Chapter 52: Inflammatory Bowel Disease

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UPDATE SUMMARY

Update Summary

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The following sections, tables, and figures were updated:

- Key Concepts: upadacitinib added to key concept 8, and rizankizuman-rzaa added to key concept 11
- Beyond The Book: part d revised
- Figure 52-2: risankizumab-rzaa added
- Table 52-4: rizankizumab-rzaa and upadacitinib added
- Figure 52-3: updated based on new guidelines to include new therapies
- Table 52-5: upadacitinib and rizankizumab-rzaa added
- Adverse Drug Effects: edits made to include upadacitinib and risankizumab-rzaa
- Special Populations, Pregnancy, and Breastfeeding: information added for upadacitinib and risankizumab-rzaa

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 26, Inflammatory Bowel Disease.

KEY CONCEPTS

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1 The exact cause of inflammatory bowel disease (IBD) is unknown. Proposed causes include infectious, genetic, and environmental factors, as well as alterations in intestinal epithelium function and systemic immune dysregulation.

2 Ulcerative colitis (UC) is confined to the rectum and colon, causes continuous lesions, and affects primarily the mucosa and the submucosa. Crohn's disease (CD) can involve any part of the GI tract, often causes discontinuous (skip) lesions, and is a transmural process that can result in fistulas, perforations, abscesses, or strictures.

3 Common GI complications of IBD include rectal fissures, fistulas (CD), perirectal abscess (UC), toxic megacolon (UC), and colon cancer. Extraintestinal manifestations include hepatobiliary complications, arthritis, uveitis, skin lesions (including erythema nodosum and pyoderma gangrenosum), osteoporosis, anemia, and aphthous ulcerations of the mouth.

4 The severity of UC may be assessed by stool frequency, presence of blood in stool, fever, pulse, hemoglobin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), abdominal tenderness, and radiologic or endoscopic findings. The severity of CD can be assessed using similar parameters, in addition to the CD Activity Index, which includes stool frequency, presence of blood in stool, endoscopic appearance, and physician's global assessment.

5 The goals of IBD treatment are resolution of acute inflammation and complications, alleviation of systemic manifestations, maintenance of remission, and improvement in quality of life (QOL).

6 The first line of treatment for mild-to-moderate extensive UC consists of oral aminosalicylates (ASAs) or oral controlled-release budesonide with prednisone as an alternative. Mesalamine enemas or suppositories are preferred for distal disease. Mesalamine is less effective for CD. Controlled-release budesonide or a tapering course of prednisone with or without azathioprine is preferred as a first-line agent for mild-to-moderate CD confined to the terminal ileum and/or ascending colon. Patients with more diffuse disease can be managed by a tapering course of prednisone with or with azathioprine.

7 Systemic corticosteroids are often required for acute moderate to severe UC or CD. The duration of steroid use should be minimized and the dose tapered gradually over 3 to 4 weeks if possible.

8 Infliximab, adalimumab, golimumab, ozanimod, and vedolizumab are treatment options for high-risk or moderate-to-severe active UC in outpatients and for those patients with UC who are corticosteroid dependent. Azathioprine or mercaptopurine may be used for maintenance of remission in UC as an alternative to or in combination with tumor necrosis factor-alpha (TNF-α) inhibitors, and in patients failing ASAs or with corticosteroid dependency. Vedolizumab with or without an immunomodulator may also be used as initial therapy or for patients failing TNF-α inhibitors. Tofacitinib and upadacitinib are used for patients with moderate-to-severe UC who have failed TNF-α inhibitors.

9 IV continuous infusion of cyclosporine or infliximab may be effective in treating severe colitis that is refractory to corticosteroids as an option to delay or prevent the need for surgery.

10 Aminosalicylates may prevent recurrence of acute UC in many patients, while corticosteroids are ineffective for this purpose.

11 Treatments for high-risk or moderate-to-severe CD include infliximab, adalimumab, certolizumab, rizankizumab-rzaa and vedolizumab. Methotrexate, azathioprine, or mercaptopurine may be used for inadequate response or to reduce steroid dosage and in combination with TNF-α inhibitors; ustekimumab (patients failing other therapies); metronidazole (for perineal or colonic disease); and cyclosporine (for refractory disease) may be used.

BEYOND THE BOOK

BEYOND THE BOOK

Several online resources about IBD are available for both patients and providers. Visit the Crohn's and Colitis Foundation webcast (http://www.crohnscolitisfoundation.org/resources/webcasts.html) and watch one the following videos.

a. IBD: Diet and nutrition

b. "Ulcerative Colitis 101"

c. "Crohn's Disease 101"

d. Comprehensive Care for IBD Wellness: Understanding Treatment Options in IBD

Identify three things you would use to educate a patient with IBD based on the information provided in the video.

INTRODUCTION

There are two forms of idiopathic inflammatory bowel disease (IBD): (a) ulcerative colitis (UC), a mucosal inflammatory condition confined to the rectum and colon, and (b) Crohn's disease (CD), a transmural inflammation of the GI tract that can affect any part, from the mouth to the anus.

EPIDEMIOLOGY

IBD is most prevalent in Western countries and in areas of northern latitude.[1] Rates of IBD are highest in North America, Northern Europe, and Great Britain.[1,2] The incidence of IBD is increasing worldwide, especially in Westernized and newly industrialized countries.[2-4] CD has an incidence of 6 to 15.5 cases per 100,000 persons per year and a prevalence of 3.6 to 214 per 100,000 persons per year.[1,2] The incidence of UC ranges from 1.2 to 20 cases per 100,000 persons per year with a prevalence of 7.6 to 246 per 100,000 persons per year.[1] Although most epidemiologic studies combine ulcerative proctitis with UC, 17% to 49% of cases are classified as proctitis.

Both sexes are affected somewhat equally with IBD, although 20% to 30% more women are affected with CD and slightly more males (60%) are affected with UC.[2] Both UC and CD tend to have bimodal distributions in age of initial presentation. The peak incidence generally occurs in the second (CD) or third (UC) decade of life, with a second peak occurring between 60 and 70 years of age.[1-3] A higher incidence of IBD occurs in the Jewish population, while Black and Asian patients have a relatively similar, and possibly lower, incidence of IBD compared to White patients.[2-4]

ETIOLOGY

1 The exact etiology of UC and CD is unknown; however, there are similar factors believed responsible for both conditions. The major theories behind the cause of IBD involve a combination of infectious, genetic, environmental, and immunologic factors. This may involve abnormal regulation of the innate immune response or a reaction to various antigens.[4-7] The microflora of the GI tract may provide an environmental trigger to activate inflammation in genetically susceptible individuals and is highly implicated in the development of IBD.[4,7]

Infectious Factors

Microorganisms are proposed to be a major factor in the initiation of inflammation in IBD. In general, there is thought to be shift toward the presence of more proinflammatory bacteria in the GI tract, often referred to as dysbiosis.[5-7] Patients with IBD have a decreased number, richness, and diversity of intestinal microbiotica compared with those without IBD as well as increases in aggressive bacterial groups and presence of mucosal and intraepithelial bacteria.[1,5-7] The development and composition of the intestinal microbiotica may also be influenced by dietary factors.[8] The pathogenesis of IBD may involve a loss of tolerance toward normal GI bacterial flora.[1,5-7]

Microorganisms may play a key role in the development of IBD. Suspect infectious agents include viruses, protozoans, mycobacteria such as *Mycobacterium paratuberculosis* or *avium*, and other bacteria such as *Ruminococcus gnavus*, *Ruminococcus torques*, *Listeria monocytogenes*, *Fusobacterium varium*, *Chlamydia trachomatis*, and adherent invasive *Escherichia coli*.[4-10] Patients with CD typically have circulating antibodies to *Saccharomyces cerevisiae*, which demonstrates some immunologic response to intestinal organisms.[5] Bacterial gene products may promote alteration of the intestinal barrier while bacterial antigens or ligands may include and propagate the inflammatory response.[5-7,10] Appendectomy has been associated with an increase in the risk of CD in White and Middle Eastern patients, while being protective against UC in White patients.[2]

Genetic Factors

Genetic factors play a significant role in the predisposition to IBD. Studies of monozygotic twins demonstrate a high concordance rate of IBD in both individuals (particularly CD).[1,12] First-degree relatives of patients with IBD may have up to a 20-fold increase in the risk of disease and risk is extended to second- and third-degree relatives.[5,13] The nucleotide-binding oligomerization domain protein 2 (NOD2), a key component involved in pathogen recognition in the innate immune system, is a major contributor of genetic predisposition to CD.[4,10,11] Other genes involved in the innate immune system autophagy, such as ATG16L1 and IRGM, as well as genes involved in the interleukin (IL) biologic pathway such as polymorphisms of the IL-23 receptor IL-23R, and IL-12B, STAT3, and CCR6, are strongly associated with CD and possibly UC (IL-23R).[1,5,10,11] The major genetic region for UC is on chromosome 6p21, in the major histocompatibility region, near human leukocyte antigen (HLA) class II genes.[10] Alterations in the genes encoding for IL-10 and the IL-10 receptor have been implicated in UC.[10,11] Emerging areas of interest in IBD pathogenesis are the role of microRNAs and the interface between environmental factors and peroxisome proliferator-activated receptors (PPARs).[12,13]

Immunologic Mechanisms

Potential immunologic mechanisms contributing to IBD include both autoimmune and nonautoimmune phenomena. NOD proteins involved in recognition of organisms and toll-like membrane receptors (TLRs) are involved in intestinal surveillance and can lead to release of antibacterial peptides such as defensins, among other functions.[1,5] Reduction in defensin secretion by Paneth cells is thought to be one contributing factor in the loss of effective intestinal barrier function.[5,14] Consequently, the bowel wall in CD is infiltrated with lymphocytes, plasma cells, mast cells, macrophages, and neutrophils, often leading to formation of granulomas. Similar infiltration has been observed in the colonic mucosal layer in patients with UC. Given that inflammation is limited to the colon in UC, dysfunction of colonocytes is highly implicated.[1] The colonic mucosal layer in UC may be thinner and less effective in protecting the epithelial cells. This may be due to reduced mucin secretion secondary to defective goblet cell differentiation.[1,5] Autoimmune features may be directed against mucosal epithelial cells or against neutrophil cytoplasmic elements. Innate lymphoid cells are also thought to possibly play a role in IBD pathogenesis.[1,5]

Antineutrophil cytoplasmic antibodies are found in a high percentage of patients with UC (70%) and less frequently in CD.[1,3,6,10] Overproduction of circulating IgG1 antibodies in UC may react with epithelium in the eyes, skin, joints, and biliary tract.[1] Dysfunction or reduced expression of the PPAR γ in colonocytes may play a role in this process.[1,13]

Th1 cytokine activity is excessive in CD and increased expression of interferon-γ in the intestinal mucosa and excess production of IL-12, IL-17A, and IL-22 are features of the immune response in CD.[3,5,10] In contrast, Th2 cytokine activity is excessive with UC.[1,5] This is mediated by excess production of IL-13, which contributes to epithelial cell dysfunction by enhancing natural killer T-cell cytotoxicity, and IL-5, which is involved with eosinophil recruitment and activation.[1] Activated epithelial cells secrete a variety of substances involved in the recruitment of inflammatory cells, including IL-1β, epithelial neutrophil-activating peptide 78, IL-8, and monocyte chemoattractant protein 1.[1]

Tumor necrosis factor-alpha (TNF-α) is a pivotal proinflammatory cytokine that is increased in the mucosa and intestinal lumen of patients with CD and UC. TNF-α can recruit inflammatory cells to inflamed tissues, activate coagulation, promote the formation of granulomas in patients with CD, and possibly modify epithelial cell apoptosis.[1,3,5,10]

Psychological Factors

Complex interactions between the enteric and central nervous systems, as well as contributions from the endocrine and immune systems can lead to

alterations in secretion, mobility, and alterations in the intestinal barrier in patients with IBD.[15,16] Mental health changes, particularly stress, possibly correlate with disease flares in IBD, but whether psychological factors are true etiologic factors in the pathophysiologic process is unclear.[15-17] Pain, anxiety, and depression are more common in patients with IBD compared to the general population, and are reported in up to 19% to 21% of patients.[15] In some instances symptoms of mood disorders, such as anxiety, may precede the onset of IBD symptoms.[16] Perceived stress has a great bearing on frequency of symptomatic flares.[17] While perceived stress and psychological factors may not be a direct cause of IBD, they significantly affect QOL.[16] This is compounded by the need for surgical intervention and temporary or permanent ostomy placement in young patients. Patients should be screened for the presence of anxiety and depression as part of their ongoing assessment, and have ongoing assessment of their QOL. Stress reduction should be an integral part of the treatment approach for IBD symptoms.[16]

Lifestyle, Dietary, and Drug-Related Causes

Several theories regarding dietary influence on the development of IBD have been proposed. Intake of refined sugars and animal fats has been associated with development of CD, while increased protein intake has been associated with a higher risk of developing IBD.[8,9] Diet composition and food derivatives may directly influence the makeup of the gut microbiotica, alter intestinal permeability, and affect immune function possibly triggering IBD.[8,9] Diets low in fruits and vegetables and high in ω-6 polyunsaturated fats may increase the risk of CD.[8] Changes in expression of the aryl hydrocarbon receptor, a transcription factor activated by dietary ligands and involved in the maintenance of the innate immune response, may increase development of IBD.[8] Interest has arisen in vitamin D deficiency as a possible cause of IBD given that vitamin D is involved with NOD2 gene induction.[9] Diets low in fermentable oligo-, di-, and monosaccharides and polyols, referred to as FODMAPs, improve IBD symptoms in some patients by reducing the osmotic load and fermentation of these sugars.[8] Tea or coffee consumption are protective against development of IBD in Asian patients.[2,8]

Smoking plays an important but contrasting role in UC and CD. It appears to be protective for UC and is associated with fewer disease flare-ups and reduced disease severity.[1,2,10] The risk of developing UC is increased for 2 to 3 years after smoking cessation in patients without IBD. In contrast, smoking is associated with increased frequency and severity of CD, and appears to worsen ileal disease more than colonic.[4,10] Patients with CD who stop smoking have a disease severity that is similar to nonsmokers. Smoking cessation should be offered to all patients. There are data to support transdermal nicotine replacement as an adjunctive therapy in UC.[18]

Use of nonsteroidal anti-inflammatory drugs (NSAIDs) may trigger disease occurrence or lead to disease flares by impairing mucosal barrier protective mechanisms.[25,30] Alteration in platelet function, release of inflammatory mediators, and alteration in the microvascular response to stress are other potential mechanisms of worsening of IBD. Cyclooxygenase-2 inhibitors and cyclooxygenase-1 inhibitors increase risk; however, it is unclear whether cyclooxygenase-2 inhibitors may be safer in select patients with IBD.[2] Despite the association between NSAID use and IBD flares, there is conflicting evidence regarding the consistency of this association.[19] There was no major impact on clinical outcomes with daily use of aspirin in patients with IBD.[20] Use of NSAIDs may be warranted in some patients with IBD, particularly those with arthritic symptoms, if the benefit outweighs the potential risk of disease flare. Oral contraceptives may also confer increased risk of IBD in susceptible patients.[22,23]

Development of IBD in White patients is associated with antibiotic use in childhood, while risk may be reduced in Asian and Middle Eastern patients.[2] There is a higher association of antibiotic use with development of CD.[21] Since antibiotics alter the intestinal flora, this appears to be a viable mechanism; however, delineating antibiotics as a causative factor is difficult given that symptoms may not manifest for several weeks to years following a treatment course. Furthermore, antibiotics may induce *Clostridioides difficile* infection, which is a cause of colitis. Patients presenting with severe diarrhea for whom a diagnosis of IBD is being entertained should be asked about recent antibiotics, and should be tested for *C. difficile* infection.

