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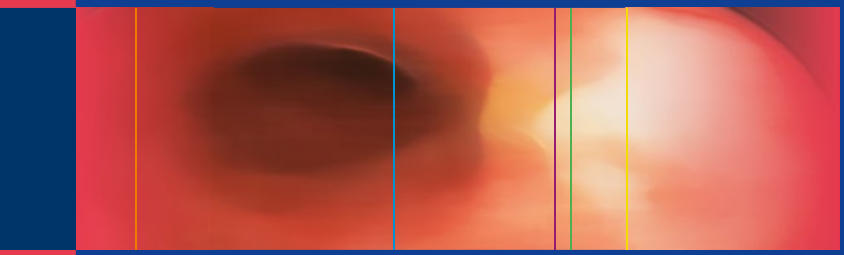

Inflammatory Bowel Disease

A Point of Care Clinical Guide

Springer

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Preface

Inflammatory bowel disease (IBD) is a chronic relapsing and remitting disease comprised of Crohn's disease (CD) and ulcerative colitis (UC). Each disease has a complex set of overlapping signs and symptoms that frequently lead to lifelong complications. The diagnosis of these diseases is often viewed as being somewhat algorithmic. Everyone remembers the two column textbook table that lists the signs and symptoms that are "specific" to CD and UC; however, anyone in clinical practice knows these diagnoses are rarely straightforward and often confusing. Similarly, the approach to managing IBD, both surgically and medically, has also been viewed as being algorithmic; however, once again those that care for IBD patients know that this is rarely the case. Frequently financial, compliance, intolerance, or medication complications arise as roadblocks to optimally managing IBD patients.

The newly diagnosed IBD patient is often filled with anxiety, fear, and confusion that lead to many questions for their providers. This is often the case for long-standing IBD patients as well, and perhaps more so for those patients failing therapy or who have experienced disease complications. Every IBD provider has been faced with the patient questions: "Why did this happen to me?", "So do I have UC or CD?"," "What happens if I do nothing for my disease?", "Do I really have to take these medications even when I feel fine?", "What if I get pregnant?", "I heard these medications

give you cancer, is that true?", or "What alternative therapies can I try?" These questions, while seemingly straightforward, require the provider to boil down a complex, overlapping, and sometime contradictory volume of literature into a simple answer the patient can comprehend.

This book will focus in on answers to the patient questions that are frequently posed to providers who care for IBD patients. Additionally, it will guide clinicians through the complicated therapeutic management of IBD including drug initiation, medications side effects and complications, therapeutic level monitoring, and accurate disease monitoring. Pre- and postsurgical patient management will be addressed in a way it can best be conveyed to patients as well. Lastly, this book will address special situations such as alternative therapies, pregnancy, fertility, and stress.

While an understanding of the immunology, microbiology, pathobiology, and pathophysiology is very important for IBD providers, our current understanding of underlying mechanisms of disease is still poorly defined and will largely be outside the scope of this book.

The purpose of this book is to be a point-of-care reference for busy clinicians who need the best evidence-based answers to patient questions at their fingertips

How to Use This Book

Each chapter is predicated on a real patient question that has been encountered in the Inflammatory Bowel Disease Program at the Medical College of Wisconsin. Every clinician early in his/her training has found themselves struggling to answer complicated IBD patient questions in a simple coherent manner. To answer these questions properly requires the provider to spend a great deal of time researching and evaluating the literature in order to formulate a succinct, yet detailed answer. In speaking with gastroenterologists who focus on IBD, it was found that many have shared this same experience and have honed their responses to patient's ques-

tions over years of experience. This shared experience was the origin of the concept for this handbook: put the experts answers to common patient questions in the hands of busy IBD providers right at the point-of-care.

The title of each chapter starts with a patient question, which leads into the review of the underlying topic. For example, the question "Why did this happen to me?" leads into the topic: Epidemiology, Genetics, Environment, and Etiology of IBD. Each chapter then begins with the suggested provider response to the patient question. This expert's response to the patient question is worded in a fashion to best facilitate patient understanding of the topic. The answers are meant to be as comprehensive as possible but also easily adaptable for unique patient situations.

Following the suggested response portion of the chapter is a brief review of the literature as it pertains to the patient question and the chapter topic. These reviews are designed to be read in a few minutes and provide high yield information. This information will further enable the provider to adapt their response and answer any follow up questions patients may have. It is written at the level of a clinician rather than at the level of a patient's comprehension. It is hoped that all levels of clinicians will benefit from this review; students, midlevel providers, GI fellows, and busy general gastroenterologists alike.

Topics are arranged in an order in which they would most commonly arise in the sequence of a patient's disease course. For this reason questions and chapters about epidemiology and etiology are in the beginning of the book, followed by discussion on therapeutics. Disease and therapeutic monitoring is then followed by surgical issues in IBD. Lastly special situations such as pregnancy and stress in IBD are discussed.

We hope you will find "Inflammatory Bowel Disease: A Point-of-Care Reference" to be a valuable clinical tool when it comes to managing your inflammatory bowel disease patients.

Milwaukee, WI, USA

Sincerely,
Daniel J. Stein, M.D.
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Chapter 1
Why Did This Happen to Me? Epidemiology, Genetics, and Pathophysiology of IBD

Ashwin Ananthakrishnan

Suggested Response to the Patient

Crohn's disease and ulcerative colitis, together termed inflammatory bowel diseases, are diseases that affect mostly the large and small intestine. They are characterized by inflammation in the intestine that sometimes is more active and, at other times, stays quiet or in remission. The exact reason why people develop these conditions is not known, but several possible reasons have been proposed. As infants develop over the first 2–4 years of life, they establish a pattern of bacteria in their intestine. This varies between different individuals but there are broad patterns. There are also immune cells that develop in the lining of the intestine that is meant to ignore one's normal bacteria or "good bacteria" but attack potential invading organisms such as those causing food poisoning or "bad bacteria." For reasons that are not completely clear, in some individuals the immune cells lose the ability to recognize the bacterial pattern as being normal

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or your own and start making chemicals called cytokines that lead to inflammation and subsequent damage to the lining. We think that there is a definite contribution of genetics to this; a family history of IBD is one of the strongest risk factors for developing disease in an individual. But there are also additional important contributions from the patterns of bacteria in the intestine; for example, studies have shown that the patterns of bacteria in people developing Crohn's disease or ulcerative colitis are different from those who do not. Additionally there is also an important contribution of the external environment in influencing both the pattern of bacteria and the immune system response. These may include factors such as smoking, diet, use of antibiotics, and stress or depression. There are approximately 1–1.5 million people in the USA with inflammatory bowel disease, so most people know at least one person with IBD.

Brief Review of Literature

Epidemiology

Inflammatory bowel disease that consists of Crohn's disease and ulcerative colitis is most commonly found in North America and Europe, but it can be found worldwide. There are approximately 1–1.5 million people with IBD living in the USA and 2.2 million people in Europe. The incidence of UC ranges from 0.6 to 24.3 persons in Europe and North America with a lower incidence in Asia. The incidence of Crohn's disease is similar as well between 0.3 and 20.2 per 100,000 persons in North America. The estimated prevalence of these diseases is as high as 505 per 100,000 individuals for ulcerative colitis and 322 per 100,000 persons for Crohn's disease in Europe. The incidence and prevalence of these diseases appear lower in Asia but are increasing. The peak age of diagnosis is between 20 and 30 years with a second peak variably reported between 60 and 70 years. The incidence seems similar across both genders. There are also some ethnic differences

with these diseases being more common in those of Jewish ancestry but uncommon in other populations like the First Nations population in Canada.

Genetics

Host genetics is an important contributor to the pathogenesis of these conditions [1, 2]. Approximately 10–20 % of patients will report a family history of IBD in a first-degree relative, and having a first-degree relative increases risk of disease between two- and tenfold. The concordance rate is also higher in monozygotic twins compared to dizygotic twins. The first single nucleotide polymorphism (SNP) to be associated with Crohn's disease was the NOD2 gene located at chromosome 6 in landmark publications in 2001. Since then, our understanding of host genetics has increased at a rapid rate. The recent international genome-wide association study (GWAS) published by the Immunochip consortium identified 163 different individual SNPs associated with these diseases with a substantial portion (110 loci) shared between both diseases [1]. Most of these variants that have been identified occur at a frequency of 1 % or higher but have modest effect sizes. The expanded understanding of the risk loci suggested several important pathways for disease pathogenesis. These include the innate immune response, autophagy, antimicrobial sensing, endoplasmic reticulum stress, epithelial barrier function, microbial defense, and adaptive immune response. Many of the genes appear to be involved in the recognition of gut microbiota through recognition of pathogen-associated molecular patterns such as muramyl dipeptide (MDP), a component of the bacteria cell wall. In response to this sensing through cells such as the dendritic cells, there is activation of the inflammatory signaling through the NF-kB as well as NF-kB-independent pathways. There is considerable cross talk between the different signaling pathways and risk loci. While most variants confer a modestly increased risk, some variants in a receptor involved in the adaptive

immune response, the IL-23R, as well as some rare variants in another gene called CARD9 appear to protect against Crohn's disease. There also appears to be a considerable overlap in risk loci for Crohn's disease and ulcerative colitis with other autoimmune diseases like psoriasis and celiac disease as well as infectious diseases like tuberculosis and leprosy and primary immunodeficiency states.

Microbiome

There is an important role for the gut microbiome in the development of both Crohn's disease and ulcerative colitis. Patients with IBD demonstrate a reduced diversity of intestinal flora. In addition, there appears to be a loss of anaerobic bacteria like *Bacteroidetes* and *Firmicutes* and an increase in *Proteobacteria*, *Actinobacteria*, and species belonging to *Enterobacteriaceae*. However, some species of bacteria appear to confer protection against inflammation. For example, *Faecalibacterium prausnitzii* is found less commonly in patients with IBD, and Crohn's disease patients undergoing ileocecal resection have a higher rate of disease recurrence if they have a reduced count of *F. prausnitzii* prior to surgery.

The External Environment

Various environmental factors play an important role in the development of these diseases [3, 4]. The earliest and most consistently described risk factor is smoking. Cigarette smoking confers a twofold increase in risk of CD in individuals who are still smoking, with the risk reducing a little but remaining elevated for a decade or longer in former smokers. In contrast, current smoker appears to be protective against ulcerative colitis with risk of disease actually lower than in never smoker. However, former smoking is associated with a considerable increase, nearly doubling, of the risk of ulcerative colitis. The mechanism for this divergent effect

is unclear. Smoking has similar influences on established disease as well with current smoking being associated with more aggressive Crohn's disease including a greater need for therapy escalation, increased rates of surgery and hospitalization, and disease recurrence after surgery. Early appendectomy before the age of 20 years is associated with a reduced risk of ulcerative colitis.

Several additional risk factors have been identified in the past decade. Antibiotic use, particularly early on in life, appears to be associated with an increased risk of IBD even when the exposure is in adulthood. IBD is more common in higher latitudes and in the northern parts of countries leading one to hypothesize that reduced UV exposure and low vitamin D levels may influence disease risk. Indeed this has been demonstrated in large cohort studies where low vitamin D levels even before the diagnosis were associated with an increased risk for Crohn's disease in particular. Studies have also linked low vitamin D levels to increased disease activity and need for surgeries and hospitalizations in patients with IBD and that normalization of vitamin D levels may reduce this risk and prevent relapse. Stress, depression, and sleep all have important effects on the immune system. Studies have suggested an association between depression, stress, coping, and impaired sleep and increased risk of disease relapse. Stress symptoms even before diagnosis also appear to increase ones risk. Medications such as NSAIDs that disrupt the epithelial barrier may also increase risk of these diseases. Finally, there is considerable interest and biological plausibility in the role of diet in the development of both Crohn's disease and ulcerative colitis. A diet high in fiber, particularly from fruits and vegetables, appears to be associated with reduced risk of both pediatric-onset and adult-onset Crohn's disease. A high-protein diet or high-saturated-fat diet has been variably associated with ulcerative colitis, while a diet high in n-3 PUFA appears to reduce the risk of UC. The role of diet in established disease and as a trigger of relapses is still unclear.

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Chapter 2
Was There Something I Did to Get Inflammatory Bowel Disease? Environmental and Dietary Factors That Contribute to IBD

Vikram Kanagala and Daniel J. Stein

Suggested Response to the Patient

Crohn's disease (CD) and ulcerative colitis (UC) are called "idiopathic" inflammatory bowel diseases (IBD) which is the fancy medical way of saying we don't know what causes them. Bottom line, it is not likely to be something you did that caused your disease; however, there are some things that may contribute to your disease. Smoking plays a big role in CD. Patients that smoke are more likely to get CD and to have worse outcomes if they continue to smoke. On the other hand, patients that stop smoking are more likely to develop UC in the year after quitting smoking, but we do not encourage our UC patients to smoke. Low vitamin D levels appear to be a risk for developing CD and high levels may be protective,

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so we encourage our patients to have adequate daily intake of vitamin D. A "Westernized" diet may play a role in the development of IBD. A diet high in soluble fiber appears to be protective of IBD, but a diet high in animal protein and fats may contribute to the development of IBD. However, no dietary change has been shown to improve the long-term outcomes of patients with IBD, but they may improve your symptoms. If you have noticed that a particular diet improves your symptoms and are able to eat a healthy, well-rounded diet, I would encourage you to continue.

Brief Review of the Literature

Several environmental and dietary factors have been implicated in the etiology of inflammatory bowel disease (IBD), Crohn's disease (CD), and ulcerative colitis (UC), although no single unifying causative agent has been identified. The onset of inflammation is a complex interaction between a patient's genetic makeup, the environment, and the patient's diet. This chapter will focus on three main environmental factors that affect IBD and then discuss the role of diet in the onset and management of IBD (Table 2.1).

Smoking

Perhaps, the best known and risk factor for Crohn's disease is cigarette smoking which has been associated with a doubling of the risk for CD when compared to those that have never smoked [1]. This risk for CD associated with smoking may linger for several years even after quitting smoking. Additionally, smoking is a risk factor for more aggressive Crohn's disease [2]. Smokers have higher incidence of surgery and higher rates of disease recurrence postoperatively compared to nonsmokers [1]. The exact mechanism of action of smoking in Crohn's disease is not clear at this time, and all CD patients should be strongly encouraged to quit smoking.

Current smokers appear to be protected against development of UC, and smoking cessation increases the risk of UC

Table 2.1 Summary of the key environmental and dietary factors that affect the onset of inflammatory bowel disease and affect ongoing disease activity

	Crohn's disease	Ulcerative colitis
Associated with disease onset or worsening of disease activity	Smoking Low levels of vitamin D Recent enteric infections *C. difficile* infection Diet high in animal protein	Recent enteric infections *C. difficile* infection Diet high *in linoleic acid* and *arachidonic acid*
Protective of disease onset or improvement of disease activity	High levels of vitamin D Diet high in soluble fiber Elemental or enteric feeding	Smoking Diet high in soluble fiber Diet high in *n-3 polyunsaturated fatty acid* and *docosahexaenoic acid*
No effect on disease	Diet high in carbohydrates	Low vitamin D Diet high in carbohydrates Elemental or enteric feeding

onset, especially within the first year of quitting. This risk may persist for more than 10 years after cessation [3]. The effect of smoking is also seen on the disease course. Active smoking in UC has been shown to be weakly associated with a trend toward lower colectomy rates, and smoking cessation has been associated with an increased need for hospitalization and escalation of medical therapy [3–9]. The mechanism of the effect of smoking on UC onset and disease course is unclear. Overall smoking is not recommended as a therapeutic option for UC given its many deleterious side effects.

Vitamin D

While its role in regulating calcium and bone heath is well understood, Vitamin D plays a role in regulating many different aspects of the immune system that we are just starting to understand [10]. Vitamin D metabolism requires exposure to UV light to create the active metabolite, 1,25-dihydroxy D3.

There is known to be a north-south gradient when it comes to the incidence of IBD, in that there is a higher risk of IBD in residents of northern latitudes. It has been suggested that reduced ultraviolet light exposure in northern latitudes may cause reduced active vitamin D (1,25-dihydroxy D3 active metabolites) which may then explain the increased IBD incidence in more northern latitudes [11]. For this reason several people have looked at vitamin D levels as a possible factor in the development of IBD. Analysis of the Nurses' Health Study showed that women with the highest predicted serum levels of vitamin D had a 40 % reduction in the risk of being diagnosed with Crohn's disease when compared to women with the lowest predicted levels of vitamin D [12]. They were unable to show a correlation between vitamin D and UC in this same study. Additionally, when compared to other CD patients with normal vitamin D levels, Crohn's patients with low vitamin D levels have a poorer quality of life and tend to have increased disease activity scores [13].

Enteric Infections

Enteric infections appear to increase the risk of UC onset which is evidenced by the association of *Clostridium difficile* infection (CDI) with about 40 % of UC flares [14]. CDI is more common in patients with inflammatory bowel disease (IBD) and is associated with increased morbidity and mortality [15]. Interestingly, the common predisposing risk factors for CDI such as recent antibiotic use and exposure to health care appear to be less common in the IBD population [14]. *Salmonella* or *Campylobacter* infections have been shown to have a three-time increased risk for IBD onset [16].

Diet

Given the higher incidence of IBD in developed countries and that the incidence of IBD appears to be increasing in developing countries, it only seems logical to look at the

Western diet as a possible etiology for IBD. This "Western diet" is typically low in fiber and high in animal fats and processed food, and we see it slowly becoming adopted in developing countries where we see the increasing incidence of IBD. While several studies have been inconclusive or conflicting, there does appear to be some correlations with diet and the development of IBD. In particular, a high dietary fiber intake has been shown to reduce the risk of both CD and UC onset, particularly soluble fiber from fruits and vegetables as opposed to insoluble fiber from cereals and bran [17]. High intake of linoleic acid and arachidonic acid has been associated with increased UC risk [18, 19], and dietary n-3 polyunsaturated fatty acid and docosahexaenoic acid intakes were associated with reduced UC risk [20]. There is limited data about the effect of protein intake on UC incidence, and high animal protein intake has been associated with increased risk of CD [21]. Carbohydrates do not seem to influence UC or CD risk. The effect of diet or dietary modifications on IBD needs further evaluation in larger intervention studies.

Treating inflammatory bowel disease with a particular diet is very attractive to physicians and patients alike; unfortunately, there is very little data to guide recommendations in this area. While it has not been extensively studied, a low-residue diet (low insoluble fiber) plays a role in the management of stricturing Crohn's disease. Although this is not typically a good long-term solution (it can be deficient in some essential vitamins), it can help to alleviate symptoms while awaiting surgery or medical therapy. While several popular exclusion diets have been proposed for treatment of IBD (e.g., gluten-free diet and specific carbohydrate diet), no elimination diet has been found on a prospective basis to be effective in treating IBD. Elemental and enteral feedings have been shown to be effective for treatment of Crohn's disease, but not ulcerative colitis. Although this may be effective in the short term, patients frequently relapse when resuming a regular diet and the long-term sustainability is often limited by cost and palatability of these diets [22].

Conclusions

Ultimately the cause of both ulcerative colitis and Crohn's disease is multifactorial. There is likely a genetic susceptibility of the patients that interact with the environment and their diet to trigger their disease. What is clear at this time is that Crohn's patients should clearly stop smoking by whatever means are available to them. Maintaining normal vitamin D levels in patients may have a protective effect in patients with Crohn's disease and may influence quality of life for these patients. *C. difficile* infections can complicate the disease course of IBD patients and should aggressively be ruled out in all flaring patients. And lastly, while diet may play a role in the development of IBD, it is not clear at this time that dietary changes will improve the overall outcomes in patients with IBD. Patients should be encouraged to eat a well-rounded healthy diet when it is at all possible.

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Chapter 3
So What Is Crohn's Disease and Ulcerative Colitis? Pathophysiology of Crohn's Disease and Ulcerative Colitis

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Suggested Response to the Patient

Crohn's disease and ulcerative colitis make up a pair of diseases called inflammatory bowel disease. We do not fully understand the exact cause of IBD, but basically it is what we call an autoimmune disease. This means that your immune system, which normally fights infections, is attacking your intestines causing ulcers and sores inside your intestines leading to your symptoms. The cause of Crohn's disease and ulcerative colitis is a result of several factors that we are just now starting to understand. It is most likely a result of several factors including genetics, environmental factors, immune system defects, and interactions with gut bacteria. Ultimately it is not one single factor that caused your inflammatory bowel disease, but rather an interaction of several factors that has caused your IBD.

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Brief Review of the Literature

Inflammatory bowel disease (IBD) is an immune-mediated disease affecting the gastrointestinal tract. There are two main types of IBD, ulcerative colitis (UC) and Crohn's disease (CD). Crohn's disease (CD) can affect any part of the gastrointestinal tract from the mouth to anus, while ulcerative colitis (UC) typically affects only the large intestines. These are mainly diseases of the Western world, suggesting that the lifestyle and dietary factors play an important role in these disorders. But on closer look, they are much more complex in nature with multiple factors such as heredity also playing a part.

Incidence and Prevalence

The incidence of IBD is increasing worldwide. The largest number of IBD patients live in North America. IBD affects nearly 1.4 million people in the USA. The incidence of ulcerative colitis ranges from 2.2 to 19.2 cases per 100,000 person years and that of CD 3.1–20.2 cases per 100,000 person years. The prevalence of UC is 238 per 100,000 and CD is 201 per 100,000 population [1].

Symptoms

Most common symptoms of IBD are nausea, vomiting, abdominal pain, diarrhea, pain or discomfort in the rectum, urgency and blood mixed with mucus in the stools. Other symptoms include night sweats, fever, chills and weight loss. Extra-intestinal manifestations such as arthralgia, skin lesions like pyoderma gangrenosum and eye involvement (iritis/uveitis) can also occur in IBD.

Diagnosis

Colonoscopy or endoscopy with biopsy is often needed to make the diagnosis. Colonoscopy is only 70 % effective in CD as the lesions can involve other areas of the GI tract such as the small bowel. In these situations, modalities like capsule endoscopy, CT scan and MRI scans are needed to make a diagnosis.

Pathophysiology

To understand the pathophysiology of these disorders, an understanding of the disease process is essential as multiple factors alone or in combination may play a role in the causation of both CD and UC. These factors include:

1. Genetic factor
2. Immune system
3. Intestinal microbiome
4. Environment

1. Genetic factors:
   The first IBD-associated gene identified was the NOD2 gene within the IBD1 gene locus in 2001. Since then extensive genome-wide analysis studies have identified more than 160 genes linked to IBD and these numbers are constantly growing. Familial clustering and racial and ethnic differences also suggest a role for genetics in IBD. Ten to twenty percentage of the affected individuals have a family history of IBD. Caucasians have the highest rates of IBD. Ethnic predisposition is also a feature with highest rates of disease in the Jewish population especially the Ashkenazi Jews. All these associations suggest a role for genetic factors in the development of IBD [2].

2. Immune system:
   The immune system has three basic components, which must act in coordination to protect the human body from microbes and foreign particles called antigens. The immune system consists of:

   (a) The mucosal lining or the epithelium of the GI tract. In addition to being a physical barrier, the epithelium also secretes mucus and other anti-bacterial substances. This in combination with intestinal peristalsis helps in clearing harmful microbes.
   (b) The innate immune system comprising mainly of white blood cells (neutrophils, eosinophils, basophils and macrophages) and the natural killer cells. These cells have receptors which bind to specific receptors on the microbes or their products to neutralize them.
   (c) The adaptive (memory) immune system comprises of the B lymphocytes, T lymphocytes and the dendritic cells. The B lymphocytes secrete substances called antibodies and the T lymphocytes on interaction with the antigens elicit immune response through substances called cytokines. The dendritic cells help T and B lymphocytes recognize harmful antigens.

It is hypothesized that a dysfunction in the immune system contributes to IBD as follows:

- Alterations in the intestinal epithelial integrity, permeability, mucus secretion, number of bacteria and abnormal antigen processing by the immune system may all play an important role in the development of IBD. Increased intestinal permeability leads to influx of more neutrophils, macrophages and lymphocytes which causes a stronger inflammatory response. There are also studies which have described the increased expression of adhesion molecules on the immune cells and their binding to the epithelium [3].
- Increased number of B-lymphocytes and hence increased number of antibodies directed against the normal antigens in the body called autoantibodies

have been described in IBD. For example, there have been studies which link the presence of perinuclear anti-neutrophil cytoplasmic antibodies (*P-ANCA*) and absence of anti-Saccharomyces cerevisiae antibodies (*ASCA*) to ulcerative colitis more than Crohn's disease (Sensitivity—57 %, specificity—97 %). Similarly the presence of ASCA and the absence of P-ANCA is more likely to be in Crohn's disease patients than ulcerative colitis. (Sensitivity—49 %, specificity—97 %) [4].

- T-lymphocytes comprise of CD 4+ (T-helper) cells and CD 8+ (cytotoxic) cells. T-helper cells can be functionally divided into Th1, Th2 and Th17 cells. Th1 cells are predominantly pro-inflammatory secreting inflammatory substances like interferon gamma and tumor necrosis factor alpha (TNF-alpha). Th17 cells have an important role in inflammation and autoimmunity. Th2 cells help in the regulation of B-lymphocyte response to the antigens [5].
- The cells of the immune system produce mediators of inflammation called cytokines. Cytokines play a central role in inflammation by inducing cells to produce more of these substances, migration of the lymphocytes and antigen presenting cells to the target area thus causing specific pathological changes in the tissues. In both UC and CD, there is dysregulation of this response leading to chronic inflammation.

3. Intestinal microbiome:
   The human intestines are rich in microbial flora (microbiome), especially the distal part of the small intestine called the ileum and the colon. This flora includes the normal gut bacteria which are good for our health and also pathogens which can harm us. The balance of this flora is maintained by the integrity of the epithelium and the immune system. Any disturbance of this equilibrium can lead to inflammation. This alteration could be due to the pathogenic bacteria or their products

breaching the epithelium, underlying defect in the epithelial integrity or aberrant immune response against the microbial products.

4. Environmental triggers:
   High intake of meat products and unsaturated fats, low vitamin D, use of antibiotics, etc. may have a role in the development and/or relapse of inflammatory bowel disease. However this has not been conclusively established and further studies need to be done in this field.

Crohn's Disease (CD)

CD can affect any region of the intestine from the mouth to the anal canal but mostly involves the ileum and the colon. The inflammation usually begins around the glands in the intestine in spaces called crypts initially leading to superficial ulcers. Later these ulcers progress both longitudinally and transversely in the mucosal surface as well as extending into the deeper walls of the intestine, typically causing a cobblestone appearance. The diseased areas of the bowel are demarcated from the normal areas leading to characteristic lesions called *skip lesions*. Inflammation can involve the entire bowel wall (*transmural spread*) [6]. The pathognomic feature of CD is *noncaseating granuloma*, which is an accumulation of lymphocytes and macrophages within the bowel wall. These microscopic changes ultimately lead to the following symptoms and complications as described below:

1. Abdominal pain: present regardless of the disease distribution. It can occur due to the transmural nature of the disease or due to complications like obstruction of the bowel.
2. Diarrhea: is a common presentation of CD. Inflammation can increase the intestinal secretions leading to abnormal absorption and diarrhea. In patients who have undergone surgery, short gut can often lead to diarrhea.
3. Bleeding: blood in stool is often seen. Occult bleeding is also common in CD.
4. Fistula: fistulas occur due to the transmural nature of the disease process. They are abnormal connections between

the bowel and the bladder, bowel and the skin, bowel and the bowel or bowel to the vagina. They can be asymptomatic or present as urinary tract infections when they drain through the bladder, passage of feces through the vagina, or drainage of the bowel contents outside when they connect to the skin. The occurrence of fistulas can be as high as 33–50 %.

5. Intestinal obstruction: transmural disease leads to fibrosis of the intestinal walls causing narrowing of the lumen called as strictures. This leads to obstruction of the bowel.
6. Perianal disease: these include skin tags, fistulas, anal fissures, and abscesses in the perianal area. Up to one-third of the patients affected with CD can suffer from perianal disease and is often very difficult to treat.
7. Malabsorption: often due to the inflammation of the terminal ileum or removal during surgery, leading to loss of bile salts in the stools causing "bile salt diarrhea." Fat malabsorption can also occur due to the loss of bile salts leading to fatty stools called steatorrhea. Malabsorption can also predispose to the formation of gallstones and kidney stones.

Ulcerative Colitis (UC)

UC is characterized by inflammation of the colon and the rectum. It often follows a relapsing and remitting course. It always involves the rectum and spreads to the colon in a continuous fashion. The basic mechanism which triggers UC is similar to CD. Inflammation in the colonic mucosal layer leads to crypt abscesses, ulcers in the colonic wall, and increased mucus discharge from the glands lining the colon. The inflammatory process can lead to polypoid appearance in the mucosa called "pseudopolyps." Eventually blunting of the intestinal epithelial vasculature occurs. The most striking differences between UC and CD are as follows:

1. UC involves only the colon and the rectum.
2. UC involves only the superficial mucosal layer of the colon unlike transmural involvement in CD.

