization. In the future, the IBD specialty medical home model has the potential to become an integral part of centers that specialize in the care of IBD patients.

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Chapter 15
A Physician Patient's Perspective: Personal Challenges and the Role of Subspecialist Telemedicine

Nilani Kaluarachi and Rashmi Advani

My journey with ulcerative colitis (UC) began 16 years ago in 2005. It was the same year that I got married and moved from the UK, where I attended medical school and began a career in obstetrics and gynecology, to Sri Lanka for a new job and a new life. I was 27 years old.

I had always been in good health. It was October of 2005, and I was a busy registrar in obstetrics and gynecology working more nights than I liked when I had an episode of, what I assumed was, gastroenteritis. However the watery diarrhea, which was the only symptom I experienced, lasted for more than a week, and a self-ordered stool culture was negative. The symptoms didn't settle with a course of empiric antibiotics.

After completion of my year as a house officer in the UK, I spent a year as a senior house officer in gastroenterology, working for two consultants whose special interest was inflammatory bowel disease (IBD). Hence, despite the lack of rectal bleeding and abdominal pain, after a couple of weeks of diarrhea with nocturnal disturbance, I decided to consult a gastroenterologist. He performed an unprepared flexible sigmoidoscopy on me and diagnosed me with ulcerative colitis. I was commenced on a course of tapering prednisolone and then mesalazine at a dose of 200 mg bid.

IBD is rare in Sri Lanka. I believe he mentioned that, at the time, there were no more than 200 diagnosed cases in a country of 22 million people. Today however IBD is on the rise in both Sri Lanka and the Asian subcontinent.

It is of interest that my maternal grandmother, who had lived most of her life in Sri Lanka but had also resided in the UK for a period of time, had been diagnosed

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R. Rajapakse (ed.), *Inflammatory Bowel Disease*, Clinical Gastroenterology,
https://doi.org/10.1007/978-3-030-81780-0_15

with ulcerative colitis in her early 70s. Her symptoms were well controlled with sulfasalazine until her death at 84 years of age.

The Grandmother

My maternal grandmother was born in Ceylon, now Sri Lanka, in 1921 and suffered from childhood and lifelong asthma.

Arranged marriages between suitable families were the custom and practice in Sri Lanka at the time. Along with family, class, caste suitability, and the matching of horoscopes, health was scrutinized as well. Suffering from chronic diseases such as asthma or infectious diseases such as filaria set a black mark against marriage. My grandmother hailed from a relatively well to do family and was fortunate enough to have her "dowry" in the form of jewelry, money, and elephants increased yearly till the age of 30 when she was finally matched with a suitor despite the asthma!

Throughout her life, I remember her using inhalers and nebulizers and having multiple hospital admissions with acute severe asthma. However, the most distinct memory I have of her is self-medicating with oral prednisolone. She would often swallow quite a few little white tablets, and even as young grandchildren, we were familiar with the little tablets called prednisolone. Toward the latter part of her life, her asthma was relatively well controlled with presumably newer maintenance medication being available, and my mother said she used less prednisolone. I have often wondered whether her UC was kept under "check" with the long-term use of prednisolone which she took liberally for her asthma. She was a very active lady and didn't suffer from significant osteoporosis or any obvious side effects from the prednisolone.

Over the next couple of years, I suffered a few relapses requiring oral prednisolone, including one hospital admission at which time it was noted that my pancreatic enzymes were elevated, and a diagnosis of acute pancreatitis was queried and disregarded following normal radiology. Since that admission, whenever I felt that my bowel symptoms were recurring, I got into the habit of checking my amylase and lipase when I did my own blood work. Despite not being an accepted marker anywhere, in my personal experience, I discovered that I could reliably monitor my disease activity using these enzymes which started to rise before the inflammatory markers.

Sri Lanka is a small island, approximately the size of Ireland, in the Indian Ocean at the tip of India, with a population of 22 million people. It was colonized by the Dutch, Portuguese, and last of all the British, from whom she gained independence in 1948. We have an advanced public free healthcare system, based on the British model, which provides for the majority of the population. Boasting five medical schools, all of our postgraduate trainees undergo compulsory training overseas, the majority being in the UK. Our medical ties with the UK are very strong.

My father, a medical doctor who graduated in Sri Lanka in the 1960s, had moved to the UK as was common practice then and now and had a career as a GP in the UK until his retirement. Similarly, Sri Lankan doctors are scattered and practicing throughout the world and maintain a strong network of connections.

During a flare, my father contacted one of his juniors and friends who was a gastroenterologist in Dundee, Scotland, which has a very high incidence of

inflammatory bowel disease. At the time they were conducting research into the gut microbiome, probiotics, and IBD. This was when my relationship with telemedicine began in a rather primitive fashion.

When I contacted him, via telephone, he informed me that the dose of mesalazine I was on was insufficient, and I decided to fly to Scotland for a second opinion and further management. After confirming the diagnosis, he changed my maintenance medication to Pentasa at the optimal dose and added the probiotic VSL #3, which had some evidence of success in the maintenance of remission. I returned to Sri Lanka armed with a suitcase of medication that wasn't available on the island, and I was to be in touch with Dundee as necessary.

Quite quickly following this visit, I suffered one relapse despite the new medication. I was managed by the doctor in Dundee, not in any formal fashion but in a rather informal manner, via the telephone. At this time video consultations were not conducted, and I believe the only face to face communication across the oceans was via Skype, although I don't believe it was used in the medical profession where a substitute for history and examination of the patient in person was almost unheard of.

After recovering from this episode, I contracted *Shigella flexneri*, a common pathogen in Sri Lanka. I presented with bloody diarrhea which I managed conservatively, and, after this, I went through a period of complete remission where I had never felt better. I often think back on this time with awe but have not found any scientific evidence to attribute this feeling of complete wellness to the infection.