PATHOPHYSIOLOGY

UC and CD differ in two general respects: the extent and distribution of inflammation within the GI tract and depth of involvement within the bowel wall. Confusion in the diagnosis can occur, particularly when the inflammation is limited to the colon. For patients in whom it cannot be determined whether they have UC or CD, they are often classified as indeterminate colitis.[1] Table 52-1 compares pathologic and clinical findings of the two

diseases.

TABLE 52-1

Comparison of the Clinical and Pathologic Features of Crohn's Disease and Ulcerative Colitis

Feature	Crohn's Disease	Ulcerative Colitis
Clinical		
Malaise, fever	Common	Uncommon
Rectal bleeding	Common	Common
Abdominal tenderness	Common	May be present
Abdominal mass	Common	Absent
Abdominal pain	Common	Unusual
Abdominal wall and internal fistulas	Common	Absent
Distribution	Discontinuous	Continuous
Aphthous or linear ulcers	Common	Rare
Pathologic		
Rectal involvement	Rare	Common
Ileal involvement	Very common	Rare
Strictures	Common	Rare
Fistulas	Common	Rare
Transmural involvement	Common	Rare
Crypt abscesses	Rare	Very common
Granulomas	Common	Rare
Linear clefts	Common	Rare
Cobblestone appearance	Common	Absent

Ulcerative Colitis

Ulcerative colitis is confined to the rectum and colon and affects the mucosal and the submucosal layers. The disease distribution upon initial diagnosis is 30% to 60% proctitis, 16% to 45% left-sided colitis, and 14% to 35% have extensive colitis, also referred to as pancolitis.[1] In some instances,

a short segment of terminal ileum may be inflamed; this is referred to as *backwash ileitis*. Unlike CD, the deeper longitudinal muscular layers, serosa, and regional lymph nodes are not usually involved.[1] Fistula, perforation, or obstruction is uncommon because of the more superficial pattern of inflammation.

In UC, abscesses form in the crypts of the mucosa occurs (crypts of Lieberkuhn) secondary to infiltration of lymphocytes, plasma cells, and granulocytes.[1] Crypt abscesses are usually visible only with microscopy but may be visible when coalescence results in ulceration. Extension and coalescence of ulcers may surround areas of uninvolved mucosa, causing *pseudopolyp* formation. Mucosal damage and friability in UC can result in significant diarrhea and bleeding, although a small percentage of patients experience constipation.

3 Complications of UC may be local, including hemorrhoids, anal fissures, or perirectal abscesses, and are more likely to be present during active colitis.

A major complication is toxic megacolon, which is a segmental or total colonic distension of greater than 6 cm with acute colitis and signs of systemic toxicity.[1,24] It occurs in up to 7.9% of UC patients admitted to hospitals and results in death rates of up to 8% if not medically or surgically treated.[24] Patients typically have a high fever, tachycardia, distended abdomen, elevated white blood cell count, and a dilated colon observed on x-ray.[24] Colonic perforation may occur with or without toxic megacolon and is a greater risk with the first episode. Another infrequent major complication is massive colonic hemorrhage. Colonic stricture, sometimes with clinical obstruction, may also complicate long-standing UC.

The risk of colonic dysplasia with transition to colorectal carcinoma (CRC) is two to six times greater for patients with chronic UC with colonic involvement compared with the general population.[25] CRC is responsible for 10% to 15% of deaths in patients with UC.[26] Patients with ulcerative proctitis or proctosigmoiditis are generally not considered to be at increased risk.[25,26] The cumulative risk of developing CRC in patients with chronic UC may be as high as 8% at 20 years.[26] Risk factors for CRC include young age at onset, longer duration of disease, greater extent of colonic involvement, presence of primary sclerosing colangitis (PSC), active histological inflammation, family history of a first-degree relative diagnosed with CRC prior to age 50, history of dysplasia, colonic strictures, pseudopolyps, a shortened tubular colon, and male gender.[26] Screening colonoscopy with multiple biopsies should be performed at 8 years after onset of pancolitis or 15 years following onset of left-sided UC or CD-related colitis.[32,33] Patients with PSC, extensive colitis with active endoscopic or histologic inflammation, a history of dysplasia, or a family history of a first-degree relative diagnosed with CRC prior to age 5 should undergo yearly colonoscopy.[26]

Crohn's Disease

Crohn's disease is characterized as a transmural inflammatory process. The terminal ileum is the most common site of the disorder, but it may occur in any part of the GI tract from mouth to anus.[3,10,27,28] Patients often have areas of normal bowel separating segments of diseased bowel resulting in discontinuous disease. The "cobblestone" appearance of the bowel wall results from deep mucosal ulceration intermingled with nodular submucosal thickening.

Small bowel stricture and subsequent obstruction is a complication that may require surgery. Fistula formation is also common, occurring much more frequently than with UC.[10,27] Fistulas often occur in highly inflamed areas, where loops of bowel become matted together by fibrous adhesions. Perianal fistulas may occur in up to 26% of patients within 20 years of diagnosis.[27] Fistulas may connect a segment of the GI tract to skin (enterocutaneous), two segments of the GI tract (enteroenteric), or the intestinal tract with the bladder (enterovesicular) or vagina.

Bleeding with CD is usually not as severe as with UC, although patients with CD may develop hypochromic anemia. The risk of carcinoma is increased but not as greatly as with UC; however, patients with CD and a personal history of dysplasia or PSC are at higher risk, and chromoendoscopy should be used during colonscopy.[26]

Nutritional deficiencies are common with CD.[28-30] Reported deficiencies include folate, vitamin B_{12}, vitamins A and D, calcium, magnesium, iron, and zinc.[37] Major contributing factors include decreased food intake, intestinal loss, malabsorption, hypermetabolic state, drug-nutrient interactions, and those receiving long-term total parenteral nutrition.[28-30]

Extraintestinal Manifestations of IBD

Both forms of IBD are associated with development of symptoms and organ involvement outside of the GI tract referred to as extraintestinal manifestations.

Hepatobiliary Complications

Hepatobiliary complications are commonly found in patients with IBD.[1,27,31-33] Hepatic complications include non-alcoholic fatty liver disease, pericholangitis, autoimmune hepatitis, liver abscess, and cirrhosis. Biliary complications include PSC, cholangiocarcinoma, and cholelithiasis.[1,31,32] Fatty infiltration of the liver may result from malabsorption, protein-losing enteropathy, or corticosteroid use, and may be found in up to 50% of patients with IBD.[31] PSC is associated with progressive fibrosis of intrahepatic and extrahepatic bile ducts in 4% of patients with UC.[31] Cirrhosis may result from cholangitis or chronic active hepatitis. Often the severity of hepatic disease does not correlate with GI disease activity. Gallstones occur in up to 34% of patients with CD (particularly with terminal ileal disease) and are related to bile salt malabsorption.[31,32]

Joint Complications

Both peripheral and axial arthropathies may be present in patients with IBD. Peripheral arthritis is typically asymmetric, oligoarticular, non-erosive, and occurs in 5% to 20% of patients.[32,33] Symptoms may present prior to GI symptoms of IBD. Axial arthropathies include sacroiliitis, ankylosing spondylitis, and IBD-associated spondyloarthropathy. The prognosis is not as favorable as peripheral arthritis, as progression is common. Patients with axial involvement should be referred to a rheumatologist in order to assist in the disease management.[32]

Ocular Complications

Ocular complications including dry eye, blepharitis, iritis, uveitis, episcleritis, and conjunctivitis occur in up to 29% of patients with IBD.[1,32,33] Commonly reported symptoms with iritis and uveitis include blurred vision, eye pain, and photophobia. Episcleritis is associated with scleral injection, burning, and increased secretions. These complications may parallel the severity of intestinal disease, and recurrence after colectomy with UC is uncommon.

Dermatologic and Mucocutaneous Complications

Skin and mucosal lesions associated with IBD include erythema nodosum, pyoderma gangrenosum, aphthous ulceration, and Sweet's syndrome.[32,33] Raised, red, tender nodules on the tibial surfaces of the legs and arms that vary in size from 1 to 5 cm are manifestations of erythema nodosum, and may occur in 4.2% to 7.5% of patients with IBD.[39]

Pyoderma gangrenosum occurs in 0.6% to 2% of patients with IBD and is characterized by skin pustules that progress to a burrowing ulcer with violaceous edges, ranging between 2 and 20 cm.[1,32,33] They can be seen on any part of the body but commonly occur on the lower extremities.

Oral lesions are found in 4% to 20% of patients with IBD.[32,33] The most common lesion seen with CD is aphthous stomatitis. The severity of these lesions tends to parallel the disease course. Sweet's syndrome, also known as acute febrile neutrophilic dermatosis, is characterized by tender erythematous skin lesions secondary to dermal neutrophil infiltration, and is often associated with fever and a distribution on the upper trunk, face, neck, and arms.[32,33]

Hematologic, Coagulation, Pulmonary, and Metabolic Abnormalities

Patients with IBD may develop anemia, with a prevalence reported up to 74%.[1,29,32,33] The anemia may present as iron deficiency related to chronic blood loss, ongoing inflammation, malnutrition, hemolysis, or bone marrow suppression from drug treatment.[32,33] Alternatively, it may be more characteristic of anemia of chronic disease. Patients with IBD are at a 1.5 to 3.6 times higher risk of venous thromboembolism (VTE) compared with the general population.[32] This is secondary to activation of the clotting cascade and platelet activation secondary to inflammation. Occurrence of VTE is higher during disease flares and occurs more often in peripheral veins.[1,32,33] Patients should be considered for pharmacologic VTE prophylaxis when admitted to the hospital for a disease flare. Patients with IBD may be at increased risk for metabolic bone disease. Osteopenia may be present in 32% to

36% of patients, while osteoporosis is reported in 2% to 15%.[33,34] Bone disease may be related to a combination of nutritional deficiencies, especially calcium and vitamin D, chronic cytokine-related inflammatory effects on bone, disease-associated hypogonadism, and use of corticosteroids.[33,34] Pulmonary manifestations occur from the glottis all the way to the small airways, but most commonly involve the large airways and may include cryptogenic organizing pneumonia, bronchiectasis, and bronchiolitis obliterans.[32]

CLINICAL PRESENTATION

Clinical Presentation: Inflammatory Bowel Disease

The patterns of clinical presentation of IBD can vary widely. Patients may have a single acute episode that resolves and does not recur, but most patients experience acute flares with alternating periods of remission.

Ulcerative Colitis

There is a wide range of presenting symptoms in UC, ranging from mild abdominal cramping with frequent small-volume bowel movements to profuse diarrhea (Table 52-2). Most patients with UC experience intermittent bouts of illness after varying intervals of remission.

TABLE 52-2

Clinical Presentation of Ulcerative Colitis

Signs and symptoms

- Abdominal cramping
- Frequent bowel movements, often with blood in the stool
- Weight loss
- Fever and tachycardia in severe disease
- Blurred vision, eye pain, and photophobia with ocular involvement
- Arthritis
- Raised, red, tender nodules that vary in size from 1 cm to several centimeters

Physical examination

- Hemorrhoids, anal fissures, or perirectal abscesses may be present
- Iritis, uveitis, episcleritis, and conjunctivitis with ocular involvement
- Dermatologic findings with erythema nodosum, pyoderma gangrenosum, or aphthous ulceration

Laboratory tests

- Decreased hematocrit/hemoglobin
- Increased ESR, CRP, and fecal calprotectin
- Leukocytosis and hypoalbuminemia with severe disease
- (+) perinuclear antineutrophil cytoplasmic antibodies

4 While various disease classifications for UC exist, a standard disease severity scoring system is not universally accepted.[18,35] The American College of Gastroenterology (ACG) UC Activity Index uses designations of mild, moderate-severe, and fulminant disease activity using clinical signs and symptoms and laboratory data[18]:

1. Mild: Fewer than four stools daily, with intermittent blood, mild or occasional urgency, normal erythrocyte sedimentation rate (ESR <30 mm/hr [8.3 µm/s]), normal hemoglobin, and elevated C-reactive protein (CRP) and fecal calprotectin (FC).
2. Moderate-Severe: More than six stools per day with frequent blood and urgency, fever, tachycardia, anemia, elevated CRP and FC, ESR greater than 30 mm/hr (8.3 µm/s).

3. Fulminant: More than 10 bowel movements per day with continuous bleeding and urgency, toxicity, abdominal tenderness, requirement for transfusion, elevated CRP and FC, and possible colonic dilation.

Guidelines from the American Gastroenterological Association (AGA) focusing specifically on moderate-to-severe UC utilize similar definitions; however, they define a subset of severe patients with acute severe UC (ASUC) as requiring hospitalization and having greater than six bloody stools per day and at least one marker of systemic toxicity, including heart rate greater than 90 beats per minutes, temperature greater than 37.8°C, hemoglobin less than 10.5 g/dL (105 g/L; 6.52 mmol/L), and/or ESR greater than 30 mm/hr (8.3 µm/s).[35]

A clinical care pathway for UC assesses the severity of UC based on risk for colectomy.[36] Patients are stratified according to low risk for colectomy (limited anatomic extent and mild endoscopic disease) or high risk for colectomy (extensive colitis, age less than 40 years, deep ulcers, high ESR/CRP, steroid dependence, history of hospitalization, and *C. difficile* or cytomegalovirus infection).

Determining disease extent, that is, which sections of the colon are involved, is important. This is accomplished via endoscopy. Patients with "distal" disease have inflammation limited to areas distal to the splenic flexure (also referred to as *left-sided* disease), while those with "extensive disease" have inflammation extending proximal to the splenic flexure.[1,18] Inflammation confined to the rectal area is referred to as *proctitis*, while disease involving the rectum and sigmoid colon is referred to as *proctosigmoiditis*. Inflammation of the majority of the colon is called *extensive disease*, sometimes referred to as *pancolitis*. Disease activity may be assessed upon endoscopy using common scoring systems, such as the UCEIS or Mayo Score.[18]

The diagnosis of UC is made on clinical suspicion and confirmed by biopsy, stool examinations, sigmoidoscopy or colonoscopy, or barium radiographic contrast studies.[35,37] Evaluation of CRP, and FC, a protein released during leukocyte trafficking, may also assist in identifying the presence of intestinal inflammation, and are also helpful in monitoring response to therapy.[37] The presence of extraintestinal manifestations may also aid in establishing the diagnosis.[18,32,33]

Crohn's Disease

The time between the onset of CD complaints and the initial diagnosis may be as long as 3 years. The patient typically presents with diarrhea and abdominal pain. Hematochezia occurs in about one-half of patients with colonic involvement and much less frequently when there is no colonic involvement. A patient may first present with a perirectal or perianal lesions, or extraintestinal manifestations in up to 50% of cases[10] (Table 52-3). The diagnosis should also be suspected in children with growth retardation, especially with abdominal complaints.