The common symptoms and complications of UC are:

1. Diarrhea: patients with UC have diarrhea much more common than CD and are associated with abundant mucus discharge. Urgency to have a bowel movement and a feeling of constantly needing to pass stools, despite an empty colon (tenesmus), are characteristic.
2. Abdominal pain: this is also a common manifestation of UC. Due to colonic involvement, the pain can be diffused all over the abdomen.
3. Bleeding: bloody diarrhea is common in UC. Rectal bleeding can also occur without diarrhea.
4. Systemic features: include fever, weight loss and fatigue. The presence of these symptoms and their severity correlate with the activity of the disease and such systemic features are much more common in UC than CD.
5. Toxic megacolon: this is one of the dreaded complications of UC which causes massive dilatation of the colon with abdominal pain, bloating, tenderness, fever, rapid heart rate, and sometimes low blood pressure leading to shock. The incidence of perforation is high and can sometimes result in death.

Extraintestinal manifestations of Crohn's disease and ulcerative colitis:

Apart from the intestines, many extraintestinal organs can also be affected in IBD. The incidence of individual manifestations varies between UC and CD. They constitute about 10 % of the initial presentation symptoms in IBD and patients with IBD have a 25 % lifetime risk of developing these manifestations:

1. Musculoskeletal: arthritis or joint pain is the most frequent extraintestinal manifestation (EIM) in IBD. They primarily involve the large joints of the back leading to low back pain and associated with a condition called ankylosing spondylitis [7].
2. Skin: the skin lesions associated with IBD are erythema nodosum, which mainly involves red, tender nodules in the shin region associated with pain and pyoderma gangrenosum causing deep ulcers around the leg region [8].

3. Eye: the most frequent eye manifestations in IBD are called uveitis and episcleritis. These manifest as pain, burning sensation in the eyes, itching and redness.
4. Liver and bile ducts: primary biliary cirrhosis and autoimmune liver disease are the main conditions associated with IBD. Common symptoms are pain in the right upper side of the abdomen, itching, fever, fatigue and jaundice [9].
5. Hematopoietic system: patients with IBD are associated with an increased risk of clotting in the blood leading to symptoms like stroke. Iron deficiency anemia and autoimmune hemolytic can be seen in IBD [10].

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Chapter 4
Are You Sure I Have Crohn's Disease? Making the Proper Diagnosis, Avoiding IBD Mimickers, and Diagnostic Pitfalls

Sunanda Kane

Suggested Response to the Patient

Inflammatory bowel disease (IBD) means that there is chronic inflammation within the gastrointestinal tract. Under the microscope there are certain features or characteristics to the tissue that is most consistent with Crohn's or ulcerative colitis. In the absence of factors such as infection, drugs, cancer, or other known autoimmune disease, the likelihood of this being IBD is high.

Brief Review of the Literature

Discrimination of IBD from other conditions can be based on location, symptoms, and endoscopic, radiographic, or histologic appearance (Table 4.1) [1]. That is why a combination of tests is necessary before the diagnosis can be confirmed. Serologic tests alone are *not* sufficient for a diagnosis—they

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Table 4.1 Common mimics of IBD

Infection	Mechanical	Inflammatory	Neoplastic
HIV	Pill esophagitis	Celiac sprue	Lymphoma
HSV	Rectal prolapse	Behcet's disease	Leukemia
CMV	Solitary rectal ulcer syndrome	Segmental colitis associated with diverticular disease	Kaposi's sarcoma
Clostridium difficile	Radiation damage	Autoimmune enteritis	
Tuberculosis	Meckel's diverticulum	Endometriosis	
Histoplasmosis		Colon prep effect	
Yesinia		Ipilimumab-induced colitis	
LGV			

are neither sensitive nor specific enough to do this despite some marketing claims [2]. A proper history and physical exam are very important when trying to make an initial diagnosis. Patients who complain of diarrhea should be asked if it awakens them from sleep, as functional diarrhea will rarely if ever disturb sleep. If bleeding is bright red and occurs after a bowel movement, it could be outlet bleeding and not be associated with a sinister process from within the bowel itself. Weight loss should be carefully documented as primary or secondary. Some patients will go on strict elimination diets and lose weight from improper caloric intake rather than from protean losses. Fatigue and arthralgias are noninflammatory and highly nonspecific symptoms and can be associated with many different diagnoses. While a family history of IBD is important, it does not mean that the patient automatically has IBD. Abdominal pain is also a common complaint and needs to be further clarified—is it present consistently, its relation to food and having a bowel movement, exacerbating factors, etc.

If we make our way down the gastrointestinal tract, mimics of Crohn's disease in the esophagus include viral infections like herpes simplex virus (HSV) and human immunodeficiency virus (HIV). Pill esophagitis also causes dysphagia with deep, single ulcers. In the small bowel, infections that can mimic Crohn's disease include tuberculosis and *Yersinia*. While *Giardia* lives in the small intestine, it does not cause mucosal damage. Medications like nonsteroidal anti-inflammatory drugs (NSAIDs) and angiotensin-renin blockers (ARB) can cause ulcerations and enteritis [3]. Celiac disease and otherwise unspecified autoimmune enteritis cause chronic diarrhea, pain, and malabsorption syndromes with inflammatory changes on imaging. Neoplasm like lymphoma, infiltrative leukemia, and metastatic lesions can look like Crohn's. Endometrial implants can cause pain and bleeding and cause an abnormal appearance to the lumen. A Meckel's diverticulum that has become ulcerated can mimic Crohn's disease as well.

Colonic mimics of IBD include prep effect histologically, and infections like histoplasmosis, tuberculosis (TB), and cytomegalovirus (CMV) or *C. difficile* infection can be mistaken for IBD as well [4, 5]. Neoplasm like Kaposi's sarcoma or an infiltrative process like leukemia will cause a colitis-like appearance. Segmental colitis associated with diverticular disease can look like either UC (ulcerative colitis) or Crohn's because of its inflammatory and patchy nature. Solitary rectal ulcer syndrome can also look like a proctitis or single ulcer confused for Crohn's disease. Rectal prolapse can cause a proctitis-like appearance as well. Recently the chemotherapy ipilimumab has been associated with a severe inflammatory colitis that mimics UC. Scope trauma with some mild erythema and a pathology report that reads "nonspecific chronic inflammation" is normal. There needs to be crypt architecture distortion with plasmacytosis and mucin depletion to be considered IBD.

Mimics in either the small or large bowel include radiation change, ischemia, or Behcet's. Irritable bowel syndrome can also mimic many of the symptoms of IBD without any

mucosal damage and will often be misdiagnosed as IBD especially in combination with abnormal serologies.

Mimics of Crohn's disease in the perianal region include trauma and obstetric, gynecologic, or colorectal surgery. Infection includes anal warts, TB, and lymphogranuloma venereum (LGV). Ischemia is not as likely unless there has been previous surgery. Neoplasm also can cause fistulas and anatomic deformity.

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Chapter 5
Do I Have Crohn's Disease or Ulcerative Colitis? Identifying Factors That Distinguish CD from UC and Indeterminate Colitis

Joel Pekow

Suggested Response to the Patient

Inflammatory bowel diseases (IBD) are commonly defined as either Crohn's disease or ulcerative colitis. There is substantial overlap, however, in clinical symptoms, genetics, and treatment response between the two. As such, it is not uncommon for your physician to change your diagnosis based on development of new clinical information over time. There are several factors that can help distinguish between the two diseases. In ulcerative colitis, inflammation only occurs in the colon; the area of inflammation is also continuous extending from the anus to an area in the colon where the inflammation ceases and there is normal-appearing colon. Crohn's disease may also involve only the colon, termed Crohn's colitis, which makes distinguishing between the two diseases difficult. In patients who have features of both Crohn's colitis and ulcerative colitis, they are often given the

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diagnosis of "indeterminate colitis." Crohn's disease is more likely; however, if there is inflammation in the small bowel or upper GI tract, the inflammation occurs in a patchy distribution, or a patient has perianal disease (anal fistulas, fissures, or inflamed skin tags). In addition, long-standing bowel inflammation in Crohn's disease may result in bowel narrowings, termed strictures, or abscesses adjacent to the bowel from connections, termed. There is also an interesting association between smoking and IBD. Although the majority of patients with Crohn's disease are nonsmokers, patients who smoke and are diagnosed with IBD are much more likely to have Crohn's disease, whereas ulcerative colitis is more common in former smokers and nonsmokers.

Brief Review of the Literature

Traditionally, inflammatory bowel disease (IBD) has been subgrouped into two diseases, Crohn's disease (CD) and ulcerative colitis (UC). As the clinical presentation, endoscopic findings, disease course, and treatment response are heterogeneous in both CD and UC with significant overlap in both diseases, however, grouping IBD into two subtypes is likely an oversimplification of numerous distinct, yet related diseases. This is reflected in genome-wide association studies which have identified over 160 loci associated with IBD, many of which overlap between CD and UC [1]. Despite the disease heterogeneity, there are several clinical, endoscopic, histologic, and serologic clues to help distinguish between CD and UC. Still, approximately 10 % of patients whose disease cannot be differentiated between the two are diagnosed with indeterminate colitis. Although the term "indeterminate colitis" was originally proposed as a pathological diagnosis for colectomy specimens which could not discriminate between Crohn's disease and ulcerative colitis, it has been widely adapted into a clinical classification [2].

In patients who have isolated colitis, differentiating between Crohn's disease and ulcerative colitis can be difficult,

although there are several endoscopic and histologic clues that can help set apart the two. Perianal disease involving fistulas, abscesses, fissures, or inflamed skin tags is more common in Crohn's disease. Findings of upper GI involvement are suggestive of Crohn's disease, although several studies have demonstrated that inflammation in the esophagus, stomach, and duodenum can be seen at the time of diagnosis in patients with UC [3]. Inflammation involving the terminal ileum is also common in CD. However, inflammation in the terminal ileum in a patient with pan-colitis is not diagnostic of CD as approximately 20 % of patients with pan-UC can have backwash ileitis [4]. Ulceration or stenosis of the ileocecal valve, ulcerations in the ileum, and granulomas on histology can aide in distinguishing between CD of the ileum and UC with backwash ileitis. Although disease distribution by endoscopy or pathology can be confounded by treatment, patchy inflammatory activity, granulomas, and inflammation extending deeper than the mucosa are also suggestive of Crohn's disease.

In addition to endoscopic and histologic findings, assessing a patient's history of smoking can aid in making a definitive diagnosis of CD or UC. In patients who quit smoking, there is an increased risk in developing UC after smoking cessation [5]. In fact, former smokers with UC will often have a response in disease activity with resuming cigarette smoking [6]. In contrast, current smokers are more likely to have Crohn's disease as smoking is an independent risk factor for the development of Crohn's disease [7].

In patients with indeterminate colitis, the role of additional diagnostic tests is controversial. Video capsule endoscopy can evaluate for small bowel ulcerations and has been proposed for use in patients with indeterminate colitis [8]. However, patients with UC may have nonspecific small bowel mucosal damage from other etiologies. In contrast, some patients with CD may have an initial negative video capsule study and subsequently develop small bowel inflammation. Serological markers including antibodies against microbial antigens (ASCA, OmpC, Cbir1, A4-Fla2) and pANCA are also often

used in the diagnosis of IBD. Yet, investigations have demonstrated that these serologies have a limited sensitivity and specificity to distinguish between Crohn's disease and ulcerative colitis. The addition of genetic tests and inflammatory markers to the serologic profile may improve the diagnostic yield, although this approach of integrating different diagnostic platforms has not been validated in patients with indeterminate colitis to guide a diagnosis of CD or UC [9]. Because of a lack of diagnostic accuracy in currently available tests to classify CD vs. UC, there is extensive ongoing research examining the diagnostic yield of genetic testing as well as other novel molecular markers in tissues and peripheral blood for this purpose.

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Chapter 6
What If I Do Not Get Myself Treated for Crohn's Disease? Natural History of Crohn's Disease

Tauseef Ali

Suggested Response to the Patient

Crohn's disease is a chronic inflammatory disease of your intestinal tract. The majority of patients with Crohn's disease are diagnosed in the second or third decade of life. The process of inflammation in Crohn's disease can involve any part of the intestinal tract, from the mouth to anus. Your intestinal tract is made of different layers just like layers of onion. Unlike ulcerative colitis, which involves only the inner most layer also known as mucosa, Crohn's disease can affect all the different layers of your intestine. To date, we don't have a cure for this inflammation, and the goal of our therapy is to suppress and keep the inflammation down and prevent the complications of the disease. If left untreated, most patients will have intermittent periods of worsening of disease called flares followed by period of feeling better called remission. Some patients can go in remission for a long time after their first flare. It is hard to determine which patients will follow

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that pattern. However, without treatment most patients will have repeated attacks of mild to severe symptoms with ongoing damage to the lining of the GI tract. This ongoing process of inflammation can lead to scar formation that may cause abnormal narrowing of the intestine called a stricture or abnormal communications between different parts of intestinal tract called fistulas. Fistulas may also form between the intestinal tract and other organs as the vagina and urinary bladder or to the skin. All of these lead to an increased need of surgery with recurrence afterwards. Long-term difficulty to absorb nutrition in untreated CD can also lead to severe malnutrition, anemia, dehydration, weight loss, and lack of immunity to fight infections. All these complications can be debilitating and even life threatening if not recognized and treated in timely fashion. The risk of complicated disease increases if you are diagnosed at an early age or smoke cigarettes. Different types of immunosuppressive medications are prescribed not only to bring inflammation down but also keep it suppressed with the goal to keep the symptoms away; prevent flares, hospitalization, and surgical and nutritional complications; and improve the quality of life.

Brief Review of Literature

Crohn's disease is a chronic, transmural immune-mediated inflammatory disease of the gastrointestinal tract that also can have extraintestinal manifestations. The current prevalence of Crohn's disease in North America is 144 ± 198 cases per 100,000 persons [1, 2]. The goal of therapy is not only to control the symptoms but to also prevent structural bowel damage and disability. We now recognize mucosal healing, prevention of relapse, and prevention of hospitalization and surgery, offering cost-effective therapy and improving quality of life as evolving goals of managing our IBD patients. Most, if not all, patients will progress toward complicated course of the disease without medical therapy. Population-based studies have shown that majority of patients who initially have

inflammatory disease phenotype at the time of diagnosis will progress to penetrating or fibrostenotic disease over the course of 10–20 years. Young patients, particularly those with perianal disease at the onset, are more likely to need surgery and several courses of steroids to control their disease. Delayed or inadequate therapy to control inflammation can lead more complicated course such as permanent ostomy or even short bowel syndrome.

Location of CD: At the time of diagnosis, approximately, 40 % of patients present with ileocolonic disease, about 30 % have isolated ileitis, and other 20–30 % patients have disease limited to the colon [3]. Approximately one-third of patients have perianal disease. Approximately, 5–15 % patients have upper gastrointestinal tract involved and 20–30 % of patients have perianal involvement. The localization of Crohn's disease changes minimally over time, with only 10–15 % of patients will have a change in the location of their disease after 10 years [4].

Pattern of exacerbations and remission: The natural course of CD is marked by recurrent flares alternating with periods of remission. Population-based studies have shown that after the first year of diagnosis, 50–65 % of CD patients will be in remission, 15–25 % of CD patients will have mild disease, and 10–30 % will have highly active disease with relapses and exacerbations. Follow-up over 10–15 years has shown that 10–13 % of patients remain in remission for several years, 67–73 % of patients experience a chronic intermittent course, and 13–20 % of patients have a chronic course with continuous activity [4]. It has also been seen that the activity of the disease in the previous year predicts the course in the subsequent years. If a patient has been in remission for full 1 year, there is an 80 % chance of remission in the following year. On the other hand, a recent flare only has a 30 % chance of remission in the following year. This pattern of disease activity highlights the need for effective drug therapy, both for the control of active disease and for the maintenance of disease remission.

Fistulas, strictures, and abscesses: At diagnosis, 70 % of patients have nonstricturing or non-penetrating disease, 17 % have strictures, and 13 % have penetrating disease. At 10-year follow-up, there has been a reported change from nonstricturing to either stricturing in 27 % or penetrating disease in 28 % of patients. The terminal ileum is the most likely point of origin for abscesses and they occur in 15–20 % of patients with CD. Internal fistulas occur in 5–10 % of patients with CD and they are more frequent in patients with ileal disease. The occurrence of perianal fistulas varies between 21 and 23 % [5].

Progression to need of surgery: More than 80 % of patients will end up needing some form of surgery in their lifetime. About 40–60 % of patients with CD in terminal ileum will need surgery during the first 10 years of symptoms. However, 50–60 % of CD patients who undergo surgery develop recurrent disease within 10 years [6, 7]. Patients with perforating disease have a higher likelihood of more rapid recurrence compared to those who have a stricturing disease.

Progression of complications: Even in patients who are treated for CD, progression of intestinal and extraintestinal may occur. Therefore it is reasonable to assume that in untreated patients these complications may ensue sooner and be more aggressive. CD can affect organs outside the GI tract in up to 25 % of patients. To list a few, malabsorption, malnutrition, bile salt diarrhea, small intestinal bacterial overgrowth, osteoporosis, kidney stones, anemia, and altered immunity all may hasten an adverse outcome in an untreated CD patient.

Impact of medical therapy: With advancement in the knowledge of pathophysiology and natural history of Crohn's disease, the goals of our therapy to manage this disease have also evolved. More attention is being paid to mucosal healing with an effort to modify the disease course and avoid disabling complications. Anti-TNF therapy has been shown to reduce the need for disease-related hospitalizations and surgery, though the duration of these effects is unknown at this point [8]. Similarly, studies have shown that combination therapy of immunomodulators with anti-TNF therapy is superior to both

anti-TNF and immunomodulator monotherapy [9]. A crucial point is the timing of commencement of early treatment. In clinical practice, early CD is usually considered as a newly diagnosed case, and this does not always correspond to onset of the early purely inflammatory form of the disease. Approximately 30 % of patients already present a stricturing or penetrating disease at the time of diagnosis, thus indicating a late disease which may be more resistant to treatment with immunosuppressive medications.

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Chapter 7
What Happens If I Do Nothing for My Ulcerative Colitis? The Natural History of Untreated Ulcerative Colitis

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Suggested Response to the Patient

Ulcerative colitis is a chronic, lifelong, inflammatory disease where the body's immune system (the system that normally fights infection) is attacking your colon which causes ulcers and bleeding from the lining of the colon. Symptoms typically occur in periods of attacks we call flares and can last from months to years at a time. These flares are different for every patient and can be characterized by abdominal pain, diarrhea, bloody diarrhea, nausea, vomiting, and/or weight loss. This leads to loss of quality of life, frequent doctor's visits, and hospitalizations, and some patients require removal of the colon due to worsening of the disease. Most patients have up to two flares in a 5-year period, but this will be very different for every patient. For many patients who go untreated, ulcerative colitis tends to get progressively worse over time. Flares tend to get more frequent and more severe, putting patients at risk for hospitalizations and even surgery to remove the colon (colectomy). Additionally, if left untreated,

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UC can put patients at a higher risk of developing colon cancer over time.

Once the diagnosis has been made, early treatment is recommended to decrease how often these flares occur and decrease the severity of each flare. Due to the development of newer medical treatments, the possibility of disease worsening is lesser today than it was a few decades ago. These treatments have also reduced the need for colon removal (colectomy) and possibly decreased the risk of colon cancer. It is important to understand that UC is a lifelong diagnosis and that medical therapy cannot cure ulcerative colitis, but it is very good at controlling the disease.

Brief Review of the Literature

Ulcerative colitis (UC) is a chronic inflammatory disease characterized by recurrent episodes of acute flares followed by periods of remission. Earlier population-based studies have revealed that without treatment, these patients have a higher risk of colorectal cancer and increased mortality [1], although this risk has decreased over the decades owing to successful immunosuppressive and biologic medical therapies [2–7]. An untreated disease pathology has the potential for extension throughout the colon leading to systemic symptoms which may require a colectomy.

Disease Course in Relation to Disease Extent

UC is classified, based on disease extent, into ulcerative proctitis, left-sided colitis, and extensive colitis. The Montreal classification includes disease extent, symptom severity (number of bowel movements per day), and signs of systemic involvement (ESR, temperature, hemoglobin) [8]. Identification of disease severity and extent serves as a useful prognostic indicator. Ulcerative proctitis is the most frequent form at diagnosis (30–60 %), and left-sided colitis (10–40 %) and extensive colitis (10–35 %) are less frequent [9–15]. The risk of proximal

progression is estimated to be around 10–20 % at 5 years and up to 30 % at 10 years [9, 16].

Disease extent is a major factor predicting the progression of disease which can signify increase in disease activity with worsening outcomes. Patients with ulcerative proctitis were shown to progress to extensive colitis at the rate of 14 % over 10 years after diagnosis. A higher rate of progression was seen in patients with left-sided colitis at 28 % in the IBSEN Norwegian cohort [7]. Young age at diagnosis and primary sclerosing cholangitis were strong and independent predictors of proximal progression in a prospective study of 420 patients [17]. The median time of progression from proctitis or left-sided colitis to extensive colitis in this study was 5.25 years.

Expected Frequency of Disease Flare-Ups

Most UC patients have at least two flare-ups in 5 years but less than 1 yearly flare-up [10]. About half of the patients in the IBSEN Norwegian cohort experienced the most severe flare-up at diagnosis, and one third of the patients had subsequent flare-ups of similar severity [13]. Younger patients at diagnosis had a trend towards higher relapse rate. In fact, patients diagnosed over the age of 50 years had a significantly lower relapse rate and colectomy rate. These findings were also corroborated in the EC IBD multicenter study [7, 18, 19].

Long-Term Complications

Disease progression in ulcerative colitis can lead to benign colonic strictures due to hypertrophy and irreversible contraction of muscularis mucosae that is eventually detached from the submucosal layer [20]. These strictures become problematic in that it is difficult to completely rule out an occult malignancy within these strictures, often leading to surgery. Also, there is a reduction in the number of neuroglial cells leading to dysmotility, and persistent diarrhea in spite of

mucosal healing seen on endoscopy, and reduced rectal accommodation leading to fecal urgency and incontinence, when the anorectal compartment is involved [21]. These changes may persist even after mucosal healing is achieved, which is thought to play a role in continued symptoms in some patients without active mucosal inflammation.

Risk of Colectomy

Colectomy is a curative procedure for patients with ulcerative colitis and significantly improves general health, but dealing with an ostomy or J pouch can be debilitating for some patients. About 50 % of the colectomies performed for UC are done emergently [22]. Colectomy has not been shown to increase mortality, but a delay in surgery has been shown to increase postoperative complications and mortality [23]. The rates of colectomy have declined over the years, and two separate studies showed this decline in 1-year colectomy rate in UC patients from 9 % in 1962–1987 to 6 % in 2003–2005. This decline is most likely due to the increasing use of azathioprine/6-mercaptopurine across these time periods [24, 25]. In the recent EC IBD study, average colectomy rate in UC patients was at 8.7 % after 10-year follow-up. The difference in colectomy rates between northern (10.4 %) and southern centers (3.9 %) in this study suggests that the disease process might be more pronounced in patients living in cooler and more sterile areas [2, 12]. Patients with extensive UC and severe refractory disease constitute more than 90 % of the colectomies. Consistent with the prior knowledge that in most cases, severe disease flares might be seen earlier in the course of the disease, about two thirds of the colectomies occurred in the first 2 years after diagnosis [12, 13]. Extensive colitis at diagnosis is an independent predictor of colectomy up to 10 years after diagnosis, based on the IBSEN study [7, 26]. Extensive colitis patients have a fourfold higher risk of colectomy compared to those with ulcerative proctitis [26]. However, in this same cohort, patients with proximal extension were shown to have a tendency towards higher rate of colectomy when compared to

patients with extensive colitis at diagnosis [7]. Overall, younger patients (<30 years old), extensive colitis, ESR > 30 mm/h, and corticosteroid requirement at diagnosis were associated with a 15 times higher risk of colectomy [2].

The presence of systemic symptoms such as weight loss and fever in addition to extensive colitis at diagnosis further increased the risk of colectomy. These factors however did not influence the risk of relapse, suggesting that severe disease might be associated with more drastic outcomes [27]. The minor fraction of patients with extensive colitis and systemic symptoms at diagnosis, that were able to avoid colectomy through timely response to medical therapies, have lesser risk of relapses when compared to patients lacking systemic symptoms, based on the IBSEN and Copenhagen cohort studies [7, 27, 28]. Endoscopic findings in these patients also corroborate the epidemiologic findings with increased mucosal healing at 1 year in patients with extensive colitis and systemic symptoms that showed good response to medical treatment [28].

Colorectal Cancer

Colonic mucosal inflammation and associated stress from reactive oxygen species can lead to genetic alterations and carcinogenesis [29]. According to a Belgian national registry study, 73 % of the UC patients developed colorectal cancer (CRC) only in areas of colitis [30]. Follow-up of unselected patients from population-based cohorts showed a cumulative CRC incidence of 0.4 and 1.1 % after 10 and 20 years, respectively [31]. The overall risk of CRC in UC patients was comparable to the background risk of CRC in the general population, in a meta-regression analysis of the same study [2, 31]. Cumulative CRC incidence was greater in other studies, up to 10–20 %, by the second and third decades of the disease process, but this was mainly noted in pancolitis patients seen at referral centers. A higher incidence of CRC was seen in UC patients with long duration of disease, coexistent primary sclerosing cholangitis (PSC), and young age at diagnosis, although the Belgian study showed that older age

at diagnosis was an independent risk factor for CRC and these patients had early cancer within 8 years from diagnosis [2, 30, 31]. Extensive colitis, male sex, and young age at diagnosis were the factors that were associated with increased mortality in UC patients with CRC. The incidence of CRC in UC patients has declined over time periods with only a third of the relative risk present in 1999–2008 compared to 1979–1988 [31], most likely due to successful use of biologics and immunomodulatory therapies. The IBSEN study also corraborates the existing evidence that CRC does not significantly increase the mortality risk in UC patients compared to the general population [2]. Presently, the prognosis is similar in UC patients compared to the general population with a 5-year survival of approximately 50 % [32]. 5-aminosalicylic acid (5-ASA) agents have been shown to reduce the incidence of CRC in a meta-analysis of 1,932 UC patients [33]. Due to the decreasing incidence of CRC in UC patients, the role of 5-ASA agents for chemoprevention may be less important than previously thought. For UC patients with coexistent PSC, where there is a significantly increased risk of CRC, ursodeoxycholic acid (UDCA) has shown some promise by reducing the levels of secondary bile acids which serve as carcinogens leading to increased risk of CRC, especially in the right colon [34]. But recent 2010 guidelines have advocated against the use of UDCA for chemoprevention based on prospective evaluation of patients who had a higher incidence of dysplasia and colorectal cancer after receiving high dose UDCA [35].

Screening for colorectal cancer in UC patients is recommended at 8–10 years for patients with pancolitis and at 15 years for patients with left-sided colitis. No surveillance is required for patients with ulcerative proctitis, and further surveillance can be based on risk factors [36–40]. The Belgian national registry study reported that time to CRC incidence was independently affected by age of IBD onset in addition to IBD duration with older age of diagnosis of IBD predisposing a shorter interval to CRC onset [30]. The high number of patients who were diagnosed with CRC concurrently with UC

in this study probably indicates a need for a more stringent surveillance approach in older patients at diagnosis. For patients with UC and PSC, the risk of CRC or dysplasia is threefold higher than for patients with UC alone [30]. In this patient group, the cumulative incidence rates were 33 and 40 % after 20 and 30 years after UC diagnosis, respectively [41]. For UC patients with coexistent PSC, annual surveillance colonoscopy is required from diagnosis [38, 42]. In patients newly diagnosed with PSC, a colonoscopy is recommended to diagnose coexistent UC [42]. Further, UC patients with a first-degree relative with history of CRC have a two- to threefold increased risk of CRC, and if the first-degree relative had CRC before the age of 50 years, the risk is ninefold compared to patients with no significant family history [43]. Chromoendoscopy was found to be superior to conventional colonoscopy with random biopsies in detecting dysplastic lesions [44]. Confocal laser endomicroscopy has a 2.5 times increased detection rate of dysplastic lesions compared to chromoendoscopy and has a 4.75-fold higher detection rate compared to conventional colonoscopy with random biopsies [45, 46].

UC patients do not have a higher mortality rate when compared with the general population. A slightly increased mortality is seen in patients older than 60 years with comorbidities undergoing emergency colectomy [4, 6, 7, 47].

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Chapter 8
What Factors of My Crohn's Disease Put Me at Higher Risk of Complications? Identifying Crohn's Patients with Severe Disease

Liliana Oliveira

Suggested Response to the Patient

Although not all patients with Crohn's disease will develop irreversible bowel damage leading to complications such as strictures and fistulas, there is a large number that will. Identifying those people at higher risk of developing these complications is not always easy, but there are certain risk factors that have been associated with disease that is more likely to progress over time.