In the meantime, another close Sri Lankan family friend, also a gastroenterologist and IBD specialist in New York, was visiting Sri Lanka and conducting a series of lectures on IBD at the request of a teaching hospital in Sri Lanka. She connected me with the Sri Lankan colleague who had invited her to lecture and said she would be happy to guide him through my future care via email or telephone. This was very reassuring as I felt that I had someone who would be happy to manage me, with expertise from New York.

In 2008 we decided to start a family and I was pregnant by March of the same year. Unfortunately, I suffered severe hyperemesis gravidarum during my first trimester. I did manage to continue working through this period but, following this, suffered a relapse of my colitis. During this time, I was referred to a senior gastroenterologist in Sri Lanka, for management of UC during the pregnancy, who informed me that I required a course of prednisolone but that I would also have to terminate the pregnancy. This was an extremely difficult time for me, and despite academically having the knowledge and the ability to research medical data, as a pregnant mother, there was always a "what if" in my mind. I contacted my friend, the consultant in New York, by phone. She reassured me that this was not in fact the case and commenced me on a high dose of prednisolone to be tapered slowly. She managed my UC remotely via telephone. I was on steroids throughout my pregnancy discontinuing them at 36 weeks, a week prior to elective LSCS which I underwent with steroid cover and minimal antibiotics. I delivered a healthy baby of normal weight with no complications. Being a doctor working in obstetrics and gynecology and part of the team that did the section, I was in the fortunate position to make sure that ideal management was followed.

I had a very uneventful postpartum period and enjoyed 3 years in remission. I continued Pentasa and intermittent VSL #3, both of which had been brought down by family and friends on private prescriptions, for which I had to rely on physicians overseas.

As a new mum on extended maternity leave, I enjoyed the following year with no relapses or steroids, and, as I believe happens to most people when the good times roll, one forgets the bad times. I didn't have any medical follow-up. While the advantage of being a physician is that one is able to manage oneself to a certain extent and navigate one's own care, it can also make one complacent and undisciplined with regard to the regular follow-up a nonmedical person would follow.

By the end of 2009, I had stopped taking VSL #3, and by the end of 2010, my compliance with Pentasa was very poor.

At the beginning of 2011, we decided to expand our family, and I was pregnant very early in the year. Unlike the first pregnancy with severe hyperemesis and a relapse of colitis requiring a course of steroids, the second pregnancy was rather uneventful. I was far more relaxed about my health, busy with work, and being a mother to a toddler and had almost forgotten about the chronic underlying illness that lay hidden. I feel that with IBD, which often has no visible extra intestinal manifestations and often only symptoms experienced by the patient, it is only the patient who truly understands how it can affect one, both physically and emotionally. People around the "patient" often don't realize that one is in fact ill, because no signs are visibly evident. Most nonmedical people often confuse inflammatory bowel disease with irritable bowel syndrome and don't recognize its gravity. In my case this was always a positive because I have never been regarded as a "patient" or restricted in my activities or seen as disabled or challenged in any manner. My life was subjectively and objectively the same if not busier than anyone else's.

With no symptoms and life not revolving around taking medications multiple times a day (owing to my poor compliance with Pentasa) and importing medication, life was relatively stress free. I often wonder if that had something to do with the extended remission. In hindsight I wish I had struck the correct balance of being stress free but still continuing to diligently take my medication and having regular follow-up with a physician, at least via telemedicine, in order to keep me in check.

I delivered my daughter by LSCS on the 1st of September 2011, and the postnatal period is when my troubles truly began.

Although I should have known better, both being an IBD patient and having trained in obstetrics and gynecology, I wasn't compliant with my colitis medication even in the postnatal period despite knowing that the puerperium was the period when I was at the highest risk of a relapse. Looking back now I am unsure of whether it was denial, wishful thinking, or simply not thinking on my part.

One month after delivery, I started having bloody diarrhea. After a trial of Pentasa and adding Asacol enemas (which had to be couriered from the UK) which I didn't respond to, I began to feel systemically unwell for the first time, with an acute severe colitis requiring hospital admission and IV steroids. Fortunately, I responded quite quickly and was discharged on oral prednisolone.

The following 2 years were the most eventful of my colitis career. After discharge, I kept relapsing every time I tapered down the steroids, and I required four back-to-back courses of prednisolone through 2012. During this time, I was in touch with my

friend in New York, and she recommended I trial a course of azathioprine as this was the only medication available in Sri Lanka at the time. Keeping the previous local doctor informed but managing my medication and doses on advice via email and telephone from New York, I commenced the azathioprine. Unfortunately, I had to discontinue the AZA a few months later as I developed low-level transaminitis. Following this setback, again on the advice over the telephone from New York, I cautiously trialed 6-MP and this led to acute pancreatitis and hence had to be discontinued as well. Though I was admitted to hospital for the pancreatitis under the local doctor here, I had daily telephone conversations with the consultant in New York, and after discharging, it was she who insisted I diligently remain on a fat free diet and monitored my blood work from across the world. The local doctor was happy and relieved to share and, more often than not, shift the responsibility of care to an overseas expert.

The next recommendation from my friend in New York was to trial one of the biologics, Infliximab. Remicade had never been used for IBD in Sri Lanka but had been used sparingly by the dermatologists and hence had approval by the Ministry of Health and was available on the island. The local doctor who my friend in New York knew had absolutely no experience with biologics. I managed to find a new consultant who practiced in the government/public sector and had a few IBD patients. He had never used infliximab for his patients but was happy to administer it under the guidance of my friend in New York.