TABLE 52-3

Clinical Presentation of Crohn's Disease

Signs and symptoms

- Malaise and fever
- Abdominal pain
- Frequent bowel movements
- Hematochezia
- Fistula
- Weight loss and malnutrition
- Arthritis

Physical examination

- Abdominal mass and tenderness
- Perianal fissure or fistula

Laboratory tests

- Increased white blood cell count, ESR, CRP, and fecal calprotectin
- (+) anti–*Saccharomyces cerevisiae* antibodies

Much like UC, global classification guidelines for scoring severity of active CD are not available. For patients with luminal nonfistulizing CD, the Crohn's Disease Activity Index (CDAI) is used most often to gauge response to therapy and determine remission and is employed mostly in the research setting. This score system ranges from 0 to 600, with score greater than 150 defined as active disease. The Harvey-Bradshaw Index (HBI) is another scoring system that is also used for CD, and tends to correlate well with the CDAI. A decrease of 3 points in the HBI is defined as a clinical response with complete remission defined as a score of less than 4. Treatment guidelines use the presence of signs and symptoms as their marker for disease activity and severity.[27]

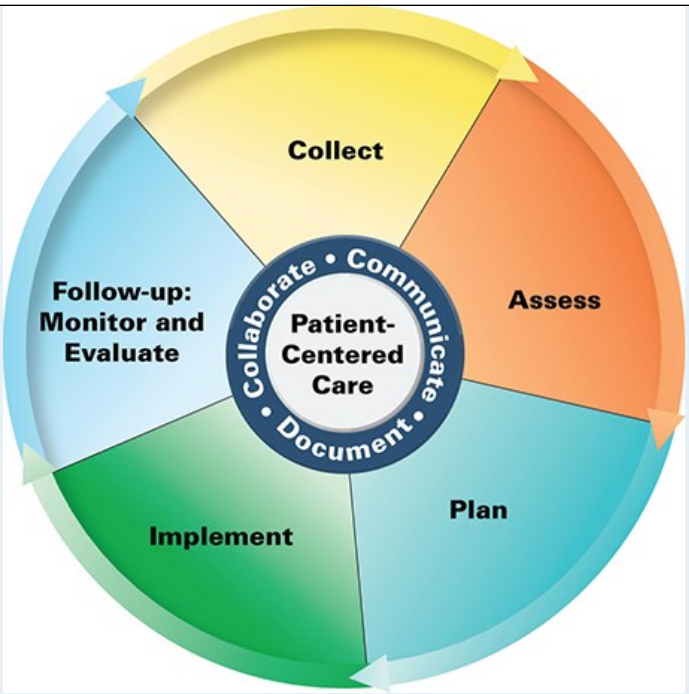
The classification of CD severity is similar to UC.[3,10,27] Patients with mild-to-moderate CD are typically ambulatory and have no evidence of dehydration, systemic toxicity, less than 10% loss of body weight, or abdominal tenderness, mass, or obstruction. This correlates to a CDAI of 150 to 220. Moderate-to-severe disease is considered in patients who fail to respond to treatment for mild-to-moderate disease or those with fever, weight loss, abdominal pain or tenderness, vomiting, intestinal obstruction, or significant anemia. Severe-to-fulminant CD is classified as the presence of persistent symptoms or evidence of systemic toxicity despite corticosteroid or biologic treatment or presence of cachexia, rebound tenderness, intestinal obstruction, or abscess with a CDAI more than 450. Disease activity may be assessed and correlated by evaluation of CRP concentrations.

Similar to UC, the AGA has developed a clinical decision support tool for assessing CD severity.[38] Patients are stratified as low risk (age at initial diagnosis over 30 years, limited anatomic involvement, no perianal and/or severe rectal disease, superficial ulcers, no prior surgical resection, and no stricturing and/or penetrating disease) or moderate to high risk (age at initial diagnosis less than 30 years, extensive anatomic involvement, perianal and/or severe rectal disease, deep ulcers, prior surgical resection, stricturing and/or penetrating disease).

The course of CD is characterized by periods of remission and exacerbation. Patients may be symptom-free for years, while others experience chronic symptoms in spite of medical therapy. As with UC, the diagnosis of CD involves a thorough evaluation using laboratory, endoscopic, and radiologic testing to detect the extent and characteristic features of the disease.[10,27,37,38] Small bowel involvement, strictures detected on radiographs, and presence of fistulae are characteristic of CD.

PATIENT CARE PROCESS

Patient Care Process for Inflammatory Bowel Disease



Collect

- Patient characteristics (eg, age, sex, weight, vital signs)
- Patient symptoms, including evidence of abdominal pain, stool frequency, presence of hematochezia, weight loss, or extraintestinal manifestations
- Patient medical, family, and social history (in particular tobacco use)
- Surgical operations (site, date, procedure) and abdominal imaging findings (CT, MRI, ultrasound)
- Thorough medication history at hospital admission (include prescription, non-prescription medications, and other substances), and drug allergies and intolerances
- Laboratory results for evidence of inflammation (CRP, ESR, WBC), major organ function (particularly kidney and liver), hemoglobin and hematocrit, nutritional status (serum albumin and transferrin), vaccination status, pregnancy status, and pANCA or anti-*Saccharomyces cerevisiae* antibodies if initial diagnostic workup, and pharmacogenomics status for TPMT, if applicable

Assess

- Determine severity of illness based on symptoms, vital signs, stool frequency, and inflammatory markers. Consider use of Crohn's Disease Activity Index to assess disease progress. Include assessment of fluid and electrolyte status
- Determine extent and location of inflammation in the gastrointestinal tract based on endoscopic and imaging procedures
- Assess if extraintestinal disease manifestations and comorbidities are present that may affect section and outcomes of medication regimens
- Evaluate current medication regimen for potential drug-induced exacerbating factors and for efficacy and toxicity of current IBD treatment regimen
- Assess if disease complications are present that may require surgical intervention (abscess or fistulae)
- Estimate creatinine clearance for drug dosing

Plan*

- Determine goals of therapy with monitoring parameters for each goal
- Based on severity and location of Illness, determine the appropriate medications to induce and maintain remission considering severity and site of disease (Figs. 51-1 and 51-2)
- Initiate adjunctive medications for pain and diarrhea, if needed
- Check for adverse drug reactions and interactions and dose adjustments based on end-organ function (Table 51-4)

Implement

- Initiate medications for short-term induction of remission and subsequent maintenance
- Discontinue medications that may be exacerbating symptoms
- Provide patient education on appropriate use of oral, parenteral, or rectally administered medications
- Assure that corticosteroids doses are tapered during discontinuation

Follow-up: Monitor and Evaluate

- Determine if patient shows improvement in the signs and symptoms within 24 to 48 hours for hospitalized patients, and 7 to 14 days for outpatients
- Evaluate laboratory parameters for evidence of drug efficacy and potential toxicity
- Monitor for adverse effects of medications
- Assess adherence to current medication regimen and address barriers to medication use
- Determine the need for dose reduction or tapering of medications intended for short-term use, such as corticosteroids

****Collaborate with patient, caregivers, and other healthcare professionals.***

TREATMENT

Desired Outcomes

5 The clinician must have a clear concept of realistic therapeutic goals for each patient with IBD. Goals may relate to resolution of acute inflammatory processes, resolution and prevention of complications (eg, fistulae, abscesses, and CRC), alleviation of extraintestinal manifestations, maintenance of remission, or surgical palliation or cure.

When determining goals of therapy and selecting therapeutic regimens, it is important to understand the natural history of IBD.[18,27,39] Some cases of acute UC are self-limited. Following remission, up to 43% of patients may experience relapse in the first year, and almost half may require hospitalization at some point during their disease course.[39] Being young at the time diagnosis, female sex, presence of extraintestinal manifestations, nonsmoking status, and higher levels of education have been associated with higher risk of relapse.[39] With severe colitis, improvement without treatment cannot be expected. The response to medical management of toxic megacolon is variable and emergent colectomy may be required. CD tends to be progressive and destructive, with only 20% to 30% having an indolent course.[3,9,27] Patients at risk for progression of CD include young age at diagnosis, extensive bowel involvement, perianal or severe rectal disease, or stenosis.[27] Up to 80% of patients will require hospitalization at some point during their disease course, and there are high rates of steroid dependence and the need for surgical intervention.

There has been a movement toward use of the “Treat-to-Target” approach.[10,40] This involves use of specific targets, such as mucosal healing and endoscopic remission, or resolution of symptoms such as abdominal pain and diarrhea, as the main indicators of treatment efficacy. Mucosal healing, defined as the absence of ulceration, has become an important target and is accessed via endoscopy with specific scoring systems used to determine if this outcome has been assessed. Mucosal healing can be used as a monitoring parameter for treatment efficacy, particularly in CD, and if achieved may be predictive of steroid-free sustained remission.[27,40] Biomarkers, such as CRP and FC, have also become important adjunctive monitoring parameters to endoscopic approaches.[27,37,40]

General Approach to Treatment

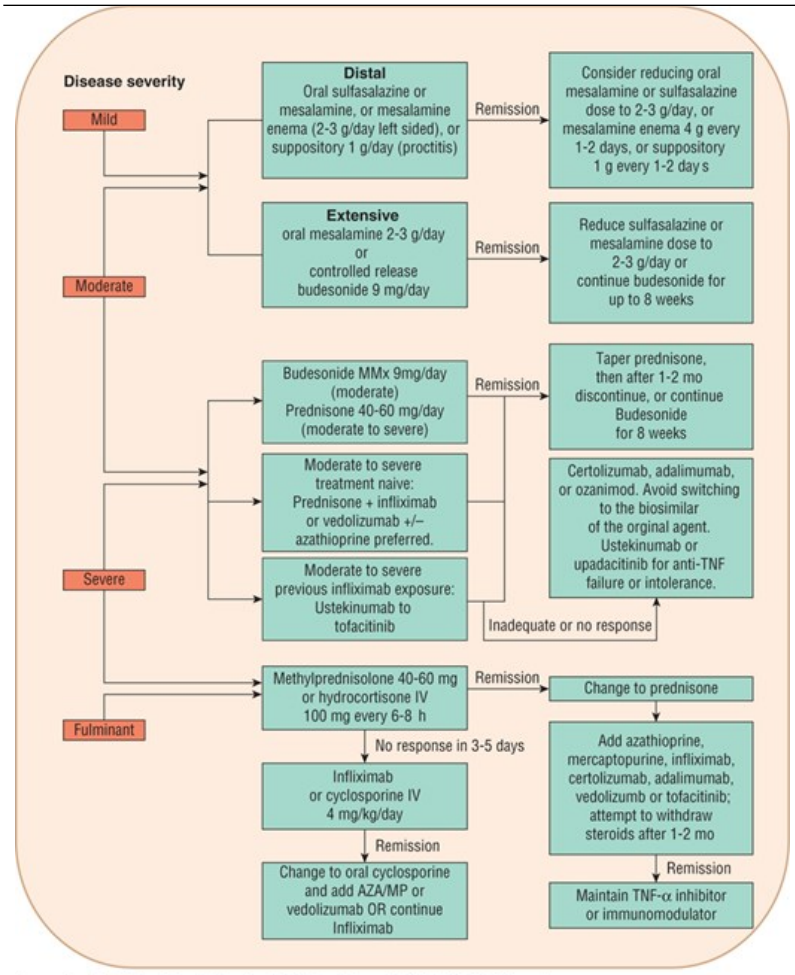
Treatment of IBD centers on agents used to suppress the inflammatory process, induce, and then maintain disease remission. The severity and extent of the disease should be taken into account, as this will often dictate the dose, route, frequency, and formulation of drug therapies that will be most effective. Patient preference for different drug formulations and cost of therapies should also be taken into account.

Surgical procedures are sometimes performed when active disease is inadequately controlled with drugs, or when the required drug dosages pose an unacceptable risk of adverse effects. Nutritional considerations are also important because many patients may develop malnutrition. A variety of adjunctive therapies may be used to address complications or symptoms of IBD.

FIGURE 52-1

Treatment approaches for ulcerative colitis.

Treatment approaches for ulcerative colitis.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Nonpharmacologic Therapy

Nutritional Support

Malabsorption or maldigestion may occur secondary to the catabolic effects of the disease process. Patients with IBD have a fivefold higher risk of malnutrition compared to those without IBD.[28] Patients with CD have continued risk, even when their disease is quiescent, while patients with UC are more at risk during times of active disease.[30] Unnecessary food restriction during hospitalization also places patients at higher risk for malnutrition.[28] Patients who have undergone multiple small bowel resections may have reduction in the absorptive surface of the intestine (ie, "short gut"). Maldigestion with accompanying diarrhea can also occur if there is a bile salt deficiency in the gut. Patients should be screened for malnutrition upon diagnosis and assessed intermittently for the presence of micronutrient deficiencies.[30]

Elimination of specific foods that appear to exacerbate symptoms can be tried; however, exclusion diets are generally not endorsed, even in the setting of severe disease.[30] Increased intake of red meat, protein, sulfur and sulfates, and alcoholic beverages have been associated with disease flares.[8] If attempted, the elimination process must be conducted cautiously, as patients may exclude a wide range of nutritious products without adequate justification. Some patients with IBD may have lactase deficiency as well; therefore, diarrhea may be associated with intake of dairy products. For these patients, avoidance of dairy products or supplementation with lactase generally improves the patient's symptoms. Patients with small bowel strictures due to CD should avoid excessive high-residue foods, such as citrus fruits and nuts, in order to prevent obstruction. Increases in soluble fiber may induce the production of intestinal short chain fatty acids, which may have intrinsic anti-inflammatory effects.[8]

Many specific diets have been tried to improve nutritional status and symptoms in IBD. Use of diets low in FODMAPs may help improve IBD symptoms.