In general, people who develop strictures or intestinal fistulas tend to have small bowel or upper GI tract inflammation as opposed to inflammation in the colon. The location of the disease is therefore an important factor but alone is not enough to predict complications. If however the Crohn's is in the colon, having deep colonic ulcers is a predictor for severe disease, and these patients are more likely to require a colectomy.

Perianal fistulas are also considered a marker of severe disease, not only because they are themselves difficult to treat

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and often require surgical intervention, but because they may be predictive of the progression of small bowel disease.

The age at which a person is diagnosed is also an important factor. Crohn's disease in children and adolescents tends to be more severe and is more likely to result in complications. A patient requiring steroids for treatment of a flare-up within the first 3 months of diagnosis is also a risk factor for severe disease.

Lastly, smoking is a well-known environmental risk factor for Crohn's disease. Patients with Crohn's disease who smoke are more likely to develop strictures and fistulas. Furthermore, these complications tend to develop faster in smokers compared to nonsmokers.

The more the above characteristics are present, the higher the likelihood it is to develop strictures and fistulas long term. Once these complications occur, it means that there has been irreversible damage to the bowel at which point surgery is often the only option. Because of this, it is important to identify people at higher risk early as they may benefit from aggressive medical treatment to prevent progression of the disease to strictures, fistulas, and eventually surgery.

Brief Review of the Literature

Crohn's disease is a chronic relapsing inflammatory condition that is progressive and characterized by the development of complications over time. Of patients presenting with uncomplicated Crohn's disease, it has been estimated that between 40 and 60 % will develop either stricturing or penetrating complications over a 10-year period [1, 2]. These complications have a detrimental effect on quality of life and in many cases require surgical intervention [3, 4].

The ability to predict which patients are more likely to develop complications would potentially allow us to aggressively treat those patients at the highest risk with effective medicines early on in their disease to prevent disease progression.

There have been a number of studies aimed at predicting the patient characteristics that increase the risk of developing penetrating and stricturing disease over time.

Disease location, specifically ileal, ileocolonic, or upper GI involvement, has been shown in several studies to be significantly associated with disease progression [5–7]. It has been proposed that the reasons behind the differences in the rates of disease progression between small bowel and colonic disease are potentially related to differences in the diameter of the lumen and the intensity of inflammation leading to permanent bowel damage [8].

Other characteristics that have been shown to independently be associated with disabling disease include young age at diagnosis (<40 years) and the need to use steroids for the first flare [9, 10]. The definition of disabling disease in these studies however is much broader and includes not only the development of stricturing and penetrating complications but also multiple steroid courses, hospitalizations, and disabling symptoms. This likely explains the finding that these two characteristics, although likely associated with more severe disease, have not been consistently shown to increase the risk of disease progression when the definition of progression is limited to stricturing and penetrating disease behavior [11].

Perianal disease has been associated with a disabling disease course in multiple studies [9, 12], but whether it is an independent risk factor for intestinal fistulization is controversial. A population-based cohort showed a strong association between intestinal and perianal fistulization [13], and in another more recent study, perianal disease was of borderline significance in predicting progression of disease [5]. Other studies however have shown that perianal disease is not a risk factor for intestinal penetrating disease [6, 14].

Smoking has also been found in several studies to predict a change in disease behavior from inflammatory disease to stricturing or penetrating disease [8, 15], and it has also been shown to accelerate the rate of progression to complicated disease [16]. In addition, Eglington et al. [15] showed that smoking is a risk factor for disease progression independent of medical therapy and disease location.

When considering colonic disease specifically, a colectomy would be considered a severe complication. In this case, the presence of deep ulcers covering at least 10 % of a colonic

segment has been associated with up to 60 % risk of colectomy over a 3-year period [17].

Serological markers have also been found to be predictive of complicated disease. Reactivity to ASCA (anti-Saccharomyces *cerevisiae* antibody), OmpC (*E. coli* outer membrane porin C), antiI2 (anti-CD-related bacterial sequence I2), and CBIr1 flagellin has been associated with early onset Crohn's disease, fibrostenotic disease, penetrating disease, and the need for early small bowel surgery [18–20]. Furthermore, it appears that the more antigens that are present and the higher their titers, the higher the frequency of disease complications [21]. These serological markers, however, may increase with disease duration in parallel with the development of complications. This may limit the prognostic value of these antibodies.

Finally, genetic factors may also be useful in predicting Crohn's disease complications. Many susceptibility loci have been identified in Crohn's disease, but so far, most have not been linked to disease outcome. The NOD2 polymorphism however has been associated with a more aggressive Crohn's disease phenotype and a higher likelihood of intestinal strictures and surgeries [22–24].

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Chapter 9
What Is the Best Possible Therapy for My Crohn's Disease? State-of-the-Art Therapy for Newly Diagnosed Crohn's Disease

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Suggested Response to the Patient

Crohn's disease is an inflammatory disease whereby the immune system attacks the intestines, causing the inflammation and ulceration that results in abdominal pain, diarrhea, fevers, fatigue, and other symptoms. Some Crohn's patients suffer from fistulas (inflamed tunnels from the intestines to surrounding skin or other organs). It is believed that the white blood cells are primarily responsible for the damage caused by Crohn's disease; thus, most therapies are aimed at either directly stopping the white blood cells from being produced or preventing them from recruiting other white

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blood cells and from attacking the bowel. Genetic studies have suggested that this "attack" is an attempt by the body's immune system to get at the bacteria and other organisms in the gut [1, 2].

When choosing "the best possible therapy" for your Crohn's disease, your physician considers factors such as *where in the body* the Crohn's disease is active, *how severe* the inflammation is, *what previous medications succeeded (or failed)*, as well as factors such as smoking (bad), family history, and previous surgery. Unfortunately, the only effective medication for many years was steroids (i.e., prednisone, hydrocortisone), which only temporarily helped to decrease the inflammation. However, steroids do not work well long term, and they have very substantial side effects that require us to use other types of agents. Budesonide is a steroid with far fewer side effects; it is preferred over prednisone or hydrocortisone but still is not a long-term option.

There are four major categories of medications currently available for patients with Crohn's disease; in many instances, your doctor may use multiple medications to get the best results. The four main categories are as follows:

1. Antibiotics. Most commonly used are ciprofloxacin and metronidazole. These are very important in patients who have active infections, fistulas, and abscesses ("pus pockets"), but also can help with patients who have partially blocked intestines by decreasing pain, gas, bloating, and diarrhea that may result from bacteria building up behind the narrowed segments of bowel.
2. Anti-inflammatories. These include medicines such as sulfasalazine and the related mesalamine pills, enemas, and suppositories. Unfortunately, they are only effective in patients with very mild Crohn's disease.
3. Immunosuppressants. Azathioprine and the closely related 6-mercaptopurine are effective pills that target the production of the white blood cells. Due to their slow onset of action, they are often prescribed initially along with a faster acting medicine (such as steroids) and then used long term to keep patients well. Methotrexate is another

option; this is typically given as a tiny shot under the skin once a week (or as a pill). The immunosuppressants are also commonly given to patients on biological agents (see the next group) to help prevent the body from making antibodies against the biological drug.

4. Biologics. These are all currently only available as in intravenous infusion or as an injection. The most common family is those biologics that target "tumor necrosis factor," effectively blocking much of the immune system's destructive impact on the intestines. These fast-acting agents, adalimumab, certolizumab, and infliximab, are all used in Crohn's disease. A newer family is drugs that block "adhesion molecules," effectively preventing the white blood cells from leaving the bloodstream and entering the intestines, as well as some other functions. Appealing due to their being very focused on only those parts of the body that need their help, natalizumab and vedolizumab are the current members of this slower-acting biological family.

It is important to realize that Crohn's disease is a chronic, relapsing condition that will recur if effective medications are stopped. As a result, medicines that are working are typically not stopped long term; the only exception is the steroids, which have a short-term role only.

Brief Review of the Literature

Given the progressive disease course in Crohn's disease, medical therapies in Crohn's disease are targeted to altering the dysregulated inflammatory responses with goals of altering the natural history of disease. The only available therapies for decades, corticosteroids and sulfasalazine, were ineffective in impacting the natural course of disease. This is in contrast to the immunosuppressants and biologics, which have been shown in multiple areas to impact the progression of Crohn's disease, perhaps reversing the disease course [3, 4]. With the ability to alter the natural history of a progressive gastrointestinal

condition, the goals of treatment include the induction and maintenance of mucosal (and histologic) healing [2].

In choosing the most appropriate therapy for newly diagnosed Crohn's disease, a number of topics often arise including the use of aminosalicylates, avoidance of corticosteroids, earlier use of biologic agents, and combination therapy with a biologic and immunosuppressant.

Aminosalicylates

Sulfasalazine and the mesalamine conjugates have had mixed results in the trials designed to determine if they are effective in treating active Crohn's disease [5, 6]. A meta-analysis of placebo-controlled trials of active Crohn's disease over 16 weeks found a statistically significant but clinically insignificant improvement in Crohn's Disease Activity Index (CDAI) [7, 8]. Their role as maintenance therapy has not been supported by the literature [5, 9, 10]. Overall, the mesalamine agents have a role limited to patients with mild Crohn's disease, and their efficacy should be proven with periodic objective assessments of disease activity (endoscopic and/or radiographic).

Corticosteroids

Corticosteroids have a deservingly bad reputation in Crohn's disease; although they might temporarily alleviate some of the signs and symptoms, they do not change the disease course, and their long-term side effects can be catastrophic. Budesonide, which is available as a controlled-ileal release capsule targeting the small intestine and right colon, has been shown comparable to prednisolone in inducing clinical remission (53 % vs. 66 %) with far fewer side effects [11]. The maintenance benefits of budesonide have yet to be proven; a systematic review of budesonide use as a maintenance therapy did not demonstrate efficacy beyond 3 months following the induction of remission [12].

Thiopurines

The thiopurine agents (azathioprine and 6-mercaptopurine) are slow-acting agents; induction of remission typically requires the use of a fast-acting corticosteroid or biological agent. Treatment with thiopurine therapy has demonstrated effectiveness in the discontinuation or reduction of steroid use, although often with up to a 3-month delay in response [13]. Further studies assessing the withdrawal of thiopurine therapies leading to clinical relapse provide proof of concept for the beneficial effects of thiopurine therapy in the long-term maintenance of disease control [14–17]. However, thiopurine monotherapy has been tempered by the lack of improved outcomes as an induction therapy in the early diagnosis of Crohn's disease, as well as the associated rare risks of lymphoproliferative disorders, myeloid disorders, and nonmelanoma skin cancers [18–22].

Methotrexate

Methotrexate also requires a faster-acting agent to induce remission in Crohn's disease (such as corticosteroids or biologics). The administration of injectable methotrexate (25 mg once weekly) when compared to placebo resulted in clinical remission (defined by a score ≤150 CDAI) at the end of a 16-week trial in 39.4 % of patients receiving methotrexate compared to 19.1 % on placebo [23]. In a maintenance study arm, among those patients achieving clinical remission after 16–24 weeks of therapy, those randomized to receive 15 mg of intramuscular methotrexate compared to placebo maintained remission at 40 weeks of therapy (65 % randomized to methotrexate compared to 39 % with placebo) [24]. Therefore, methotrexate use has demonstrated effectiveness for the induction and maintenance of clinical remission in an era prior to the initiation of biologic therapies.

Anti-TNF Agents

The advent of biologic therapies has revolutionized treatment strategies and endpoints in clinical trial design with demonstrated effectiveness in the induction and maintenance of clinical disease activity. In addition, biologic therapy use has introduced the concept of early aggressive medical therapy in those with a short duration of disease and prognostic factors associated with the development of disease complications. A meta-analysis of ten studies demonstrated that, when compared to placebo, anti-TNF therapies resulted in an increased likelihood of induction of remission (RR: 1.66, 95 % CI: 1.17–2.36) as well as maintenance of remission (RR: 1.78, 95 % CI: 1.51–2.09) [25]. Furthermore, recent studies have extended the results of steroid-free remission to 4 years of therapy with decreases in the rates of hospitalization and surgery among those receiving scheduled therapy [26–30]. With a safety profile that does not include the development of malignancy and an increased risk of serious infection of 0.64 per 100 patient-years (compared to conventional Crohn's disease therapies), biologic therapies have been advocated as the initial therapy in individuals with poor prognostic factors [31–33].

Anti-integrin Agents

The anti-integrin antibodies are also proven effective in the induction and maintenance of remission in patients with Crohn's disease. Early enthusiasm over natalizumab, used mostly in multiple sclerosis as it targets adhesion molecules in the central nervous system as well as the gut, quickly vanished when reports appeared of disabling or fatal progressive multifocal leukoencephalopathy. Subsequent investigations identified this as a complication of infection by the John Cunningham (JC) virus. Current treatment paradigms require first a blood test for antibodies to the virus; if these are not present, natalizumab monotherapy can be instituted, but

should be discontinued if the patient subsequently tests "positive" for the JC virus on annual or semiannual testing. Natalizumab's long-term efficacy in Crohn's disease patients, including those who were nonresponders to infliximab, keeps this alive as a backup option in these patients.

Vedolizumab's emergence into the field in mid-2014 has supplanted natalizumab; this anti-integrin antibody targets only the gut; there have not been any PML infections seen nor expected. The excellent safety profile of this agent is tempered only by its short time on the market, as well as a slower onset of action than the anti-TNF biologics.

Combination Therapy

Given the success rates achieved with biologic therapies, the state of the art in Crohn's disease therapy comes in the optimization and prolongation of biologic therapy responses [34, 35]. With the demonstration of antibody formation to biologic therapies and decreased immunogenicity with concomitant immunosuppressive therapy, approaches to combined immunosuppression have been introduced. An open-label 2-year trial randomizing 133 patients to early combined immunosuppression with azathioprine and infliximab (utilizing an episodic dosing schedule) compared to a conventional approach of corticosteroids followed in sequence by azathioprine and infliximab demonstrated rates of corticosteroid-free remission in 60 % in the early combined immunosuppression arm compared to 35.9 % in the conventional therapy arm at 26 weeks [36]. The subsequent SONIC trial randomized 508 patients with moderate-severe Crohn's disease to infliximab monotherapy, azathioprine monotherapy, or combined immunosuppression. With a primary outcome of corticosteroid-free remission at 26 weeks, the endpoint was met in 56.8 % randomized to combination therapy, 44.4 % receiving infliximab alone, and 30 % receiving azathioprine alone. Furthermore, mucosal healing occurred in 43.9 % in the combination therapy group, 30.1 % in the infliximab monotherapy arm, and 16.5 % receiving azathioprine [37].

The increased use and recognition of biologic therapies has led to increasing evidence with respect to the optimal use and monitoring of drug therapy. Factors associated with improved treatment responses have included early initiation of biologic therapy, maintenance biologic therapy as opposed to episodic dosing schedules, the use of concomitant immunosuppression, and the use of premedication to suppress antibody responses to biologic therapies [37–40]. In addition, increased monitoring of drug levels has led to preliminary work resulting in predictive values of clinical response [41–43]. Future works will continue to include therapy optimization algorithms in addition to incorporation of novel therapeutic agents and objective disease monitoring [44–52].

Targeting sustained clinical and endoscopic remission aims to interrupt the naturally progressive and destructive disease course that culminates in the development of intestinal failure and associated disease complications. The choice of initial therapy should incorporate the individual profile in order to make more potent compounds available to high-risk patients. Surgery remains an indication in complex Crohn's disease and although not curative, when used restrictively is effective in providing prolonged disease control [1, 53, 54]. Future studies will continue to guide the optimization of drug therapies in order to create personalized algorithms with respect to disease activity and therapy monitoring while maintaining a focus on altering the natural history of the disease.

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Chapter 10
What is the Best Possible Therapy for My Mild to Moderate Ulcerative Colitis? State-of-the-Art Therapy for Mild to Moderate Ulcerative Colitis

Alexis P. Calloway and David A. Schwartz

Suggested Response to the Patient

Once clinical severity is determined and infectious etiologies are ruled out, the therapy to treat mild to moderate ulcerative colitis is directed by the extent of involvement during colonoscopy. The goal is to gain control of active inflammation and maintain remission once achieved. Therapies used to treat the active disease are generally combinations of topical and/or oral 5-aminosalicylic acids (5-ASAs) and corticosteroids. Looking forward, medications to maintain remission aim to limit prolonged corticosteroid use given its side effects, such as infections and osteoporosis, and include continued use of 5-ASAs and often addition of thiopurines. Regardless of therapy selection, the control of disease is ultimately important in decreasing the overall risk for developing advanced colorectal cancer in patients with long-standing ulcerative colitis by decreasing the time of severe inflammation.

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Brief Review of Literature

Mild to Moderate Active Proctitis

The cornerstone for induction and maintenance of remission in mild to moderate ulcerative colitis is 5-ASA agents which are thought to act by activating nuclear receptors that influence inflammation, cell proliferation, apoptosis, and the metabolic function of colonic epithelial cells [1]. In active proctitis, the therapy is targeted directly to the rectum with mesalamine suppositories which have been found to be more effective than oral 5-ASA formulations showing remission as early as 2 weeks in a meta-analysis comparing the two forms of delivery (oral vs. topical) [2]. This medication is usually given in a dose of 500 mg twice daily or 1 g daily and is considered safe, well tolerated, and effective in patients with active proctitis and distal colitis [3, 4]. The selection for the type of topical therapy is dependent on the extent of involvement with suppositories reaching 10–15 cm and foams reaching 15–20 cm, while enemas may reach up to the splenic flexure. Disadvantages include bloating and leaking which may lead to noncompliance. Topical corticosteroids are also used to assist in induction of remission but are not effective in maintenance [2, 5]. However, topical steroids have been found to be as effective as systemic corticosteroids with significantly lower inhibition of cortisol levels for patients with left-sided colitis [6]. At times, complete response is not obtained with topical therapy alone. In these instances, oral mesalamine may be added to the regimen as it has been found to provide quicker and more complete relief of rectal symptoms than oral or rectal formulations used alone [7].

Mild to Moderate Distal Active Colitis

As in patients experiencing difficulty controlling active proctitis, combination therapy is more effective than monotherapy for induction of remission. In a randomized double-blinded study, oral mesalamine in combination with mesalamine

enemas induced remission in 64 % of patients within 8 weeks compared to 43 % of patients taking oral mesalamine with a placebo [8]. There is, however, a dose-related effect of oral 5-ASA therapy. The ASCEND III trial, a non-inferiority study, found that 70 % of the 389 patients receiving delayed-release mesalamine 4.8 g daily achieved treatment success at 6 weeks compared to 66 % of those receiving a dose of 2.4 g daily. However, significantly more patients who received 4.8 g daily achieved clinical remission at weeks 3 and 6 compared to those receiving 2.4 g daily [9]. In the ASCEND I trial, a statistically significant difference in treatment success was found in a subgroup of patients with moderate active colitis receiving delayed-release mesalamine at 4.8 g compared to those receiving 2.4 g, 72 % and 57 %, respectively [10]. Patients with moderate disease benefit the most from higher doses when considering balance of side effect profile to therapeutic response.

In general 5-ASAs are affordable and well tolerated; however, some patients experience nausea, vomiting, dyspepsia, headache, and anorexia in varying degrees making full compliance with this medication difficult. More severe reactions including pancreatitis, hepatotoxicity, bone marrow suppression, interstitial nephritis, and anemia have also been found. Additionally, 5-ASAs specifically sulfasalazine can affect sperm morphology which is reversible when discontinued [5]. In 1–2 % of the population, 5-ASA therapy can cause worsening of ulcerative colitis and should be discontinued in this group.

Mild to Moderate Extensive Colitis

Patients with disease activity extending beyond the distal colon should be started on an oral 5-ASA. Time to resolution of stool frequency and rectal bleeding was found to be significantly shorter in patients receiving mesalamine at 4.8 g daily in comparison to those receiving 2.4 g. 73 % versus 61 % of patients noted improvement of symptoms at 2 weeks in these groups [11]. Additionally symptom relief at 14 days was

associated with continued symptom relief at 2 weeks and thus is a reasonable time for consideration of modification of therapy. Oral prednisone should be added to the regimen if symptoms are not controlled with oral 5-ASA therapy alone. A dose of 20–60 mg is usually recommended balancing therapeutic dosing with potential risk for side effects. The relative risk for development of opportunistic infections in the setting of prolonged corticosteroid use is higher in patients over the age of 50 and should be used with caution [12]. Though there are no randomized trials comparing steroid tapers, it is generally recommended to begin slowly tapering the dose by 5 mg weekly to 15–20 mg after symptom relief is obtained.

Incorporating Uceris (Budesonide) into Practice Management

An alternative to prednisone has been introduced which has minimal corticosteroid activity due to first-pass hepatic metabolism. Uceris (budesonide), an extended-release synthetic corticosteroid tablet with enteric coating that dissolves directly in the terminal ileum, has been approved for the management of mild to moderate extensive ulcerative colitis. In a randomized control trial comparing Uceris given in a dose of 6 mg or 9 mg, mesalamine, and placebo, remission rates at 8 weeks in subjects were 17.9 %, 13.2 %, and 12.1 %, respectively, compared to 7.4 % for placebo. Uceris given at a dose of 9 mg was found to be more effective in inducing clinical remission in patients with active mild to moderate UC than those taking placebo [13]. As this medication still has some of the side effects of traditional corticosteroids, its use should ideally be limited to 8 weeks.

Maintenance of Remission

The extent of disease influences strategy for continuance of therapy for remission in ulcerative colitis. Azathioprine or 6-MP may be useful as a steroid-sparing agent in patients

who are corticosteroid dependent or not adequately sustained by monotherapy with aminosalicylates. In an RCT comparing azathioprine 2 mg/kg/day to mesalamine 3.2 g/day in steroid-dependent UC patients, 53 % of those receiving azathioprine achieved clinical remission versus 21 % receiving mesalamine [14]. The side effects include bone marrow suppression (primarily leukopenia), liver abnormalities, and allergic reactions such as fever, rash, myalgias, or arthralgias. Prior to initiation, TPMT genotyping should be obtained as it may assist in optimizing dose and identifying those at risk for potential drug-induced toxicity [15]. Prolonged severe inflammation has been found to be an independent risk factor for neoplasia [5, 16]. Mucosal healing is important, not only to decrease this risk, but, in a prospective study, was also found to be associated with a decreased need for colectomy and future steroid use [17].

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Chapter 11
What Is the Best Therapy for My Moderate to Severe Ulcerative Colitis? State-of-the-Art Therapy for Moderate to Severe Ulcerative Colitis

Ayal Hirsch and David T. Rubin

Suggested Response to the Patient

The symptoms of ulcerative colitis (UC) are caused by inflammation of the large intestine, which is composed of the colon and the rectum. Most of the symptoms of UC are caused by inflammation of the rectum. The severity of your symptoms and additional factors help us choose the appropriate therapy for you. Patients having, for example, four or more bowel movements per day or other symptoms like fever or anemia are categorized as having moderately to severely active colitis. Because of your current symptoms, we believe your UC belongs to that category.

Your treatment will include a phase for induction of remission, in which our goal would be to suppress the inflammatory activity so you feel well, and a second phase for maintenance of remission in order to keep you well and to avoid future flares. Because UC is a chronic condition, it does

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require chronic therapy so that the condition stays under good control, and, ultimately, so we can avoid future complications and the rare risk of colorectal cancer.

For moderately active UC, the most common therapy is a class of drugs called "aminosalicylates." Aminosalicylates are a family of non-immunosuppressive drugs that act locally on the bowel wall to reduce inflammation. The agents, of which there are many different ones, can induce and maintain remission in this type of UC and can be given in combination with other medications for more severely active UC. They can be administered both orally and rectally to increase their effectiveness. These medications are exceptionally safe, but 3 % of the population may be intolerant to them and actually have more diarrhea when they start them. In addition, there is a rare risk of kidney insufficiency which is monitored with periodic kidney function blood tests.

Most patients with moderately to severely active UC will require corticosteroids. Steroids are very effective and fast at inducing remission and are used mainly for their rapid effect. They are generally safe for short-term treatment, but we really work hard to limit your exposure to them due to an unfavorable long-term safety profile and taper down rapidly in case we do. The rectum and lower part of the colon can be treated with topical steroids given by foam or by enema. The most common side effects of short-term steroid use include sleep disturbances, weight gain, anxiety, acne, and mood changes. Steroids have no role in maintaining remission. A newer type of steroid called "budesonide MMX" (Uceris) works primarily topically on the colon and has fewer side effects than prednisone and may have some benefit for milder disease.

An additional class of immunosuppressant therapy, called thiopurines, has benefit in some UC patients. Thiopurine therapy includes azathioprine (Imuran or Azasan) and 6-mercaptopurine (Purinethol) and is used when patients needed steroids in order to get them off of them and keep them off. They are given orally, once daily, and their mechanism of action is not fully understood, although we know these drugs have suppressive effects on white blood cells that play a key role in inflammatory activity. Common but preventable side

effects include suppression of blood counts, which is reversible when the drug is stopped and is monitored by periodic blood work. Some of the side effects depend on the individual's ability to metabolize the drug. Fortunately, this can be tested with a simple blood test before treatment initiation. The rarer side effects include infections and minor increases in the rates of non-melanoma skin cancer and lymphoma. These risks can be decreased with flu and pneumonia vaccines and sun exposure protection measures combined with annual dermatologic screening. The risk of lymphoma is rare but slightly increased compared to the general population. It increases the longer a patient is on this medication and the older the patient is, but the risk goes away when the drug is discontinued.

Another class of therapy for moderately to severely active UC is the biological therapies known as anti-TNF therapies. Anti-TNF therapies are antibodies to an inflammatory mediator called TNF. Because these therapies are proteins, they must be administered intravenously or subcutaneously. Currently, there are three anti-TNFs approved for the treatment of UC in the USA including infliximab (Remicade), adalimumab (Humira), and golimumab (Simponi). These therapies are very effective for this type of UC and work even better when in combination with the thiopurine therapies. The side effects include rare risks of infection and, rarely, allergic reactions to the therapy that may also predict a loss of response. In order to protect our patients, we screen for tuberculosis and hepatitis B prior to treatment initiation and recommend influenza and pneumonia vaccines.

A recent addition to our therapeutic options is vedolizumab (Entyvio) which is also an intravenous biological therapy, but this drug works by inhibiting white blood cells, movement from the bloodstream to the gut. Because of this specific mechanism, vedolizumab is a more targeted approach to treating UC and has a very favorable safety profile, but does have a small risk of nasal and throat infections. Vedolizumab can be used to induce and to maintain remission.

There are occasions when more severe UC will require hospitalization, during which time intravenous treatment can be administered to induce remission. In a minority of the

patients, surgical treatment may be required. The surgery for severe UC is removal of the entire colon and rectum. By removing the large intestine, UC is also removed from the body. Most patients have a new rectum made from small intestine, called a "J pouch."

Brief Review of the Literature

Moderately active UC is characterized by four or more bowel movements per day and minimal signs of toxicity, while patients with more than six bloody bowel movements and overt signs of toxicity (fever, tachycardia, anemia, or elevated ESR) are categorized as severely active UC [1].

The primary treatment goal is to rapidly induce remission, followed by developing a plan for steroid-free maintenance. In general, the choice of maintenance agent is determined by the agent required for induction. A more strict aim, currently emerging, is achieving endoscopic remission (mucosal healing) which has been associated with decreased need for corticosteroids, lower hospitalization rates, sustained clinical remission, decreased colectomy rates, and cancer risk [2–5].

Aminosalicylates are preferred as initial treatment of mildly to moderately active UC for their convenient dosing and favorable safety profile. Sulfasalazine, in a daily dose of 4–6 g, is an effective, low-cost treatment for induction and maintenance of remission, but carries a higher incidence of side effects. Mesalamine, olsalazine, and balsalazide have been shown to be as effective in inducing and maintaining remission in moderate UC [6, 7]. This effect may be more pronounced at a dose of 4.8 g per day and with concomitant topical rectal therapy in the form of either suppository or enema [8, 9]. Intolerance to sulfasalazine is common, but is rarely seen with mesalamine.

Many patients with moderately active UC and patients with severely active UC will require immune-based therapeutic strategies. Thiopurines may be effective as maintenance therapy in patients who failed aminosalicylates or are steroid dependent, but because of their slower onset of

action, they are not practical for induction of remission and therefore usually require concomitant administration of steroids or anti-TNFs. The use of thiopurines in the management of UC is not based on high-quality evidence; it remains unclear if they should be given with aminosalicylates or as monotherapy [10, 11].

Thiopurines are metabolized by the enzyme thiopurine methyltransferase (TPMT) to 6-thioguanine (6-TGn) and 6-methylmercaptopurine (6MMP). 6-MMP is associated with elevated liver enzymes [12]. 6-TGn is associated with relapse-free remission, but also with bone marrow suppression in patients with low TPMT activity and high 6-TGn levels [13, 14]. In patients wtih normal TPMT activity, dosing is weight based with a target dose of 2–3 mg/kg for azathioprine and 1–1.5 mg/kg for 6MP.