Despite being a small island, our public healthcare system is entirely free, and being a government sector consultant, this new consultant organized the costly infliximab/Remicade free of charge, for which I was extremely grateful. Having had to buy and bring down most of the medication to date and having no medical insurance, this was a truly welcome change.

After a workup as advised from NY, I commenced infliximab at 5 mg/kg while on 10 mg of prednisolone and moved up to 7.5 mg/kg when I failed to respond adequately. Despite starting in January and being fully loaded, I relapsed again in March requiring 40 mg of prednisolone again. After my fourth dose of infliximab at 7.5 mg/kg, for the first time, I seriously started considering surgery. My first surgical house job in the UK had been with one the pioneers in complex colorectal laparoscopic surgery in the UK and now a professor, dean, and lead laparoscopic trainer at St. Mark's Hospital, one of the only hospitals in the world to specialize entirely in intestinal and colorectal medicine, a national and international referral center for intestinal and colorectal disorders.

When I contacted him via email regarding surgery, he advised me to meet with the now professor of gastroenterology, himself, and the lead pouch care nurse at the same hospital. In April 2013, I flew to the UK, and a colonoscopy by the gastroenterologist showed a relatively well-healed mucosa. I was on 20 mg of prednisolone at the time. They jointly concluded that there was no indication for surgery at that time, but the surgeon, my former boss, explained all the surgical options to us, should I require them at some point in the future. I returned to Sri Lanka with a plan to continue the infliximab and Asacol and taper the steroids.

In May after returning to Sri Lanka, as I was reducing the steroids, my bowels started becoming a bit more "active" and I was advised to increase the 5th dose of infliximab to 10 mg/kg. Infliximab levels and antibodies were not available in Sri Lanka.

Around the same time, I started experiencing various skin lesions. It started with a mild folliculitis-type picture on the thighs, a few small abscesses/boils, a seborrheic dermatitis-type picture of the scalp, a plaque psoriasis-type picture of the back, and a persistent furuncle of the lower leg. I saw several dermatologists, all with varying diagnoses, and by the time I saw the last dermatologist, I had such severe rashes that I was admitted to hospital with a possible diagnosis of Von Zumbusch! It was the most difficult time of my life with no proper diagnosis, independent consultants disagreeing, and no centralized care, management plan, or proper treatment other than some topical steroids, antibiotic creams, and emollients.

As I had run out of options in Sri Lanka and everyone was at sea, the closest place for me to fly to was Singapore. I met with one of the leading dermatologists at Singapore General Hospital because I had the advantage of medical connections in Singapore. In Singapore it was concluded that I had a general psoriasiform picture and that my leg lesion was likely pyoderma gangrenosum, and biopsies were taken. Whether the skin lesions were due to the colitis or the treatment was a mystery. My steroid dose had been tapered down to almost nothing and sadly I appeared to be relapsing with the colitis as well. I returned to Sri Lanka on only topical treatment for the skin and awaiting biopsy results.

In Sri Lanka I started getting more abscesses of varying sizes, from the size of a pea to the size of a ping pong ball, from my groin to my axillae to my face. The frequency of my bowels was getting worse as well, and I couldn't find a doctor who could treat me. This was the hardest time in my life as I simply didn't know what to do. Sri Lanka didn't seem to have a solution, and Singapore hadn't proved very useful with management. I had the option of returning to the UK where the private healthcare system was not logistically geared for emergencies as such, and I would have to find independent consultants privately. My friend in New York suggested I go to the USA for further evaluation and treatment. One of my closest friends, who was now working at the Mayo Clinic in Rochester and had incidentally delivered both my children, recommended I try treatment at the clinic.

I took a 36-hour flight with three connections accompanied by my father, abscesses oozing with what looked like pus and having diarrhea more than 30 times on the 36-hour journey.

I landed in Rochester late at night, and the following morning, I had my first appointment with a gastroenterologist who was to later become one of my long-term caregivers.

After seeing me, his impression was that this terrible skin reaction was infliximab related, and he explained that he had seen similar manifestations on different patients but not all of them on any one patient at one time! He referred me to a dermatologist the same morning, and he too concluded that, while he couldn't say for certain whether these manifestations were part of the illness or the treatment, temporally he felt that it was more likely due to the Remicade. All the consultations and investigations were performed as an outpatient within a day. Having experienced private healthcare as a patient in Sri Lanka, Singapore, and London and having worked for the NHS and both state and private sectors in Sri Lanka, I had never encountered anything as unique as I did at the Mayo Clinic. The efficiency,

multidisciplinary approach and teamwork, the quick decision-making, and the "one stop shop" geared to health tourism, not to mention the aesthetics, were unparalleled to anything I had ever seen. It gave me a sense of comfort and confidence, and I felt I had finally found a place I could trust and stop having to self-manage and burden my friends and colleagues all over the world.

After discussion between the gastroenterologist and dermatologist, I was commenced on 60 mg of prednisolone a day for both the skin and the bowel, the first time I had been on such a high dose. I spent 5 weeks with my friend in Rochester, and my bowels settled very quickly on the high dose of oral steroids, and my skin began to start healing as well.

The biopsy results/histology from all the lesions which had manifested in different ways throughout the body returned all showing the same features under the microscope, "sterile pus," and diagnosis of neutrophilic dermatoses likely secondary to infliximab was given. The results from Singapore came in with similar findings.

At this point the next hurdle was finding safe maintenance medication as I had reacted to azathioprine, mercaptopurine, and lastly infliximab as well. I was commenced on subcutaneous methotrexate, 25 mg per week, to self-administer, with careful monitoring of liver function. I returned to Sri Lanka 6 weeks later.

The Mayo Clinic registers all its patients on to a "patient portal" which is essentially an application that is downloaded on to one's mobile telephone or electronic device. This portal is unique to each individual, and one is able to be in touch with one's doctor, send reports, book appointments and receive reminders, and view all previous medical records and results through this. It gave me a great sense of comfort that I had access to such a formal and easily available service which could be accessed from anywhere in the world.