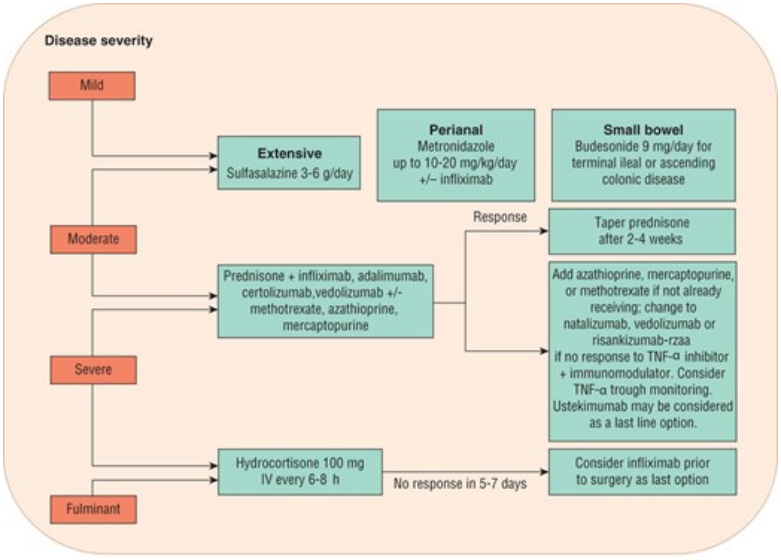
The specific carbohydrate diet (SCD) is another option that involves restriction of all carbohydrates except monosaccharides (glucose, fructose, and galactose), as well as restriction of milk, canned fruits and vegetables, and processed meats.[9,28,30] Some studies have demonstrated improvement in symptoms and inflammation; however, these diets are difficult to follow and patient adherence may by problematic.[28,30] Exclusive enteral nutrition, which involves use of elemental, semi-elemental, and defined formulas, has shown some benefit in increasing nutritional status and reducing intestinal inflammation and cytokine production.[8,28,30] While this approach may lead to a greater chance of induction of remission, particularly in patients with CD, most data are in pediatric patients and are lacking regarding its use as a maintenance diet.[28,30]

Parenteral nutrition is generally reserved for patients with severe malnutrition or those who fail enteral therapy or have a contraindication to receiving enteral therapy, such as perforation, protracted vomiting, short-bowel syndrome, or severe intestinal stenosis.[30] Parenteral therapy is not preferred as primary therapy for IBD even in the setting of acute disease flares in hospitalized patients, and should be reserved for those patients with the most complicated disease.[30] Home parenteral nutrition may be necessary for patients requiring long-term therapy, particularly those with short-bowel syndrome. Parenteral nutrition is more costly and is associated with more complications, such as serious infections, compared with enteral nutrition.

Probiotic administration as an adjunctive treatment of IBD has been explored. Postulated mechanisms for using probiotics in IBD include reestablishment of normal bacterial flora within the gut, reduction in bacterial adhesion and competition for nutrients with pathogenic bacteria, production of antibacterial substances, and promotion of favorable effects on the host immune response.[7] Probiotic preparations often contain various organisms such as nonpathogenic *E. coli Nissle*, bifidobacteria, lactobacilli, *Streptococcus thermophilus*, or *Saccharomyces boulardii*. While probiotics were effective in inducing and maintaining remission in some trials for patients with UC, differences in methodology, probiotics used, and underlying treatments for IBD make comparison of trials difficult.[40,41] A formulation of *Bifidobacterium*, lactobacilli, and streptococci (VSL #3) is marketed specifically for use in UC as an adjunctive therapy and for patients who have a surgically constructed ileal pouch anal anastomosis (IPAA) to prevent or treat pouchitis.[18,41,42] Evidence of probiotic use for the induction and maintenance of CD is less compelling and has led to recommendations not supporting widespread use, but rather further investigation.[27,42] While probiotics are considered to be generally safe in patients with IBD, the added cost, requirement to take multiple doses per day, coupled with the lack of quality data to support their use, should also weigh into the decision to use them in IBD.

FIGURE 52-2

Treatment approaches for Crohn's disease.



Surgery

Patients with IBD often require surgery. Surgical procedures may involve resection of segments of intestine that are affected, as well as correction of

complications (eg, fistulas) or drainage of abscesses.

Rates of colectomy over 20 years UC are reported as 0.55% to 20%.[18,39,43] Colectomy may be necessary when the patient has disease uncontrolled by maximum medical therapy or when there are complications of the disease such as colonic perforation, toxic megacolon, uncontrolled colonic hemorrhage, or colonic strictures.[1,24,43] Colectomy may be indicated for patients with long-standing disease (greater than 8-10 years), as a prophylactic measure against the development of CRC, and for patients with premalignant changes (severe dysplasia) on surveillance mucosal biopsies.[42] Proctocolectomy, after which the patient is left with a permanent ileostomy, is generally considered curative for UC; however, the decision to perform this should take into account the effects on the patient's QOL. Restorative proctocolectomy with construction of an IPAA is the most common surgical procedure performed in UC. This procedure is typically well tolerated with approximately 29% of patients developing long-term complications such as pouchitis, pelvic floor abscess, or bowel obstruction.[43]

Surgery in patients with CD is usually reserved for patients with intractable hemorrhage, perforation, persistent or recurrent obstruction, abscess, dysplasia, cancer, or medically refractory disease.[27,44,45] The 10-year cumulative risk of surgical intervention is 40% to 55%, with the 5-year postoperative recurrent rate reported as approximately 50%.[27] The surgical procedures performed most often include resections of the major intestinal areas of involvement. Patients who undergo multiple resections of the small intestine may develop malabsorption related to short-bowel syndrome. For some patients with severe rectal or perianal disease, particularly abscesses, diversion of the fecal stream is performed with a colostomy.

TABLE 52-4

Drug Monitoring Guidelines

Drug(s)	Adverse Drug Reaction	Monitoring Parameters	Comments
Sulfasalazine	• Nausea, vomiting, headache • Rash, anemia, pneumonitis • Hepatotoxicity, nephritis • Thrombocytopenia, lymphoma	• Folate, complete blood count • Liver function tests, Scr, BUN	Increase the dose slowly, over 1-2 weeks
Mesalamine	Nausea, vomiting, headache	GI disturbances	
Corticosteroids	Hyperglycemia, dyslipidemia	Blood pressure, fasting lipid panel	Avoid long-term use if possible or consider budesonide
	Osteoporosis, hypertension, acne	Glucose, vitamin D, bone density	
	Edema, infection, myopathy, psychosis		
Azathioprine/mercaptopurine	Bone marrow suppression, pancreatitis, lymphoma	Complete blood count	Check TPMT activity or NUDT15 phenotype

	Liver dysfunction, rash, arthralgia	Scr, BUN, liver function tests, genotype/phenotype	May monitor TGN
Methotrexate	Bone marrow suppression, pancreatitis	Complete blood count, Scr, BUN	Check baseline pregnancy test
	Pneumonitis, pulmonary fibrosis, hepatitis	Liver function tests	Chest x-ray
Infliximab Adalimumab Certolizumab Golimumab	• Infusion-related reactions (infliximab), infection • Heart failure, optic neuritis, demyelination, injection site reaction, signs of infection	• Blood pressure/heart rate (infliximab) • Neurologic exam, mental status • Trough concentrations (infliximab) • Antidrug antibodies (all agents)	Need negative PPD and viral serologies
Natalizumab Vedolizumab	Infusion-related reactions	Brain MRI, mental status, progressive multifocal leukoencephalopathy	Vedolizumab not associated with PML
Ustekinumab	Infections, skin cancers	Signs/symptoms of infection, annual skin exam	Rare instances of reversible posterior leukoencephalopathy syndrome (RPLS)
			Avoid live vaccines
Risankizumab-rzaa			Obtain LFTs and bilirubin prior to initiation of theraphy; monitor frequently for first 12 weeks
Upadacitinib	Risk of infection, higher rate of MACE (CV death, stroke, MI), bone marrow suppression, thrombosis, increase lipids and LFTs, lymphoma, fetal toxicity	Symptoms of infection, thrombosis, chest pain, neurologic deficits	Avoid live vaccines and use with strong CYP 3A4 inducers or inhibitors. Avoid with azathioprine or cyclosporine
Tofacitinib	Infection, thrombosis, lymphoma, elevated cholesterol, CPK, LFTs, lymphopenia, neutropenia, anemia	Symptoms of Infection or thrombosis	Avoid live vaccines. Screen for baseline TB. Do not initiate in patients with lymphocytes < 500/mm^3(0.5 × 10^9/L), ANC <1000/mm^3(1 × 10^9/L), or hemoglobin <9 g/dL (90 g/L; 5.59 mmol/L). Monitor lipids and LFTs every 4-8 weeks. Gastrointestinal perforation has been reported with use of the XR formulation. Drug interactions with CYP3A4 and 2C19 inhibitor

Ozanimod	Infection, heart rate, blood pressure, LFTs, respiratory rate, fetal abnormalities, macular edema, headache	Symptoms of infection or respiratory dysfunction, changes in vision	Need baseline ECG, WBC, LFTs, ophthalmic assessment, and testing for varicella zoster antibodies. Contraindicated if patient has experienced MI, unstable angina, stroke, TIA, decompensated heart failure, or Mobitz type II second- or third-degree AV block, sick sinus syndrome in the last 6 months, presence of sleep apnea, and concomitant use of MAOI. Women of childbearing age should use effective contraception during and for 3 months after use

Pharmacologic Therapy

The approach to treatment of IBD should consider all aspects of each individual patient in order to maximize therapy, improve patient symptoms and QOL, and prevent complications. To ensure optimal drug therapy, an assessment of each patient's health literacy and potential barriers to understanding and adherence should be performed. Involving the patient in the care process will help to keep him or her engaged. Since patients with IBD are often seen by GI specialists or surgeons, ensuring that each provider has a current, accurate, and complete medication list will help to prevent potential medication errors. Female patients of childbearing age should discuss with their providers their goals for becoming pregnant, as this may dictate the choice of drugs used.

None of the drugs used for IBD are curative; therefore, reasonable goals of drug therapy are resolution of acute disease symptoms and induction and maintenance of remission.

Sulfasalazine is the prototypical ASA, and is composed of a sulfonamide moiety (sulfapyridine) and mesalamine (5-aminosalicylate acid [5-ASA]) joined by a diazo bond in the same molecule.[46] Sulfasalazine has been used for years to treat IBD but was originally intended to treat arthritis. It is cleaved by gut bacteria in the colon to sulfapyridine (which is mostly absorbed and excreted in the urine) and mesalamine (which mostly remains in the colon and is excreted in stool).[46,47]

The active component of sulfasalazine is mesalamine, which exerts its effects locally in the GI tract; however, the mechanism of action is not completely understood. Beneficial effects of mesalamine may include scavenging of free radicals, inhibition of leukocyte motility, interference with TNF-α, transforming growth factor-β (TGF-β) and nuclear factor κB (NF-$\kappa\beta$), suppression of IL-1 production, inhibition of leukotriene and prostaglandin production, and induction of PPARy.[13,18,46,47]

Because the effectiveness of sulfasalazine is not related to the sulfapyridine component and since sulfapyridine is believed to be responsible for many of the adverse reactions to sulfasalazine, mesalamine can be administered alone. Given that mesalamine is rapidly and completely absorbed in the small intestine but poorly absorbed in the colon, drug formulations must be designed to deliver mesalamine to the affected areas in the GI while preventing premature absorption. Mesalamine can be used topically as an enema, to treat left-sided disease, or as a suppository for treatment of proctitis (Fig. 52-3).[48-50] The use of topical mesalamine preparations, such as enemas and suppositories, is more effective than oral preparations.[48-50] These therapies may be used concomitantly with the oral mesalamine preparations, which may result in additive efficacy in patients with UC.[49,50] Oral slow-release formulations will deliver mesalamine to the small intestine and/or colon based on the product design (Table 52-5). Slow-release oral formulations of mesalamine (eg, Pentasa) release mesalamine from the duodenum to the ileum, with up to 59% of the drug passing into the colon.[46,47] Some dose forms (Asacol, Asacol HD, Delzicol) utilize a pH-dependent coating that releases in response to intestinal pH.[46] Another tablet formulation of mesalamine (Lialda) uses a pH-dependent coating that releases at a pH of 7, in combination with a polymeric matrix core, referred to as the Multi-MatriX (MMX) system, and releases drug evenly throughout the colon also allowing for once-daily dosing.[51] A capsule formulation of mesalamine (Apriso) utilizes enteric-coated mesalamine granules in a polymer matrix for delayed and extended delivery of mesalamine to the colon and also allows for once-daily dosing.[46] Use of once-daily oral mesalamine preparations may enhance adherence, which may help to prevent relapse.[46-48] Olsalazine is a dimer of two mesalamine molecules linked by an azo bond. Mesalamine is released in the colon after colonic bacteria cleave the azo bond.[46] Balsalazide is a mesalamine prodrug that couples mesalamine with the inert carrier molecule 4-aminobenzoyl-β-alanine and is also enzymatically cleaved in the colon to release mesalamine.[46] Because the oral mesalamine formulations are delayed-release coated tablets or granules, they should not be crushed or chewed. Unlike sulfasalazine, all of these agents are safe to use for patients with sulfonamide allergies.

FIGURE 52-3

Site of activity of various agents used to treat inflammatory bowel disease.

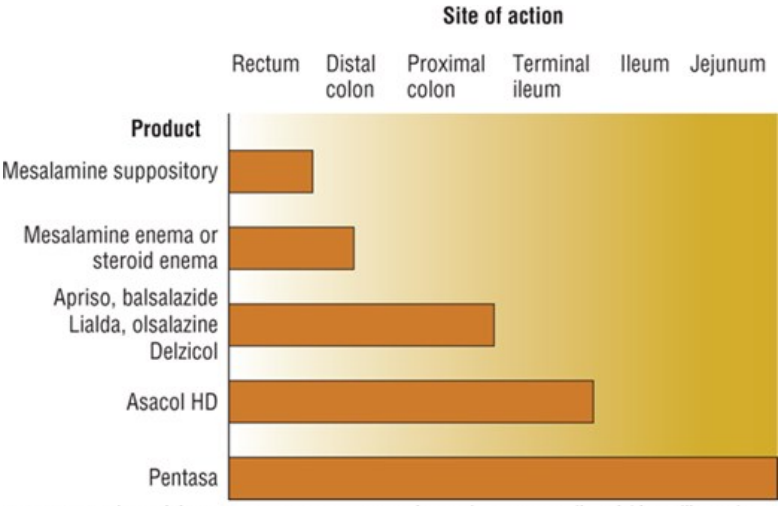


TABLE 52-5

Agents for the Treatment of Inflammatory Bowel Disease

Drug	Brand Name	Initial Dose	Usual Range
Sulfasalazine	• Azulfidine • Azulfidine EN	• 500 mg to 1 g • 500 mg to 1 g	• 4-6 g/day • 4-6 g/day
Mesalamine suppository	Canasa	1 g	1 g daily to three times weekly
Mesalamine enema	Rowasa	4 g	4 g daily to three times weekly
Mesalamine (oral)	• Asacol HD • Apriso • Lialda • Pentasa • Delzicol	• 1.6 g/day • 1.5 g/day • 1.2-2.4 g/day • 2 g/day • 1.2 g/day	• 2.8-4.8 g/day • 1.5 g/day once daily • 1.2-4.8 g/day once daily • 2-4 g/day • 2.4-4.8 g/day
Olsalazine	Dipentum	1.5 g/day	1.5-3 g/day
Balsalazide	Colazal	2.25 g/day	2.25-6.75 g/day
Azathioprine	Imuran, Azasan	50-100 mg	1-2.5 mg/kg/day
Cyclosporine	• Gengraf • Neoral, Sandimmune	• 2-4 mg/kg/day IV • 2-8 mg/kg/day oral	2-4 mg/kg/day IV

Mercaptopurine	Purinethol, Purixan	50-100 mg	1-2.5 mg/kg/day
Methotrexate	No branded IM injection	15-25 mg IM weekly	15-25 mg IM weekly
Adalimumab	Humira	160 mg SC day 1	80 mg SC 2 (day 15), and then 40 mg every 2 weeks
Adalimumab-atto	Amjevita[a]		
Adalimumab-abdm	Cyltezo[a]		
Adalimumab-adaz	Hyrimoz[a]		
Adalimumab-afzb	Abrilada[a]		
Adalimumab-bwwd	Hadlima[a]		
Certolizumab	Cimzia[a]	400 mg SC	400 mg SC weeks 2 and 4, and then 400 mg SC monthly
Infliximab	Remicade	5 mg/kg IV	5 mg/kg weeks 2 and 6, 5-10 mg/kg every 8 weeks
Infliximab-dyyb	Inflectra		
Infliximab-abda	Renflexis		
Infliximab-qbtx	IXIFI		
Infliximav-axxq	AVSOLA		
Natalizumab	Tysabri	300 mg IV	300 mg IV every 4 weeks
Budesonide	Entocort EC capsule, Uceris tablet	9 mg orally once daily	6-9 mg daily
	Uceris rectal foam	2 mg twice daily	2 mg daily
Vedolizumab	Entyvio	300 mg IV	300 mg IV weeks 2 and 6 and then every 8 weeks
Golimumab	Simponi	200 mg SC	100 mg SC weeks 2 and 4
Ustekinumab	Stelara	Weight based initial IV dose <55 kg (260 mg), 55-85 kg (390 mg), >85 kg (520 mg)	90 mg SC every 8 weeks

Tofacitinib	Xeljanz, Xeljanz XR	10 mg twice daily or 22 mg XR for 8 weeks; may continue for max of 16 weeks	5 mg twice daily or 11 mg once daily
Ozanimod	Zeposia	0.23 mg orally once daily days 1-4, then 0.46 mg once daily days 5-7	0.92 mg orally once daily starting day 8 of therapy
Upadacitinib	Rinvoq	45 mg orally once daily for 8 weeks	15 mg orally once daily
Risankizumab-rzaa	Skyrizi	600 mg IV weeks 0, 4, 8	180 or 260 mg Subcutaneously at week 12 then every 8 weeks

[a]Not available until 2023

SC, subcutaneous; IM, intramuscular.