It is currently considered a quality measure to assess TPMT activity prior to initiation of treatment with a thiopurine [15]. Absence of enzyme activity (0.3 % of the population) precludes treatment with thiopurines. Patients with intermediate enzyme activity (11 %) should be started on a low dose (25–50 mg) and increased gradually (25–50 mg/week), while patients with normal enzyme activity treatment can be initiated at the target dose [16]. Patients should be monitored for bone marrow suppression and liver enzyme elevations, and although not standard of care, we recommend thiopurine metabolite measurement for drug optimization [17]. Liver enzyme elevation and bone marrow suppression are reversible dose-dependent side effects, while allergic reactions such as fever, rash, arthralgia, and myalgia usually require trial of a different thiopurine. There is still a 50 % risk of cross-reaction. Pancreatitis is class-related side effect and precludes further treatment with thiopurines [18]. Thiopurines also carry the risk for increased rate of nonmelanoma skin cancers, overall infections and serious infections, and lymphoma [19–21].

Anti-TNF therapy is an effective therapeutic option for patients with moderately to severely active UC, patients with steroid-dependent or refractory disease, and patients refractory or intolerant to aminosalicylates or thiopurines. Infliximab, adalimumab, and golimumab are approved in the

USA for inducing and maintaining remission in UC [22–26]. Concomitant therapy of anti-TNFs and thiopurines leads to higher rates of remission induction, maintained remission, and mucosal healing [23]. Concomitant therapy also results in decreased immunogenicity (anti-drug antibodies) and higher drug trough levels [23, 27, 28]. This was shown for infliximab/adalimumab and thiopurines in UC; however, recent evidence supports the use of methotrexate, which may be preferred in patients that have higher risk of lymphoma (males younger than 30 or older than 50) [28]. We also generalize the current knowledge to utilize golimumab in combination therapy.

Secondary loss of response to anti-TNF therapy is well described. When it occurs, it is recommended to assess for infection and to consider the possibility of increased clearance due to anti-drug antibodies [29]. Infliximab and adalimumab have commercially available assays for their serum levels and anti-drug antibodies. In a patient who previously responded to anti-TNF therapy and has now developed anti-drug antibodies and undetectable drug levels, switching to another anti-TNF within the same drug class makes sense [30–34]. There has been a movement in the field to monitor for subclinical disease activity in order clinical relapse and colonic dysplasia; details regarding appropriate interventions and monitoring strategies have not been formulized [35]. However, there is considerable interest in utilizing fecal calprotectin for noninvasive monitoring of disease activity [36].

Vedolizumab, an $\alpha_4\beta_7$ integrin inhibitor, is effective for inducing and maintaining remission in anti-TNF naïve and experienced patients with moderately to severely active UC [37]. Current data suggest an excellent safety profile, low immunogenicity, and high rates of sustained response.

Patients with fulminant UC or patients with severe UC who are intolerant or failing remission induction with maximal therapy of oral steroids, oral and topical aminosalicylates, and anti-TNFs require admission and initiation of intravenous steroid treatment [38]. Failure to achieve remission with IV steroids in 3 days is associated with ongoing failure of this

treatment strategy, so additional therapy with infliximab or calcineurin inhibitors should be considered [39].

Medical salvage therapy for induction of remission with calcineurin inhibitors, tacrolimus or cyclosporine, achieves up to 82 % colectomy-free survival in patients with steroid-refractory severe colitis [40–42]. Patients who achieve remission must then be maintained on thiopurines or anti-TNFs. The overlap of immunosuppression during transition to maintenance phase requires careful monitoring for infectious complications. We have recently described using calcineurin inhibitors for induction, followed by vedolizumab for maintenance of remission. 10–17 % of all UC patients will eventually require colectomy 10 years from diagnosis, and 27 % from the patients admitted for severe UC will require emergent colectomy [43, 44]. The current gold standard surgery is a staged ileal pouch-anal anastomosis (IPAA), either stapled or hand sewn.

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Chapter 12
Can I Stop My Medications Now that I Am Feeling Well? Why Maintenance Therapy Is Important in Preventing Recurrence in Crohn's Disease

Daniel J. Stein

Suggested Response to the Patient

It is important to understand that although you may be feeling well while taking medication for your Crohn's disease, we have not cured you of Crohn's disease. At this time we are only controlling your disease. As of right now we have only limited information on what happens when we stop medications for Crohn's disease. The limited information we do have seems to show that Crohn's disease will have a high likelihood of coming back if we were to stop your medications. While it may take a year or more for the Crohn's disease to come back, it will recur in most patients that stop their therapy. Also when your disease comes back, there is no guarantee that restarting the medications will work when they are restarted. For this reason it is important to continue on your current therapy that has been successful at inducing and maintaining your remission.

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Brief Review of the Literature

Reasons for Discontinuation

Crohn's disease and ulcerative colitis are chronic, lifelong diseases that have no known medical cure at this time. However, effective immunosuppressive therapy has become the mainstay of inducing and maintaining remission in IBD patients. It has been shown in both Crohn's disease and ulcerative colitis that combination therapy with thiopurines and infliximab is more effective than either one alone to achieve clinical and endoscopic remission [1, 2]. Therefore, we have effective therapy to treat patients with IBD.

However, patients who achieve remission no matter how it is defined frequently ask if their immunosuppression can be stopped or reduced. This may occur for any number of reasons including: potential for infection, potential for malignancy, newly diagnosed malignancy, cost of the medication, pregnancy, intolerance, or desire to take a drug "holiday" to name a few. Clearly patients suffering from a serious complication related to the immunosuppression should have their therapy held. What about the patients that are doing well and are not having a complication of their therapy? Is it safe to withdraw or reduce therapy in this population? These are the questions this chapter will attempt to answer.

Given the limited data on withdrawal of medications and that the two conditions respond similarly to immunosuppression, this chapter will review the literature for both UC and CD.

Dose Reduction of Thiopurines

The therapeutic benefit of combination therapy is largely thought to be a result of increased anti-TNF trough levels and decreased levels of immunogenicity to the anti-TNF antibodies. There have not been any studies investigating dose reduction of thiopurines in IBD patients on combination therapy or monotherapy. However, it has been reported that

higher 6-thioguanine levels, but not thiopurine dose, are associated with higher tough levels of infliximab suggesting dose reduction may be possibly in the setting of high 6-thioguanine levels [3].

Dose Reduction of Biologics

There is very little evidence to discuss when it is safe to decrease the dose of biologics in IBD patients. One part of the TAXIT trial decreased the frequency of infliximab infusion based on elevated infliximab levels without effect on disease remission rates [4]. Adalimumab de-escalation was also evaluated in patients that had achieved clinical remission on weekly dosing. Decreasing the adalimumab dosing from every week to every 2 weeks was only successful in 47 of the 75 patients (63 %) after 6 months [5]. Decreasing the dose of anti-TNF therapy should not be done routinely, but patients in remission with elevated trough levels of infliximab could be considered for dose reduction.

Discontinuation of Immunomodulator Monotherapy

There have been several trials looking at the discontinuation of immunomodulator (azathioprine or 6-mercaptopurine) therapy in both UC and CD. A randomized controlled trial in UC looking at stopping azathioprine showed that the relapse rates at 1 year were 36 and 59 % in patients taking AZA and placebo, respectively ($P=0.039$) [6]. Additionally, a retrospective observational study showed a relapse rate of approximately one third, one half, and two thirds in UC patients in steroid-free remission who stopped their azathioprine at 1-, 2-, and 3-year follow-up, respectively [7].

Similarly in CD, a placebo-controlled trial looking into azathioprine withdrawal found relapse rates of 14, 53, and 63 % at 1, 3, and 5 years, respectively, for patients having stopped azathioprine [8]. Additionally a large meta-analysis on relapse

rate in patients stopping azathioprine monotherapy showed similar findings [9]. Overall patients that are doing well on their immunomodulator therapy should be continued on their therapy unless a serious side effect or contraindication develops.

Discontinuation of Biologic Monotherapy

Currently there are no trials looking at stopping anti-TNF monotherapy in a randomized placebo-controlled fashion. However, we know from the clinical trials that were designed to look at anti-TNF therapy efficacy that patients randomized to placebo after induction therapy were significantly more likely to have disease recurrence than those continued on anti-TNF therapy [10, 11]. For this reason continuing maintenance therapy with anti-TNFs monotherapy in patients doing well is recommended.

Discontinuation of Immunomodulator Therapy, Continuing Biologics

A randomized controlled trial specifically looked at stopping immunomodulator and continuing infliximab in patients receiving combination therapy was undertaken randomizing 80 patients in clinical remission for at least 6 months to immunomodulator withdrawal. A significant number of patients in the immunomodulator withdrawal arm had lower infliximab trough levels and higher C-reactive protein levels compared to patients that continued their immunomodulator [12]. Additionally, a retrospective observation study looked at predictors of infliximab failure following azathioprine withdrawal in CD patients in remission for at least 6 months. They found that the probability of effective therapy with infliximab were 85 % at 12 months and 41 % at 24 months. Predictors of infliximab failures were a short infliximab-azathioprine exposure duration (≤811 days), C-reactive protein >5 mg/l, and platelet

count >298 10(9)/l [13]. Withdrawal of immunomodulator therapy in patients doing well on combination therapy should be undertaken with great caution. When undertaken it should certainly limited to patients who have a long duration of remission without elevated markers of inflammation.

Discontinuation of Biologic Therapy, Continuing Immunomodulators

Withdrawal of anti-TNF therapy in steroid-dependent Crohn's disease patients receiving combination therapy with azathioprine was looked at in a study from the GETAID group. Patients received induction dosing of infliximab (0-, 2-, and 6-week infliximab) along with azathioprine. They were then maintained on azathioprine alone. This resulted in an initial remission rate of 75 % following the induction doses at 12 weeks, but this fell to 57 and 40 % at 24 and 52 weeks, respectively [14, 15]. A newer prospective cohort study (STORI) looked at infliximab withdrawal in a group of CD patients in steroid-free remission for at least 6 months on combination therapy with azathioprine and infliximab. Of the 115 patients, 44 % had relapsed over the first year and 52 % had relapsed by the 2-year mark. The risk factors associated with relapse were male gender, no prior operation, WBC $>6.0 \times 10(9)$/L, hemoglobin ≤145 g/L, C-reactive protein ≥5.0 mg/L, and fecal calprotectin ≥300 μg/g. Patients who had complete endoscopic healing at the time of withdrawal had a significantly decreased risk of relapse [16]. A retrospective study looked at infliximab withdrawal in a group of IBD patients, 87 % of whom were treated with combination immunomodulators. At the end of 1-year follow-up, only 61 % of CD and 75 % of UC patients were in remission and only 12 % of CD patients were in remission at the end of 10 years and 40 % of UC patients at 4.5-year follow-up [17]. Another retrospective study looked at the withdrawal of infliximab (73 % immunomodulator use) and showed a relapse rate of 35 % at 1 year [18]. Lastly a group of 121 CD patients in remission were prospectively

observed following withdrawal of their anti-TNF therapy showing that 45 % relapsed irrespective of their thiopurine use [19]. Overall, withdrawal of anti-TNF therapy in CD patients in remission should be discouraged and reserved for special situations and then only in patients that have no objective findings of disease activity.

Conclusions

It is important to remember that while we have very effective therapy to treat patients with Crohn's disease, we are not curing their disease, we are only controlling a lifelong chronic disease. While there may exist a subset of patients that enter into remission or deep remission who can successfully stop therapy, we do not have the ability to confidently identify these patients prospectively. While the lack of objective inflammation serologically, endoscopically, and histologically may be an indicator that the therapy could be safely reduced or withdrawn, there is very little evidence to support this practice on a routine basis at this time.

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Chapter 13
"My Medications Are Not Working, What Can I Try Now for My Crohn's Disease?" Options for Refractory Crohn's Disease

Jonathan C. Chapman

Suggested Response to the Patient

The use of medications other than biologics to treat moderate-to-severe Crohn's disease has been proven in the recent past to be less effective to induce or maintain remission. If you are not currently employing biologic therapy to treat your Crohn's, this should be a consideration. If you are currently taking or have just begun a biologic, it does require time to become therapeutic. Clinical improvement should be seen in the range of 2–4 weeks, but maximal improvement may take up to 3 months [1]. It's also very important to discontinue tobacco, as this is related to worse disease course and decreased response to biologics. Studies show you are close to three times more likely for your biologic treatment to stop working if you abuse cigarettes [2].

Other possible causes for your medication not working also need to be explored. This includes infections which you

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may be susceptible secondary to your Crohn's and/or your current therapy. These are known as opportunistic infections. These are defined as infections that under normal circumstances possess little or no pathologic capabilities [3]. Other reasons, which may be perceived as medication failure, are those not caused by infection or inflammation. These may include a stricture or scarring of the small intestine, previous surgical changes, or even overgrowth of bacteria in the small intestine. Prior to deciding that your medication has failed, data will need to be collected. This will likely include laboratory, ileocolonoscopy, and/or imaging. In the absence of any of the aforementioned possibilities, we will need to discuss the possibility of adding a second medication known as an immunomodulator or checking levels if you are already taking one to ensure therapeutic dosing. After taking the above steps, if it does prove to be a medication failure, then using a drug of the same class with a different delivery mechanism or one with a different mechanism of action may be required.

Brief Review of the Literature

One of the feared scenarios for a gastroenterologist dealing with Crohn's disease is when a patient states, "I don't think my medications are working." When dealing with Crohn's disease, it is especially important to establish a relationship with your patient allowing you to open up a clear line of communication where the patient is not afraid to share the truth about anxiety, stress, financial difficulty, and an active description of their current disease state. Without these details, it is difficult to assess wellness, increased disease activity, or medication failure.

Despite the scientific evolution of therapy ushered in by biologics in the recent past, we need to remember approximately one third of patients will not respond to anti-TNF-alpha therapy [4]. Those patients who have been treated and failed to respond to therapy are deemed primary nonresponders. While those who initially responded then lose response or become intolerant are known as secondary nonresponders [5]. The latter may represent 30–40 % over the first year. Another surprising statistic is

that two thirds of all nonresponders, regardless of cause, will lose response within the first 12 months [6]. With these numbers illustrating an all-too-familiar scenario, we as clinicians must have an approach to managing these patients. Correct identification and appropriate timely treatment changes, when needed, optimize patient outcomes by improving quality of life while decreasing surgery and hospitalization [7].

Before deciding medication nonresponse in a patient, we must first verify actual nonresponse. Some patients may be labeled nonresponders when actually "failure" is attributable to a non-IBD cause. This is due rather to unrecognized complications of the disease including a structural lesion, a superimposed infection or abscess, and even those symptoms not arising from inflammation such as IBS.

We as clinicians may benefit from using a standard approach when a patient with Crohn's has a change in disease activity suspicious for nonresponse. First and foremost, and often easily treated, is the topic of superinfection posing as nonresponse. Viral, bacterial, parasitic, and fungal infections all pose a risk to our patients regardless if treated with immunomodulator or biologic therapy [8]. Testing should always be done for *Clostridium difficile* as well as other infections such as CMV at which the patient may be at risk. These can be related to age, vaccination history, antibiotic exposure, or recent travel (Table 13.1).

While ruling out opportunistic infection, it can also be very important to assess for inflammation as well as drug levels of the medications currently used in treatment. Drug levels paired with inflammatory markers can give important information as to what is causing the current issue with suspected nonresponse.

When beginning the initial laboratory assessment, objective data such with CRP and fecal biomarkers have proven valuable when evaluating for inflammation. The two currently commercially available fecal biomarkers are stool calprotectin and lactoferrin. Fecal biomarkers are helpful as an adjunctive management tool in those with inflammatory disease to monitor disease activity and predict relapse [9]. Obtaining one or both of these biomarkers at significant waypoints in

Table 13.1 Possible mechanisms of worsening on anti-TNFs

Low drug level; + positive evidence of inflammation
Loss of anti-TNF activity due to antidrug antibodies
Interminable inflammation "consuming" anti-TNFs Ab
Noncompliance to therapy
Loss of anti-TNF activity due to nonimmune drug clearance
Adequate drug level + evidence of inflammation
Shift of disease pathway away from TNF to other mediators
Infection
Others (vasculitis, ischemia)
Adequate drug level, no evidence of inflammation
Fibrostenotic stricture
Cancer
Irritable bowel syndrome
Miscellaneous (amyloid, bacterial overgrowth, bile salt diarrhea, celiac disease, etc.)

Adapted from Allez M, Journal of Crohn's Colitis 2010

treatment, such diagnosis or treatment onset can provide valuable information. Once inflammatory results are obtained, they can be paired with drug levels giving us valuable insight into disease activity, medication dosing, and even compliance. Superimposing the above data upon clinical suspicion and if needed radiologic and/or endoscopic testing is necessary when making the decision of medication failure or nonresponse.

When treating with TNF-alpha agents, it's important to realize and correctly identify lack or loss of response to anti-TNF agents thereby avoiding complication of inadequately treated disease. To begin a causal investigation, we must first identify if inflammation is present before increasing, changing or checking levels of medication. Once completed this will allow placement of the patient into one of three categories—(1) low drug level, (2) adequate drug level and increased inflammatory biomarkers, and (3) adequate drug level and normal biomarkers (Table 13.1).

Those patients with low drug level must first be evaluated for compliance. Other causes of low levels may include high inflammatory disease burden or clearance of drug due to antidrug antibodies (ADAs). It may be important to check serum for ADAs at this time to aid in treatment decisions.

If it's discovered that the patient has adequate drug level and high inflammatory biomarkers, this may be indicative of an inflammatory shift of the disease to a non-TNF-alpha pathway. It may also indicate another disease process such as infection, vasculitis, or ischemia.

Lastly are those patients with normal biomarkers and adequate drug level. Patients may have one of the many causes of noninflammatory-related complications of Crohn's disease including a fibrostenotic stricture, IBS, neoplasm, choleretic diarrhea, SIBO, or even amyloid deposition.

Based on the proposed categories, we should have a fairly accurate idea of which category our patient may fit. Based on these data, further diagnostic work-up may be selected. This may include ileocolonoscopy, CT/MRI-based studies, or wireless capsule endoscopy. Capsule endoscopy has been shown superior to all other modalities for diagnosing non-stricturing small bowel CD [10]. One important note to remember is that a capsule can be retained if a stricture is present. Employing an Agile (brand name) patency capsule prior to deploying the video capsule could prove beneficial to prevent capsule retention [11].

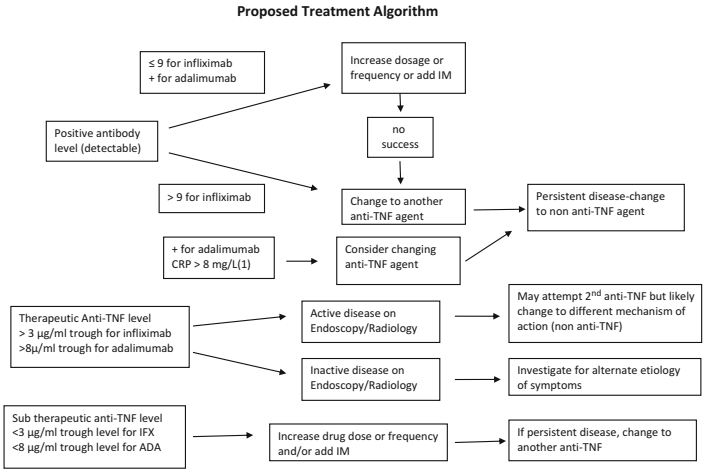
Remember, the first step to treating loss of response is prevention. This is done by avoiding episodic therapy and ensuring adequate drug levels. This will avoid subtherapeutic drug levels and minimize antibody formation [12].

If the patient is in fact experiencing loss of response, options include the addition of an immunomodulator, dose escalation of their current TNF therapy, or changing to a different therapy of the same or different mechanism of action.

The addition of an immunomodulator can help to revert immunogenicity and restore efficacy [13]. Remember that with patients on an immunomodulator such as 6-MP or azathioprine, assessment of metabolite levels of 6-thioguanine(6-TG) and 6-methylmercaptopurine(6-MMP) is important to optimize outcome and decrease side effects [14].

Dose escalation or intensification can recapture response by allowing adequate drug available to meet the inflammatory demand. This can be accomplished by increasing frequency

TABLE 13.2 Proposed treatment algorithm



ADA adalimumab, *IFX* infliximab

Table adapted from Afif W et al. Am J Gastroenterol 2011; 105:1133–1139. 1—Baert FJ, Lockton S, Hauenstein S, Singh S, Gils A, Vermeire V. Antibodies to adalimumab predict inflammation in Crohn's patients on maintenance adalimumab therapy [DDW abstract Sa1247]. *Gastroenterology*.2014; 146(suppl 1):S242

or dosage of the respective medication. Both options have been proven effective [15]. Drugs may then be de-escalated after desired response is achieved.

If the cause off LOR has been verified and no strategy listed above has proven beneficial, then moving to a drug with a non-TNF mechanism of action or referring your patient to a center with active clinical trials may be needed (Table 13.2).

In summary, when a patient enters your office and states they don't believe their medication is working, it's important to first know your patient and be able to make accurate assessment using history combined with objective data. Proper objective assessment may include drug levels, inflammatory markers, imaging, and/or ileocolonoscopy.

Remember: (1) Verify the cause or LOR and (2) ask, "Is it related to Crohn's disease activity?"

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Chapter 14
What About Alternative Therapies I Can Try? Dietary Supplements, Probiotics, Prebiotics, and Alternative Therapies in IBD

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Suggested Response to the Patient

Complementary and alternative medicine is a growing area of research in inflammatory bowel disease (IBD). While it is clear that patients with IBD should take calcium and vitamin D supplements to prevent osteoporosis, the role of dietary and herbal supplements to treat the inflammation in IBD is still under investigation. Scientific studies have shown that probiotics are effective in treating pouchitis and ulcerative colitis. In addition to probiotics, prebiotics, omega-3 fatty acids, herbal supplements, and helminth (worm) therapy are examples of alternative treatments that are being studied. We are still learning about their treatment potential, as well as possible side effects.

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Brief Review of Literature

Complementary and alternative medicine continues to grow in popularity and is being utilized with increasing frequency among inflammatory bowel disease (IBD) patients [1]. Despite its popularity, the evidence to support dietary therapy, probiotics, and alternative therapy in patients with IBD is limited. Some studies suggest a potential therapeutic effect of these therapies; however, the scientific rigor of these studies varies greatly. Concomitant IBD therapy, disease severity, duration, phenotype, and patient demographics are among several possible confounders that are often not adjusted for in the observational investigations. Focusing specifically on existing randomized trials, data for curcumin and helminth therapy is the strongest to suggest a potential treatment benefit. Conversely, data are weak to support the use of aloe vera, dietary fish oil, or *Boswellia* as IBD therapy. There is good evidence that probiotics, specifically VSL#3, prevent the first and recurrent episodes of pouchitis and treat active pouchitis and ulcerative colitis [2].

Choosing the right treatment for IBD can be a complicated endeavor. Fortunately, many treatment options have emerged in the past several decades; thus, we are no longer limited to steroids as the only available, effective medical therapy to treat IBD. Newer steroid-sparing agents, including immunosuppressant and biologic therapies, have shown efficacy in clinical trials in both inducing and maintaining remission in IBD. That said, the costs of these therapies can be prohibitive, especially with long-term use, and they are not without their own set of undesirable side effects, including but not limited to an increased risk of infection, hepatotoxicity, bone marrow suppression, and malignancy. While these risks are low, and typically are outweighed by the benefits of therapy, patients and physicians alike would welcome effective treatment options that do not carry these risks.

Dietary Supplements and Dietary Therapy in IBD

Although not used specifically to treat IBD, vitamin and mineral supplements are used often by patients. Since vitamin and mineral deficiencies may be a result of the inflammatory process, reevaluation of the need for supplementation after the inflammation has been controlled and the symptoms have abated is reasonable. Low bone mass occurs in 18–42 % of IBD patients [3]. Steroid exposure increases this risk; however, osteoporosis has also been noted to occur more frequently even in steroid-naïve patients with IBD compared to matched controls [4], suggesting the inflammatory process itself confers additional risk, independent of steroid use. Such patients should be treated with calcium and vitamin D supplementation, typically under the guidance of an endocrinologist or rheumatologist.

To date, data are conflicting on the benefit of elemental nutrition in IBD. A prospective pilot study reported improvement in clinical symptoms, endoscopic scores, histopathology, and inflammatory cytokines in 28 patients with CD given an enteric elemental diet [5]. Some participants experienced diarrhea and abdominal colic, but, there were no instances in which the side effects required interruption of therapy. Occasionally antidiarrheals were also utilized. After 4 weeks of elemental diet, 71 % of patients achieved clinical remission. Endoscopic and histologic improvement was also demonstrated. Among those with endoscopic healing, previously elevated inflammatory cytokines were reduced to levels equivalent to healthy controls [5]. Elemental diets have not proven superior to standard medical therapy, as was reported in a meta-analysis reviewing trials that compared elemental diets to steroids [6].

Prebiotics and Probiotics in IBD

It has been long suspected that gut microbiota plays an important role in the pathogenesis of IBD, though we are still learning about the complex interplay between diet,

the gut microbiome, and the interaction with the host immune system. Prebiotics and probiotics have been studied as potential therapies that treat IBD by altering the intestinal bacterial milieu. Prebiotics are nondigestible carbohydrates, which yield a lower intestinal pH, favoring certain bacterial populations and theoretically helping to treat IBD. In a small study of ten patients with UC, the use of butyrate enemas decreased bowel movement frequency and bleeding and induced mucosal healing when compared to placebo [7]. Another study utilized oral ingestion of germinated barley with standard therapy to yield improved maintenance of remission in patients with UC [8]. Probiotics, which are strains of favorable intestinal microorganisms such as *Lactobacillus* and *Saccharomyces*, are recognized as effective therapy for antibiotic-induced diarrhea [9] and recurrent *C. difficile* infection [10], and in the IBD population they are best utilized in the treatment of pouchitis and ulcerative colitis [11, 12]. The data for VSL#3 in the treatment of pouchitis is strong and in a randomized trial was associated with 85 % of treated patients maintaining remission compared to only 6 % in the placebo group ($p < 0.0001$) [13]. VSL#3 has been evaluated in five studies in patients with ulcerative colitis. A meta-analysis of these studies reported a response rate of 53 % and a remission rate of 44 % in VSL#3-treated patients compared to 29 and 25 % of placebo-treated patients [2]. Outcomes for data on the use of probiotics in CD are less impressive. A recently published double-blinded, placebo-controlled trial compared maintenance of remission in CD patients treated with *Saccharomyces boulardii* or placebo and found no significant difference between the treatment groups [14]. Several meta-analyses failed to demonstrate a beneficial effect of probiotics in maintenance of remission or prevention of postoperative recurrence of CD [15–17]. Further investigation on the use of prebiotics, probiotics, and synbiotics (the combined use of pre- and probiotics) is needed to more definitively clarify their role in IBD therapy.

Alternative Therapies in IBD

Many other alternative therapies believed to possess anti-inflammatory qualities have been investigated as possible treatment for IBD, such as aloe vera, fish oil, curcumin, marijuana, helminths, and *Boswellia serrata*. In vitro studies have demonstrated that aloe vera reduces inflammation in rat models of colitis [18], as well as in human colonic mucosa [19]. In clinical studies, a randomized, double-blinded, placebo-controlled trial demonstrated a trend toward symptom remission and response in UC patients given dietary aloe supplementation [20]. After 4 weeks of oral aloe vera gel supplementation, 30 and 47 % of the patients in the aloe vera group achieved clinical remission or response, respectively, compared to only 1 % remission and 1 % response in the placebo group. Mucosal healing was not significantly different between treatment arms.

Omega-3 fatty acids are well known for their anti-inflammatory effects and can be found in several dietary sources including fish oil, walnuts, flaxseed oil, and olive oil. These essential fatty acids have demonstrated beneficial effects in multiple pro-inflammatory conditions such as cardiovascular disease and rheumatoid arthritis [21] and consequently may be candidates for therapy in IBD. Dietary fish oils have demonstrated positive effects in rat models of colitis [22]. In CD, two large randomized trials reported no difference in relapse rates between patients treated with 4 g/day of omega-3 fatty acids compared to placebo [23]. A recently published systematic review compiling data from randomized trials performed in UC and CD demonstrated no effect with dietary fish oil supplementation [24].

Curcumin, a natural food additive known as turmeric, has also been described to exhibit anti-inflammatory effects in cell culture and animal studies [25]. In IBD, a small open-label pilot study evaluated the effects of curcumin as adjunctive therapy in five patients with ulcerative proctitis and five patients with CD [26]. Patients were allowed to continue existing

therapy at entry including aminosalicylates, mercaptopurine, and budesonide. All patients but one (who discontinued the medication due to worsening fistula output) exhibited improvement in clinical symptoms and endoscopic scores. In a double-blinded, placebo-controlled trial, curcumin therapy resulted in decreased relapse rates in UC [27], and a recently published Cochrane systematic review deemed curcumin as safe and effective adjunctive therapy in UC [28].