Over the next couple of years, I adjusted the dose of oral prednisolone, initially in response to the activity of the skin lesions and not the bowels, and later taking into account side effects such as muscle spasms and fatigue, likely effects of steroid withdrawal.

Methotrexate was a drug easily available in Sri Lanka and I self-administered it weekly. Once again, I was leading a normal life working and doing all the usual things I would have done otherwise.

The next few years from 2014 to 2019 were spent with annual visits to Mayo Clinic for surveillance colonoscopies. I reduced and stopped the steroids entirely in 2018. I had to discontinue both five ASAs and methotrexate due to abnormalities in liver functions tests. In addition there were queries of pancreatitis, autoimmune hepatitis, and primary sclerosing cholangitis as well as a very manageable residual palmer pustular psoriasis.

In addition, I was diagnosed with a thyroglossal cyst, erythema nodosum of my upper arm, and a recurring sebaceous cyst all of which were self-limiting. I also had an unfortunate accident in the Arctic Circle where I suffered a compound fracture of the head of humerus requiring plating and pins (notably, I did not have any osteopenia at the time).

Despite a list of diagnoses that sounds rather long, I had never felt "unwell" or unable to successfully do everything I wanted to, including taking care of patients.

I monitored my health under guidance of the Mayo Clinic and my friend in New York. I could check the Mayo portal for results of regular blood work, eye, and bone checks, and, apart from mild osteopenia, the steroid side effects have been thankfully relatively minimal except for a moon face which settled with time.

By 2019, I was in complete remission clinically, endoscopically, and histologically but was very aware that I was not on any maintenance medication as the newer drugs recommended were not available in Sri Lanka, nor the expertise to monitor administration.

I was on a combination of regular turmeric tablets, a local fruit called bael and psyllium husk for my bowel, and topical coconut oil which worked better than topical steroids for my residual intermittent pustular psoriasis. I informed dermatology colleagues, a couple of patients, and my friend of this, and they all had the same unexpected positive response to their conditions. During my visits to the Mayo Clinic, I was pleasantly surprised to be informed of studies being done on turmeric and the use of psyllium husk which were both easily available and had been used for centuries in Asia. Being a western qualified doctor, I had never really looked into complementary or alternative therapies, but after trial and error over the years, I found that, for me, the above worked very well.

Over the last few years**,** the incidence of IBD in Sri Lanka has continued to rise perhaps partly due to more awareness of the diagnosis of IBD and more doctors returning from training overseas, bringing with them expertise and knowledge. However, with regard to medication, the newer biologics such as vedolizumab, tofacitinib, and ustekinumab are still unavailable; both azathioprine and infliximab are being used by gastroenterologists.

The Explosion of Telemedicine

After a relatively calm period, 2020 has proven to be an impossibly difficult year. With an ongoing global pandemic and Sri Lanka being in lockdown for the past 7 months and my inability to return to Mayo Clinic, I have relied almost entirely on telemedicine, which has shown an explosion in growth worldwide.

In February of 2020, I became systemically unwell with fevers, exhaustion, abdominal pain, very high inflammatory markers, and a very high alkaline phosphatase level. As these symptoms didn't initially feel like a relapse of the colitis, after discussion with my overseas doctors, I contacted a local physician and was then referred to a surgeon and admitted to hospital. I then developed my usual symptoms of watery diarrhea, but the local doctors convinced that this was a picture of sepsis, despite the daily consultations with the USA via telemedicine and there was a long delay before steroids were started, and I was extremely unwell. Fortunately, I responded quite quickly to the steroids and was discharged home.

Unfortunately, I have been relapsing whenever I reduce the steroids to low doses and have since required three back-to-back courses of high-dose oral steroids. I was unable to travel to the Mayo Clinic this year but have been managing myself since discharge via video consultations with the Mayo Clinic and my consultant friend in

New York. As it appears that I have become steroid dependent, the next step in my care is to escalate medical management for maintenance or undergo surgery. The medications are not available on the island. I am not able to import them, and even if I could, I can't find a local doctor to administer the new medications. In addition, because of lockdown, I cannot travel across to India where they are available. I find myself in an impossible and frustrating situation.

St. Mark's Hospital in London has commenced video consultations in a simple manner as well. So I set up appointments with the same gastroenterologist and surgeon I had seen in 2013 in case it is easier for me to travel to the UK rather than the USA. While the consensus of management is the same from both the USA and UK, which is to first trial the newer medical therapies, they both agree that this is logistically not a possibility at this given juncture. Hence, I am relying entirely on video consultations for maintenance of my symptoms with oral steroids and monitoring of side effects due to the long-term use of steroids.

A silver lining of this pandemic is the explosion in telemedicine which has given patients like me not only sound and safe medical management but also great psychological comfort at a time of travel restrictions.

I have no idea what the future holds for my colitis, but I am taking each day as it comes. These unprecedented times have humbly shown me how much of life is out of our control. We can only really control our reaction to the unexpected circumstances life throws at us.

While I wait hopefully for the next chapter of my health, I remain optimistic and supported by the exponential development in telemedicine which I have always relied on in some form or the other and which now many other patients with chronic conditions can access more readily at both national and international levels.

Journey Through Telemedicine

Rashmi Advani

What Is Telemedicine?

Telemedicine also known as telehealth is a platform where health-related services and medical information are provided and distributed through electronic and telecommunication devices. It can utilize audio and/or visual technology to help provide these services between a patient or client and a healthcare provider (i.e., physician, nurse practitioner, physician assistant, or nurse).