Picking the appropriate ASA formulation and dose of drug for the disease severity and extent is key. Enemas and suppositories, while generally more effective than oral preparations, may not be as acceptable for use, particularly by younger patients. Therefore, individuating the patient's preference for a specific formulation should be taken into account when choosing ASA preparations. Consideration can be given to the use of once-daily products if there is evidence that multiple-daily dosing is affecting patient adherence.[18,46-51]

7 Corticosteroids are used to suppress acute inflammation in the treatment of IBD, and may be given parenterally, orally, or rectally.[52] They modulate the immune system and inhibit production of cytokines and mediators. It is not clear whether the most important steroid effects are systemic or local (mucosal). Budesonide is a corticosteroid that is administered orally in a controlled-release formulation designed to release in the terminal ileum or the colon depending on the product, or as a rectal foam. The drug undergoes extensive first-pass metabolism; so systemic exposure is thought to be minimized.[50,52]

Immunomodulators such as azathioprine, mercaptopurine, methotrexate, or cyclosporine are also used for the treatment of IBD (see Table 51-4). Azathioprine and mercaptopurine are effectively used in long-term treatment of both CD and UC.[18,27,53,54] These agents are generally reserved for patients who fail ASA therapy or are refractory to or dependent on corticosteroids. They may be used in conjunction with mesalamine derivatives, corticosteroids, TNF-α antagonists, and vedolizumab, and must be used for extended periods of time, ranging from a few weeks up to several months, before benefits may be observed.[53,54]

Cyclosporine has a short-term benefit in the treatment of acute, severe UC to avoid colectomy in patients failing corticosteroids, but has little efficacy in CD.[18,35] It is used initially as a continuous IV infusion of 2 to 4 mg/kg daily.[35] Cyclosporine poses a risk of nephrotoxicity and neurotoxicity. Studies evaluating tacrolimus for the treatment of IBD suggest a potential role for short-term use in patients with perianal or fistulizing CD; however, results have been variable with few data to support its routine use.[27] There are limited data to suggest routine use of tacrolimus in UC as well.[18] Methotrexate 15 to 25 mg given intramuscularly or subcutaneously once weekly may useful for maintenance therapy of CD and may result in steroid-sparing effects, while data supporting use in UC are lacking.[27,55]

Antimicrobial agents have limited roles as adjunctive therapies in IBD. Metronidazole can be used as adjunctive therapy for simple perianal fistulaes and may be combined with infliximab.[27] Risks of long-term antibiotic use include the development of antibiotic resistance, predisposition to *C. difficile* infection, and adverse effects such as neurotoxicity secondary to metronidazole use.

Biologic agents that target TNF-α have become a key class of agents in the treatment and maintenance of IBD.[56-58] Infliximab is an IgG1 chimeric monoclonal antibody that utilizes 25% murine variable regions and is administered IV. Infliximab binds TNF-α and inhibits its inflammatory effects, resulting in reductions in pro-inflammatory cytokines, such as IL-1 and IL-6. Adalimumab is also an IgG1 antibody to TNF-α; however, this agent, unlike infliximab, is fully humanized and contains no murine sequences. It is administered subcutaneously. Theoretically, the lack of a murine component in adalimumab reduces antibody development seen with use of infliximab. Certolizumab pegol is a humanized pegylated Fab fragment directed against

TNF-α that is also administered subcutaneously. Golimumab is similar in structure to adalimumab and offers similar efficacy to the currently approved agents.

Biosimilars are highly similar to the FDA-approved biologic agents. There are no clinically meaningful differences in efficacy or adverse effects from the reference products. Biosimilars have a nonproprietary name plus an FDA-designated suffix consisting of four lowercase letters that have no intended meaning. Some are considered to be interchangeable with the reference product.[56] Several infliximab biosimilar agents are approved for use in UC and CD, including infliximab-dyyb, infliximab-abda, infliximab-qbtx, and infliximab-axxq. There are several adalimumab biolsimilars, including adalimumab-adbm, adalimumab-atto, adalimumab-adaz, adalimumab-afzb, and adalimumab-bwwd. Legal disputes involving the manufacturers of the adalimumab reference products have led to delays in the commercial availability of the biosimilar products.

Natalizumab and vedolizumab are biologic agents that inhibit leukocyte adhesion and migration by targeting the α_4 subunit of integrin.[59,60,70] Vedolizumab works similar to natalizumab but is more specific for the $\alpha_{4\beta7}$ subunit of integrin, which targets leukocyte trafficking in the gut.[59]

Ustekinumab is a biologic agent that blocks IL-21 and IL-23 action by binding to the p40 protein subunit used by these cytokines.[61,62] It is approved for use in moderate-to-severe CD in patients who failed immunomodulators or corticosteroids but have not received anti-TNF therapy. It can also be used for patients who have failed anti-TNF therapy and in combination with immunomodulators. Risankizumab-rzaa is more specific for the p19 subunit of IL-23 and is also indicated for moderate to severe active CD. Tofacitinib and upadacitinib inhibit intracellular Janus kinases (JK) proteins, which are responsible for the signal transduction of multiple cytokines involved in the inflammatory cascade.[63] They are approved for patients with moderate-to-severe UC who are unresponsive to TNF-α inhibitors. Ozanimod is a small molecule that inhibits sphingosine-1 phosphate (S1P) which inhibits lymphocyte egress from lymph nodes and subsequent migration to the intestinal tract.[57] It is approved for the treatment of moderate to severely active UC in adult patients.

Ulcerative Colitis

Induction Therapy for Mild-to-Moderate Active Disease

Most patients with mild-to-moderate active UC can typically be managed on an outpatient basis with oral and/or topical ASAs or oral or rectal budesonide (Fig. 51-1; Table 51-6). Mesalamine preparations are typically better tolerated than sulfasalazine and thus are often chosen preferentially as first-line therapies. For patients with extensive disease, oral once daily mesalamine is generally preferred at a dose of 2 to 3 g/day (see Table 51-2).[18,64] Doses of greater than 3 g/day are reserved for lack of response to standard doses. Topical mesalamine in an enema or suppository formulation is more effective than oral mesalamine or topical steroids for distal disease. Mesalamine suppositories will only reach to approximately 10 to 20 cm within the lower GI tract and thus are reserved for patients with proctitis. Enemas will reach to the splenic flexure and are preferred for left-sided disease. Combining suppositories or enemas with oral mesalamine preparations has additive effects and is preferred in patients with extensive or left-sided disease if patients are willing to use both preparations.[18,64] Sulfasalazine, at doses of 2 to 4 g/day, may be considered in patients already receiving it in remission, or in those with prominent arthritic symptoms.[44]

TABLE 52-6

Levels of Evidence for Therapeutic Interventions in Inflammatory Bowel Disease

Interventions	Evidence Grades[a]
Ulcerative Colitis	
Rectal mesalamine is recommended at a dose of 1 g/day for induction of remission in mildly active UC	Strong
Mesalamine enemas at a dose of 1 g/day is preferred over rectal steroids for induction of remission in mildly active left-sided colitis	Strong
Rectal mesalamine at a dose of 1 g/day in combination with oral mesalamine at a dose of 2 g/day is preferred for induction of remission of	Conditional

mildly active left-sided UC	
Oral budesonide 9 mg/day is preferred in patients who fail or are intolerant of oral or rectal mesalamine for induction of remission in mildly active UC	Strong
High-dose mesalamine (>3 g/day) is suggested in patients who have suboptimal response to standard dose mesalamine	Conditional
Oral mesalamine at a dose of at least 2 g/day is recommended for induction of remission in patients with mildly active extensive colitis	Strong
Oral systemic corticosteroids are recommended for induction of remission in patients with UC of any extent who fail to respond to mesalamine	Strong
Sulfasalazine, mesalamine, or balsalazide is effective in maintenance of remission of distal disease; combining oral and topical mesalamine is more effective than is either alone	Strong
Sulfasalazine, olsalazine, mesalamine, and balsalazide are effective in preventing relapses in patients with mild-to-moderate extensive disease	Strong
Corticosteroids are not effective as maintenance treatment	Strong
Oral budesonide is recommended for induction of remission in patients with moderately active UC	Strong
Monotherapy with thiopurines or methotrexate is not recommended for induction therapy in patients with moderate-to-severe active UC	Strong
Infliximab, adalimumab, and golimumab are effective for induction of remission in moderate-to-severe active UC	Strong
Infliximab combined with a thiopurine is effective for induction therapy in moderately severe active UC	Strong
Tofacitinib is effective for induction and maintenance of remission for patients with moderate to severely active UC	Strong
Vedolizumab is effective for induction of remission in moderate-to-severe active UC	Strong
Tofacitinib is effective for induction of remission in patients with moderate-to-severe UC	Strong
Crohn's Disease	
Sulfasalazine is effective for treating mild-to-moderate active colonic CD	Conditional
Mesalamine has not consistently been demonstrated to be effective in active CD	Strong
Ileal release budesonide is effective for mild-to-moderate ileal or right-sided colonic disease	Strong
Metronidazole is not effective for treatment of luminal CD	Conditional
Ciprofloxacin should not be used for treatment of luminal CD	Conditional
Systemic corticosteroids are effective for short-term treatment of moderate to severely active CD	Strong
Conventional corticosteroids do not consistently achieve mucosal healing	Weak
Thiopurines should be considered for steroid sparing in CD	Strong

Azathioprine and mercaptopurine are not effective to induce short-term remission	Strong
Azathioprine and mercaptopurine are effective for maintenance of remission	Strong
TPMT testing should be considered prior to use of azathioprine or mercaptopurine	Strong
Anti-TNF agents should be given in patients refractory to azathioprine or methrotrexate	Strong
Vedolizumab with or without an immunomodulator should be considered for induction of remission in symptomatic patients	Strong
Natalizumab can be considered for induction of remission	Strong
Infliximab, adalimumab, and certolizumab are effective in lowering or eliminating corticosteroid use in corticosteroid-dependent patients	Strong
Ustekinumab should be given in moderate to severe CD in patients who fail treatment with corticosteroids, thiopurines, methotrexate, or anti-TNF agents or who have no prior exposure to anti-TNF agents	Strong
Cyclosporine, mycophenolate mofetil, and tacrolimus should not be used for CD	Strong
Methotrexate maintenance therapy (15-25 mg IM weekly) is effective for steroid sparing and for maintenance of remission	Conditional
Intravenous corticosteroids should be used for severe to fulminant CD	Conditional
Infliximab, adalimumab, and certolizumab are effective in severely active CD	Strong
Infliximab can be administered for treatment of fulminant CD	Conditional
Infliximab is effective for perianal fistulas	Strong

[a]Strong (desirable effects outweigh undesirable), conditional (uncertainty about trade-offs).

Data from References 6,8,18,27, and 35.

Controlled-release budesonide (Uceris) is an alternative for mildly active extensive UC, and is typically recommended in patients unresponsive to mesalamine. While budesonide foam may be used for distal disease, it has a limited role and is reserved for patients who are intolerant or unresponsive to topical mesalamine.[18,52,64] Oral budesonide MMX at a dose of 9 mg/day is preferred for patients who are unresponsive to optimized doses of mesalamine.[18,64] Oral corticosteroids in doses of 40 to 60 mg/day prednisone equivalent can be used as an alternative to budesonide for patients with moderately active extensive disease who are refractory to oral ASAs or require more rapid control of symptoms.[18,64] Topical corticosteroids, given as foams, enemas, and suppositories, while effective for patients with distal disease, are generally less effective than mesalamine but can be used for patients with tenesmus or intolerance to meslamine.[18,52,64]

Induction therapy for Moderate-to-Severe Active Disease

Patients with moderate-to-severe active disease require prompt initiation of therapies to quickly suppress inflammation. While oral mesalamine products may be effective for moderately severe UC, oral budesonide MMX is the preferred alternative prior to use of more systemic corticosteroids and for moderate disease.[18,35,64] Systemic corticosteroids are an alternative for the treatment of moderate-to-severe active UC regardless of disease location or in those patients who are unresponsive to maximal doses of oral and/or topical mesalamine derivatives.[18,35] Oral doses of 40 to 60 mg prednisone equivalent daily are recommended.[18,52,64]

Use of TNF-α inhibitors or vedolizumab are the main options for patients with moderate-to-severe disease who are unresponsive to aminosalicylates

or corticosteroids, or are corticosteroid dependent, and are more effective than immunomodulator monotherapy for induction of remission.[18,35] The choice of agent depends on previous exposure to biologic agents. For treatment-naive patients, infliximab or vedolizumab in combination with an immunomodulator (eg, azathioprine) is recommended preferentially.[18,35] Vedolizumab is superior to adalimumab in this setting.[65] Certolizumab is not approved for use in UC in the United States. Combining infliximab or vedolizumab with a thiopurine is more effective in inducing corticosteroid-free remission in patients with moderate-to-severe UC and is the preferred approach.[35,60] Vedolizumab should not be used in combination with TNF-α inhibitors. For patients previously exposed to infliximab, ustekinumab, tofacitinib or upadacitinib are preferentially recommended over vedolizumab or adalimumab.[35] Ozanimod is an alternative for induction and subsequent maintenance therapy in moderate to severely active UC.[66]

Therapy for Acute Severe or Fulminant Disease

Patients with ASUC or those with incapacitating symptoms require hospitalization for effective management. Under these conditions, patients generally receive nothing by mouth to promote bowel rest. Medications are given by the parenteral route, and oral sulfasalazine or mesalamine derivatives are not typically beneficial in this setting because of rapid elimination of these agents from the colon with diarrhea. Patients should be tested for *C. difficile* infection and receive VTE prophylaxis.