Cannabis was recently studied in a prospective trial as induction therapy for CD [29]. Interestingly, patients included in this study had symptoms that were refractory to steroids, immunomodulators, or antitumor necrosis factor-α agents. After 8 weeks of cannabis therapy administered via cigarettes, clinical remission rates were higher in the cannabis compared to placebo group (45 % vs. 10 %, $p = 0.43$), and 90 % of those who received cannabis experienced a clinical response, compared to 40 % in the placebo group ($p = 0.028$). No changes in quantitative c reactive protein were noted in either treatment group, raising the question of whether cannabis decreases inflammation or only treats symptoms. There are obvious issues related to the use of cannabis in the treatment of IBD such as the fact that it is still illegal under Federal law and that chronic cannabis use is associated with a risk of significant cognitive, neuromuscular, and respiratory side effects [30]. Additional studies are needed to confirm the effectiveness of cannabis in the treatment of IBD and to evaluate if other delivery systems (oral intake) are efficacious.

Boswellia serrata is an Indian frankincense utilized in Ayurvedic medicine for centuries, primarily for the treatment of arthritic symptoms. Given its anti-inflammatory properties, it has also been considered as an IBD therapeutic candidate. Early studies examining the effect of *Boswellia* in animal models of colitis demonstrated no significant reduction in inflammation and more notably found higher doses of the herb to be hepatotoxic [31]. This was further investigated in a randomized trial that evaluated the safety and efficacy of *Boswellia* compared to placebo in patients with CD. *Boswellia* was well tolerated with a low side effect profile [32]. Unfortunately, there

was no improvement in relapse rates among patients who received *Boswellia* compared to placebo.

Helminth therapy is perhaps among the most creative of the potential alternative IBD therapies and has received considerable attention. Hookworm is thought to have a protective effect in the development of CD [33], and in particular, the porcine whipworm *Trichuris suis* has been studied extensively in IBD. In an open-label study, 29 patients with active CD were randomized to ingest 2,500 live *T. suis* ova every 3 weeks for 24 weeks. At week 24, 72 % of patients achieved clinical remission and 79 % achieved a clinical response [34]. Subsequently, Summers et al. demonstrated that 2,500 *T. suis* ova every 2 weeks for 12 weeks in patients with UC was well tolerated and that 43 % of patients treated with *T. suis* improved compared to 17 % of placebo ($p = 0.04$) [35]. A recent study using up to 7,500 *T. suis* ova did not find a higher rate of adverse events with increasing dose [36]. Large-scale therapeutic trials for *T. suis* therapy are ongoing.

Summary

Many alternative and complementary methods of treating IBD are under investigation. Probiotics are useful in patients with IBD being treated with antibiotics to prevent antibiotic-associated diarrhea and in some cases to prevent recurrent *C. difficile* infection. Probiotics, specifically VSL#3, prevent the first and recurrent episodes of pouchitis and treat active pouchitis. There is also evidence that high doses of VSL#3 improve outcomes in UC. Although early studies of cannabis are promising, the use of cannabis in clinical practice should be discouraged because cannabis is a Federal I-controlled substance and because of its long-term adverse health effects. The use of helminths, specifically *Trichuris suis*, should be restricted to a research protocol until further studies emerge regarding its efficacy and safety. This is also true for other herbal supplements which may have a beneficial effect in treating IBD but require further study. Research in this area

will need greater scientific rigor, with adjustment for confounding factors and attention to response rates, which have been comparable to the high placebo response rates seen in larger IBD clinical trials [37]. Because these are "natural" substances, they are often perceived as harmless, and their lack of regulation results in unlimited access. As providers we should ask patients about the use of nontraditional therapies and recognize their evolving role in the treatment of IBD.

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Chapter 15
Why Can't I Just Stay on Prednisone? The Long-Term Adverse Effects of Steroids

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Suggested Response to the Patient

Steroids do an excellent job of treating active inflammation associated with ulcerative colitis or Crohn's disease and are often used to bring severe disease into remission. Unfortunately, there are numerous adverse effects that occur with prolonged use, and they have even been shown to overall shorten patients' life-spans. Potential complications can vary dramatically, from acne and irritability to life-threatening infection and suicidality. Other complications include weight gain, diabetes, high blood pressure, osteoporosis, death of a bone in your hip, anxiety, depression, and serious infections. The risks increase with higher doses and longer duration of therapy. For this reason, we prefer to use other medications with better safety profiles for long-term use to maintain your disease under good control.

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Review of the Literature

Glucocorticoids have been used for the treatment of inflammatory bowel disease for over 50 years. Pivotal randomized controlled trials from the 1950s and 1960s in ulcerative colitis [1, 2] and from the 1970s and 1980s in Crohn's disease [3, 4] showed superior efficacy compared to placebo at inducing clinical remission. This effectiveness was confirmed in the more recent GETAID study whereby oral prednisolone administered for 3–7 weeks induced clinical remission in 90 % of patients with active Crohn's disease [5]. Though glucocorticoids are effective at achieving remission, they perform poorly as maintenance agents. A meta-analysis of RCTs showed that over a 2-year period, patients with quiescent Crohn's disease who were given glucocorticoids did not have any reduction in risk of relapse [6].

Though the numerous adverse effects of glucocorticoid use have been well known and described, IBD-specific outcomes have been documented only more recently. For example, results of prospective, observational, treatment registry data for Crohn's disease have suggested an increased risk of serious infections and death associated with glucocorticoid use even after adjusting for other factors [7]. Based on these data and data from additional observational studies, recent treatment guidelines have strongly denounced the long-term use of glucocorticoids, especially given the wide availability of newer agents with better safety profiles [8, 9].

Long-term glucocorticoid use can result in adverse effects involving virtually any organ system, and in general, risk tends to correlate with both dose and duration of use. The concept of a maximum tolerable amount is controversial and poorly defined, as studies looking at even relatively low-dose prednisone have demonstrated safety concerns with chronic use [10]. Prednisone—the prototypical oral glucocorticoid used in treatment of IBD—exerts its effects primarily via inhibition of the hypothalamic-pituitary-adrenal axis, leading essentially to iatrogenic Cushing's syndrome. With its predominate function being a glucocorticoid agonist, it lacks significant mineralocorticoid as well as gonadotropic activity.

Cardiovascular

Among the adverse effects of greatest concern are those related to increased cardiovascular risk. Glucocorticoid use has been demonstrated to accelerate the development of atherosclerosis and consequently is associated with increased risk of ischemic heart disease and congestive heart failure. A large population-based study showed that glucocorticoid users had a significantly higher risk of cardiovascular disease, defined as a composite outcome of myocardial infarction, coronary revascularization, angina, heart failure, stroke, or transient ischemic attack [11]. Additionally, glucocorticoid use has been found to be arrhythmogenic, and is associated with higher rates of atrial fibrillation and atrial flutter, even independent of the presence of preexisting cardiovascular or pulmonary disease [12]. Hypertension is also common with glucocorticoid administration. Interestingly, although hypertension is seen in 70–80 % of patients who develop Cushing's syndrome [13], rates among patients taking exogenous glucocorticoids tend to be lower—roughly 20 % [14]. This difference is postulated to be a result of improvement in the underlying inflammatory state for which steroids were initiated.

Endocrine

Glucocorticoids have long been associated with disorders of glucose metabolism and are the most common causative agents of drug-induced diabetes. The effect is predominately through increased insulin resistance, which occurs via alterations in glucose utilization as well as upregulation of hepatic gluconeogenesis. Glucocorticoid-induced hyperglycemia tends to manifest as postprandial elevations in blood glucose more so than elevated fasting levels. One study of patients with rheumatoid arthritis found that 9 % of patients started on glucocorticoids developed diabetes within 2 years [15]. Another analysis of a large group of Medicaid enrollees found that glucocorticoid use portended a RR of 2.23

(95 % CI 1.92–2.59) among patients newly initiated on hypoglycemic therapy. The RR rose to 10.3 among patients taking an equivalent of 30 mg/day of prednisone [16]. In addition to diabetes, weight gain is among the most common adverse events, occurring in 70 % of long-term glucocorticoid users [17]. The pattern of weight gain tends to involve a redistribution of body fat and the development of truncal and central adiposity, with the so-called moon facies and buffalo hump.

Musculoskeletal

The impact of glucocorticoid use on bone health is significant. The increased predilection toward the development of osteoporosis, and in turn fragility fractures, imposes a significant morbidity and mortality burden. Glucocorticoid use is the leading cause of secondary osteoporosis [18]. This is achieved through a variety of mechanisms which serve to increase bone resorption while decreasing bone formation. Glucocorticoids inhibit the differentiation and maturation of osteoblasts through interference with several cell signaling pathways and are also detrimental to the function of mature osteoblasts and osteocytes by inhibiting the expression of IGF-1 resulting in decreased production of type I collagen and higher rates of apoptosis [19]. Osteoclast formation is conversely promoted by glucocorticoids, as a result of decreased apoptosis and alterations of signaling cascades which upregulate differentiation of this cell line, leading to higher levels of osteoclasts and an increase in bone resorption [20]. Another mechanism by which resorption is increased is via glucocorticoid-mediated reduction in levels of gonadotropins, leading to lower levels of serum androgens and estrogens [21].

Glucocorticoids impact bone health through significant interactions with the Ca^{2+}-Vitamin D-PTH axis as well. This is felt to occur via two main mechanisms. First, glucocorticoids decrease gut absorption of calcium via antagonism of vitamin D and downregulation of duodenal calcium channels [22].

Second, renal tubular reabsorption of calcium is inhibited thus promoting urinary calcium loss. Whether this leads to a form of secondary hyperparathyroidism remains uncertain as studies have failed to demonstrate elevations in parathyroid hormone levels among patients taking glucocorticoids [23]. Moreover, IBD may not actually be an independent risk factor for hypovitaminosis D, and the overall incidence of osteomalacia is actually not increased [24].

Fracture risk, especially of the vertebral body, is increased among glucocorticoid users, with risk rising steadily early after the initiation of steroid therapy, as this tends to correlate with the period of most rapid bone loss [23]. Despite clear evidence of steroid impact on bone density, other factors likely contribute to an increased fracture risk. A 2005 study showed that fracture risk remained elevated in glucocorticoid users even with normal BMD values [25]. A comprehensive systematic review of bone disease in IBD patients found that fracture risk in general is only modestly elevated (RR 1.4), though glucocorticoid use was consistently the largest independent risk factor [24].

An additional musculoskeletal concern among glucocorticoid users is steroid myopathy, a well-described phenomenon characterized typically by proximal muscle weakness and wasting, as a result of direct catabolic effect of steroids on skeletal myocytes [26]. Lower extremities tend to be involved more severely than upper extremities, and typically pain and myalgia are not seen. Serum muscle enzyme levels may be normal, and EMG or muscle biopsy may either be normal or show mild nonspecific findings. Diagnosis can thus be difficult to establish, but improvement in muscle strength upon dose reduction or discontinuation of the offending glucocorticoid is expected. Avascular necrosis or osteonecrosis is also seen more commonly among patients on glucocorticoids and potentially at a higher rate in IBD patients as compared to patients taking glucocorticoids for other indications [27].

Gastrointestinal

Despite potent efficacy in IBD, glucocorticoids carry a significant number of potential adverse effects targeting the gastrointestinal system, including gastrointestinal hemorrhage, predilection or exacerbation of ulcer disease, gastritis, and bowel perforation. A large meta-analysis found a RR of 2.3 and 1.5 for peptic ulcer disease and GI hemorrhage, respectively, among glucocorticoid users compared to controls [28]. The risk of ulcer formation and hemorrhage in this analysis was exacerbated by concomitant use of NSAIDs. Another investigation found an overall RR of 2.0 for ulcer disease among glucocorticoid users; however, subgroup analysis among patients not using NSAIDs found this risk was no longer significant [29]. In general the risk of significant bleeding may be small, and concomitant NSAID use clearly plays a role.

Psychiatric

A host of psychiatric disturbances can be attributed to glucocorticoid use as well. These include changes in cognition, memory impairment, sleep disturbances, delirium, depression, mania, anxiety, or psychosis [30]. The more activating effects, such as mania and anxiety, tend to occur earlier on in a course of therapy, whereas depressive symptoms are often seen after more prolonged periods of use. Typically the neuropsychiatric effects are reversible on discontinuation or lowering of the glucocorticoid dose.

Immunologic

Glucocorticoid use leads to an increased risk of infections via effects on both the innate and acquired immune systems. Identification of infections may be made more challenging due to masking of the typical cytokine-mediated inflammatory effects which are inhibited by steroids. In IBD patients,

the use of corticosteroids is associated with a significantly increased risk of opportunistic infection, similar to that seen with thiopurines and biologic agents; however, this risk rises exponentially when these agents are used in combination [31]. In patients with inflammatory bowel disease undergoing elective bowel surgery, the preoperative use of glucocorticoids was associated with an increased risk of postoperative infectious complications. This association was not seen with use of other immunomodulators [32].

Others

Chronic glucocorticoid use is associated with several skin and ocular manifestations. Thinning of the skin, easy bruising, and the development of purpura are common. Nearly half of all patients using prednisone for more than three months in one analysis reported changes in their skin [33]. Steroid-associated purpura is typically non-palpable and affects the sun-exposed areas disproportionately. An additional dermatologic concern is nonmelanoma skin cancers. Chronic glucocorticoid use is associated with an OR of 2.31 and 1.49 for squamous cell and basal cell carcinomas, respectively. Both glaucoma and cataracts are seen more commonly in patients taking long-term glucocorticoids. Patients taking an average of 6 mg prednisone daily for an average period of 6 years had greater than threefold increase incidence of cataract development [10].

Conclusions

Glucocorticoid use is associated with a wide array of adverse effects impacting multiple organ systems and leading to a myriad of disease states. Risks in general tend to increase with prolonged use and with higher mean dose. Glucocorticoids are very effective at inducing clinical remission and are well tolerated when used for brief periods, but these medications should not be utilized as long-term therapy for the maintenance of remission in IBD.

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Chapter 16
Why Can't I Continue to Take My Narcotics? The Long-Term Negative Effects of Narcotics

Ayan Rage and Daniel J. Stein

Suggested Response to Patient

As a patient with inflammatory bowel disease (IBD), specifically Crohn's disease, you may develop abdominal pain at some point. Pain is a way for our body to communicate that there might be something wrong. As there are multiple causes of pain, it's crucial to identify the exact cause so that the right treatment can be offered. Narcotics can be thought of as a "Band-Aid" since they only treat symptoms, not the cause (inflammation) of pain in IBD. By masking pain, narcotics interfere with our ability of judge if your disease is active or not.

Narcotics not only mask the underlying cause of pain, they can make the inflammation worse [1]. Research has shown that patients with IBD who use narcotics are more likely to have severe abdominal infections (abscesses), strictures (bowel narrowing), and intestinal obstruction (blockages) [1]. While narcotics have a role for short-term relief of pain, we try to avoid prescribing narcotics for patients with IBD

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because they seem to be harmful in the long run. Additionally, if narcotics are needed, you should work with your physician to limit their use and explore alternate pain medications that are less harmful than narcotics.

Brief Review of the Literature

The adequate management of pain is paramount in caring for patients with IBD. Narcotics have been shown to cause undesirable outcomes in both short- and long-term use. A landmark study looking at the safety of infliximab showed increased mortality and morbidity rate in those using narcotics [1]. Paradoxically, narcotics themselves can cause abdominal pain, the very thing that they were prescribed for in the first place. By causing constipation, bloating, nausea, emesis, and ileus, narcotics further complicate pain management in the IBD population [2]. Despite the available data clearly outlining the detrimental effects of narcotics in the IBD population, up to 13 % of IBD patients are on chronic narcotics [3]. The following will highlight the important studies looking at narcotic administration in both the outpatient and inpatient setting followed by the alternatives to narcotics for our IBD patients.

Inpatient Narcotics in IBD

In a study looking at narcotic administration in IBD patients who were hospitalized, narcotic administration was significantly correlated with a diagnosis of irritable bowel syndrome (IBS), psychiatric illness, and tobacco use but not associated with the severity of inflammation [4]. Although the previous study was retrospective in design, it highlights the role that psychiatric conditions play in the administration of narcotics even in the inpatient setting where patients are presumably in an IBD flare. Recognizing that IBS can coexist with IBD and then treating underlying anxiety disorders and/or IBS is crucial to avoiding unnecessary narcotics [4].

Ulcerative colitis (UC) patients who receive narcotics during hospitalization are at theoretically at higher risk for developing a toxic megacolon given their negative effects on colonic motility. However, this has not been borne out in the literature and there does not appear to be an increased risk of colectomy in UC patients receiving narcotic when looked at retrospectively [5].

Outpatient Narcotics in IBD

In the outpatient setting, the use of narcotics can lead to unintentional consequence of drug abuse, drug dependence, or narcotic bowel syndrome (NBS) [6]. NBS is a condition where patients experience chronic worsening abdominal pain while on narcotics [6]. A vicious cycle develops where the patient complains of worsening abdominal pain in which more narcotics are prescribed [6]. NBS usually occurs when accelerating doses of narcotics are prescribed over a period of the time. In such instances, patients might need to be admitted for a narcotic detox [6].

Causes of Abdominal Pain Other than Active Inflammation

Abdominal pain in IBD is multifactorial, and identifying the cause of pain will increase the success rate in alleviating pain (Fig. 16.1) [7]. Reviewing patient's medication list and asking about over-the-counter (OTC) medications can uncover oral iron and nonsteroidal anti-inflammatory drug (NSAID) use which can mimic the signs and symptoms of active IBD. One study did show that NSAIDS could cause IBD flare and thus be a source of abdominal pain although other studies have been contradictory [8].

Given the high prevalence of psychiatric disorders and functional pain syndromes in the IBD population, the use of psychiatric consultation and antidepressant medications is a powerful tool [7]. Medications such as tricyclic antidepressants

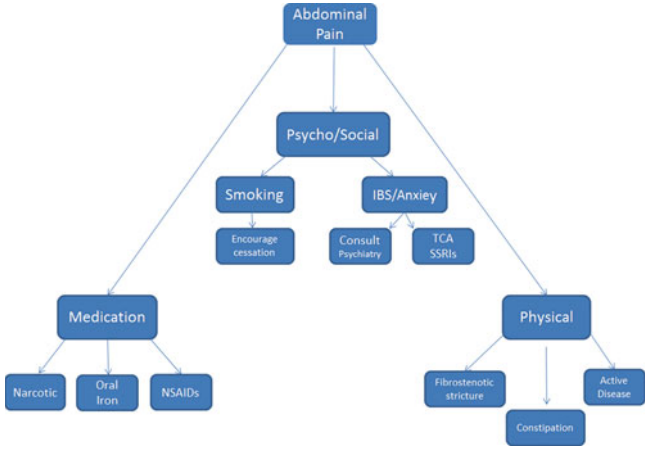

FIG. 16.1 Algorithm for abdominal pain management in inflammatory bowel disease patients (Adapted with permission from Srinath et al. [7])

and selective serotonin reuptake inhibitors (SSRIs) have been shown to be effective in treating pain in patients with underlying psychiatric illness or functional pain syndrome (most commonly IBS).

Constipation as a result of intestinal dysmotility can be a significant player in the development of abdominal pain in IBD that is rarely recognized or addressed. This issue often has a good deal of overlap with IBS and psychiatric disorders clinically. The cycles of inflammation and healing in patients with IBD can lead to damage of glial cells and the interstitial cell of Cajal and to the calcium channels in intestinal smooth muscle resulting in dysmotility and/or pain even when inflammation has resolved [9–11]. With the aid of detailed history taking and abdominal x-ray, constipation and/or dysmotility can be diagnosed and thus treated appropriately.

Additionally, when patient's Crohn's disease appears to be endoscopic in remission, but continues to have ongoing abdominal pain, one can consider the possibility of fibrostenotic strictures or intra-abdominal adhesions as a cause for

the pain. These being either beyond the reach of standard or extraluminal endoscopy can be missed by standard evaluations. Collaboration with a GI radiologist and or an advanced endoscopist may be helpful in evaluating these patients when this is suspected. If either is present, surgery would be the appropriate treatment to alleviate the pain rather than continued narcotics.

When Is It Ok to Use Narcotics

There are instances where using narcotics in IBD patients is reasonable provided the goal is a short time frame with a definitive end date. During the immediate postoperative period and during induction therapy period, narcotics can be safely used. However, the lowest dose possible for the shortest duration possible should be the goal. Examples of when narcotics can be used would include active perianal fistulizing disease and a bowel obstruction awaiting operative evaluation. Situations in which a timetable can be set for the withdrawal of narcotics in conjunction with a primary care physician or a pain management specialist are ideal.

Conclusion

In conclusion, causes of pain are multifactorial in the IBD population. Not all abdominal pain in the IBD patient is secondary to intestinal inflammation or uncontrolled disease. It is important to realize that IBS, anxiety disorders, and depression are prevalent in this population and that they can all be partially alleviated by narcotics. It is also important to remember that narcotics do not treat these disorders and to consider using antidepressant medications in these patients with help from their psychiatrist or primary care physician.

Additionally looking for dysmotility-related issues can be very helpful and uncover underlying constipation as the cause of their symptoms. Lastly, vigilant evaluation for fibrostenotic disease, particularly in Crohn's patients, is essential. Minimizing the use of narcotics and setting limits and setting

goals of narcotic use when they are unavoidable are essential to providing optimal outcomes for our IBD patients when narcotics have to be used.

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Chapter 17
I Heard These Medications Give You Cancer. Is That True? Risks of Malignancy with IBD Therapy

Ryan R. Gaffney and Andrew Tinsley

Suggested Response to the Patient

"Thiopurines (azathioprine and mercaptopurine) and biologic anti-TNF agents (infliximab, adalimumab, certolizumab, and golimumab) are some of the most effective medications that we have for treating inflammatory bowel disease. However, it is important to recognize that these therapies have been associated with an increase in the risk of developing certain cancers including lymphoma and skin cancer. Fortunately, the total number of people who develop these cancers while on therapy

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is very small. There is also little evidence that thiopurines and anti-TNF drugs significantly increase the risk of other types of cancers. Before initiating treatment with these types of medications, we need to review your cancer risks and weigh them against the considerable benefits these therapies can offer."

Brief Review of the Literature

Immunosuppressive agents are widely used for long-term maintenance therapy of inflammatory bowel disease (IBD). While the benefits of these medications are well established, their use may occasionally be limited by concerns over cancer risk. However, practitioners and patients are often unfamiliar with the specific types of malignancy and exact magnitude of risk associated with the use of immunosuppressive therapy. Most of the data regarding IBD medications and malignancy center on the increased risk of non-Hodgkin's lymphoma (NHL) and skin cancer in patients on thiopurines and/or anti-TNFs. To date, there is little evidence that these drugs significantly increase the risk of other types of cancers.

There is an increasing amount of data to suggest that thiopurines (azathioprine [AZA], 6-mercaptopurine [6-MP]) increase the likelihood of developing lymphoma, particularly NHL. Factors that also appear to be associated with increased NHL risk include male sex, age >50, prior exposure to Epstein-Barr virus (EBV), and longer duration of IBD [1, 2]. A 2005 meta-analysis on this topic demonstrated a fourfold increased risk of lymphoma in IBD patients treated with AZA and 6-MP compared to the rate expected in the general population [3]. Since this publication, several population-based and referral center studies have demonstrated similar findings [4–7]. Importantly, a large prospective cohort study of over 20,000 IBD patients found that, in patients who discontinued thiopurines, the lymphoma incidence rate appeared to revert back to that of the general population [8]. The most recent meta-analysis reported a very low overall absolute risk of lymphoma for patients treated with thiopurines [9]. The risk for patients younger than 50 was estimated at less than 1:2,000 per year. Patients aged over 50 had

an absolute risk closer to 1:350 per year. Thus, caution may be required when prescribing thiopurines to an older population.

Use of anti-TNF agents has also been associated with an increased risk of developing NHL. However, TNF inhibitors are often prescribed to current or past users of thiopurines, making it difficult to determine the exact risk attributable solely to anti-TNF drugs. A meta-analysis by Siegel et al. reported a threefold risk of NHL in anti-TNF users compared to the general population. Of note, most cases of NHL occurred in patients with current or prior exposure to AZA, 6-MP, or methotrexate [10]. Other studies have not demonstrated significantly higher rates of cancer in IBD patients on anti-TNF agents. A large Danish population-based cohort study of over 4,000 IBD patients exposed to anti-TNFs alone found no increased cancer risk over a median follow-up of 3.7 years [11]. Additionally, a systematic review and pooled analysis of all available randomized controlled trials of anti-TNF therapies used in IBD failed to show any conclusive evidence of an increased risk of any malignancy with these drugs [12].

It is important that providers be aware of reports regarding anti-TNF therapy and the extremely rare development of hepatosplenic T-cell lymphoma (HSTCL), a peripheral T-cell lymphoma with an estimated survival of less than 1 year from diagnosis. HSTCL has been reported in 36 IBD patients receiving immunosuppressive medications. Twenty of these patients were on anti-TNF agents. There may be an increased risk of HSTCL in men <35 years of age receiving combination thiopurine and anti-TNF therapy. While the risk of HSTCL with combination immunosuppressive therapy in this group of patients needs to be acknowledged, the absolute risk still appears to be low (1:3534) [13].

Immunosuppressive therapy in IBD has also been associated with an increased risk of both melanoma and non-melanoma skin cancer (NMSC). Immune dysfunction in IBD may be a risk factor for the development of melanoma, independent of therapy. While the use of anti-TNF agents may increase this baseline risk, the absolute risk of melanoma has been found to be low at 57 per 100,000 person-years [14]. Therefore, in most clinical situations, an IBD patient's mela-

noma risk likely does not outweigh the benefits of anti-TNF therapy. With respect to NMSC, current and past thiopurine use in IBD has been associated with increased risk in several retrospective studies [15–17]. Combination therapy with an anti-TNF and thiopurine may further increase the risk [18]. Based on this data, providers may consider withdrawing thiopurines in high-risk patients on concurrent anti-TNF agents. Furthermore, patients with IBD on combination therapy should be monitored for suspicious skin lesions and advised to minimize sun exposure, use physical barriers such as sunscreen and protective clothing, and consider annual dermatologic assessment.

There may be an increased risk of cervical dysplasia in female patients exposed to immunosuppressive medications. To date, only three studies have addressed this question, each with conflicting results and significant differences in study design. Therefore, it is difficult to draw definitive conclusions about the baseline risk of cervical dysplasia in women with IBD or the potential for therapy-related effects [19]. At present, enhanced cervical screening for female IBD patients on immune suppressants on an annual basis can be considered.

There are other important issues that arise when assessing cancer risk in the setting of immunosuppressive therapy for IBD. The risk of malignancy with other agents used in the treatment of IBD is not well defined. Limited data exists regarding the risk of hematologic and other malignancies in IBD patients exposed to methotrexate. The anti-integrins, natalizumab and vedolizumab, have also not been specifically studied with regard to cancer risk. However, post-marketing surveillance has not revealed an increased risk of malignancy with these agents. As for patients with a prior history of malignancy, a recent prospective cohort study of several hundred IBD patients found no increase in the risk of recurrent cancer with exposure to immunosuppressants [20]. While this data is certainly reassuring, providers need to carefully consider a variety of factors before prescribing immunosuppressive agents in this setting. These variables include the severity of an individual's inflammatory bowel disease and potential for recurrence of their prior malignancy (based on specific type of cancer and duration of remission) [21]. In most cir-

cumstances, patients with an active malignancy should not receive thiopurines or anti-TNF therapy. The decision to start or resume immunosuppressive therapy after cancer treatment has been completed should typically be made in conjunction with an oncologist.

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Chapter 18
Are All of These Vaccinations Really Needed? Vaccinations and Inflammatory Bowel Disease (IBD) Patients

Y.T. Nancy Fu and Gil Y. Melmed

Suggested Response to the Patient

Patients with inflammatory bowel disease (IBD) are at increased risk for vaccine-preventable illnesses. Some of these infections can be devastating, especially in immunocompromised patients. Several reports have demonstrated that patients with IBD have low overall vaccination rates. Furthermore, immune response rates to vaccinations may be impaired, especially when vaccines are administered while patients are on immunosuppressive therapies. Therefore, patients with IBD should be up-to-date with recommended vaccinations. Most vaccinations can be administered regardless of immune suppression status and have not been shown to cause flares of disease activity. There are several commonly recommended vaccinations for adult IBD patients (listed in Table 18.1). IBD patients should consider obtaining these vaccines prior to starting immunosuppressive therapies, although most vaccinations are safe and at least partially effective even when administered to patients on immunosuppression.