Telemedicine serves as a way to initiate and continue clinical services, while providing access to patients in settings where physical visits are not feasible. It can also help improve equity of access to healthcare, the quality of that care, and efficiency by which it is delivered [1]. Telemedicine not only serves as a vital tool to bring healthcare to rural areas of the world, but it also helps deliver acute, chronic,

specialty, and primary care to patients. Although it has been used to deliver care in special circumstances in the past, this modality became crucial in our efforts to deliver standard healthcare during the COVID-19 pandemic.

The main barriers that were mitigated by the implementation of telemedicine included access to healthcare for patients who were unable to seek care due to lack of transport, access, and mobility [2]. On a larger level, telemedicine provides services in times of decreased funding, lack of staff, and most recently, in the era of a world pandemic where, due to public safety, a reduction of physical visits and contact is implemented.

Three modalities of telemedicine delivery and receipt have been recognized: synchronous, asynchronous, and remote patient monitoring. Synchronous modalities utilize audio and/or visual technology (via smartphone, computer, or tablet) to allow for real-time and direct healthcare. Asynchronous telemedicine, also known as the "store-and-forward technology," involves stored messages, data/labs, or images obtained at an earlier time point that is then interpreted, analyzed, and responded to at a later time point via another modality (i.e., patient portals, encrypted emails/messages, audio/visual technology, telegram). Remote patient monitoring involves direct transmission of health-related patient measurements which may be obtained in real time or at an earlier time point, to their healthcare provider (i.e., blood glucose monitoring, blood pressure, heart rate/rhythm monitoring systems) [3].

A Snapshot in the History of Telemedicine

As early as the 1960s, telemedicine was garnered as a tool to bring healthcare to populations with limited access. It became especially popular in rural communities. One example of this was the Space Technology Applied to Rural Papago Advanced Health Care (STARPAHC). STARPAHC was a government project between NASA and Indian health services that helped bring telemedicine to Native Americans of the Papago reservation in Arizona using the same technology astronauts used on space missions [4]. A more recent example is Project ECHO (Extension for Community Healthcare Outcomes) which is a telementoring program where virtual communities of expert teams and healthcare providers are brought together to help improve patient care outcomes. Project ECHO doesn't provide care to patients directly but uses telemedicine technology to increase specialty treatment in underserved areas by providing frontline physicians with the knowledge and support to help manage patients with many conditions such as hepatitis C, chronic pain, HIV, etc. Virtual lecture presentations and cases using videoconference technology are utilized to accomplish this goal, thereby allowing local providers to deliver the best-in-practice care to their communities [5].

Since the 1990s, research and growth of telemedicine have risen exponentially with the invention of the Internet and advancement of technology. Even before the

COVID-19 pandemic, telemedicine was a tool implemented by many hospital systems throughout the world. In 2016, the Department of Health and Human Services estimated that more than 60% of all healthcare institutions and 40–50% of all hospitals in the USA used some form of telehealth [6]. Telemedicine was and is still used as a way to fill gaps in care due to provider shortages and allows for care past normal clinic hours. It eases patient and family travel burdens and provides a way to help set up appointments and prescription refills [7, 8].

Challenges and Limitations with Telemedicine

From its inception, telemedicine has been under the microscope for several recurrent concerns regarding usage by health systems, providers, and patients. On multiple levels, the legality and regulatory measures by which telemedicine was/is performed are ongoing concerns with palpable barriers. As a telemedicine provider, one must be able to legally provide virtual services to patients traveling to or from a different state/country. This involves credentialing and knowledge of the local and state laws surrounding the appropriate licenses and credentials to treat patients virtually, i.e., physically located elsewhere [9]. In addition to laws surrounding prescription of controlled substances, some states also require providers to see patients in person prior to offering a telemedicine service. During the COVID-19 pandemic, some of these rules were relaxed to help meet growing healthcare demands.

Reimbursement of telehealth services and protection of patient health information also posed a challenge. A service that provides telemedicine should rightfully protect patients under Health Insurance Portability and Accountability Act (HIPAA). Meeting the requirements under HIPAA is a prerequisite prior to engaging in any virtual patient encounter. Reimbursement for telemedicine also remains a consistent challenge. Reimbursement varies depending on the type of patient insurance (i.e., private insurance, Medicare) and can also be based on the state-level decision for reimbursement of telehealth services (i.e., Medicaid programs). A way this barrier was mitigated during the COVID-19 pandemic was when The Centers for Medicare and Medicaid Services provided flexibility in granting payment by issuing multiple waivers.

Telemedicine also may pose several logistical/situational challenges. Its implementation may be affected by patients who may not have access to or feel comfortable with using devices that utilize audiovisual technology for virtual visits. In the same vein, virtual provider visits may conflict with patients' cultural and/or religious beliefs surrounding their medical care.

Telemedicine is importantly limited by the inability to perform a physical examination which may be important in certain clinical situations and in scenarios of acute, potentially life-threatening problems.

Another recurring concern of telemedicine is the ability to objectively measure quality of care and standards of care of the services delivered. More formal research and studies are needed. Lastly, realistic outcome expectations as well as the ability

to establish long-term working relationships with telehealth providers may pose a challenge.

Use of Telemedicine in the Era of COVID-19

Telemedicine during the COVID-19 pandemic was nothing less than a blessing. Despite the aforementioned concerns and issues with its utilization, it became the backbone for the delivery of health services and care to patients. Not only did telemedicine provide access to healthcare, but it helped preserve vital personal protective equipment (PPE) and helped minimize the impact of patient surges on facilities [2]. It provided a safer, yet still effective, option for both patients and providers to continue vital healthcare. Telehealth services were used to provide inpatient care by reducing exposure, screen, and triage patients with possible symptoms of COVID-19, provide mental and behavioral health services, and increase access to primary doctors and specialists for management of chronic health conditions and medication refill/management. It also served as a tool for post-hospitalization follow-ups, care to long-term facility residents, and continued access to rehabilitation services such as occupational and physical therapy (CDC).