Systemic corticosteroids are used in the treatment of severe disease and may allow some patients to avoid colectomy. Methylprednisolone IV at a dose of 40-60 mg daily is considered a first-line agent.[35] A trial of corticosteroids is warranted in most patients before proceeding to colectomy, unless the condition is grave or rapidly deteriorating. The length of corticosteroid therapy before consideration of surgery is open to debate, with recommendations ranging from 3 to 5 days.[18,52] Steroids do increase surgical risk, particularly infectious, if an operation is required later.

8 Patients, who are unresponsive to parenteral corticosteroids, have the option of receiving higher-potency agents such as cyclosporine or infliximab.[18,35] Among those unresponsive to corticosteroids, 76% to 85% will typically respond to IV cyclosporine.[64] Infliximab as a single 5 mg/kg IV dose or a continuous IV infusion of cyclosporine 2 to 4 mg/kg/day, with goal serum levels of 200-400 ng/mL (mcg/L), is the typical dose range utilized and may delay the need for colectomy.[18,35] Patients with ASUC who respond to infliximab should be continued on this agent, while those who are controlled on IV cyclosporine can be transitioned to maintenance therapy with azathioprine.

Maintenance of Remission

9 After remission from active disease is achieved, the goal of therapy is to maintain remission for as long as possible. Various agents can be used and the choice may depend on the initial response to treatment, patient specific factors, and safety.

For patients with previously mildly active extensive or left side disease the oral aminosalicylate agents are preferred for maintenance therapy at a dose of at least 2 g/day.[18] The newer mesalamine derivatives are generally better tolerated than sulfasalazine and are associated with fewer adverse effects, making them a preferred choice.[1,18] For patients with proctitis, mesalamine suppositories are preferred at a dose of 1 g/day.[18,48,49] The frequency of administration of topical agents may be lessened to every third night over time.[18,48,49] For patients with previously moderate-to-severe active disease, the aminosalicylate products can be continued if remission is achieved initially with an aminosalicylate agent; however, the likelihood of sustaining remission is significantly lower, especially if more severe disease is present. Thiopurine monotherapy is recommended for maintenance in the setting of corticosteroid induced remission for moderate-to-severe disease.[18,35]

Corticosteroids have no role in the maintenance of remission, as they are ineffective and are associated with serious adverse effects with long-term use.[18,35,52] Budesonide oral MMX may be continued for up to 8 weeks for patients with moderate disease; however, systemic corticosteroids should be tapered over 4-12 weeks in moderately active UC patients achieving remission.[18,35,52] For patients who are steroid dependent, there is a strong justification for use of alternative therapies to allow for steroid withdrawal. Azathioprine may be effective in preventing relapse of UC for patients who fail ASAs or who are steroid dependent.[52-54] Approximately one-third of patients will maintain remission on azathioprine; however, the onset of action is slow and 3 to 6 months may be required before beneficial effects are noted.[52-54]

The TNF-α inhibitors, vedolizumab, ustekinumab, tofacitinib, or upadacitinib are all options for maintenance in patients with moderate-to-severe UC following successful induction of remission, and in those who are steroid dependent or have failed azathioprine. Once patients with moderate-to-severe disease achieve remission with a biologic therapy or azathioprine there is no further role for aminosalicylate agents, so these should be

discontinued.[35] For patients with ASUC, if remission with infliximab is achieved, this agent can be continued as maintenance therapy, while azathioprine or vedolizumab are recommended as maintenance therapies in patients achieving remission with cyclosporine.[35]

Crohn's Disease

Management of CD often proves more difficult than management of UC because of the greater complexity of presentation and the aggressive nature of the disease (Fig. 52-2; see Table 52-3). There is a greater potential for reliance on drug therapy with CD because resection of involved areas of the GI tract may not be possible. Surgical intervention is often required with rates of recurrence of CD following surgery reported in up to 80% of patients.[10]

Drug treatment of CD involves many of the same agents used for UC. While the treatment strategy for CD has often followed a similar "step-up" pattern as seen with UC, there has been more interest in the Treat-to-Target approach in patients with severe disease, which often involves more of a "step-down" approach of using more effective agents earlier in the disease course.[10,27,40]

Mild-to-Moderate Active Crohn's Disease

While effective in UC, ASAs have not demonstrated significant efficacy in CD. Sulfasalazine is reported to have marginal efficacy when compared with placebo for patients with mild-to-moderate CD, while the newer mesalamine derivatives are generally considered to have minimal efficacy.[27] Despite limited and variable effectiveness, the mesalamine derivatives are often tried as an initial therapy for mild-to-moderate CD in low-risk patients given their more favorable adverse effect profile.[67] Since CD often involves the small intestine, formulations such as Pentasa, which release in the small intestine, may be used to target areas of inflammation.

Systemic corticosteroids are frequently used for the treatment of moderate-to-severe active CD; however, controlled-release budesonide (Entocort) at a dose of 9 mg daily is a preferred first-line option for patients with mild-to-moderate ileal or right-sided (ascending colonic) disease.[27,52] This agent is superior to placebo and has demonstrated superiority to mesalamine and is preferred for patients with ileal disease.[27,52,67]

Antibiotics have little to no efficacy in treating luminal CD and are not recommended.[6,7,27] Broad-spectrum agents may be used for treatment of abscess formation in CD.[34] Metronidazole may have some role in prevention of postoperative recurrence of CD, and is also recommended for use in patients with perianal fistulas, particularly in combination with infliximab.[27]

Moderate-to-Severe Active Crohn's Disease

Patients with moderate-to-severe active CD require rapid suppression of inflammation for symptom improvement and prevention of complications. Oral corticosteroids, such as prednisone 40 to 60 mg/day, are generally considered first-line therapies for moderate-to-severe active CD who are unresponsive to ASAs.[10,27,52,60] Traditional oral systemic steroids have greater efficacy in inducing remission compared with budesonide in patients with moderate disease; however, the potential for adverse effects is greater, even with short-term use.[10,27,52] Hospitalized patients with moderate-to-severe disease who are unable to tolerate oral therapy are candidates for administration of parenteral steroids, with methylprednisolone or hydrocortisone being first-line options.[10,27] Systemic steroids do not appear to be effective for treatment of perianal fistulas, nor do they induce mucosal healing.[27,58]

10 Azathioprine, mercaptopurine, and methotrexate are generally not recommended for induction of remission as monotherapy in moderate-to-severe CD.[6,7,10,27] These agents are largely used for maintenance of remission, and are effective in maintaining steroid-induced remission and reducing steroid dependency, either as monotherapy or in combination with TNF-α inhibitors or vedolizumab.[10,27,53,54] Clinical response to azathioprine and mercaptopurine may be related to whole-blood concentrations of the metabolite 6-thioguanine (TGN). Concentrations of TGN between 230 and 450 pmol/8 × 10^8 erythrocytes have beneficial effects when used as monotherapy, but monitoring is not routinely performed or may not be available at some sites.[54,68]

11 Methotrexate given weekly intramuscularly or subcutaneously in doses of 15 to 25 mg is effective in reducing steroid dependency and maintaining remission, and may be considered as an alternative to azathioprine or mercaptopurine.[27]

The TNF-α inhibitors, including the biosimilar agents, are the preferred agents in the management of moderate-to-severe CD, especially those with high-risk features.[27,55,60,67] All agents in this class, with the exception of golimumab, which is not approved for use in CD in the United States, have similar rates of efficacy. The choice of agent depends on patient preference, route of administration, and cost. Adalimumab and certolizumab have the advantage of subcutaneous administration and may be considered alternates to infliximab as initial therapy or in those patients losing response to infliximab. Collectively these agents have demonstrated higher likelihood of induction of remission, reductions in hospitalization and the need for surgery, and lower rates of endoscopic recurrence.[10,27,57,58,60,67]

The use of TNF-α inhibitors in combination with thiopurines has quickly become the preferred approach to treatment of moderate-to-severe CD. Combination therapy results in added efficacy and reduction in antibody formation to the TNF-α inhibitor, which extends the duration of efficacy. Studies comparing infliximab to azathioprine combined with infliximab demonstrate greater rates of remission, steroid-free remission, and mucosal healing.[10,27,58] For this reason combination therapy is preferred unless patients have contraindications.

The integrin antagonists are options for patients who do not respond to steroids or have lost efficacy to or are intolerant of TNF-α inhibitors. Vedolizumab is also considered a first-line alternative to TNF-α inhibitors for moderate-to-severe disease.[27,59,60] These agents should not be used in combination with TNF-α inhibitors, but may be used with immunomodulators, which will also result in lower rates of antibody development.[27] Vedolizumab is preferred over natalizumab due to the reduced risk of adverse effects, particularly progressive multifocal leukoencephalopathy (PML) and has similar efficacy and safety outcomes compared to anti–TNF-α therapies.[59,60,69] If natalizumab is used, a baseline John Cunningham (JC) virus antibody must be negative prior to initiating therapy, and then should be monitored every 6 months. Therapy should be discontinued if a positive JC virus antibody is detected.[27]

Ustekinumab or risankizumab-rzaa can be considered for moderate-to-severe CD in patients who have failed previous treatment with corticosteroids, immunomodulators, or TNF-α inhibitors, in patients with no prior exposure to TNF-α inhibitors.[27] These agents may be a preferred option for patients at higher risk of infections, those with advance age or multiple comorbidities, or in patients with prior malignancies.[27,56,60,62,67]

Severe/Fulminant Active Disease

Patients with severe or fulminant disease require prompt management in the inpatient setting and are often considered for surgical intervention. Parenteral corticosteroids at a dose equivalent of 40 to 60 mg prednisone should be instituted once the presence of abscess has been excluded.[27] TNF-α inhibitors may be used in severe disease, and infliximab may be considered in fulminant disease.[27] There are no data to support the use of cyclosporine, tacrolimus, or mycophenolate in patients with severe or fulminant disease.[27] TNF-α inhibitors are also considered first-line agents for fistulizing disease, with azathioprine and mercaptopurines as alternatives.[27] Patients may require surgical intervention in the setting of medically refractory disease.

Maintenance of Remission

Maintaining remission is typically more difficult with CD than with UC. Sulfasalazine may be considered in low-risk patients with disease confined to the colon who initially respond.[66] There is minimal evidence that oral mesalamine derivatives are effective therapies for maintenance of CD following medically induced remission, and therefore these agents are not preferred.[27,70] Mesalamine appears to have limited efficacy in preventing postsurgical relapse following resection, but can be considered in patients with isolated ileal resection with no risk factors for recurrence.[27] Metronidazole, 1 to 2 g/day, may also be used to prevent postoperative recurrence, but is not recommended for use in medically induced remission.[27]

Systemic corticosteroids have no role in maintenance of remission or prevention of recurrence of CD. These agents do not alter the long-term course of the disease and predispose patients to serious adverse effects with long-term use.[27] Despite a lower potential for systemic adverse effects, use of budesonide as maintenance therapy is only recommended for a duration of up to 4 months.[27]

All of the TNF-α inhibitors currently approved for use in CD are viable options for maintenance of remission.[27] Combination therapy with a thiopurine should be highly considered to further improve efficacy and to extend the duration of TNF-α inhibitor efficacy by reducing the immunogencity.[27] If surgical resection is being considered, TNF-α inhibitors should be started within 4 weeks of surgery in high-risk patients (age 2 prior resections for

penetrating disease) in order to prevent postoperative recurrence.[71] Methotrexate may be considered as an alternative to thiopurines to maintain corticosteroid-induced remission.[27] Vedolizumab, natalizumab, risankizumab, and ustekinumab can be used for maintenance in patients who initially achieve induction of remission with these agents.[34]

Selected Complications

Toxic Megacolon

The treatment required for toxic megacolon includes general supportive therapy, consideration for early surgical intervention, and drug therapy.[24] Perforation can significantly worsen outcomes, with up to 44% of patients requiring surgery.[24] Aggressive fluid and electrolyte management is required for dehydration. Transfusion may be necessary if significant blood loss has occurred. Opiates and medications with anticholinergic properties should be discontinued because these agents enhance colonic dilation, thereby increasing the risk of bowel perforation. Broad-spectrum antimicrobials that include coverage for gram-negative bacilli and intestinal anaerobes should be used as preemptive therapy in the event that perforation occurs. If the patient is not receiving corticosteroids, then high-dose IV therapy with hydrocortisone 100 mg every 6 to 8 hours should be administered to reduce acute inflammation.[24] Emergent surgical intervention, mainly an abdominal colectomy with formation of an ileostomy, is an important consideration for patients with toxic megacolon and prevents death in some patients.[43-45]

Extraintestinal Manifestations

For some extraintestinal manifestations of IBD, specific therapies can be instituted, whereas for others the treatment that is used for the GI inflammatory process also addresses the systemic manifestations.

Anemia secondary to blood loss from the GI tract can be treated with oral ferrous sulfate. If the patient is unable to take oral medication and the patient's hematocrit is sufficiently low, blood transfusions or IV iron infusions may be required.[32] Anemia may also be related to malabsorption of vitamin B_{12} or folic acid, particularly for patients who have had ileal resection, so supplementation may be required.[28,29] Screening for osteoporosis does not differ significantly from the general population. Patients with conventional risk factors for abnormal bone density should be screened for osteoporosis with dual x-ray absorptiometry and then periodically thereafter.[72] Screening should also occur in patients starting oral corticosteroids, particularly in patients who have received greater than 7.5 mg/day equivalent of prednisone for longer than three consecutive months.[72] If the patient is deemed high risk for osteoporosis, such as those receiving corticosteroids, or exhibits a reduced serum vitamin D concentration, vitamin D supplementation should be instituted.[29] If osteoporosis is present, then calcium, vitamin D, and a bisphosphonate or possibly teriparatide are recommended.[32] Corticosteroid use should be avoided or limited, and weight-bearing exercise initiated if possible.

There are no consistently recommended therapies for aphthous ulcers; however, topical viscous lidocaine may provide symptom relief while topical corticosteroids may promote healing.[32] Episcleritis or uveitis is often worse during exacerbations of the intestinal disease, and measures improving intestinal disease will improve these systemic manifestations. Cool compresses and topical corticosteroids or NSAIDs may provide symptomatic relief, while immunomodulators and TNF-α inhibitors when in use may also provide benefit.[32] For arthritis associated with IBD, short-term NSAID or corticosteroids may be considered. However, NSAID use may exacerbate the underlying IBD and predispose patients to GI bleeding, so COX-2 inhibitors may be considered.[33,73] Intra-articular corticosteroids may be tried to limit the adverse effects of systemically administered agents.[32] Skin manifestations often require local wound care and use of topical or systemic corticosteroids.[32,33] Anti–TNF-α therapies may also improve severe dermatologic manifestations.