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Table 18.1 Recommended vaccinations for adult patients with inflammatory bowel disease

Vaccine	Dose	Recommendation	Check titer first	Safe for immunocompromised
Inactivated vaccines				
HAV[a]	2 doses	Adults ≥19	Yes	Yes
HBV[a]	3 doses	Adults ≥19	Yes	Yes
HAV and HBV[a]	3 doses	Adults ≥19	Yes	Yes
HPV	3 doses	Females 11–26 Males 11–26 at risk[b]	No	Yes
Influenza (trivalent)[c]	Annually	Adults ≥19	No	Yes
Meningococcal[a]	≥ 1 dose	Adults ≥19	No	Yes
Pneumococcal[a]	1 dose and 1 booster in 5 years	Adult ≥19	No	Yes
Tetanus and diphtheria	Every 10 years	Adults ≥19	No	Yes
Live attenuated vaccines				
MMR	1 or 2 doses[d]	Adults born after 1957	Yes	Contraindicated
Varicella[a]	2 doses	Adults ≥19	Yes	Contraindicated
Zoster	1 dose	Adults ≥60	Yes	Contraindicated

[a]Hepatitis A, hepatitis B, meningococcal, pneumococcal, and varicella vaccines are not universally recommended. Specific recommendations regarding these vaccines are listed below:

- *Hepatitis A vaccine* is recommended for persons with chronic liver disease, receive clotting factor concentrates, travel to high or intermediate endemic area, use illicit drugs, or men who have sex with men.
- *Hepatitis B vaccine* is recommended for persons with diabetes younger than age 60 years, end-stage renal disease, HIV infection, or chronic liver disease; healthcare personnel at risk of exposure to blood or other infectious body fluids; clients and staff of institutions for persons with developmental disabilities; persons at risk of sexually transmitted disease including those not in a monogamous relationship and men who have sex with men; current or recent injection drug users; household contacts and sex partners of hepatitis B surface antigen-positive persons; and international travelers to countries with high or intermediate prevalence of chronic HBV infection.

- *Meningococcal vaccine* is recommended for first-year college students, military recruits, persons with asplenia, persons with persistent complement deficiencies, and persons traveling to hyperendemic or epidemic areas. Revaccination every 5 years is recommended for adults who remain at increased risk for infection such as adults with asplenia or persistent complement component deficiencies.
- *Pneumococcal conjugate (PCV13) vaccine* is recommended for adults aged 19 years or older with immunocompromising conditions, asplenia, cerebrospinal fluid leaks, or cochlear implants.
- *Pneumococcal polysaccharide (PPSV23) vaccine* is recommended for adults aged 65 or older; adults younger than 65 years with chronic lung disease, chronic cardiovascular diseases, diabetes mellitus, chronic renal failure, nephrotic syndrome, chronic liver disease, alcoholism, cochlear implants, cerebrospinal fluid leaks, immunocompromising conditions, and asplenia; residents of nursing homes or long-term care facilities; and adults who smoke cigarettes. One-time revaccination 5 years after the first dose of PPSV23 is recommended for persons aged 19 through 64 years with chronic renal failure or nephrotic syndrome, asplenia, or immunocompromising conditions.
- *Varicella vaccine* is recommended for all adults without evidence of immunity. Immunity is indicated by documentation of two doses of varicella vaccine at least 4 weeks apart, US-born before 1980, history of varicella or herpes zoster based on diagnosis or verification of disease by a healthcare provider, or laboratory evidence of immunity or confirmation of disease.

[b]Male IBD patients with perianal Crohn's disease on immunosuppressive therapies and men who have sex with men.

[c]Intranasal influenza vaccination (LAIV) is live attenuated and should be avoided in immunocompromised patients.

[d]Students attending colleges or other post-high school educational institutions, healthcare personnel, and international travelers should receive two doses of MMR vaccine.

Brief Review of Literature

Common vaccine-preventable illnesses include influenza, pneumococcus, varicella, hepatitis A and B (HAV and HBV), and tetanus (with diphtheria). At the time of IBD diagnosis, most children have been vaccinated against common childhood illnesses including measles, mumps, and rubella (MMR), polio, tetanus, diphtheria, and pertussis. However, despite being at high risk for infection, many adult IBD patients do not have up-to-date vaccinations. Most vaccine response studies report normal antibody response rates in non-immunosuppressed IBD patients, but reduced rates in those who are immunocompromised, particularly those on combined anti-TNF and immunomodulator regimens [1].

Vaccination Strategies

Recommended vaccinations for patients with IBD are listed in Table 18.1. All adults with IBD should receive annual killed influenza vaccination and should be considered for hepatitis B, pneumococcal, and TdAP booster vaccinations. Live attenuated vaccines should ideally be administered prior to initiation of immunosuppressive therapies, and immunosuppressive therapies should not be initiated within 4–12 weeks after live attenuated vaccines. In general, immunocompromised patients should not receive live attenuated vaccines. However, there may be exceptions to this rule when the benefits of vaccination outweigh theoretical risks of vaccination. For example, high rates of herpes zoster infection warrant consideration for vaccination against herpes zoster (a live attenuated vaccine) even among patients on "low doses" of immunosuppression, which includes treatment with corticosteroids at ≥20 mg/day of prednisone daily, 6-mercaptopurine at 1.5 mg/kg/day or less, and azathioprine at 3 mg/kg/day or less. Recent data suggests that zoster vaccine may even be appropriate for patients on anti-TNF therapy, although this has not been recommended in guidelines as yet [2–6].

IBD patients planning for travel abroad should seek advice regarding travel vaccinations. Most travel vaccinations

are inactivated. However, yellow fever and oral typhoid are live attenuated and are contraindicated in immunocompromised patients [2–6].

Consideration should be given to offering human papillomavirus (HPV) vaccines to female as well as male IBD patients younger than 26 years, to protect against cervical and anal cancer. Additionally, those that received HBV vaccinations but remain HBV surface antigen negative should be offered a booster shot [2–6].

Family Members Receiving Vaccinations

Household contacts and other close contacts of immunocompromised patients may receive all age-appropriate vaccines except smallpox vaccine. They should also receive annual injectable (non-live) influenza vaccination. Family members who develop a rash after varicella or zoster vaccination should avoid direct contact with the immunocompromised patients until the rash resolves. All members of the household should wash their hands after changing the diaper of an infant vaccinated against rotavirus to minimize the risk of transmission [2–6].

Suggested Approaches

At the initial IBD consultation:

- Obtain a vaccination history.
- Screen for risk factors for vaccine-preventable illnesses, including occupational and travel risk.
- Offer influenza and pneumococcal vaccines and others as appropriate.
- Assess for protective titers against MMR, HBV, and varicella if immune status is unclear.

At subsequent visits:

- Reinforce the importance of up-to-date vaccinations.
- Offer annual influenza vaccination.

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Chapter 19
Do I Really Need to Come for Blood Testing So Often? Appropriate Monitoring of Therapy and Disease by Laboratory Testing

Laura E. Raffals

Suggested Response to the Patient

We are fortunate to have many effective treatments for inflammatory bowel disease (IBD). Most of our treatments work by modulating or suppressing the immune system, which is overactive in patients with IBD. While our treatments can often induce a remission and maintain a remission, they can also be associated with side effects. Close monitoring of our patients on these medications allows us to prevent complications of treatment. Mesalamine drugs, often used to treat ulcerative colitis, can rarely be associated with damage to the kidneys. Due to this rare, but potentially serious side effect, all patients taking this class of drug should have their kidney function tested every 6–12 months. Immunomodulators, such as azathioprine or 6-mercaptopurine, can cause a drop in one's blood counts and an increase in liver enzymes. As a patient begins these medications, frequent monitoring of blood counts and liver enzymes is needed. Once a stable dose is established, blood tests are often monitored every few

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months indefinitely. Likewise, patients on methotrexate also require frequent blood work to monitor for drops in blood counts or signs of liver inflammation. Patients on biologic therapies (such as infliximab, adalimumab, golimumab, certolizumab, natalizumab, and vedolizumab) also require routine blood work, although typically only every 6–12 months. For several biologic therapies and immunomodulators, we are able to monitor drug levels which allow us to optimize an individual's treatment or assess for intolerance to a given drug. Routine blood work helps monitor tolerance of therapy and also can provide clues to a patient's disease state. Although frequent blood tests may seem inconvenient or uncomfortable, it is important to remember that proactive care is much more effective than reactive care, particularly for our patients with IBD.

Brief Review of the Literature

There is little literature to support or guide routine blood testing for patients with inflammatory bowel disease. However, most of the medical therapies used for the treatment of IBD are associated with potential side effects which can be reflected in routine blood tests. For example, interstitial nephritis is a rare but serious side effect associated with mesalamine treatment [1]. There are no published guidelines on monitoring of kidney function in patients treated with mesalamine, but generally kidney function (serum creatinine) should be performed prior to starting treatment and every 6–12 months thereafter. Immunomodulators, azathioprine and 6-mercaptopurine, can be associated with bone marrow suppression, often manifested as leukopenia and elevation of liver enzymes. The leukopenia is often a result of elevated 6-TGN levels, and elevation in the metabolite 6-MMPR is associated with a rise in liver enzymes. Complete blood counts should be monitored closely after initiation of treatment and every 2–3 months indefinitely. Liver enzymes

are also commonly monitored after initiation of treatment and every 3–6 months indefinitely. Methotrexate is also associated with myelosuppression and hepatotoxicity. Patients receiving methotrexate should have close monitoring of complete blood counts and liver enzymes. Blood work is commonly performed frequently upon initiation of treatment (every 1–2 weeks) and every 1–3 months thereafter.

There are no clear recommendations for frequency of blood testing in patients receiving biologic treatment with anti-TNF agents or anti-integrin treatments including natalizumab and vedolizumab. Patients on biologic agents might benefit from routine blood tests (comprehensive metabolic panel and complete blood count) every 6 months. Patients on natalizumab should also have a JC virus antibody screen every 6 months due to the increased risk of progressive multifocal leukoencephalopathy (PML) which is associated with the JC virus. This does not appear to be necessary for patients on vedolizumab.

Recent studies in the IBD field have also highlighted the opportunity of therapeutic drug monitoring (TDM) in patients treated with azathioprine, 6-mercaptopurine, or anti-TNF agents (adalimumab and infliximab). Azathioprine or 6-mercaptopurine metabolite levels (6-TGN and 6-MMPR) can be measured in patients with inadequate response to treatment, allowing for adjustment of dosing [2]. In patients with an elevation of liver enzymes, metabolite levels can identify whether a patient metabolizes the drug in an unfavorable manner resulting in elevation of the 6-MMPR metabolite, often in the setting of subtherapeutic 6-TGN levels (<235 pmol/8×10^8 RBC). Likewise, for patients receiving infliximab or adalimumab, drug levels and levels of antibodies to drug allow a practitioner to determine if a patient's primary or secondary failure to respond to treatment is a result of underdosing of treatment or the development of antibodies to drug [3]. This information helps guide optimization of treatment or switching of therapeutic agent when appropriate.

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Chapter 20
"Do I Really Have to Have *Another* Colonoscopy or *Another* CT Scan?": Appropriate Disease Monitoring of Newly Diagnosed and Established Inflammatory Bowel Disease

Karen A. Chachu and Gary R. Lichtenstein

Suggested Response to the Patient

The symptoms that are associated with IBD such as diarrhea and abdominal pain can also be seen in other conditions such as bowel infections and diseases of other abdominal organs. Since the symptoms of many disease states or intestinal conditions are similar, it is important to identify what the exact problem is since your doctor will choose different treatments for each condition. For example, a bacterial infection would be treated with antibiotics, while an IBD flare might be treated with steroids. However, it would not be a good idea to treat an infection with steroids, having assumed that it was an IBD flare. In other situations, symptoms may be related to irritable bowel syndrome (IBS), and this is also important to distinguish from IBD.

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Brief Review of Literature

Patient's Symptoms

The principal question to be answered is whether the patients' symptoms are related to inflammation from IBD, infections, strictures leading to bowel obstruction, irritable bowel syndrome or related to a condition of another abdominal organ. There is no single gold standard test that provides all the information that is needed for clinical decision making about a patient's symptoms. Most of the time, a combination of tests is needed.

Options

The options for testing include laboratory testing, radiographic imaging, and endoscopy.

Laboratory Tests

Laboratory tests that are of value in helping to determine the cause of a patient's abdominal pain are complete blood count (CBC), fecal calprotectin (FCP), C-reactive protein (CRP), and stool studies, such as stool cultures, stool for ova and parasite examination, and especially stool for *Clostridium difficile* toxins A and B.

A complete blood count (CBC) can be used to evaluate the patient's overall health and detect a wide variety of disorders, including anemia, infection, and leukemia. On evaluation of the CBC, an acute or progressive decline in hemoglobin, even in the absence of overt bleeding, would suggest ongoing blood loss which would be concerning for inflammation. In addition, an elevated white blood cell (WBC) count, would be more concerning for active infection (possibly due to bowel inflammation or even an abscess) and prompt further evaluation. An elevated platelet count or thrombocytosis can suggest either infection or inflammation; however, it is not

specific for these and can just be elevated in the presence of iron deficiency anemia. It is worth noting that the WBC can also be altered by treatments for IBD. For example, leukocytosis can occur with the use of steroids, and leukopenia can occur with immunosuppressants such as azathioprine and 6-mercaptopurine.

FCP has been extensively studied in the evaluation and monitoring of IBD. FCP levels are higher in patients with definite IBD compared to non-IBD controls, and in addition, elevated FCP is positively related to clinical disease activity and endoscopic grade of inflammation with high sensitivity and specificity [1–5]. FCP can also be used as a predictor of relapse [6] with a rise in FCP levels prior to the onset of symptoms. More severe disease phenotypes (those that have a worse future outcome) like stricturing disease were associated with even higher levels of FCP.

Many studies show that CRP is also associated with both clinical and endoscopic disease activity [6, 7]. However, CRP is not consistently elevated in all individuals with active IBD. Therefore, it is important to establish at the outset whether an individual is prone to demonstrating elevations in CRP in the setting of active disease; this will then determine it will be worthwhile to follow CRP as a measure of disease activity in a specific patient. Additionally, CRP is not specific for IBD and may be elevated in other inflammatory conditions.

Radiologic Imaging

Radiologic imaging remains an important tool in the monitoring of IBD. Cross-sectional imaging is a discipline of radiology that encompasses the use of a number of advanced imaging techniques that feature in common the ability to image the body in cross section. This discipline typically focuses on the diagnosis and characterization of abnormalities of the chest, abdomen, and pelvis. The scope of the discipline is broad and ranges from the assessment of emergency conditions and trauma to the detection and follow-up of malignancies.

Primary imaging modalities include computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound. The use of cross-sectional imaging, especially computed tomography (CT) studies such as CT of the abdomen and pelvis, has dramatically increased in general and specifically for IBD-related diagnoses [8].

The use of CT is widespread, and it has the advantage that CT studies can be obtained in a rapid fashion, allowing them to be used to quickly evaluate sick patients, especially in emergency departments. Reliable information can be obtained about abscesses, intestinal obstruction, intestinal perforation, and any other abdominal pathology that may explain patients' symptoms. However, concerns have emerged about the long-term consequences of exposure to repeated amounts of ionizing radiation and possible contribution to a risk of malignancy [9, 10].

Magnetic resonance imaging (MRI) of the pelvis is key in the evaluation of patients with known or suspected fistulizing Crohn's disease (CD), as well as abscesses in the pelvis and perineum as an adjunct to an examination under anesthesia (EUA). An EUA consists of visual inspection, palpation, and the passage of metal probes into fistula tracks under general anesthesia performed by an experienced surgeon. In addition, in patients with primary sclerosing cholangitis (PSC), magnetic resonance cholangiopancreatography (MRCP) helps evaluate and guide the management of biliary strictures.

Imaging with CT enterography or MR enterography is overall safe and useful. These cross-sectional imaging modalities complement laboratory testing and endoscopy in the initial evaluation, monitoring, and preoperative evaluation of patients with IBD [11]. Both tests allow easier determination of the extent of disease, especially small-bowel Crohn's disease at the time of initial diagnosis, as well as determining the response to treatment with no significant differences in diagnostic accuracy between the two [12]. The advantage of MR enterography is that patients are not exposed to ionizing radiation; however, CT enterography is more commonly available.

Factors that may limit the use of CT in some patients include allergies to contrast reagents, concerns that preexisting chronic kidney disease may be worsened by intravenous contrast administration, and concerns about the cumulative dose of radiation received. Claustrophobia, prior metallic implants, and the increased risk of nephrogenic systemic fibrosis related to gadolinium administration in patients with chronic kidney disease may also limit the use of MRI.

In the era of CT and MR enterography, the use of small-bowel follow-through (SBFT) x-rays has declined, likely associated with a decline in the number of radiologists in community practice able to expertly perform and interpret SBFT. However, in geographical regions where expertise remains, SBFT remains an option in the mucosal evaluation of suspected or known small-bowel CD. It provides useful information about small-bowel luminal disease, strictures, and motility [13]. However, SBFT is limited in its ability to detect extramural complications, with the exception of intestinal fistulae.

Endoscopy

The gold standard for the initial diagnosis of both ulcerative colitis (UC) and CD remains confirmation of the diagnosis with tissue pathology of tissues obtained in areas of the mucosa that are endoscopically abnormal. Once the diagnosis has been made, mucosal healing is increasingly accepted as an important endpoint for management of patients with IBD and is associated with sustained clinical remission [14, 15], prevention of complications, and reduced rates of surgery [16–18]. There are a number of scoring systems that integrate endoscopic findings into the assessment of patients including the Mayo score [19] and the Simple Endoscopic Score for Crohn's Disease (SES-CD) [20]. These are mostly used in clinical trials and less often in routine clinical practice. However, these scoring systems reinforce the importance of endoscopy in evaluating symptoms, such as abdominal pain

and diarrhea where the etiology is unclear, and determining the appropriate treatment response.

Video capsule endoscopy (VCE) is another modality for initial diagnosis and monitoring of CD. While it may have more similarities to radiographic imaging, it is well within the armamentarium of many gastroenterology practices. VCE is sensitive for the detection of small-bowel CD at both the early and late stages of IBD [21, 22], and especially in the initial diagnosis of CD, it can provide target locations to acquire tissue via deep enteroscopy to confirm a diagnosis of small-bowel CD. It is also an alternate strategy for evaluating the small bowel instead of using CT or MR enterography. In approximately 1 % of patients who have a capsule endoscopy performed, the capsule can become lodged above a stricture or an area of narrowing in the bowel. Individuals who have Crohn's disease or have had abdominal surgery in the past are at increased risk for this complication. If an obstruction or stricture prevents passage of the capsule, endoscopic retrieval or surgery may be required for removal. An abdominal x-ray may be ordered in the weeks after the procedure if the physician is not able to determine that the capsule passed into the large intestine during the course of the study.

The Patency® capsule is a new non-endoscopic dissolvable capsule which has as an objective of checking the patency of digestive tract in a noninvasive manner. The available clinical trials have demonstrated that the Patency® capsule is a good tool for assessment of the functional patency of the small bowel, and it allows identification of those patients who can safely undergo a capsule endoscopy, despite clinical and radiographic evidence of small-bowel obstruction. When using cross-sectional imaging with combined use of a patency capsule, VCE can likely be safely used in selected patients with strictures or who have undergone prior surgical resection [23].

Endoscopic procedures can be therapeutic as well as diagnostic in the evaluation and treatment of IBD-related strictures. Endoscopic balloon dilation can be safely used to treat strictures to allow adequate evaluation of mucosa, to relieve symptoms, and to avoid the need for surgical resection of the affected area.

A colonoscopy is the most effective test to examine the colon and the terminal ileum. Colonoscopy is the primary modality used for the detection of colorectal cancer (CRC), i.e., screening. Screening colonoscopy is recommended in individuals in the general population over age 50 and those with concerning family histories of colon cancer as recommended at an earlier age [24]. In addition, specifically for patients with ulcerative colitis with left-sided colitis or more extensive disease, colonic Crohn's disease, and primary sclerosing cholangitis who are at increased risk of CRC, it may be necessary to begin CRC screening at an earlier age depending on the duration of their IBD [25, 26]. The risk of colorectal cancer increases over time in ulcerative colitis, from 2 % at 10 years to 8 % at 20 years and 18 % at 30 years [27]. Meta-analysis has shown that the risk of CRC is similar for colonic Crohn's disease and UC [28]. National guidelines recommend screening colonoscopy after 8 years of disease (either UC or Crohn's colitis) and surveillance colonoscopy every 1–2 years thereafter [26].

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Chapter 21
"What Can I Do to Avoid Getting Too Much Radiation and What Imaging Test Is Right for Me?" Selecting the Best Imaging Test for the Right Patient and the Right Reason

William J. Tremaine

Suggested Response to the Patient

The best imaging test for you depends on the specific medical questions that need to be answered and if you have other medical conditions that limit the choices. Limiting conditions include allergy to intravenous contrast, kidney disease, pregnancy, or a pacemaker or other metal implant. The best test is the one with the highest likelihood of providing correct information with a low risk of harm. In some situations, the best test involves radiation.

Brief Review of the Literature

Computed tomography enterography (CTE) and magnetic resonance enterography (MRE) both use a large volume of oral contrast to provide superb visualization of the small bowel to assess for the presence and severity of Crohn's disease. A head-to-head comparison showed similar accuracy for CTE and MRE in detecting small bowel inflammation [1].

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Computed tomography (CT) and magnetic resonance imaging (MRI) without enterography demonstrate complications of Crohn's disease and ulcerative colitis including bowel obstruction, megacolon, abscesses, and some fistulas. Ultrasound of the small intestine is an alternative to CT and MRI for evaluating small intestinal Crohn's disease that requires a high level of expertise. Barium studies, either orally or as a barium enema, are sometimes the best method for confirming partial small bowel obstruction. Each of these imaging techniques has advantages and shortcomings.

CTE is less expensive, more widely available, less claustrophobic, and takes less time in the machine for the patient than MRE. The image quality is better with CTE than MRE, but the sensitivity and specificity for Crohn's disease is similar [2]. CT is inferior to MR for demonstrating perianal fistulas and abscesses due to Crohn's disease. The main drawback to CT studies is the radiation exposure. The risk of a single CT scan is small: the amount of radiation is about 1–14 mSv (millisieverts) which is similar to the annual radiation exposure of most Americans from naturally occurring radon and cosmic radiation [3]. Although the risk of a single CT scan is low, there is epidemiologic evidence from atomic bomb survivors and radiation workers in the nuclear industry that exposures of 30–90 mSv increase the risk of cancer, particularly in children [4]. Having three or more CT scans could place a patient in that range of exposure. The risk is lower in people age 35 and older [4].

MR enterography has an 80 % sensitivity and a 90 % specificity for detection of disease severity in Crohn's disease [5]. MRI is similar to colonoscopy for assessing disease activity in Crohn's colitis [6]. The main drawback to MRE is the expense—about 1.5–5 times the cost of CTE. Some patients find the body MR scanner to be too claustrophobic to tolerate. Glucagon, given intravenously to reduce small bowel contractions and motion artifact, can cause nausea and vomiting for hours after the procedure. Both CTE and MRE can cause renal failure due to the contrast agents. Gadolinium, the contrast used for MRE, is contraindicated during the first trimester of pregnancy. MRE is contraindicated in patients with implanted metal such as a pacemaker [2]. MRE is a better

choice than CT for most patients who require repeated exams for IBD.

Ultrasound of the abdomen for assessment of IBD is more popular in Europe and Canada than in The United States and it is endorsed by Europeans as a suitable test for diagnosis and follow-up of Crohn's disease [5]. Ultrasound is an attractive option for avoiding radiation and reducing costs. However, expertise is limited among North American radiologists and gastroenterologists for performing and interpreting ultrasound in IBD [7].

Barium small intestinal x-rays are a good choice for patients with complicated anatomy due to previous surgery and for patients in whom intravenous contrast is contraindicated [2].

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Chapter 22
"Will this affect my or my partner's fertility?": Fertility and Women's Issues in Inflammatory Bowel Disease

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Suggested Response to the Patient

Fertility is an important issue for both women and men. Studies thus far have not revealed a great difference in the capacity to conceive or induce conception in a patient with IBD when compared to the non-IBD patient. In general, IBD patients have normal fertility except in a certain subgroup of populations: women after surgical resection with ileal pouch-anal anastomosis (IPAA), men on sulfasalazine, and the use methotrexate (MTX). Subfertility or the inability to conceive has been seen in patients with active CD.

IBD medications have not been shown to affect fertility in women, but MTX around the time of conception can lead to recurrent miscarriage and significant birth defects.

Sulfasalazine results in reversible male subfertility by causing low concentration of sperm or abnormal sperm. Methotrexate's effect on male fertility is controversial with limited studies reporting reversible changes in the sperm.

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Brief Review of the Literature

IBD affects patients in their peak reproductive years, and pregnancy counseling should ideally occur before conception. Fertility is the ability to conceive while Infertility or subfertility is typically defined as the failure to conceive after 1 year of unprotected, regular sexual intercourse. The general consensus is that IBD patients have normal fertility except for a subset of patients. Interpretation of the studies on fertility and IBD is difficult due to the fact that many IBD patients choose not to conceive and this "voluntary childlessness" complicates the data.

CD and UC

Older studies have estimated infertility rates between 32 and 42 % in women with CD but more recent reviews indicated infertility rates closer to 5 and 14 % which is similar to the general population [1–4]. When looking at population and referral center-based studies, the majority of studies have found involuntary infertility in IBD patients to be similar to the general population [5]. It is felt that fertility in a CD patient in remission is equivalent to a healthy woman but may be decreased with active inflammation with subfertility seen in CD patients with active disease [6, 7]. Overall, most studies have not seen a decrease in fertility in UC women when compared to the general population except with surgical resection and ileal pouch-anal anastomosis (IPAA) [5, 8, 9]. In quiescent disease, male and female fertility is not significantly affected in the nonoperated IBD patient [10].

IPAA

IPAA can increase the risk of subfertility in women by approximately threefold [11]. When defining infertility as the inability to achieve pregnancy within 12 months, the rates increase from 15 to 48 % in women post IPAA for UC [9, 11–14].

It is important to remember that the IPAA may result in a mechanical infertility (tubal factor) in these patients and there is a reduced probability of conception rather than a true infertility [13]. More recently, pregnancy rates have been shown to be significantly higher after laparoscopic IPAA and that in vitro pregnancy outcomes and success rates after IPAA are similar to the general population [12].

Fertility and IBD Medications

IBD medications do not negatively impact fertility except for sulfasalazine and MTX. Sulfasalazine in men can induce oligospermia, decreased sperm motility, and abnormal morphology which cause a reversible infertility [15–17]. Sperm quality is restored within 2 months or two full cycles of spermatogenesis after drug cessation or switching to another 5-ASA agent [7, 10].

Methotrexate has been reported to cause reversible oligospermia and has known teratogenic properties [18]. Despite the fact that no increase in congenital abnormalities in children conceived by fathers on MTX has been reported, it is still recommended to wait at least 3–6 months prior to conception. MTX does not affect a female's ability to achieve pregnancy; however, due to adverse fetal effects and early pregnancy loss, discontinuation is recommended 6 months prior to conception.

Infliximab therapy in men may affect sperm but further information is needed on whether this translates into impaired male fertility [19].

Fertility in the IBD Patient

In a systematic review of the literature, women and men with CD had a reduction in fertility compared to controls, and the higher infertility observed in nonsurgical IBD patients was due to voluntary childlessness (patient's choice typically driven by fear) [5]. It has been seen that the IBD-related

reproductive risks are often overestimated by women due to misperceptions. Education prior to conception and patient awareness of disease with accurate knowledge on medication risks are essential to optimal management of the IBD patient.

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Chapter 23
What Do I Do with My Medications If I Become Pregnant? Safety of IBD Medications During Pregnancy

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Suggested Response to the Patient

One of the most important things a mother can do to help decrease risk to her baby is to have her inflammatory bowel disease (IBD) under good control during the pregnancy. If IBD is uncontrolled, nutrition and growth of the baby may be suboptimal. Babies born to mothers with poorly controlled IBD may have low birth weight and may be vulnerable to infections and other health problems after birth. Additionally, some studies suggest that there could be miscarriages or premature births associated with active IBD. For many IBD patients, more harm can be done to the baby by stopping all IBD medications and causing a flare-up, than continuing most of the IBD medications. You and your doctor should evaluate each and every medication you take and determine the ones that you need to continue, by weighing the benefit of the medication in controlling your IBD against the risks

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associated with the medication. Before the discussion, you should also look up each of your medications in Table 23.1 at the end of this chapter and see how the US Food and Drug Administration (FDA) rates them in terms of their pregnancy risk. Here are some general guidelines about IBD medications with regard to pregnancy.