Similar to the personal account by Dr. Nilani Kaluarachchi, telemedicine during the COVID-19 pandemic provided a platform for patients to continue receiving care from their providers. It also promoted patient confidence in the health system and reduced patient and clinician anxiety. Telemedicine allowed for a synchronous, real-time delivery of medical care that was not only efficient but also effective as well.

Future Directions of Telemedicine

In a medical system that is currently suffering through a second wave of the COVID-19 pandemic, telemedicine may once again allow for the conversion of scheduled office visits to telehealth visits for patients. It will provide a way for our medical system to stay afloat through protecting and preserving provider manpower by reduction of nonessential in-person exposure to patients. Conversely, it will also reduce patient exposure to clinical "higher risk of exposure" settings and will offer a way for exposed or quarantined providers to still provide care remotely [10].

With the rapid growth of telemedicine-based applications in the last year, access to services and provider reimbursement will become more streamlined. Smart device, application-based services (i.e., MDLIVE, Lemonaid, DocsApp, Spruce, and Teladoc), hospital system-specific platforms, and other encrypted audiovisual aids will continue to be developed and perfected to fit the needs of a growing society of telemedicine. A world pandemic skyrocketed the trajectory of telemedicine, and it will only continue to grow at an accelerated rate. With the standardization of telemedicine as an offered service across all care settings, patient wait times to see a

specialist will improve, and patients will not face geographic limitations for the providers that they wish to see virtually. For example, in Dr. Nilani Kaluarachchi's personal account, telemedicine provided her the option of continuing her visits virtually with two specialists, one at the Mayo Clinic and one in New York who helped comanage her care. She was also able to reconnect with her specialists in the UK during the pandemic. Telemedicine truly allowed her to experience care on an international level.

Of note, it is still important to consider the limitations listed previously that will need to be tackled on both a local, state, and federal level. Not all services can be provided virtually, especially when it comes to specific medication delivery and/or procedures. Telemedicine, in this case, may be used as a way to help determine the acuity of such procedures and medication administration. For example, a patient who complains of weight loss and rectal bleeding may need a colonoscopy sooner than the patient who has no symptoms but is due for colon cancer screening.

Resources will need to be put in place in order to streamline and provide devices for those without access to the Internet, smart devices, or laptops. Education on how to use virtual platforms, and on the benefits of telemedicine to patients may also be needed in order to increase acceptance of virtual basic medical care. For this to occur, medical institutions will also need incentivization. Recognition that this shift to virtual platforms poses a business opportunity with the potential for revenue growth will encourage investment in growth of the services.

Updated laws and regulations will need to be implemented to allow for easier credentialing and reimbursement for providers. Lastly, objective quality of care and standards of care will need to be researched and formalized in order for telemedicine to survive as a viable option for the delivery of healthcare [9].

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Chapter 16
IBD in the Time of COVID-19

Ramona Rajapakse and Aman Sharma

Introduction

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization on March 11, 2020 [1]. COVID-19 is caused by SARS-CoV-2, a single-stranded RNA virus, belonging to the *Coronavirus* family responsible for a wide range of upper respiratory infections such as the common cold. The majority of patients inflicted with this virus have minimal or mild illness, but some go on to develop severe pneumonia, acute respiratory distress syndrome, and multi-organ failure caused by cytokine storm. A significant number of patients also develop gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and diarrhea [6]. Risk factors for severe illness appear to be older age, obesity, comorbidities, and immunosuppressive medications. As of March 2021, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused cases in 219 countries worldwide and 2.73 million deaths. As the pandemic unfolded, gastroenterologists in the Inflammatory bowel disease (IBD) community were tasked with trying to determine if IBD patients were at increased risk from the disease and what constraints the disease posed to the management of IBD. In this chapter we will discuss briefly the pathogenesis of COVID-19 and how it has affected IBD patients.

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R. Rajapakse (ed.), *Inflammatory Bowel Disease*, Clinical Gastroenterology,
https://doi.org/10.1007/978-3-030-81780-0_16

Pathophysiology

Coronavirus is a family of viruses that can cause illnesses such as the common cold, severe acute respiratory syndrome (SARS), and the Middle East respiratory syndrome (MERS). SARS-CoV-2 belongs to the ß-coronavirus family. Its origin is unknown but it was first identified in China. It is an RNA virus with an envelope that contains three glycoproteins: the spike, membrane, and envelope proteins and, within this, a nuclear capsid protein. This N protein is bound to a single strand of RNA. The spike protein on the envelope is the antigen-binding site. Binding of the virus to the host membrane depends on an interaction between the spike protein and the angiotensin-converting enzyme 2 receptor (ACE2). The transmissibility and pathogenicity of the virus depend on the affinity between these two [17]. In addition to lung alveolar pneumocytes, ACE2 is widely expressed in other tissues, including the gastrointestinal tract. It is found in the duodenum and other parts of the small intestine as well as the colon. This expression of ACE2 may be responsible for gastrointestinal symptoms in patients with COVID-19 [2]. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and loss of appetite. Laboratory findings include leukopenia, lymphocytopenia, elevated transaminases, and elevated inflammatory markers like C-reactive protein. One study showed that 35% of patients with COVID-19 had gastrointestinal symptoms, and these patients were more likely to have a prolonged illness [5].

The pathogenesis of diarrhea in COVID-19 is unknown but may be related to increased intestinal permeability.

