

INFLAMMATORY BOWEL DISEASE



Jeffrey F. Binkley, Pharm.D., BCNSP

Reviewed by Michelle M. Chapman, Pharm.D., FCCP, BCPS; Joseph T. DiPiro, Pharm.D., FCCP; and Karen Whalen, R.Ph., BCPS

Learning Objectives

1. Based on a patient's signs and symptoms, history, and diagnostic findings, distinguish between the characteristics of Crohn's disease (CD) and ulcerative colitis (UC) and understand how the site and type of disease can influence treatment options.
2. Given patient-specific parameters and indicators, assess a patient's severity of CD or UC and risk of disease progression or cancer development.
3. Based on a patient's history, symptoms, and type and site of disease, design and implement the best pharmacological interventions using antibiotic drugs, anti-inflammatory drugs, corticosteroids, immunomodulators, and adjunctive drugs to treat CD or UC and evaluate the effectiveness of treatment.
4. Evaluate and justify the appropriate use of infliximab to treat CD based on the efficacy, toxicity, and cost-effectiveness.
5. Design appropriate pharmacological therapies to maintain remission for patients with inflammatory bowel disease (IBD).
6. Given patient-specific information, design appropriate nutritional interventions for patients with IBD.
7. Given patient information regarding response to pharmacotherapy, design appropriate monitoring plans and evaluate appropriate counseling requirements to optimize treatment outcomes and prevent treatment failures.
8. Based on patient-specific needs, recommend resources for patients with treatment, economic or psychological challenges due to refractory IBD.

Introduction

Inflammatory bowel disease (IBD) is a grouping of two similar disorders: ulcerative colitis (UC) and Crohn's disease (CD). Although the pathogenesis of these disorders

is complex and has not been fully elucidated, both have distinct and overlapping clinical manifestations and pathology. These disease processes can have broad social, economic, and health-related quality of life influences that significantly impact patients and their families. Treatment options include medical and surgical interventions, but results are variable, depending on the type, severity, and location of disease. This chapter addresses the pathogenesis and treatment of these two potentially debilitating diseases, offering guidance to pharmacists who can help patients achieve optimal pharmacological therapy and improve their quality of life. Comparisons of UC and CD will be made throughout the chapter, noting similarities and highlighting differences in manifestations, diagnosis, and treatment of these disorders.

Pathophysiology of IBD

Definitions

Although there are many similarities between UC and CD, the basic defining differences involve the location of disease and the extent of inflammation. Ulcerative colitis is characterized by inflammation limited to the superficial mucosal layer of the colon and does not affect other areas of the gastrointestinal tract. Crohn's disease is characterized by transmural, or deeper, mucosal inflammation and can be present throughout the gastrointestinal tract. Other distinguishing characteristics for UC and CD are listed in Table 1-1.

For patients with UC, the rectum is almost always affected, but disease also may extend proximally and continuously to involve other locations within the large bowel. When only the rectum is inflamed, the disease is known as ulcerative proctitis. Distal colitis or proctosigmoiditis describes disease extending into the midsigmoid colon. Left-sided UC reaches the splenic flexure. Disease involving the entire colon, including

Abbreviations in this Chapter

CD	Crohn's disease
IBD	Inflammatory bowel disease
pANCA	Perinuclear antineutrophilic cytoplasmic antibody
Th1	Type 1 helper T cell
TNF	Tumor necrosis factor
UC	Ulcerative colitis

sections beyond the splenic flexure, is described as pancolitis.

For patients with CD, the severity of mucosal inflammation may lead to the development of fibrosis, which may result in obstructive symptoms, which are not seen in patients with UC. Sinus tracts may burrow and penetrate the serosa, giving rise to bowel perforations and fistula formation. Crohn's disease may involve any area of the gastrointestinal tract from the mouth to the anus, and areas of involvement may be patchy and affect multiple, discontinuous areas. The majority of patients with CD have some small bowel involvement, usually in the distal ileum; about 66% of patients with CD exhibit colonic disease. Crohn's disease of the colon sometimes spares the rectum, unlike UC which usually involves the rectum. Fewer patients have disease involvement in other areas of the gastrointestinal tract, such as the mouth, esophagus, stomach, and duodenum. Sometimes interchangeable terminology is used to describe CD in a specific location, such as Crohn's colitis or Crohn's ileitis. Patients who have involvement of both the ileum and colon are said to have ileocolitis.

Remission for IBD defined as the absence of symptoms of disease without the continued use of significant drugs, such as corticosteroids. Maintenance therapy is pharmacological intervention used to maintain remission and reduce the incidence of disease exacerbation or recurrence.