5-Aminosalicylates (5-ASAs)

Most medications in this category are safe to take during pregnancy, even though there are few case reports of babies with kidney insufficiency born to mothers taking 5-ASA-based drugs during pregnancy. Some medications may be safer than others. For example, certain 5-ASA pills are coated with a chemical called DBP (dibutyl phthalate), which has been associated with malformations of the skeleton in animal testing. Others can interfere with folic acid which is essential for nervous system development and its metabolism. Patients on these types of 5-ASAs should consider switching to a different 5-ASA medication. Enemas and suppositories of 5-ASAs are often given for ulcerative colitis (UC), but there is little to no information on the outcomes in pregnant patients. There are theoretical concerns that anything placed into the rectum may induce uterine contractions prematurely.

Purine Analogues (Thiopurines)

Case reports of congenital anomalies do exist, and animal studies suggest increased risks of cleft palate, skeletal, and urogenital anomalies. However, most studies in humans have not found a difference in congenital birth defects, tumors, or infections in pregnant women on these medications.

Methotrexate

This should not be used in pregnancy and should be stopped several months before conception.

Corticosteroids

Steroids may cause an increased risk of cleft lip and cleft palate in the baby if used in the first trimester of pregnancy and therefore should be avoided, if possible, early in pregnancy. If needed, steroids can be used in the second and third trimester of pregnancy and may also help with lung development in a premature baby. Some steroids have disadvantages in pregnancy. For example, dexamethasone can pass into the fetus without being inactivated by the placenta and can theoretically cause more adverse effects. Prednisolone can be more efficiently metabolized by the placenta than other steroids and may be preferred.

Biologic Medications

Most medications in this category are too large to cross into the baby through the placenta. However, the placenta is thought to actively concentrate and transport significant amounts of medications in this category (except one) into the baby's circulation, especially in the last trimester of pregnancy. If your IBD is severe, you should strongly consider continuing on the biologic medication that controls your disease. If you remain on a biologic medication (other than certolizumab) throughout your pregnancy, you need to inform your pediatrician before the delivery, so that live vaccines are not given to your baby for a period of approximately 6 months after birth. Alternatively, if you have low risk factors for a flare, biologic medications can be held during the last 10 weeks of pregnancy to limit your baby's exposure to the drug. After delivery, the biologic medication can then be restarted.

Calcineurin Inhibitors

These types of medications are sometimes used to induce remission in IBD when other therapies fail. Solid organ transplant patients usually take one of these medications to prevent the rejection of transplanted organs. A study of pregnant transplant patients taking cyclosporine showed the incidence of congenital malformations to be similar to that of the general population.

Table 23.1 Use of medications in inflammatory bowel disease in pregnancy

Medication	FDA category	Summarized data	Recommendation
5-ASA derivative			
Dibutyl phthalate (DBP)-coated mesalamine (e.g., Asacol HD®)	C	• Cleft palate, skeletal defects, and adverse effects related to androgen-dependent development of the male reproductive organs were seen in rats [1] • Urine concentrations of DBP metabolite is 200× higher in women [2] • No human studies with increased birth defects exist	• Likely low risk, may consider alternative 5-ASA
Non-DBP coated 5-ASAs and balsalazide (e.g., Pentasa®, Delzicol®, Lialda®, Apriso®) (e.g., Giazo®, Colazal®)	B	• Meta-analysis of seven studies (2,200 pregnant women with IBD); 642 received 5-ASA drugs and 1,158 received no medications → no significant difference between groups [3] • Increased risk of adverse outcomes in women with ulcerative colitis who were not on 5-ASA in the 2nd/3rd trimesters [4] • Case report of interstitial nephritis and renal insufficiency in infant with prenatal exposure linked to drug [5]	• Low risk, continue medication
Olsalazine (Dipentum®)	C	• Reduced fetal weight, retarded ossification, and immaturity of the fetal visceral organs in rats • No human data	• Likely low risk, may consider alternative 5-ASA
Sulfasalazine (e.g., Azulfidine®, Sulfazine®)	B	• No increased risk of fetal congenital malformations in multiple studies [6, 7] • One study shows a trend toward increased congenital malformation risk with exposure during conception and first trimester [4] • Initial concerns about kernicterus have not been validated in later studies	• Low risk, consider stopping 3 months prior to conception (for men and women) and during first trimester; or consider switching to alternate 5-ASA • Must supplement with folic acid (1 mg BID)

Enema and suppository preparations of 5-ASAs (e.g., Canasa®, Rowasa®)	B	• Drug FDA rating is based on mesalamine component only	• Low risk; no data to suggest increased risk of preterm labor or miscarriage, however general obstetric concerns about rectal stimulation causing uterine contractions may outweigh benefits, especially in third trimester or in select cases
Thiopurines			
Azathioprine (AZA) and 6-mercaptopurine (6MP) (e.g., Azasan®, Imuran®) (e.g., Purinethol®, Purixan®)	D	• Increased teratogenicity with cleft lip, skeletal, and urogenital anomalies in animal models [8] • Some guidelines suggest AZA/6MP to be safe and well tolerated in pregnancy [9] • No increased risk of congenital malformation, spontaneous abortion, neoplasia, or risk of infection in pregnant IBD patients or with paternal exposure during conception in IBD or in pregnant renal transplant recipients in several studies [8, 10–17] • Increased risk of preterm labor and increased risk of low birth weight in some studies [10, 11, 18] • Increased risk of ventricular/atrial septal defects in one study [11]; however confounding factor of IBD activity • Nonsignificant increased risk of spontaneous abortions; higher rate of elective terminations of pregnancy in the exposed group with paternal exposure during conception [17] • Anemia in some infants born to mothers on purine analogues reported in a small study [19]	• Probably low-risk; likely safe to continue medication if patient has been stable on drug • Possible adverse effects of bone marrow suppression and pancreatitis need to be considered when initiating medication during pregnancy • May consider checking infant for anemia after birth

(continued)

Medication	FDA category	Summarized data	Recommendation
Corticosteroids			
Prednisone, prednisolone, dexamethasone	C*	• Increased risk of oral cleft in newborns, with nonsignificant risk of other major malformations in some studies [20–22] • No increased risk of oral cleft in one study [23] • Increased risk of premature rupture of membranes; increased risk adrenal insufficiency in pregnant organ transplant recipients and rarely in newborn [24] • Reduced head circumference, birth length or birth weight in a systemic review of studies in which pregnant women received dexamethasone or betamethasone [25] • Dexamethasone and betamethasone (i.e., fluorinated steroids) pass through the placenta without inactivation; risk of increased exposure [26] • Non-fluorinated steroids (such as prednisone, prednisolone, methylprednisolone, and hydrocortisone) are better suited to treat IBD as they are metabolized by the placenta and have less effects on the fetus until 36 weeks, when the fetal liver can resynthesize the original steroid from the placental metabolites	• Probably avoid in the first trimester due to increased but small risk of orofacial clefts • Lower risk in second and third trimesters and may be used to acutely control IBD flare • Monitor for hypoadrenalism; rare but may occur in infants
Oral budesonide (e.g., Entocort®, Uceris®)	C	• Teratogenic and embryocidal in rabbits and rats with increases in fetal loss, low weight in fetus, and skeletal abnormalities • No maternal side effects or fetal congenital abnormalities in eight pregnant women with Crohn's disease on budesonide for 1–8 months [27]	• Likely low risk, may consider alternate medication

Calcineurin inhibitors			
Cyclosporine (CS) and tacrolimus (e.g., Neoral®, Gengraf®, Sandimmune®) (e.g., Prograf®)	C	• Embryo- and fetotoxic in animals exposed to 2–5 times the human dose. Reduced numbers of nephrons, renal hypertrophy, systemic hypertension and progressive renal insufficiency in rabbits, and increased ventricular septal defects in rats with CS • Unclear how much of drug crosses the placenta • Case report of tacrolimus used successfully as maintenance therapy for ulcerative colitis in pregnancy [28] • Case report of cyclosporine used successfully to treat a 27-week pregnant woman with fulminant, steroid-refractory ulcerative colitis [29] • No increase in risk of congenital malformations or prematurity in a meta-analysis of 15 studies of pregnant women taking CS for transplant/autoimmune disease [30] • Out of 116 patients on CS and other drugs for transplant → 16 fetal losses; 47 % premature deliveries with 85 % of patients with pregnancy complications, 27 % with neonatal complications, and seven congenital anomalies; results confounded with concomitant meds [31] • Congenital anomalies in transplant recipients receiving tacrolimus are comparable to the general population, but high rate of prematurity (57 %) and maternal and neonatal complications [32]	• May be suitable for use in acute colitis unresponsive to other therapies

(continued)

Medication	FDA category	Summarized data	Recommendation
Biologic agents			
Infliximab (IFX) (Remicade®)	B	• IFX (an IgG1 subclass molecule) and other biologics with an Fc portion can concentrate in the fetus by crossing the placenta at a high rate [33]; IgG transfer starts early as 13 weeks and increases linearly with the most transferred after 32 weeks and especially in the third trimester [34]; levels are high in newborn if drug is given in the last few weeks; drug is detectable in newborns up to 6 months after birth [33] • Pregnancy outcomes with IFX in women with rheumatoid arthritis and Crohn's disease are similar to the general population with regard to live births, miscarriages, and therapeutic terminations [35] • TREAT registry → no difference in congenital malformations, miscarriage, or neonatal complications in 36 women with Crohn's disease [36] • PIANO registry → no increase in risk of birth defects with exposure to biologic agents or in combination with AZA/6MP in IBD [16] • No increase in infection or developmental milestones in infants [16], but possible increased risk of newborn infection when given with AZA • Fatal case reported of disseminated BCG infection after vaccination of infant with in utero exposure to IFX [37]	• Low risk; continue drug • Consider holding IFX at about 30 weeks of gestation and restarting immediately after delivery if risk of flare is low, weighed against risk of infection in the newborn by continuing drug throughout pregnancy • Live vaccinations (e.g., BCG vaccines) are not recommended for the first 6 months of life to newborns whose mothers have received IFX throughout the pregnancy

Adalimumab (ADA) (Humira®)	B	• Animal models with ADA show no increased obstetric risks and no teratogenic effects [38] • Actively transported across placenta; detectable in newborns up to 6 months after birth [33] • No reports of congenital abnormalities in 155 pregnancies [39, 40] and in IBD pregnancies in the PIANO registry • No changes in growth status or rate of infection in IBD pregnancies [41] • No increased risks of miscarriage or congenital anomalies in rheumatoid arthritis patients exposed in the first trimester and beyond [42]	• Low risk; recommendations are the same as IFX
Certolizumab (CZ) (Cimzia®)	B	• Minimal placental transfer; minimal blood levels in newborns and cord blood [33] and drug levels are less compared to IFX and ADA • No increased risk of congenital abnormalities, growth status changes or increased rate of infection in 47 pregnancies in the PIANO IBD registry [16]	• Low risk; continue drug • Probably can continue throughout pregnancy • No change needs to be made to newborn immunization schedule, although data is limited
Golimumab (Simponi®)	B	• Adverse events not observed in animal reproductive studies; the drug was noted to cross the placenta reaching 50 % of the maternal levels in the fetus • No human data available	• Consider limiting exposure after 30 weeks of gestation • Live vaccinations are not recommended to newborns whose mothers have received the drug throughout the pregnancy

(continued)

Medication	FDA category	Summarized data	Recommendation
Natalizumab (Tysabri®)	C	• In monkeys, the drug at 2.3 times human dose causes anemia, low platelets, lower weight of spleen, liver, and thymus in the fetus • Thought to actively across the placenta • No increase in birth defect risk in exposed multiple sclerosis patients [43]; or in the natalizumab global safety database with 164 pregnancies [44] • In one observational study of 13 pregnancies with multiple sclerosis exposed during third trimester → mild to moderate hematologic abnormalities in 10 of 13 infants [45] • In another observational study of 35 pregnancies with multiple sclerosis exposed to drug → 28 healthy births, 1 with hexadactyly; 5 with early miscarriage; 1 with elective abortion [46]	• Likely low risk • Live vaccinations are not recommended for newborns whose mothers have received the drug throughout the pregnancy
Vedolizumab (Entyvio®)	B	• No adverse effects reported in animal models given 20 times the recommended human dose • Transported across placenta in a linear fashion as pregnancy progresses, mostly transferred during the third trimester, with adverse effects probably greater during second and third trimester • No human data available, however a registry of pregnancy outcomes has been established	• Consider limiting exposure after 30 weeks of gestation • Live vaccinations are not recommended for newborns whose mothers have received the drug throughout the pregnancy

Other			
Methotrexate (MTX) (e.g., Otrexup®, Rheumatrex®, Trexall®)	X	• Causes fetal death/congenital abnormalities • British registry showed higher rate of spontaneous abortion among patients exposed to anti-TNF with MTX/leflunomide at the time of conception [47] • Small study reviewed paternal exposure to MTX at time of conception or up to 3 months before conception → no major adverse effect to baby [48]	• Contraindicated during pregnancy • Should be stopped in women 6 months prior to conception and in men 3 months prior to conception, based on limited data
Ciprofloxacin (Cipro®)	C	• Causes arthropathy in children • Study of 200 pregnant women exposed to ciprofloxacin showed low risk of birth defects and clinically significant musculoskeletal dysfunction [49]	Avoid in pregnancy since alternate drugs with lower risks exist
Metronidazole (e.g., Flagyl®, Metro®)	B	• Teratogenic in animal studies and mutagenic in vitro • Increased rate of oral cleft malformations in one large case-control study with exposure in 2nd and 3rd months of pregnancy [50]; although the absolute risk was small and may not be clinically significant • No increase in preterm birth, low birth weight, or congenital malformations in a large retrospective study with use of drug at any time during pregnancy [51] • Multiple studies in bacterial vaginosis treatment have not shown any increased in congenital anomalies or other adverse fetal outcomes following metronidazole exposure during pregnancy [52] • Center for Disease Control does not restrict the use for bacterial vaginosis in the first trimester for a duration of 7 days [53]	Consider avoiding during the first trimester; however if needed, short term use (up to 7 days) probably safe in all trimesters

(continued)

Medication	FDA category	Summarized data	Recommendation
Bismuth subsalicylate (Pepto-Bismol®)	C* (first and second trimester) D* in third trimester	• Bismuth and salicylates cross the placenta • Fetotoxic effects of bismuth; exposure in late pregnancy may increase risk of pulmonary hypertension [54, 55] • Salicylates have reduced mean birth weight in limited animal and human studies, may cause prolongation of labor, increase in blood loss at delivery [56]	• Avoid in pregnancy since alternate drugs with lower risk exist
Diphenoxylate with atropine (Lomotil®)	C	• Teratogenic in animal studies • 187 cases of first-trimester exposure showed no evidence of developmental toxicity [57]	• Likely low risk based on limited data
Loperamide (e.g., Imodium®, Diamode®)	B	• 108 pregnancies with first trimester exposure showed five unexpected birth defects of which three were cardiovascular in nature [57] • No increased risk of congenital malformations, possibly lower birth weight in 105 pregnancies exposed to drug [58]	• Likely low risk; can be used with discretion • Ideally avoid during first trimester

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Chapter 24
Is It Safe for Me to Breastfeed While on My IBD Medications? Safety of Lactation and IBD Medications

Kimberly A. Harris and Sara Horst

Suggested Response to the Patient

Most medications used to treat inflammatory bowel diseases (IBDs) including ulcerative colitis and Crohn's disease are safe to continue while breastfeeding. Medications including 5-aminosalicylic acids (5-ASAs), thiopurines, and anti-tumor necrosis factor medications are excreted in minimal concentrations in breast milk and cause little to no known adverse side effects in the breastfed infant. An important exception to this rule is methotrexate, which is pregnancy category X and

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should not be used in pregnant or breastfeeding mothers. Also, several antibiotics sometimes used in the treatment of IBD, including metronidazole and ciprofloxacin, can be excreted into the breast milk, and long-term use should be avoided if possible. Additionally, some experts recommend that lactating mothers withhold breastfeeding for 4 h after taking a dose of a thiopurine agent (azathioprine or 6-mercaptopurine) to help decrease infant exposure to this medication, although long-term studies on this medication have failed to show any increased risk of infections in breastfed infants of mothers taking azathioprine. Anti-tumor necrosis factor agents (infliximab, adalimumab, and certolizumab) have little to no excretion in breast milk and are likely compatible with breastfeeding. Finally, although there is little data available on the safety of breastfeeding with anti-integrin antibody agents (natalizumab, vedolizumab), they may be detected in breast milk and caution should be used when administering to nursing women.

Brief Review of the Literature

5-Aminosalicylate Acid Medications

5-Aminosalicylate (5-ASA) medications and their metabolites pass into breast milk at relatively low concentrations (30–50 % of maternal plasma concentrations) and are generally considered safe in breastfeeding moms [1]. There are rare reports of diarrhea in breastfed infants of mothers taking 5-ASA medications. Therefore, the infant should be monitored for such symptoms with consideration of discontinuing the medication if these symptoms persist in the infant [2, 3].

Antibiotics

Metronidazole is excreted in breast milk and is generally not recommended for long-term use in breastfeeding mothers. If a single dose is given, the American Academy of Pediatrics recommends waiting 12–24 h before breastfeeding [4].

Very small quantities of ciprofloxacin are excreted into breast milk; however, given the concern for potential arthropathies in children, the Summary of Product Characteristics recommends that mothers wait 48 h before breastfeeding after a single dose [5].

Given the limited evidence to support antibiotic use for the treatment of IBD and the need for an extended course of therapy if used, antibiotics should generally be avoided in breastfeeding mothers [6]. Short courses of ciprofloxacin and/or metronidazole can be considered for the treatment of pouchitis, or alternatively, a different antibiotic, such as amoxicillin/clavulanic acid (pregnancy category B), can be considered.

Glucocorticoids

Glucocorticoids are considered safe in breastfeeding due to low levels of excretion in breast milk [7]. Safety of budesonide in lactation is not known.

Immunomodulators

Methotrexate is pregnancy category X. It is excreted in breast milk and is contraindicated in breastfeeding mothers [4]. Possible adverse effects to the infant include immunosuppression, neutropenia, and possible link to carcinogenesis [8].

Thiopurine agents including azathioprine and 6-mercaptopurine have been detected in the breast milk of lactating mothers at negligible levels ranging from 2 to 50 μg/L with peak concentrations within 3–4 h after taking a dose [9]. These levels are far less than the infant's maximum risk-free ingestion amount of <0.008 mg/kg/day, and no studies have found detectable levels of thiopurines in the serum of breastfed infants [10]. One case-control study investigating long-term effects did not reveal any increased risk of infections in breastfed infants of mothers taking azathioprine [11].

There are no strong contraindications to breastfeeding while on azathioprine or 6-mercaptopurine, but some experts recommend that lactating mothers could be advised to wait to breastfeed for at least 4 h after taking a dose.

Biologic Agents

Biologic agents available for treatment of inflammatory bowel disease include anti-tumor necrosis factor therapy (infliximab, adalimumab, golimumab, and certolizumab) and anti-integrin antibody therapy (natalizumab, vedolizumab). Infliximab and adalimumab are excreted into breast milk in very small amounts (100–200th of the mother's serum level) [12, 13]. Certolizumab pegol has no detectable transfer in breast milk [14]. Little human data is available for the anti-tumor necrosis factor medication golimumab; in animal models, detectable but minimal concentrations were detected in breast milk [15]. The largest current prospective study to date evaluating the safety of anti-tumor necrosis factor therapy during pregnancy is called the Pregnancy IBD and Neonatal Outcome (PIANO) study. Currently in abstract format, the study reports on 1,115 women and children who are being followed throughout pregnancy and for 4 years following delivery. To date, 72 % of the infants in this study were breastfed and there was no association with increased risk of infection in these infants [16]. The World Congress of Gastroenterology recommends that infliximab and certolizumab are compatible with breastfeeding, and the American Gastroenterological Association noted that infliximab and adalimumab are likely compatible with breastfeeding [6, 17]. There is little data available for the safety of breastfeeding with natalizumab. The prescribing information from the manufacturer notes that natalizumab has been detected in human breast milk and that the effects of this exposure on infants is unknown [18]. It is currently unknown whether vedolizumab is present in human milk, and the manufacturers recommend exercising caution when administering to nursing women [19].

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Chapter 25
My Fistulas Are Just Not Healing. What Are You Going to Do About It? Surgical Management of Perianal Crohn's Disease

Timothy Ridolfi and Mary F. Otterson

Suggested Response to the Patient

The management of fistulas largely depends on the extent of the fistula and the degree of inflammation and infection present. If a large infected fluid collection is present, this is usually drained in the operating room prior to any other intervention. Treatment with antibiotics is also common. At times, a drain called a seton is placed to keep the fluid collection from reforming. It is also important to assess both the internal and external opening of the fistula and the path of the tract between them in order to determine the best treatment option. This may be accomplished by an exam under anesthesia or other radiologic studies such as an MRI or an ultrasound study. The degree of inflammation from Crohn's disease present in the rectum and anus must also be assessed.

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If inflammation is present, medical therapy is utilized first with the hopes of improving the degree of inflammation and promoting spontaneous closure of the fistula.

If there is no rectal inflammation, a surgical option may be possible. If the tract between the internal and external opening is superficial, a fistulotomy, opening of the tract, may be performed. In the case of a more complicated fistula without rectal inflammation, it may be possible to close off the internal opening with a flap of healthy rectal tissue; this is commonly done to treat a rectovaginal fistula. In many cases, however, the fistula tracts are complex and multiple and long-term use of draining setons is the preferred method of treatment. Setons are usually well tolerated and keep painful, infected fluid collections from forming. In the most severe cases of perianal fistulas and infections secondary to Crohn's disease, a temporary or permanent ostomy, where the stool is passed out of the intestine and through the abdominal wall into a bag, is required.

Brief Review of the Literature

The management of anal fistulas is challenging and is based upon the patient's presentation considering the fistula's location and complexity, the presence or absence of rectal inflammation, and the severity of accompanying anal canal disease [1]. In general, a conservative surgical approach is adopted because a more aggressive attitude often results in outcomes that are worse than the disease itself. Proper evaluation for perianal fistulas includes physical examination, an examination under general anesthesia, and possible pelvic imaging including MRI, CT scan imaging, and/or endoscopic or endorectal ultrasound imaging [2]. These techniques help define the precise extension of the disease and are needed to rule out complications such as abscesses. Adequate diagnosis has been obtained in 100 % of cases when the evaluation included pelvic MRI and examination under anesthesia or when either of these techniques was combined to endorectal ultrasounds [3]. Once the anatomy of the fistula tract and the

presence or absence of rectal inflammation have been determined, appropriate therapy can be outlined.

Surgery will eventually be required in 20–80 % of Crohn's disease patients with perianal fistulas [4–7] and about 30 % of patients with complicated perianal Crohn's disease may eventually require a permanent stoma [8, 9]. Surgical therapy has to be tailored to each case, but the overall goal of surgery should be to cure the fistulas without damaging sphincter function. If inflammation is present, surgical therapy should be aimed at draining abscesses and placing non-cutting setons to control sepsis and prevent recurrent abscess formation. The seton does delay fistula healing and closure, but medical therapy, including immunomodulators, may be given while a seton is in place. One strategy is to place setons in patients with known fistulas who are about to start therapy with infliximab, specifically for the prevention of an abscess while on therapy [10]. Setons are well tolerated by most patients and they cause no long-term harm. Patients who have responded well to infliximab will generally have the seton removed, which can be done easily and painlessly in the physician's office. After removal of the seton, medical therapy should be continued.

In the absence of rectal inflammation, more surgical options exist. Low perianal fistulas in patients without rectal inflammation can be treated by fistulotomy, with reported healing rates of 80 % or more. Another option is to use a rectal advancement flaps to cover the internal opening of the fistula. This technique is commonly used in the treatment of rectovaginal fistulas. In two studies, initial healing rates with advancement flaps were 71–89 %, but with recurrence rates of 34–63 % during subsequent follow-up [11–13].

More recently described procedures for the management of fistulas in adults with Crohn's disease entail occlusion of the fistula tract with a fibrin sealant [14] or collagen plug [15]. Results with a fibrin sealant for fistulas related to Crohn's disease have been inconsistent partially because complex fistulas tend to be less responsive to treatment, but the largest series to date revealed that more than one-half of treated fistulas remained drainage-free after nearly two years of follow-up [14]. Similar to the fibrin sealant experience, some centers

[16] have reported high success rates (>80 %) in patients with fistula tracts treated by collagen plug occlusion while others [15] have encountered somewhat discouraging outcomes.

Patients with severe perianal Crohn's disease or complications may benefit from a diverting colostomy or ileostomy. Some are able to subsequently heal enough to have the ostomy reversed; however, the risk of the ostomy becoming permanent is significant. Less than one-quarter of individuals have intestinal continuity restored [17]. Diversion is especially useful for the treatment of refractory infectious complications (cellulitis, recurrent abscesses, destructive deep infections) but sometimes disappointingly ineffective at reducing the progression of the inflammatory and fibrotic aspects of the disease (fissures, fistulas, or strictures) [16]. Patients with minimal colitis can have a sigmoid (left lower quadrant) colostomy, whereas others will require an ileostomy (right lower quadrant). Patients who have complete resolution of their perianal Crohn's disease or manageable sequelae (skin tags, epithelialized chronic fistulas) can be considered for ostomy closure, but this is typically only a consideration after 6–12 months. The majority of patients who undergo successful closure of their stoma require a secondary procedure (e.g., rectal mucosal advancement flap) to achieve stoma closure. This type of patient should also be warned about the high likelihood of recurrent symptoms and the possible need for another diversion. Ultimately, an endoanal proctectomy with end ostomy is necessary in approximately 5 % of Crohn's disease patients solely to control perianal disease, especially if high, complex fistulas, deep ulcerations, colonic disease, or anal canal stenosis is present.

Perianal manifestations of Crohn's disease can be a frustrating and painful, with significant deleterious effects on the patient's self-image and quality of life. Like all Crohn's disease, treatment is primarily medical. Surgical intervention, although rarely curative, is useful for the assessment of the extent of disease and helping to manage complications. The goals of the surgeon should be to control sepsis, relieve discomfort, and help maintain good function so that patients with the disease can have a normal lifestyle and avoid long-term complications.

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Chapter 26
Why Do I Need to Have Surgery for My Crohn's Disease? Surgical Management of Crohn's Disease

Mary F. Otterson

Suggest Response to the Patient

About 75 % of the patients with Crohn's disease will require surgery at one time or another during the course of their disease. Surgery does not cure Crohn's disease but rather treats the complications of the disease. Medical management is required to treat the actual disease process and is necessary for most patients to remain healthy after their surgery. The complications of Crohn's disease that can be addressed by surgery include: bleeding, obstruction (blockage of the bowel), perforation (hole in the bowel wall), abscess (pus pocket), fistualization (abnormal connection between bowels), incontinence (loss of stool), inability to manage the disease medically, and malignancy (cancer).

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Brief Review of the Literature

Bleeding

Bleeding is relatively uncommon as an indication for surgery in small intestinal Crohn's disease. Usually, patients that bleed are anticoagulated or are taking blood thinners for another reason, and the combination of factors results in ongoing blood loss. Repeated transfusions or ongoing iron administration without improvement may be an indication for surgical resection. Occasionally, deep ulcerations, particularly in the rectum, may result in massive bleeding requiring surgical intervention.

Endoscopy will always be the primary method for the diagnostic workup for bleeding in Crohn's disease. However, the development of video capsule endoscopy has provided a novel method of imaging for inflammatory bowel disease. The safety profile is excellent for this technique with the caveat that retention risk is increased in patients with small bowel CD or ostomies. This risk can partially be decreased with the routine utilization of a patency capsule administered prior to the ingestion of the diagnostic capsule [1].

Obstruction

Long-standing inflammation results in the remodeling of the wall of the intestine or scarring. Just as every other wound on the human body heals and gradually shrinks over time, intestinal ulcerations of Crohn's disease can cause a section of intestine to stricture. This narrowing can result in intestinal obstruction which symptomatically leads to nausea, vomiting, constipation, food intolerance, abdominal pain, and weight loss. Food and intestinal secretions cannot get past the tight and thickened area of the intestine. Much as a plumber may be called to relieve a blockage in a pipe, surgery may be necessary to relieve an obstruction and this should not be considered a failure of medical management.

Data from pediatric patients suggest that early medical therapy may resolve the inflammation without resulting in stricture formation [2]. However, once scar tissue has formed, surgical removal is typically needed. Endoscopic dilation of the stricture is not usually effective since the intestinal wall itself has thickened with the narrowest segment usually being adjacent to the blood vessels. Atreja et al. [3] have written about the safety and efficacy of endoscopic dilation of primary and endoscopic stricture. Strictures selected for intervention were no greater than 4 cm in length. Greater than 70 % of patients who underwent dilation require repeat procedures and approximately 30 % of patients required surgery in spite of dilation. The use of steroid injections at the dilation or biologic therapy did not change the results, and the success rate of dilation between primary and anastomotic strictures was similar. Forceful dilation may result in either rupture of the intestine or bleeding. In addition, not all strictures of the small intestine may be accessible using colonoscopy or endoscopy.