Effect of Inflammatory Bowel Disease (IBD) on COVID-19

Inflammatory bowel disease (IBD) is a chronic relapsing disease whose pathogenesis is believed to be due to an interaction between multiple factors including genetic variations, environmental factors, and gut microbial dysbiosis leading to a dysregulation in the innate and adaptive response. The effect of COVID-19 on IBD appears to be complex, and it is generally believed that patients with IBD alone are not at increased risk of infection with COVID-19. Although one study from Italy showed higher mortality in older patients with active IBD, another study did not show an increased risk [3, 4]. A recent case series from NYC showed similar hospitalization rates for patients with immune-mediated diseases (including IBD) as the general population [25].

Since there are known gastrointestinal symptoms in patients with COVID-19, the challenge is to distinguish symptoms related to the viral infection from those caused by IBD itself. It does not appear that IBD patients present with symptoms any different to that of the general population. Many COVID-19 patients present with abdominal pain, loss of appetite, and diarrhea, which are common symptoms of

IBD exacerbations. In addition, there are no lab abnormalities specific to the IBD patient with COVID-19.

There has been concern that the immunomodulatory medications used to treat IBD would put patients at increased risk for severe COVID-19 infection. However, a study from China which evaluated 1099 patients did not find immunomodulators to be a risk factor for severe disease [6]. In addition the international registry of COVID-19 and IBD (SECURE-IBD) published an analysis which revealed that steroid use was associated with the worst outcomes. Anti-TNFs were not associated with an increase in adverse outcomes [7].

If a patient with IBD has confirmed COVID-19, the recommendation is physical isolation and to hold dosing of immune based therapies until the infection has resolved. Therapy may be resumed after infection has resolved and/or testing for SARS-CoV-2 is negative. During the clinical infection with COVID-19, nonimmune-based therapies such as aminosalicylates and budesonide may be continued. If a patient is having a flare of IBD in the setting of COVID-19 infection, prudent and judicious use of IBD medications is suggested to control the IBD, together with consultations with other specialists, particularly infectious disease and pulmonology [8].

Effect of COVID-19 on Inflammatory Bowel Disease (IBD)

Patients with chronic medical conditions such as inflammatory bowel disease (IBD) were significantly affected by the COVID-19 pandemic. A Canadian group surveyed 1581 IBD patients about their experiences during the first wave of the pandemic. They found that closure of healthcare clinics and interruption of elective procedures in the early pandemic led to interruption in care for individuals with IBD. In addition patients reported challenges: patients on immunosuppressive therapy were fearful of infection; they were concerned about the inability to undergo procedures for routine monitoring of the disease and inability to maintain treatment programs. However, switching to virtual care was accepted by 77% of the patients, and, overall, 82.7% of IBD patients maintained their care without interruption [9].

The difficulties in obtaining care created by the pandemic were partly caused by lack of knowledge and increased fear in this population. A survey carried out with the support of the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) between March 30 and April 16, 2020, published in *The Lancet* highlighted some of these concerns. Patients were afraid that receiving treatment for IBD put them at greater risk for infection and severe outcomes due to an immunocompromised state [10]. Additional patient concerns included the fear of infection associated with contact with other individuals and fear associated with travelling for medical care. Interestingly, the survey highlighted that the majority of patients (88%, 3815 patients) who answered the survey did not want to discontinue their treatment despite ongoing concerns [10].

In the early days of the COVID-19 pandemic, outpatient clinic visits were switched over to virtual visits. Although virtual visits have limitations including the inability to perform a thorough evaluation of patients with active disease, the modality enabled patients to keep in touch with their physicians. Some nonurgent and less emergent procedures such as diagnostic endoscopies, colonoscopies, and elective surgical procedures were limited or suspended, in efforts to limit the spread of COVID-19. The inability to fully evaluate patients meant delays in starting induction therapy resulting in potential sequelae of untreated disease, and when medical therapy failed, surgery was delayed because, in many hospitals, postsurgical units were converted into makeshift ICU units as highlighted in a report from Italy [11].

Aside from the difficulties in obtaining care for symptomatic disease, there were additional subjective challenges that played a role during the early days of the pandemic. Patients avoided presenting to the hospital for symptoms they normally wouldn't have hesitated to seek care for, due to the fear of COVID-19 infection. In one study, analysis of IBD follow-up showed that 83.1% of all patients missed an IBD medical appointment, 45.5% of the patients missed laboratory tests, 41.3% missed the national flu vaccination program, 31.3% missed any radiologic exam, 17.3% missed colonoscopy, and 16.9% failed to obtain biologic therapy prescriptions [12].

The current guidelines for IBD treatment are based on pre-COVID-19 pandemic data. PROTECT-ASUC, a multicenter observational study, was carried out in the UK in an effort to study the management of ulcerative colitis during the pandemic [14]. Sixty acute care hospitals participated, and adults with ulcerative colitis or colitis unclassified admitted between March 1, 2020, and June 30, 2020, were enrolled. Patients with ulcerative colitis admitted between March 1, 2019, and June 30, 2019, were used as a historical cohort control group. The primary outcome was the number of patients receiving rescue therapy or surgery.

A total of 782 patients were included in the study, 384 patients in the historical control cohort and 398 study patients. Interestingly, the proportion of patients receiving rescue therapy (including primary induction) in the pandemic cohort was higher than in the control group (55% vs 42% $p = 0.00024$). However the overall colectomy rates were no different between the groups. In addition the rate of steroid use was no different and did not lead to either increased incidence of SARS-CoV-2 infection or an increase in adverse outcomes for the few who did become infected. At a 3-month follow-up, there was no difference in symptomatic, biochemical, or endoscopic remission of the disease in both cohorts. The study found no difference in rates of readmission, IV steroid use, and surgery between the two cohorts. Additionally this study indirectly allayed concerns regarding the use of IV steroids in IBD patients, thought to put IBD patients at a greater risk of acquiring COVID-19, based on data from the SECURE-IBD registry [15].