Epidemiology

In North America, the incidence for UC ranges from 2.2/100,000 to 14.3/100,000 person-years, and prevalence ranges from 37/100,000 to 246/100,000 people. The incidence for CD in North America ranges from 3.1/100,000 to 14.6/100,000 person-years, and prevalence ranges from 26/100,000 to 199/100,000 people. A higher incidence of IBD is observed in Jewish and Caucasian populations, and lower rates are seen in African-American, Hispanic-American, and Asian-American populations; however, studies suggest that the incidence of IBD in African Americans is approaching that of white Americans. The incidence of IBD is higher in urban areas. Although IBD can present at any age, peak incidence is observed in late adolescence and early adulthood; in addition, a second peak occurs between 50 and 80 years of age. A slight

predominance in CD has been observed in women, but predominance has been noted in men with UC.

Etiology

The pathogenesis of IBD is not known; however, three components have been established as major contributors: genetic predisposition, environmental factors, and immunologic influences. Disease development may be a result of complex interactions of all three of these influences; however, further investigation is required to fully understand the intricacies of these interactions.

Genetic Influences

Genetic factors may influence susceptibility to IBD. The majority of patients with IBD have no family history of IBD; however, in patients who have a positive family history, the most common occurrence is in first-degree relatives. Evidence derived from studies of identical twins indicates stronger genetic influences for CD than for UC. Specific genes responsible for the genetic risk of IBD have not been fully identified; however, multiple genes probably contribute to the complex IBD phenotype in humans.

Animal models with modified genes have indicated that colitis may result from alterations in many genes. Many gene alterations may impact changes in the mucosal immune system. Animal models with genetic alterations demonstrated a lack of disease when the animals were maintained in germ-free environments. This observation suggests the role of environmental factors in disease development.

Environment Influences

It has been suggested that environmental triggers play a role in the pathogenesis of IBD. Cigarette smoking, the use of oral contraceptives, nutritional deficiencies, and the presence of infectious agents have been suggested as environmental factors that possibly contribute to disease progression in susceptible patients. Although several studies have shown a negative correlation between smoking and UC, a positive correlation between smoking and CD recurrence has been demonstrated. A clear association between oral contraceptive use and IBD incidence has not been established. No specific causative factor has been identified in the diets of patients with IBD. In the setting of an underlying genetic or immune defect, pathogenic bacteria may play a role in the pathogenesis of IBD. Although some evidence has linked *Mycobacterium* species with CD, no single pathogen has been identified to have a consistent association with IBD. Microorganisms suggested as potential IBD pathogens include viruses, mycoplasmata, Chlamydia, and other bacteria. Limited evidence suggests that stress can worsen the symptoms of IBD, but the mechanism underlying this observation is unclear.

Immunologic Influences

In addition to genetic and environmental factors, altered immune response has been implicated in the pathogenesis of both UC and CD. Investigation has revealed two major areas of immune system involvement: an abnormal immune system against dietary or microbial antigens and possible alterations in mucosal barrier function.

Table 1-1. Distinguishing Characteristics of Crohn's Disease Versus Ulcerative Colitis

Characteristics	Crohn's Disease	Ulcerative Colitis
Pattern of inflammation and ulceration	Patchy, "cobblestone" appearance	Continuous and superficial
Histology	Transmural lesions and granulomas	Nontransmural and crypt abscesses
Location within the gastrointestinal tract	Any location from mouth to anus	Limited to colon and/or rectum
Presenting symptoms	Fatigue, diarrhea, abdominal pain, and fever	Rectal bleeding and bloody or watery diarrhea
Potential complications	Perineal disease, abscesses, and fistula development	Toxic megacolon
Response to surgery	Variable, not curative	Curative

During normal absorptive processes, the intestine has an effective barrier that uses both innate and acquired immune systems to discriminate harmless food antigens from infectious or toxic agents.

The innate immune system provides the initial response to a foreign antigen exposure and is composed of phagocytes and natural killer cells. The acquired immune system involves both humoral and cell-mediated mechanisms and includes B and T lymphocytes which provide specific immunity. Humoral immunity is mediated within the gastrointestinal tract by antibody-secreting B cells, primarily of the immunoglobulin A class. Cellular immunity is mediated by T lymphocytes, which include both CD4⁺ helper T cells and CD8⁺ suppressor T cells. CD4⁺ helper T cells include both type 1 (Th1) and type 2 (Th2) helper T cells. Inducers of cell-mediated immunity such as interferon-gamma, tumor necrosis factor-alpha (TNF- α), interleukin-2, and interleukin-12 are secreted by Th1 cells. B cell differentiation is regulated by Th2 cells by secreting interleukin-4, interleukin-5, interleukin-6, and interleukin-10. Animal studies suggest additional CD4⁺ subsets, which produce "down-regulatory" cytokines.