One feature of Crohn's disease is that there may be "skip" lesions—meaning that there are areas of disease interspersed with normal segments of intestine. The surgeon should examine the intestine carefully looking for additional strictures. Often a balloon is passed to search for symptomatic strictures [4]. In general, the diameter thought to be acceptable is about 2 cm. Once a stricture is identified, the stricture can either be resected or a strictureplasty can be performed. The most commonly performed strictureplasty is the Heineke-Mikulicz strictureplasty which means that the intestine is cut longitudinally through the stricture and closed transversely.

Radiologic imaging under- or overestimates the number of strictures in approximately 35 % of patients. Imaging is least accurate in patients with short-length strictures that may be amenable to strictureplasty, multiple strictures, or prior surgical procedures where adhesions are easily confused with recurrent stricture formation [4].

Perforation of the Intestine

The ulcerations of Crohn's disease can become so deep as to penetrate through the intestinal wall. When a hole develops in the intestine, this can be a life-threatening complication. The partially digested food, enzymes, and bacteria within the intestine can spill into the abdomen causing peritonitis. There is no option other than surgery when this life-threatening emergency occurs. Often the site of perforation occurs just proximal to a stricture and both the stricture and the site of perforation need to be removed. Of note is that while an abscess is a contraindication for aggressive medical management with and anti-TNF alpha, intestinal fistula is an indication for biologic therapy. Sometimes, an abscess can be successfully drained in a minimal procedure or percutaneously with radiologic guidance [5, 6], converting the infection into an intestinal fistula and allowing medical therapy while the inflammation resolves.

Incontinence

If perirectal infection has progressed too far and involved or destroyed the sphincter muscles, the patient may become incontinent. This is particularly a problem if the stool is loose because of a diseased or prior resection of the intestine. Neither repair of the sphincter muscles nor the use of implantable devices to assist with sphincter function is possible in the setting of active Crohn's disease. The patient's best option may be a diverting ostomy to prevent fecal soiling and limit ongoing inflammation.

Failure of Medical Management

Medical management failure is unusual as the sole reason for surgical resection of Crohn's disease. Some of this can be considered noncompliance. The adult patient with multiple

drug allergies and intolerances would fall into this category or the child with failure to thrive who is intolerant of medical management. Stricture formation after drug therapy would not necessarily be categorized as a medical failure since the active disease has healed with the scar tissue and the obstruction requires surgical intervention. Stricture formation does not require cessation of the current medical therapy.

Recent research into growth failure and failure to thrive in pediatric patients has identified granulocyte macrophage colony-stimulating factor autoantibodies as well as an association with CARD15 genotype. These patients have growth hormone resistance, and in the future, more specific therapy for their medical condition may be forthcoming [7].

Summary

In the recent past, surgery was a cornerstone of the therapy for Crohn's disease. Since the widespread introduction of immunomodulator drugs and the development of biologic therapies, surgery has been rightly delegated to the treatment of complications of a chronic, medical disorder. The proper use and timing of surgical intervention is of critical importance for the patient who has developed a complication of their Crohn's disease.

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Chapter 27
What Is Life Like After Colectomy for UC? Ileal Pouch-Anal Anastomosis and Pouchitis

Jason M. Swoger and Shrinivas Bishu

Suggested Response to Patient

Ileal pouch-anal anastomosis or "IPAA" is a surgical procedure to treat ulcerative colitis, where the entire colon is removed. The last portion of the small intestine is formed into a "pouch" and is attached internally to the anal sphincter muscle. This procedure is often done in two or three stages and usually involves a temporary ileostomy for 12–24 weeks, depending on the number of stages.

Because the anal sphincter is preserved and there is a "pouch" to hold the stool, you will have more control over your bowel movements. Many people may have up to ten bowel movements immediately after surgery. Over time, however, most have about six soft daytime bowel movements and one or two at night. You will be able to take antidiarrheal medications to control stool frequency. Because IPAA removes the entire colon, UC medications are usually not

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necessary, and the risk of colon cancer is significantly decreased [1–3, 10].

There are no dietary restrictions after an IPAA, and most people can eat a variety of foods. However, certain poorly digestible foods, such as nuts, can increase stool frequency [1, 9]. A significant but minor fraction of women who undergo IPAA may have difficulties becoming pregnant. Rarely, male patients may have difficulty with sexual functioning that may impact fertility and ejaculation [12, 15]. The pouch may become infected immediately after the surgery, which can be serious, and is usually treated with antibiotics or drainage.

One important complication is inflammation of the pouch, termed "pouchitis [1, 4, 5, 8]." Pouchitis usually presents with abdominal pain, cramping, and diarrhea, similar to UC. Pouchitis occurs in up to 40 % of patients and is usually treated with antibiotics, but can require more complicated medications. Most only have a few episodes; however, some patients (20 %) develop chronic pouchitis and may require repeated courses of antibiotics. The majority of patients who undergo this surgery (95 %) report a good or excellent quality of life.

Brief Review of the Literature

Indications for Surgery

Indications for surgery in UC can be either acute or elective. Acute indications encompass patients with acute severe fulminant colitis either refractory to medical therapy or with complications. Elective indications include (1) medically refractory disease, (2) intolerable side effects of medical therapy, and (3) patients who develop colon cancer or dysplasia [1]. The rate of surgery for UC reported in the literature is highly variable and depends on a variety of factors including whether studies are population or hospital based and the geographic location of the centers [6].

However, collective data indicates that the incidence of elective surgery in UC has declined, but the incidence of

acute surgery has remained steady. It is estimated that approximately 50 % of surgeries for UC are performed for acute indications. Cumulatively, these data imply that biologics and immune modulators have resulted in improved control of chronic disease, but acute presentations still plague disease management and lead to early surgical intervention.

Surgical Considerations

There are multiple surgical options for UC depending on whether surgery is acute or elective. The simplest procedures, typically performed for acute indications, are subtotal or total proctocolectomy with end ileostomy ("Brooke" ileostomy). In a subtotal colectomy with end ileostomy, the remaining distal colon is preserved in a Hartmann's pouch. This leaves all operative possibilities after recovery from the acute insult. In contrast, a total proctocolectomy with end ileostomy is the definitive procedure that precludes reversal.

The restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the most commonly performed elective surgical procedure for UC. In this surgery, the colon and rectum are removed, and the distal 20 cm of ileum is fashioned into a pouch and either stapled or hand-sewn to the proximal anal canal. A variety of pouch configurations ("S," "W," "K") are possible, but the most common is the "J [1]." The ileal pouch is anastomosed to either the anal transition zone in close proximity to the dentate line or directly to the proximal anal canal. The former is a stapled anastomosis and is associated with less nocturnal incontinence [7, 11]. This is attributed to the preservation of the anal sensation and a lower likelihood of anal sphincter complex damage [7, 11]. However, it comes with the theoretically increased risk of "cuffitis" and a small risk of cancer because of a small band of preserved mucosa, the "anal transition zone." In contrast, the hand-sewn IPAA anastomosis requires a mucosectomy, resulting in a lower incidence of cuffitis and theoretically no remaining risk of colon cancer. This surgery preserves intestinal continuity, improves quality of life, and significantly decreases the risk of colorectal cancer [2, 3, 13, 14].

The restorative proctocolectomy with IPAA is usually performed in 2 or 3 stages. The first stage involves colon and rectal resection with a diverting loop ileostomy and pouch creation. The loop ileostomy is then closed in the second stage, which is generally performed 8–12 weeks later. If a 3-stage procedure is performed, the first stage is usually a subtotal colectomy with loop ileostomy, and the second stage involves removal of the distal colon/rectum and formation of the "J" pouch. A single-stage procedure can be performed, but the majority of data indicate higher rates of anastomotic leaks and pelvic sepsis compared to multistage surgeries. In general, the optimal procedure depends on several disease and patient factors, including medication exposure, and is best considered on a case-by-case basis in consultation with an experienced surgeon in a high-volume center.

Complications

Complications can be early or late following surgery. Complications can be categorized into several broad groups, including surgical technique related, inflammatory, neoplastic, functional, and metabolic. Common early complications include obstruction (which can also occur late), anastomotic stricture, anastomotic leak, and pelvic abscess/sepsis. Almost all patients eventually develop web-like strictures of the ileoanal anastomosis that can be conservatively managed, often with digital dilation. Recalcitrant strictures may require serial dilations. The most ominous complication is the pelvic sepsis, which develops in 5–24 % of patients. Abscesses require percutaneous drainage and can result in higher rates of pouch failure and need for pouch excision [2, 3, 7, 11, 13].

The most important late complications are sexual dysfunction, reduced fecundity, cuffitis, and pouchitis. Other types of pouch dysfunction, including issues with pouch outflow (stricture, weak sphincter), pouch volume, and irritable pouch syndrome, can all occur [2, 3, 7, 9, 13, 14]. Finally, patients can develop Crohn's disease of the pouch, which is often difficult to manage, and can be associated with fistulas, strictures, and sinus tracts.

Pouchitis

Pouchitis is the most common complication of UC patients with IPAA. It occurs in 23–46 %, with an increasing incidence with time from IPAA. Importantly, pouchitis is almost exclusive to patients who undergo IPAA for IBD and is rarely seen in patients with polyposis syndromes [1]. The pathogenesis of pouchitis is complex and poorly understood, but bacterial dysbiosis is thought to be a significant contributor. Several risk factors for pouchitis have been described, including genetics (NOD2/CARD15), extensive UC, backwash ileitis, primary sclerosing cholangitis (PSC), p-ANCA positivity, and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) [16, 17]. Some degree of chronic pouch inflammation, villus distortion, and colonic metaplasia can be demonstrated in most patients with IPAA, regardless of symptoms [10].

Pouchitis typically manifests as an increase in stool volume, bleeding, and discomfort. Incontinence, systemic symptoms, and dehydration may also be present, and extraintestinal manifestations (dermatologic or rheumatologic) occur rarely. Pouchitis can be acute (<4 weeks in duration), chronic (>4 weeks), or relapsing and can be idiopathic or secondary. Acute and chronic pouchitis may be distinct entities. Most patients with acute pouchitis do not develop chronic forms, but 60 % suffer at least one relapse. Acute pouchitis in the early post-op period is associated with a higher risk of developing chronic pouchitis [5, 8, 16, 17]. Moreover, 15–19 % of those with acute pouchitis develop chronic antibiotic refractory pouchitis. Despite the high incidence of pouchitis, dysplasia and cancer of the pouch are exceedingly rare with a 5 % incidence at 25 years. Important forms of secondary pouchitis that require evaluation include *Clostridium difficile* infection, IgG4-deposition, autoimmune-associated pouchitis, Crohn's disease of the pouch, NSAID use, and pouch structural disorders.

Endoscopy and biopsy are necessary to establish the diagnosis. Pouchitis appears as friable, erythematous, inflamed mucosa with exudates and erosions or ulcerations on pouchoscopy. Histologic confirmation requires both acute inflammatory changes (neutrophil infiltrates, crypt abscesses, and

mucosal ulcerations) and chronic changes (villus blunting, crypt distortion/hyperplasia, chronic inflammatory cell infiltration, and pyloric gland metaplasia).

The first-line therapy for acute pouchitis is a 14-day course of ciprofloxacin [18–20]. Metronidazole and rifaximin are alternatives that may be used if first-line therapy is ineffective or if combination therapy is required in order to achieve remission. Patients refractory to first-line therapy or those with chronic pouchitis can be treated with an extended 4-week course or have sensitivity-guided therapy. Many of these patients may need alternating courses of antibiotics. Some studies have suggested that probiotics may be helpful in reducing the incidence of pouchitis following surgery, as well as pouchitis recurrence. Patients who are either refractory to extended courses of alternating antibiotics or who suffer frequent relapses when antibiotics are tapered off may require step-up therapy to topical and oral 5-aminosalicylate agents, topical hydrocortisone, or budesonide enemas. Patients that remain unresponsive to the latter therapies may respond to oral budesonide or oral steroids. Immune modulators and antitumor necrosis factor-α agents are typically reserved for patients who fail 8 weeks of oral steroid therapy or have underlying Crohn's disease of the pouch [20]. Finally, surgical referral remains the option of last resort with pouch excision and end ileostomy creation. Overall, pouch excision is rare, occurring in <5 % of patients at experienced centers.

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Chapter 28
What Is It Like to Have an Ostomy? Colostomy and Ileostomy Issues and IBD

Kirk Ludwig

Suggested Response to the Patient

There is no getting around the fact that having an ostomy will impact your life. Whether the ostomy is temporary or permanent, there will be body image issues, social functioning issues, intimacy issues, control issues, and simple daily living issues. Having said all that, you should understand that the vast majority of patients lead normal and fulfilling lives with their ostomies, and in fact, for most patients who ultimately need a stoma for management of their disease, the ostomy means they will get better, they may need fewer or no medications, they will often feel better and function better, and in fact their quality of life will usually, overall, improve as a result of the surgery to remove disease and construct the ostomy. In the long run, 80–90 % of patients with an ostomy report good or excellent physical well-being, 90 % work without restrictions, and only about 10 % experience significant

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restrictions when it comes to diet, sports, hobbies, travel, and clothing selections. There are over a million people in the United States with an ostomy. You probably pass one, talk with one, or work with one very day, and you probably don't even know it, and there are specific organizations designed to educate and support those with an ostomy. You should try and focus on the fact that having the ostomy will very likely be much better than being chronically ill or being constantly tied to the nearest toilet. It will be a new start.

Brief Review of the Literature

A stoma, or ostomy, is an opening, either natural or surgically constructed, which connects a portion of the body to the outside environment. A colostomy is a surgically constructed opening in the large intestine that allows passage of feces, typically constructed to take the place of a surgically removed rectum and anus. An ileostomy is a surgical opening constructed by bringing either the end or the side (loop ileostomy) of the ileum out onto the surface of the abdominal wall. An end ileostomy is typically constructed after the colon, rectum, and anus have been removed, and a loop ileostomy is constructed as a temporary stoma to divert stool from a downstream, high-risk bowel anastomosis. All patients facing a temporary or permanent stoma should visit with an enterostomal therapist before surgery, and all these patients should have a stoma marking (putting a tattoo or ink mark at the correct site on the abdominal wall) before going to the operating room. This ensures that the best site is chosen for the stoma placement which will optimize stoma care and improve the quality of life. In the IBD population, ileostomies will be constructed far more commonly than colostomies and will be the focus of this discussion (Fig. 28.1). Given the nature of the disease, obviously, a colostomy would almost never be the answer for the treatment of ulcerative colitis, and given the typical patterns of disease and the surgical options available for the treatment of Crohn's disease,

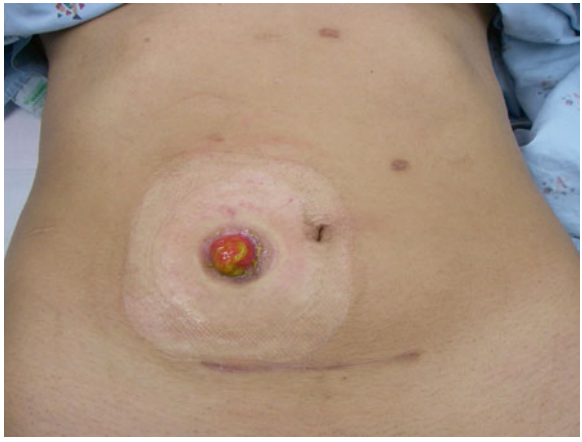

FIG. 28.1 An end ileostomy will protrude 1.5–2.5 cm above the level of the skin. While they are most commonly placed in the right lower quadrant, the most important considerations are finding a flat area on the abdominal wall, free of creases, folds, or surgical scars in an area that is easily visualized by the patient, such that appliance maintenance and care is simple

colostomy construction will be limited to those patients at the extremes of age or with the unusual situation.

In the early postoperative period, ileostomy output will be bilious and liquid. Once solid food is ingested, the effluent thickens but in the early postoperative period, the output is typically 1–1.5 l a day and at this level, some patients will need IV replacement of lost water and electrolytes. In a short time, the small bowel adapts and slows transit to the point that a well-established ileostomy will consistently put out only 200–700 cc per day with 90 % of the output being water. Within about 6 months of construction, the volume of ileostomy output will vary little and the effluent will be a yellow-brown color with a porridge-like consistency. An ileostomy will function throughout the day, but the bulk of the effluent will come within a few hours after meals. There will be some patients who, based on a number of factors, not the

least of which might be disease activity or length of the small bowel, will have chronically high ileostomy outputs of a liter or more a day. These patients will be instructed to try and control the stoma output by using antidiarrheal mediations such as Imodium, Lomotil, or codeine taken just before meals and at bedtime.

In the early postoperative period, patients should be instructed to watch their diet carefully and avoid fibrous foods (generally all raw fruits and vegetables, except bananas). The issue is that there will predictably be edema where the ostomy exits the abdominal wall and fibrous foods that do not digest easily can obstruct the ileum just beneath the stoma site causing what is known as a food bolus obstruction. These are a common cause for early postoperative visits to the office or the hospital. The classic symptoms being cramping just beneath the stoma site and reduced ileostomy output following dietary indiscretion. These food bolus obstructions can usually be broken up and cleared by aggressive irrigation of the bowel, through the stoma, using a 14 or 16Fr red rubber catheter. In the late postoperative period, the diet can be liberated. From a nutrition and metabolic standpoint, in the long term, normal nutrition is the rule. Total body water volume and exchangeable sodium are decreased leading to a slight state of chronic dehydration and perhaps an elevated serum aldosterone level. However, potassium depletion is rare and calcium and magnesium losses are unaffected. Loop ileostomies (Fig. 28.2) constructed to divert the fecal stream from an ileal pouch to anal anastomosis can be different as they are often constructed in the proximal ileum with perhaps 2–3 ft of distal bowel out of circuit, between the stoma and the ileal pouch to anal anastomosis. These stomas may have a higher output and may lead to nutritional deficits and dehydration. They are, of course, meant to be merely temporary, and the trouble will be resolved when they are closed: typically in about 12 weeks.

A well-constructed end ileostomy will protrude about 1.5 to 2.5 cm above the level of the skin. Given a nice “ileostomy spout” coupled with siting on a nice flat point on the abdominal wall, most ileostomy patients should be able to

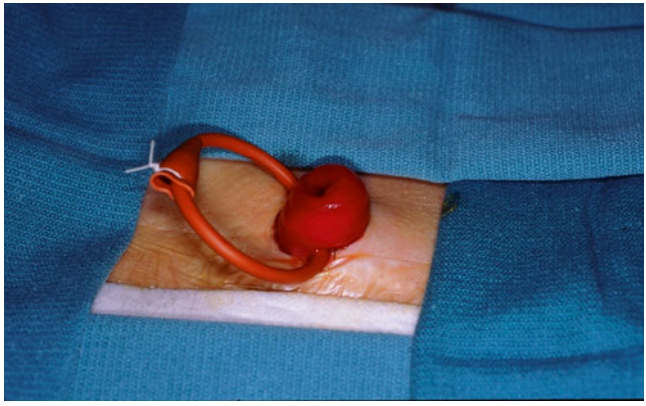

FIG. 28.2 A loop ileostomy, just constructed. The red rubber catheter is placed temporarily beneath the loop just simply to provide a day or two of support. The stoma should protrude a few centimeters above the level of the skin, just as is the case with an end ileostomy

maintain an appliance for 3-7 days and most patients empty the ileostomy pouch about 4-6 times each day [5, 6].

For the majority of patients with ulcerative colitis, the predictably good outcomes with an ileal pouch to anal anastomosis will mean that a permanent stoma may not be a necessity, with a loop ileostomy more often than not the stoma they will face [7]. For patients with Crohn's disease, while segmental colectomy with primary anastomosis or an ileorectal anastomosis after a total abdominal colectomy is a valuable technique for avoiding a permanent end ileostomy, for patients with multi-segment colitis with rectal and/or anal involvement, a total proctocolectomy with an end ileostomy may be the best option if medical therapy cannot control the symptoms [8].

Of course, for patients facing an ileostomy, there will be many physical, psychological, social well-being, and quality-of-life issues. Many patients facing a stoma may well consider that a permanent stoma may be more disabling than the disease process they are facing. This is simply just not the case. Patients should be assured that for the vast majority of those

with an ileostomy, quality of life is high. In a study from the Cleveland Clinic looking at 273 patients with an ileostomy, 72 % led normal lives without restriction, 24 % had minor restrictions, and only 4 % regretted having surgery. Eighty percent reported good or excellent emotional health, 80 % reported a positive body image, and only 10 % experienced negative feelings from employers, friends, or family [1]. A number of studies support the concept that patients adapt well to an end ileostomy with good or excellent postoperative well-being experienced by 80–90 % of patients [2, 3]. In terms of diet, sports, hobbies, travel, and clothing selection, only 10 % experience severe restrictions, 40–50 % experience moderate restrictions, and 90 % return to work after surgery without restrictions. Most patients find that they were more restricted preoperatively than they were postoperatively [4]. Overall, it can be said that the longer a patient has struggled with their disease and the better the function of the ileostomy, the better the outcome will be after ileostomy construction [1, 2]. Patients should be encouraged to consider the fact that life with a stoma may well be better than being chronically ill or being chronically tied to the nearest toilet.

A valuable resource for patients and physicians is the United Ostomy Associations of America (UOAA). This is a national network for bowel and urinary diversion support groups in the United States. Its goal is to provide a nonprofit association that will serve to unify and strengthen its member support groups, which are organized for the benefit of people who have or will have intestinal or urinary diversions and their caregivers. There are some 600 chapters and over 50,000 individual members. UOAA's website, http://www.ostomy.org/, offers much to patients with stomas and is an excellent forum for support and information.

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Chapter 29
Why Can't I Take My NSAIDs Any Longer? Avoiding Meds That May Cause a Flare

Amar Naik

Suggested Response to the Patient

Medications such as ibuprofen and naprosyn, also known as NSAIDs, have known possible toxic effects involving the small and large intestine. These range from intestinal inflammation or stricturing, iron-deficiency anemia, and even bleeding or perforation. As you can see, this is quite similar to what is seen with active IBD. NSAIDs can injure the intestinal mucosa, and their absorption into the blood stream can worsen inflammation.

For example, NSAIDs are commonly used by IBD patients for the treatment of joint pain. More than one out of four people with IBD have joint pain as a result of the condition. This joint pain might be a sign of active intestinal inflammation. Careful evaluation is important in this case, because if active IBD is discovered, appropriate treatment may improve symptoms. NSAID use would not help that situation and could actually make it worse.

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Some studies have suggested that even up to one-third of patients in remission can experience a clinical relapse of their IBD with a short course of NSAIDs. The newer NSAIDs (selective COX-2 inhibitors) might be safer to use for a short course, but this has only been evaluated in patients whose IBD was in clinical remission. Using NSAIDs to treat minor discomfort without trying other medications or local measures is not ideal. When considering these medications, setting up a personalized approach with your physician is best.

Brief Review of the Literature

IBD is a chronic inflammatory disorder of the intestines with known extraintestinal manifestations presumed to be a consequence of acute and chronic inflammation. Peripheral and axial arthralgias and arthritis occur in up to 35 % of IBD patients. In this situation, NSAIDs are commonly used for local anti-inflammatory and analgesic effects. There is an association of these medications' use and disease flares of Crohn's disease and ulcerative colitis [1–3].

There are a few proposed modalities to explain this phenomenon. Mucosal injury to the small and large intestine by tablets is felt to play a direct role by increasing intestinal permeability via damage to the intestinal barrier function. Subsequently, otherwise benign intraluminal contents such as bacteria and bile cause further injury.

From a systemic and vascular inflammation standpoint, COX inhibition, leukotriene mobilization, and NF-kB inhibition are the bases for potential explanations of this phenomenon.

Through crude COX inhibition, NSAIDs impact via decreased prostaglandin synthesis which hampers the intestines' mucosal defenses. There has been interest in selective COX inhibition's ability to mitigate these effects. A single, nonrandomized, non-blinded prospective study demonstrated IBD relapse rates of up to 5 % with selective COX-2 inhibition compared to ~20 % with nonselective NSAIDs.

Perhaps this suggests an improved safety profile from the IBD standpoint with respect to selective COX-2 inhibitors. It should be a point of emphasis, however, that there are no long-term, randomized, blinded clinical trials addressing the safety of COX-2 inhibition in IBD patients.

Additionally, NSAIDs (via COX inhibition) may affect arachidonic acid metabolism by shunting toward the lipoxygenase breakdown pathway. This results in increased leukotrienes, which incidentally have been found in IBD patients with active disease. The pathology of IBD revolves around a dysregulated immune system. NF-kB is a key player with regard to immune response in IBD patients. NSAID inhibition of NF-kB occurs fairly independent of COX inhibition and propagates inflammatory dysregulation by the immune system via effect upon pro-inflammatory signaling. Nevertheless, clinical studies have not clearly demonstrated the answers to the questions in whom and what extent NSAIDs cause IBD flares. ACG (American College of Gastroenterology) guidelines for the management of adult patients with Crohn's disease acknowledge NSAID use as a potential exacerbating factor. The CCFA (Crohn's & Colitis Foundation of America) also cautions against NSAID use in IBD [2, 4–6].

The use of NSAIDs does not negatively affect all patients with IBD. This is especially true when taken for short courses, during disease remission, and at lower doses. They can be just as effective as an analgesic when compared to non-IBD patients. Using NSAIDs to treat minor discomfort without trying other modalities, however, may not have a favorable risk/benefit profile for IBD patients.

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Chapter 30
Does Stress Play a Role in My Disease? The Role of Stress and Psychiatric Issues in IBD

Eva Szigethy

Suggested Response to the Patient

Stress, defined as any circumstance that overwhelms a person's ability to deal with it effectively, can have a negative effect on the course of inflammatory bowel disease (IBD). Stressors can be biological (e.g., infection, surgery) or environmental (e.g., life stress or trauma). If stress is extreme or chronic, it can lead to psychological reactions such as anxiety and depression as well as physical consequences such as poor sleep, worse gastrointestinal symptoms, and immune system problems. In patients with IBD, these effects have been linked to poor response to medical treatment and relapse of IBD activity. The strong bidirectional communication between the brain and gut is thought to underlie these types of stress reactions and also provide the substrate for why brain-based interventions can help reduce stress and have positive effects on the gastrointestinal tract and quality of life in patients with IBD.

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Brief Review of the Literature

There is growing evidence supporting the neurobiological manifestations of IBD including anxiety, depression, persistent abdominal pain, fatigue, and poor sleep [2]. These symptoms can occur both during periods of increased IBD-related inflammation but have also been reported during periods of relative remission of IBD. Since IBD is a lifelong disorder, the effects of stress can be cumulatively detrimental and thus important to identify and manage as early as possible in the disease process [1, 6].

Stress and IBD

The stress response and the resulting activation of a cascade of hormonal and neurochemical reactions are essential to enhance the survival of organisms in the short term. However, when stress is extreme or becomes chronic, it can lead to compromised functioning. In the face of a lifelong biological stressor like IBD, chronic stress exposure is associated with worse disease course, more chronic pain, and reduced quality of life [3]. Both experienced and perceived stress has been shown across multiple studies to contribute to the risk of relapse in IBD. Psychological stress responses can occur across a spectrum of severity from situational symptoms of emotional distress to functionally impairing psychiatric syndromes. Patients with IBD may have other factors predisposing to an exaggerated stress response unrelated to their disease such as other comorbid medical diagnoses, history of trauma, social conflict, and those with genetic vulnerability to psychiatric disorders (e.g., positive family history) [2]. Collectively, the presence and severity of these factors determine what type of stress management may help patients the most.

Psychiatric Issues and IBD

Depression has been reported in as many as 40 % of patients with IBD and up to four times higher than the rates reported

in comparison samples [8]. The highest depressive rates have been reported in patients with active disease or those with a more chronic or complicated disease course (e.g., having surgical complications or comorbid functional abdominal pain) [4, 5]. Similarly, clinically significant anxiety symptoms have been reported in patients with IBD with rates as high as 80 % during IBD relapse [8]. It is still unclear from the existing literature whether anxiety or depression precedes the diagnosis of IBD or whether there are differences in rates and underlying causal factors between patients with Crohn's disease or ulcerative colitis, the two predominant types of IBD. Regardless of the etiology, psychiatric symptoms are treatable and targeted psychosocial interventions and psychotropic medications can improve the quality of life in patients with IBD.

Neurobiology of the Stress-Brain-Gut Connection in IBD

The brain-gut interactions related to stress involve the autonomic nervous system, the central nervous system, and the hypothalamic-pituitary-adrenal (HPA) axis, as well as the enteric nervous system, microbiome, and immune response in the gastrointestinal tract [1]. There is preliminary evidence that psychosocial interventions can reduce acute inflammation in adolescents and adults with IBD and may influence these other neurobiological pathways as well [9, 10]. Future studies are needed to show that stress management alters longer-term course of IBD or could provide a protective effect against epigenetic factors underlying the pathophysiology of IBD.

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