This large series of patients provides reassurance regarding the management of UC during the pandemic and may provide guidance for any future resurgence of COVID-19 [14].

The American Gastroenterological Association (AGA) published guidelines, together with considerations from the British Society of Gastroenterology and the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) [13], on management of IBD in various COVID-19 scenarios [16]. The guidelines are stratified into different patient categories: patients with IBD without COVID-19, patients with IBD and asymptomatic COVID-19, and patients with IBD with confirmed COVID-19 with or without bowel inflammation.

In patients with IBD who do not have COVID-19, therapy is to be continued as usual, because disruption in therapy is associated with recurrence of disease. This patient population is not at greater risk than the general public for acquiring COVID-19; therefore standard precautions such as wearing a mask, washing hands, and avoiding crowded areas should be observed. Additionally, patients who receive infusion medications should continue to receive them at the infusion centers. Therapy should not be switched from infusion center to home infusions or from infusible medications to injectables. Infusion centers should prescreen patients for COVID-19 and check for fever and any additional symptoms prior to the appointments [16].

In patients who have IBD and asymptomatic COVID-19, the recommendations are to reduce prednisone dose to <20 mg/day or, if possible, switch to oral budesonide as it has a lower risk of immunosuppression. Holding thiopurines, MTX, and tofacitinib is ideal if possible. Delaying treatment with monoclonal antibodies for 2 weeks is recommended, and, in the meantime, patients should be observed for the development of signs and symptoms of active COVID-19 disease. If a patient remains asymptomatic for 2 weeks, therapy can be resumed [16].

Treatment of patients with IBD and confirmed symptomatic COVID-19 with or without bowel inflammation is more complex. Guidelines suggest that patients with active IBD or those in remission who have mild COVID-19 should continue 5-ASA. Corticosteroids should be tapered if possible and switched to budesonide, and rectal therapies can be continued. Patients should hold thiopurines, methotrexate, tofacitinib, anti-TNF therapies, and ustekinumab [16].

In patients with mild to moderate COVID-19 disease who also have severe GI symptoms, the first step is to rule out other infections such as Clostridioides difficile and other microorganisms. Differentiating COVID-19-related gastrointestinal symptoms from an IBD flare can be challenging. Disease activity markers such as C-reactive protein and fecal calprotectin should be checked. Fecal calprotectin is higher in IBD flares than in COVID-19 infection alone. Abdominal imaging can be used to further aid in the diagnosis. The treatment of primary COVID-19 infection in those with moderate to severe disease and poor outcomes takes priority over treating IBD. However patients admitted for moderate to severe IBD who get diagnosed with mild COVID-19 should first have their IBD symptoms and treatment addressed. Surgical evaluation should be obtained where needed, when dealing with severe IBD in COVID-19 hospitalized patients. Endoscopic procedures and surgical intervention should be reserved for urgent cases [16].

SARS-CoV-2 Vaccination in Patients with Inflammatory Bowel Disease

The rapid sequencing of SARS-CoV-2 has enabled pharmaceutical companies and academic institutions to develop vaccinations. Currently two mRNA vaccines and one inactivated vaccine have been authorized for use worldwide.

Many IBD patients are on immune modifying therapies such as corticosteroids, immunomodulators, and biologic agents, and the SARS-CoV-2 vaccine trials did not include this population of patients [17, 18, 19]. There are concerns that patients on immunosuppressants may not mount as robust an immune response to vaccination as those without. For example, IBD patients on infliximab were found to have inadequate rates of seroconversion after influenza vaccination [20]. Similarly in Crohn's patients receiving the pneumococcal vaccine, an impaired response was noted in those on combination immunosuppressive therapy [21]. In contrast, in a recent preprint and yet non-peer-reviewed paper, Wong et al. showed that IBD patients on biologics had good seroconversion after the Pfizer and Moderna vaccines. In addition, in patients who had previous infection with SARS-CoV-2 infection, a single dose of vaccine produced high antibody values, similar to findings in the general population [22]. Steroids and thiopurines, particularly in combination with TNF antagonists, are associated with more severe illness with COVID-19. Anti-TNF monotherapy does not appear however to increase this risk [23].Therefore the current expert consensus statement from a meeting of the IOIBD is that patients with IBD should be vaccinated against SARS-CoV-2 virus [24]. They suggest that IBD patients should receive vaccination as soon as it is available to them and that it should not be deferred if a patient is receiving immune-modifying treatments. The consensus statement suggests that patients should be made aware that vaccine efficacy may be reduced if they are receiving corticosteroids [24].

Conclusion

IBD patients should follow similar precautions to the general population. The COVID-19 pandemic has had consequences on the management of IBD in terms of delays in treatment. Every attempt should be made to continue IBD medications in noninfected patients. In asymptomatic and symptomatic patients with SARS-CoV-2 infection, treatment should be individualized based on risk/benefit assessment and expert guidelines as stated previously. IBD itself does not appear to increase the severity of infection with SARS-CoV-2, but thiopurines and corticosteroids with or without TNF antagonists can contribute to a more severe disease course. TNF antagonists alone do not seem to increase the severity of COVID-19. All IBD patients are candidates for the SARS-CoV-2 vaccine which should not be deferred in patients on immunomodulators or biologics. Patients on steroids may mount a less robust antibody response. This field is rapidly changing with the development

of mutant strains of the SARS-CoV-2 virus, new vaccines, and a greater understanding of the virus. This chapter is meant as a guide for the management of IBD patients during the COVID-19 pandemic, based on current knowledge, and should be supplemented with up-to-date reading of the literature.

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R. Rajapakse (ed.), *Inflammatory Bowel Disease*, Clinical Gastroenterology,
https://doi.org/10.1007/978-3-030-81780-0