Adverse Drug Effects

Compared with mesalamine, sulfasalazine is more often associated with adverse drug effects, and these effects may be classified as either dose related or idiosyncratic (Table 51-4).[18,27,46,47,74] The sulfapyridine portion of the sulfasalazine molecule is believed to be responsible for much of the sulfasalazine toxicity.[18] Dose-related side effects usually include GI disturbances such as nausea, vomiting, diarrhea, or anorexia but may also include headache and arthralgia. These adverse reactions tend to occur more commonly on initiation of therapy and decrease in frequency as therapy is continued. Approaches to the management of these adverse effects include discontinuing the agent for a short period and then reinstituting therapy at

a reduced dosage with subsequent slower dose escalation, administration with food, or substituting another enteric-coated 5-ASA product. Folic acid absorption is impaired by sulfasalazine, which may lead to anemia, so oral folic acid supplementation should be administered.

Idiosyncratic effects commonly include rash, fever, or hepatotoxicity, as well as relatively uncommon but serious reactions such as bone marrow suppression, thrombocytopenia, pancreatitis, pneumonitis, interstitial nephritis, and hepatitis. For most patients with idiosyncratic reactions, sulfasalazine must be discontinued. Mesalamine has been associated with development of interstitial nephritis as well; therefore, intermittent monitoring of serum creatinine is warranted.[74]

Up to 80% of patients who are intolerant to sulfasalazine will tolerate oral mesalamine derivatives.[18] The most commonly encountered adverse effects are nausea, vomiting, and headache. However, olsalazine may cause watery diarrhea in up to 25% of patients, often requiring drug discontinuation.

Adverse effects of corticosteroids include hyperglycemia, hypertension, osteoporosis, acne, fluid retention, electrolyte disturbances, myopathies, muscle wasting, increased appetite, psychosis, infection, and adrenocortical suppression.[18,52,74] To minimize corticosteroid effects, clinicians may use alternate-day steroid therapy; however, some patients do not do well clinically on the days when no steroid is given. For most patients a single daily corticosteroid dose suffices, and divided daily doses are unnecessary. Adrenal insufficiency after abrupt steroid withdrawal often necessitates gradual tapering of steroid therapy for patients using these agents daily for more than 2 to 3 weeks. Budesonide is preferred in CD involving the ileum or right colon, or in UC, and may also be substituted for prednisone in CD patients who are steroid dependent or require long-term therapy.[27,60]

Azathioprine and mercaptopurine may be associated with serious adverse effects such as lymphomas, pancreatitis, or nephrotoxicity.[18,27,53,54,74] Adverse events to thiopurines are typically divided into two groups: type A and type B.[27,35,54] Type A reactions are dose related and include malaise, nausea, infectious complications, hepatitis, and myelosuppression. Complete blood counts with differential should be monitored every 2 weeks while doses are being titrated. Type B reactions are considered idiosyncratic and include fever, rash, arthralgia, and pancreatitis (3%-15% of patients).[35,53,54] Predisposition to development of these adverse effects may be related to polymorphisms in the enzyme thiopurine methyltransferase (TPMT), which is partially responsible for activation and metabolism of these drugs. Determination of TPMT activity is recommended prior to initiation of therapy to determine which patients require lower doses of these agents.[54,74,75] Alternatively, evaluating TPMT genotype or phenotype can also assist in assessing a patient's risk for toxicity.[61,62,74,75] Doses may need to be reduced by 30% to 80% if low TPMT activity is present.[75] Adjusting azathioprine and mercaptopurine doses by measuring concentrations of metabolites, particularly TGN, may be useful, with target concentrations of 230 to 450 pmol/8 × 10^8 erythrocytes considered optimal.[61,62,68,75-77]

Variations in the NUDT15 allele also predisposes patients using mercaptopurine to excess myelosuppresion.[75,76] Assessment of the NUDT15 phenotype can be performed as well if Mercaptopurine is used, with similar recommendations for dose reductions if poor or intermediate metabolizer status is present.[75] Since the initial dosing of these agents is weight based, obtaining a current accurate weight for the patient is necessary as well. Obtaining a family history regarding lymphoproliferative disorders or lymphoma is important for determining if the potential risks outweigh the benefits of long-term use. Women receiving immunosuppressive therapy should undergo annual cervical cancer screening and all patients should be screened annually for melanoma.[72]

With the advent of coadministration of azathioprine with infliximab, development of hepatosplenic T-cell lymphoma (HSTCL) has become a concern. The overall impact of using both drugs together, the contribution of drug classes to the development of lymphoma, and the risk and effects of both drugs are unclear. Those most at risk appear to be younger male patients (<35 years) and most of the risk is thought to be conferred by the thiopurine component.[53,74] Thiopurines are also associated with the development of non-melanoma squamous cell carcinoma, with the risk being higher during combination therapy with TNF-α inhibitors.[72,74] Methotrexate is associated with the development of nausea, vomiting, pulmonary fibrosis, pneumonitis, hepatotoxicity, anemia, and renal dysfunction, and is a known abortifacient. Patients should have baseline liver function tests, serum creatinine, BUN, complete blood count, and chest x-ray prior to use. Female patients should have a negative pregnancy test prior to use. Some patients may require supplementation with folic acid. Female patients of childbearing age opting to use methotrexate should have a safe and effective method of birth control available that is based on their preference.

Most patients receiving metronidazole for CD tolerate the agent fairly well; however, mild adverse effects occur frequently. They commonly include nausea, metallic taste, urticaria, and glossitis.[27,74] More serious effects that occur with long-term use include development of paresthesias and reversible peripheral neuropathy. Other effects include a disulfiram-like reaction if alcohol is ingested in conjunction.

The TNF-α inhibitors may be associated with development of serious adverse effects and carry similar adverse effect profiles for the available agents. Patients who receive infliximab often develop antibodies to infliximab (ATIs), also referred to as antidrug antibodies (ADAs). These ADAs can develop in response to administration of the other TNF-α inhibitors as well. Overall up to 50% of patients may lose efficacy after 1 year of treatment due to ADA development.[68] The development of ADAs also results in increases in the occurrence of serious infusion-related reactions in up to 2.8% of patients.[75] Up to 10% of patients per year require discontinuation of infliximab due to adverse effects and loss of efficacy related to development of ATIs.[55,58,74,76]

Strategies to reduce ATI formation include administration of a second dose within 8 weeks of the first dose, concurrent administration of steroids (hydrocortisone 200 mg IV on the day of the infusion or oral prednisone the day prior), and use of concomitant immunomodulators agents such as thiopurines.[18,27,58,74] Loss of efficacy may be managed by a dose escalation to 10 mg/kg, reducing the dosing interval, or switching to another TNF-α inhibitor.[27,55,74,77] Delayed hypersensitivity reactions may also occur up to 14 days after administration, with 5 to 7 days being the most common time frame. Autoimmune phenomena, such as lupus and hemolytic anemia, may also occur during infliximab therapy but are uncommon, as are adverse neurologic events such as optic neuritis and demyelinating syndrome.[74,76] Anti-TNF agents may also cause worsening of heart failure and should be avoided in patients with New York Heart Association Class III or IV heart failure.

All TNF-α inhibitors predispose patients to development of serious infections, including fungal, bacterial, and viral. Patients with clinically significant active infections should not receive TNF-α inhibitors. While the overall risk of hospitalization for serious infections may be less than previously suspected, development of infection remains a serious concern and increases with age.[67,74,76] Reactivation of latent mycobacterial infections may occur because of the inhibition of TNF-protective mechanisms; therefore, patients should receive a tuberculin skin test (purified protein derivative [PPD] test) and a chest x-ray prior to initiating therapy to rule out undiagnosed tuberculosis.[67,74,76] Reactivation of hepatitis B may occur; thus, patients should also be screened for hepatitis B virus infection prior to initiating therapy. Patients should also be screened for hepatitis C infection, although it does not appear that use of TNF-α inhibitors is unsafe or significantly alters the disease course. Natalizumab is associated with development of PML and is only available via the manufacturer's TOUCH prescribing program. Patients receiving natalizumab should be monitored for development of adverse neurologic events and undergo MRI of the brain should development of PML be suspected. Vedolizumab has not been associated with development of PML and may be associated with a lower risk of infection compared to TNF-α inhibitors.[69,74,76] Ustekinumab, risankinumab-rzaa and tofacitinib carry many of the same adverse effects as the TNF-α inhibitors, and baseline screening for TB and hepatitis should be performed; however, overall risk of serious infection appears to be lower compared to TNF-α inhibitors.[67,69,74,76] Tofacitinib and upadacitinib are also associated with development of thrombosis and lymphoma, as well as neutropenia, lymphopenia, and anemia.[60,63,74,76] The risk of thrombosis for tofacitinib was observed at the higher doses of 10 mg twice daily, and in trials of patients with rheumatoid those greater than 50 years of age with at least one cardiovascular risk factor were at higher risk.[78] Tofacitinib and upadacitinib should be avoided in patients with risks for thrombosis or history of pulmonary, deep vein, or arterial thrombosis.[78] Ozanimod is associated with the development of several potentially serious adverse effects. These include increased rate of infection, macular edema, fetal abnormalities, bradycardia or atrioventricular block, liver injury, and respiratory dysfunction. This necessitates a thorough patient history be obtained for presence of cardiovascular or cerebrovascular events within the last 6 months, as well as a history of sleep apnea.

For patients receiving ustekinumab, risankizumab-rzaa, upadacitinib and tofacitinib, baseline screening for latent infections should be performed. If patients appear to be losing response to TNF-α inhibitors, evaluating for ADAs, if assays are available, in addition to evaluating serum trough concentrations may assist the clinician in determining if dose and frequency need to be altered. Recommendation trough concentrations for TNF-α inhibitors include >5 μg/mL (mg/L) for infliximab, >7.5 μg/mL (mg/L) for adalimumab, >20 μg/mL (mg/L) for certolizumab, while optimal concentrations for golimumab are unknown.[68]

Patients should be evaluated for use of recommended vaccines; however, if patients are receiving immunosuppressants or biologic agents, the use of live or attenuated vaccines may be contraindicated.[72] Patients who currently use tobacco should be encouraged to undergo tobacco cessation, as tobacco use will worsen CD.[27,72] Since nicotine often improves symptoms in UC, it may be more difficult to cease tobacco use in this patient population. Choice of tobacco cessation products should also be based on current nicotine consumption and patient preference.

Special Populations

Pregnancy and Breastfeeding

The occurrence or consideration of pregnancy may cause significant concerns for the patient with IBD. Patients with IBD have similar infertility rates as the general female population, and the rate of involuntary childlessness in IBD patients who have not undergone surgery is similar.[79-81] There is a greater risk of adverse pregnancy outcomes such as spontaneous abortion, low birth weight, cesarean section, congenital abnormalities, low Apgar scores, preterm rupture of membranes, and preeclampsia.[79-81] However, most patients can conceive normally and have a normal pregnancy. The impact of IBD disease activity on pregnancy still remains unclear. In patients in remission at the time of conception the rates of reported flares are 20% in CD and 33% in UC, and postpartum rates of relapse are reported as 14%.[78-81] Preconception counseling in patients with IBD is recommended, in addition to objective assessment of disease activity in order to optimize therapy.[1,8] Overall patients should optimally achieve at least 3 to 6 months of corticosteroid-free remission prior to conceiving.[7,9] Patients should be managed by a gastroenterologist throughout their pregnancy, and also be referred to an obstetrician who manages high-risk patients if they have active or complicated disease.[80,81]

Diligence should be given to reviewing current medications in patients with IBD who are both contemplating pregnancy or have already conceived. Sulfasalazine is generally well tolerated; however, it does interfere with folate absorption, so supplementation with folic acid 1 mg twice daily should be used during the pregnancy.[74,79,80] Sulfasalazine causes decreased sperm counts and reduced fertility in males and corticosteroids may adversely affect fertility as well.[82] This effect is reversible on discontinuation of the drug, and it is not reported with mesalamine. Other ASAs can be used as well; however, there are concerns regarding the presence of dibutyl phthalate in the coating of Asacol.[7,9] Mesalamine preparations not containing dibutyl phthalate should be preferentially used.[7,80] Steroids given systemically do not appear to be detrimental to the fetus, and in general can be used in the same manner as in non-pregnant patients.[4,7,80] Due to its lower systemic bioavailability budesonide may be considered safer than other systemic corticosteroids for pregnant patients.[4,7] Azathioprine and mercaptopurine appear to carry an overall minimal risk in pregnant patients, and should be continued in patients receiving these agents as maintenance therapy.[74,80] Given pharmacokinetic changes in azathioprine metabolism occur during pregnancy, monitoring of 6-TGN during and after pregnancy is indicated.[80] Use of TNF-α inhibitors in pregnant patients appear to carry an overall low risk, and continuation of therapy is warranted in most patients. Infliximab, adalimumab, and golimumab do cross the placenta and there are some concerns with increased exposure to the fetus in the third trimester. While the risk is low, consideration can be given to administering the last dose at 22 to 24 weeks of gestation to minimize drug transfer to the fetus in patients considered low risk for relapse.[75,80,81] For newborns of women who were receiving TNF-α inhibitors during pregnancy it is recommended that use of live vaccines be avoided.[80] In patients receiving combination therapy with azathioprine and a TNF-α inhibitor, consideration of switching to monotherapy can be given, with use of a TNF-α inhibitor as preferred therapy.[80] Natalizumab, vedolizumab, and ustekinumab appear to carry low risk when used as monotherapies; however, consideration can also be given to administering the last dose at 8 to 10 weeks prior to delivery to minimize fetal exposure.[7,9] Rizankizumab-rzaa does have a pregnancy exposure registry that female patients are encouraged to join. Tofacitinib does not appear to cause birth defects, miscarriage, or adverse fetal outcomes. There is a pregnancy registry that women who become pregnant while receiving tofacitinib are encouraged to enroll in. Upadacitinib does carry a potential risk for fetal harm, therefore a pregnancy test should be performed prior to starting therapy in women of child-bearing age. Effective contraception should be used during treatment and for 4 weeks after the final dose if applicable. Metronidazole and ciprofloxacin may be used for short courses for treatment of perianal disease, and should be avoided during the first trimester if possible.[74,79,81] Methotrexate should not be used during pregnancy, and should be stopped 3 months prior to conception. It should be stopped immediately in patients who become pregnant while taking it, with referral for obstetric counseling.[1,8]

Use of agents in breastfeeding women is also a consideration. Sulfasalazine does pose a small risk of kernicterus, as levels of sulfapyridine in breast milk are low or undetectable, and thus monitoring for this symptom should be implemented.[79-81] Other mesalamine derivatives are considered safe in breastfeeding.[78,79] Corticosteroids can be detected in breast milk, with fetal levels approximately 10% to 12% of maternal levels.[79] However, breastfeeding is believed to be safe, but mothers should optimally wait at least 4 hours after an oral dose of systemic corticosteroids before breastfeeding to limit exposure to the child.[7,9] The anti–TNF-α agents and thiopurines are generally considered safe for use in breastfeeding and carry minimal risk of adverse effects.[74,81] Breastfeeding should be avoided in patients receiving Upadacitinib or tofacitinib; including up to 6 days after the last dose of upadacitinib or 36 hours after the last dose of tofacitinib. Methotrexate should be avoided in breastfeeding mothers.[1,8] Metronidazole and cyclosporine should not be given to nursing mothers because these agents are excreted into breast milk and may cause adverse effects.[74,78-81]

Children and Adolescents

IBD can present early in life, with 6% to 15% of patients being diagnosed prior to 6 years of age, and CD being more prevalent than UC.[83,84] This distinction in pediatric patients is referred to as very-early-onset IBD (VEO-IBD).[83] Due to the aggressive nature of CD, patients may be at risk for poor nutritional status, growth failure, micronutrient deficiencies, anemia, and pubertal delay.[84,85] Patients should be assessed for nutrient deficiencies, particularly iron and vitamin D, and replacement implemented if needed.[83-87]

Drug treatment in pediatric patients is similar to adults, with mesalamine, azathioprine, and the TNF-α inhibitors all being viable options. Due to the association with development of lymphoma and pharmacokinetic changes in metabolism as patients get older, thiopurines are used less often in pediatric patients.[83] Due to the potential for adverse effects, corticosteroid use should be limited to short-term use as induction therapy. The TNF-α inhibitors have become a major drug class used in the management of pediatric patients with IBD for both induction and maintenance of remission. Infliximab is approved for use in the United States for patients 6-17 years of age with moderate-to-severe active CD. Adalimumab is also approved for use in patients 6 years of age or older with CD. Studies indicate that early use significantly improves clinical outcomes, such as remission and mucosal healing.[88] However, initial response rates in patients to infliximab with VEO-IBD may actually be lower due to differences in pharmacokinetics and immune pathways of the disease.[83] This may necessitate higher and more frequent dosing to optimize therapy. Data are lacking to support routine use of vedolizumab, ustekinumab, rizankizumab, upadacitinib, and tofacitinib in pediatric patients.

Older Adults

Up to 30% of patients with IBD develop symptoms after age 60, and prevalence in older patients appears to be increasing.[89,90] In North America the incidence of IBD is reported as 4-8 per 100,000 persons greater than age 60 and 15% of cases are diagnosed after age 60.[90] One of the difficulties in diagnosis of IBD is that patients greater than 60 years of age may have other conditions present that may mimic IBD symptoms. This includes ischemic colitis, diverticular disease, microscopic colitis, CRC, NSAID-induced intestinal changes, or radiation induced enteritis or colitis.[89,90] Older patients with CD may present more often with isolated colonic disease, while left-sided disease is more common in elderly patients with UC.[90]

The approach to drug therapy in older adults is similar to younger individuals; however, a multidisciplinary approach is favored given the greater number of comorbidities and medications that may be present.[90] Overall patient fitness and frailty should be assessed, as this may impact the potential for serious adverse effects from medications, such as infection.[89,90] The aminosalicylates can be used for both induction and maintenance therapy; however, routine monitoring of renal function should be implemented, as interstitial nephritis is a potential adverse effect.[90] Corticosteroids should still be reserved for short courses as induction therapy, as older patients may have conditions that corticosteroids may worsen, such as diabetes, hypertension, heart failure, glaucoma, or osteoporosis.[89,90] Budesonide may be preferred, if possible, due to the lower systemic bioavailability.

Thiopurines are an attractive option due to their oral route of administration; however, there are concerns about increases in hepatotoxicity and nonmelanoma skin cancers in older patients.[90,91] They should be used cautiously in this population, and methotrexate may be an alternative in some instances.[90,91] The TNF-α inhibitors can be used for induction and maintenance; however, more frail patients may be at higher risk for infection and malignancy, especially if used in combination with a thiopurine. Combination therapy should be reserved for patients with severe disease.[90] Use of ustekinumab, risankizumab-rzaa or vedolizumab may be preferred for more frail patients due to the lower overall risk for infection.[74,76,90] Tofacinib and upadacitinib are largely reserved as a second-line agent in elderly patients, due to both lack of data and increases in risk of thromboembolic disease. Lastly, older patients with IBD should have routine health screening and maintenance performed. This is important in this patient population due to the need for maintaining appropriate vaccinations and implementing screenings for osteoporosis and CRC.[72,92]

PATENTS WITH COVID-19 INFECTION

Given that patients with IBD are often receiving one or more immunosuppressive agents, concerns with the COVID-19 pandemic were that patients would be at higher risk for infection and potentially worse outcomes. In order to communicate information rapidly, an international reporting website, https://covidibd.org/, was formed to allow clinicians and investigators to report outcomes related to COVID infection in both adult and pediatric patients with IBD. This resulted in an initial report of outcomes in over 500 patients in 33 countries.[93] Based on the analysis, patients with IBD who were

older, had multiple comorbidities, or were receiving corticosteroids had more severe COVID-19 disease. Interestingly, TNF-α use was not associated with severe COVID-19 disease. A subsequent meta-analysis demonstrated that the risk of acquiring COVID-19 in patients with IBD is not significantly different than the general population and does also not differ based on subtype of IBD.[93] Worse outcomes, such as hospitalization and increased mortality was seen more in patients with UC and in patients receiving 5-ASA products or corticosteroids. TNF-α use was actually found to be a protective factor in this trial, indicating that the anti-inflammatory effects of these drugs may actually attenuate some aspects of COVID-induced inflammation. With regard to the COVID-19 vaccines, the Crohns and Colitis Foundation have released recommendations that patients with IBD should receive the vaccine, regardless of current medication use (https://www.crohnscolitisfoundation.org/coronavirus/vaccines). Both international and British guidelines also advocate for the same approach, indicating that the benefit of vaccination as soon as possible in patients with IBD outweighs the risk of potential reduced response in those receiving immunosuppressive therapies.[94-96]

EVALUATION OF THERAPEUTIC OUTCOMES

The success of therapeutic regimens to treat IBD can be measured by patient-reported complaints, signs, and symptoms; by direct clinician examination (including endoscopy); by history and physical examination; by selected laboratory tests; and by QOL measures. Evaluation of IBD severity is difficult because much of the assessment is subjective. Disease rating scales, such as the CDAI or other indices, have been created to make disease assessment more objective. The CDAI is a commonly used scale for patients with nonfistulizing disease and for evaluation of patients during clinical trials.[10,27] The scale incorporates eight elements: (a) number of stools in the past 7 days, (b) sum of abdominal pain ratings from the past 7 days, (c) rating of general well-being in the past 7 days, (d) use of antidiarrheals, (e) body weight, (f) hematocrit, (g) finding of abdominal mass, and (h) a sum of extraintestinal symptoms present in the past week. Elements of this index provide a guide for those measures that may be useful in assessing the effectiveness of treatment regimens. A decrease in CDAI of 100 points is considered a clinically significant response, with a score of less than 150 considered to be disease remission.[10,27] A subsequent scale was developed specifically for perianal CD, known as the *Perianal Crohn's Disease Activity Index* (PDAI). The PDAI includes five items: presence of discharge, pain, restriction of sexual activity, type of perianal disease, and degree of induration. The HBI may also be used in place of the CDAI.

Standardized assessment tools have also been constructed for UC.[1,18] Elements in these scales vary and include (a) stool frequency, (b) presence of blood in the stool, (c) mucosal appearance (from endoscopy), and (d) physician's global assessment based on physical examination, endoscopy, and laboratory data. While these tools are often used for assessment of patients in clinical trials, they are sometimes used in the clinical setting as well.

Additional studies that are often useful include direct endoscopic examination of affected areas and/or radiocontrast studies. Mucosal healing is considered a major end point for patients with luminal disease. For patients with acute disease, assessment of fluid and electrolyte status is important, because these may be lost during diarrheal episodes. Other laboratory tests, such as serum albumin, transferrin, or other markers of visceral protein status as well as markers of inflammation such as ESR or CRP, and fecal calprotectin, are used to monitor disease and drug therapy. Lastly assessing for both trough concentrations and presence of ADAs can help guide therapy in patients who are not responding to normal doses of TNF-α inhibitors.

Finally, a patient QOL assessment should be performed regularly.[18,27] Inquiry should be made regarding the patient's general well-being, emotional function, and social function. Social function may include assessment of the ability to perform routine daily functions and to maintain occupational activities, sexual function, and recreation. The most common tool used to assess QOL is the Inflammatory Bowel Disease Questionnaire (IBDQ), a 32-item questionnaire that covers four disease dimensions: bowel function, emotional status, systemic symptoms, and social function. The IBDQ has shown good correlation with the CDAI.[27] The standard short form 36 (SF-36) is often used as a measure of QOL in IBD intervention trials.

ABBREVIATIONS

ADA	antidrug antibody
ASA	aminosalicylate
ATI	antibody to infliximab

CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CRC	colorectal carcinoma
CRP	C-reactive protein
ESR	erythrocyte sedimentation rate
FC	fecal calprotectin
FODMAPS	fermentable oligo-, di-, and monosaccharides and polyols
HBI	Harvey-Bradshaw Index
HLA	human leukocyte antigen
HSTCL	hepatosplenic T-cell lymphoma
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IL	interleukin
IPAA	ileal pouch anal anastomosis
JAK	Janus Kinase
MMX	Multi-MatriX
NF-κ B	nuclear factor κ B
NOD2	nucleotide-binding oligomerization domain protein 2
NSAID	nonsteroidal anti-inflammatory drug
PDAI	perianal Crohn's Disease Activity Index
PML	progressive multifocal leukoencephalopathy
PPD	purified protein derivative
PSC	primary sclerosing cholangitis
QOL	quality of life
SCD	specific carbohydrate diet
S1P	sphingosine-1 phosphate

TGF-β	transforming growth factor-β
TGN	thioguanine
TLR	toll-like membrane receptor
TNF-α	tumor necrosis factor-α
TPMT	thiopurine methyltransferase
UC	ulcerative colitis
VTE	venous thromboembolism

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SELF-ASSESSMENT QUESTIONS

1. A patient with extensive ulcerative colitis has disease located:
   A. Only in the rectal area
   B. In the rectum and sigmoid colon
   C. In the terminal ileum
   D. Throughout the majority of the colon
2. In patients with ulcerative colitis symptoms may be worsened by which of the following factors?
   A. Use of ibuprofen
   B. Use of acetaminophen
   C. Nicotine use
   D. Exercise
3. Which enzyme's activity should be evaluated prior to initiation of therapy in patients receiving azathioprine?
   A. Xanthine oxidase
   B. CYP2D6
   C. TPMT
   D. HLA DRPHLA-DR2
4. Which of the following is more characteristic of ulcerative colitis versus Crohn's disease?
   A. Confinement of disease to the small intestine
   B. Fistula formation
   C. Involvement of the terminal ileum
   D. Superficial continuous inflammation of the intestinal mucosa
5. Which adverse effect may occur at a higher rate in patients receiving the combination of infliximab and azathioprine?
   A. Pancreatitis
   B. Lymphoma
   C. Hepatitis
   D. Encephalopathy
6. Which of the following drugs is administered intravenously?
   A. Golimumab
   B. Adalimumab

C. Certolizumab

D. Vedolizumab

7. Which location best describes the site of action of oral budesonide (Entocort EC)?

A. Sigmoid colon

B. Rectal area

C. Terminal ileum

D. Duodenum

8. Which one of the following is a potential adverse effect of ustekinumab?

A. Risk of infection

B. Progressive multifocal leukoencephalopathy

C. Neural tube defects

D. Heart failure

9. Antibody development to infliximab may result in:

A. Increased trough concentrations

B. Increase in duration of action

C. Reduction in therapeutic efficacy

D. Reduction in infusion related adverse events

10. Which drug is recommended for acute treatment of a hospitalized patient with fulminant Crohn's disease who has failed maximum doses of intravenous corticosteroids?

A. Azathioprine

B. Cyclosporine

C. Budesonide

D. Methotrexate

11. Which medication may induce infertility in male patients with inflammatory bowel disease?

A. Mesalamine

B. Sulfasalazine

C. Certolizumab

D. Golimumab

12. Which medication is associated with an increased risk of blood clots?

A. Budesonide

B. Tofacitinib

C. Prednisone

D. Ustekinumab

13. Which medication is most effective for treatment of mild-to-moderate proctitis in a patient with UC?

A. Sulfasalazine

B. Mesalamine suppository

C. Hydrocortisone enema

D. Ciprofloxacin

14. Which preventative measure is most appropriate for all patients with active IBD?

A. Annual influenza vaccination

B. Yearly colonoscopy

C. Thiamine supplementation

D. Folic acid supplementation

15. Which of the following is an extraintestinal manifestation of inflammatory bowel disease?

A. Pyoderma gangrenosum

B. Hypothyroidism

C. Hypertension

D. Glaucoma

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** Disease affecting the entire colon is called extensive, while left-sided refers to involvement of the sigmoid colon and rectum. Disease confined just to the rectal area in patients with IBD is referred to as proctitis.

2. **A.** Use of NSAIDs may worsen symptoms in patients with IBD, as they disrupt the intestinal barrier. Acetaminophen is generally safe for patients with IBD. Nicotine use may actually improve symptoms in patients with UC, while exercise has no effect on disease symptoms.

3. **C.** Thiopurine methyltransferase (TPMT) is a key enzyme involved in the metabolism of azathioprine. Activity of TPMT should be evaluated prior to initiation of azathioprine to determine if alterations in the dose are required.

4. **D.** The depth of inflammation is shallower than that observed in CD. For this reason, inflammation may penetrate the intestinal wall and affect adjoining structures, resulting in fistula formation in patients with CD. The small intestine is often the most common site affected in CD, while the colon and rectal area are more commonly affected in patients with UC.

5. **B.** The combination of TND-α inhibitors and thiopurines may result in higher incidences of hepatosplenic T-cell lymphoma, although the majority of risk is thought to be due to thiopurine.

6. **D.** Vedolizumab requires intravenous administration, while golimumab, adalimumab, and certolizumab may be given subcutaneously.

7. **C.** Oral budesonide (Entocort EC) is formulated to deliver budesonide to the terminal ileum, which is the most commonly affected section of the GI tract in patients with CD.

8. **A.** Usetkinumab blocks the activity of IL-12 and IL-23, which predisposes patients to an increased risk of infection.

9. **C.** Development of antidrug antibodies to the TNF-α inhibitors may ultimately neutralize the drug, resulting in loss of efficacy over time and the potential for increases in infusion-related reactions.

10. **B.** Cyclosporine or infliximab is endorsed by the AGA guidelines as a treatment option for patients with fulminant CD who fail systemic corticosteroids.

11. **B.** Chronic use of sulfasalazine had been associated with reductions in sperm count in male patients, and thus may contribute to infertility.

12. **B.** Tofacitinib has been associated with increases in pulmonary, venous, and arterial thromboembolism and should be avoided in patients with a history of clots or those at risk.

13. **B.** Topical mesalamine (suppository) delivers higher concentrations to the site of inflammation, which for proctitis would be the most effective. This results in better efficacy than orally administered aminosalicylates. Topical corticosteroids are considered less effective than topical mesalamine.

14. **A.** Patients with IBD should receive the usual annually recommended vaccinations, such as influenza.

15. **A.** Extraintestinal manifestations of IBD can affect many different organ systems, with the skin being a commonly involved site. Both pyoderma gangrenosum and erythema nodosum can be encountered in patients with IBD.