Studies show abnormally secreted immunoregulatory and inflammatory cytokines correlate with active IBD. Secretion of interferon-gamma and TNF- α by Th1 cells has a significant proinflammatory effect, whereas the secretion of interleukin-10 by Th2 cells suppresses the Th1-mediated responses. CD4⁺ T lymphocytes isolated from patients with CD secrete large amounts of interferon-gamma and TNF- α , implicating Th1 cells in the pathogenesis of IBD.

Abnormal B cell regulation may be a factor in IBD development. An increase in circulating B cells, perinuclear antineutrophilic cytoplasmic antibodies (pANCA), and other autoantibodies have been observed in patients with IBD. Studies have not shown that production of these

antibodies are directly involved in the development of IBD, and titers of pANCA are not indicative of disease activity.

An effective mucosal barrier function requires an intact intestinal epithelium, surface mucus, normal peristalsis, and the secretion of numerous protective factors. Epithelial cells provide the first barrier against pathogens crossing the gastrointestinal tract. Alterations in epithelial cells or in intestinal mucus, high concentrations of bacteria within mucus, and increased intestinal permeability may play contributing roles in the pathogenesis of IBD. Intestinal growth factors regulate the growth and differentiation of intestinal epithelial cells and may be involved in IBD pathogenesis. Excess arachidonic acid and its by-products, reactive oxygen and nitrogen products, have been implicated in IBD pathogenesis because of their potential effects on the mucosal barrier.

Clearly, researchers will continue to investigate the pathogenesis of IBD; however, the mechanisms of disease likely involve a matrix of interactions among these genetic, environmental, and immunologic influences.

Clinical Characteristics and Complications Ulcerative Colitis

Clinical Manifestations of UC

The severity of symptoms associated with UC usually correlates with the extent of colonic involvement. Initial presentation often includes an insidious onset of symptoms, often preceded by a history of self-limited, intermittent rectal bleeding. Other physical findings include abdominal tenderness, fever, weight loss, and pallor. In general, patients can be classified as having mild, moderate, or severe disease based on their symptoms and diagnostic studies.

About 33% of patients with UC experience mild disease, limited to the rectum and sigmoid colon, known as proctitis or distal colitis. Presentation of mild disease usually includes intermittent rectal bleeding, passage of mucus, and development of about four episodes of mild diarrhea daily. Tenesmus, or difficulty defecating despite urgency, mild abdominal pain, and periods of constipation are also common for patients with mild disease.

Patients with moderate UC usually have disease extending beyond the distal colon. These patients experience frequent loose bloody stools, mild anemia, moderate abdominal pain, and low-grade fever.

Patients with severe disease demonstrate extensive colonic involvement, often pancolitis. In general, these patients have frequent loose stools (as many as 10 stools/day or more) with severe abdominal cramping, fever, and significant bleeding. They also may experience rapid weight loss and malnutrition. Toxic megacolon is a condition that may occur in severely ill patients when colonic motility is impaired, the colon is dilated, and the patient's bowel movements decrease or cease. Serious consequences may result, including colonic perforation, peritonitis, and even death.

Complications of UC

Ulcerative colitis can include both local and extraintestinal complications. Local complications of UC include massive hemorrhage, fulminant colitis, toxic

Table 1-2. Extraintestinal Complications of Inflammatory Bowel Disease

Eye involvement
Uveitis
Episcleritis
Skin disorders
Erythema nodosum
Pyoderma gangrenosum
Joint disease
Peripheral arthritis (usually involves large joints with no synovial destruction)
Ankylosing spondylitis (may be the presenting manifestation of ulcerative colitis)
Sclerosing cholangitis (presents with an elevation in serum alkaline phosphatase and gamma glutamyltranspeptidase)
Venous and arterial thromboembolism

megacolon, intestinal perforation or stricture, and the development of colon cancer. Extraintestinal manifestations of UC can include eye involvement, skin disorders, joint disease, primary sclerosing cholangitis, and venous and arterial thromboembolism as described in Table 1-2.

Potential development of colon cancer is a major concern for patients diagnosed with UC. The risk of colon cancer is related both to the extent and duration of the disease. Patients with UC who have proximal disease involvement or who have a family history of colon cancer are at increased risk of developing colon cancer. In addition, patients with UC and primary sclerosing cholangitis may be at increased risk for colorectal cancer compared to those without primary sclerosing cholangitis. Compared to an age-matched population, the risk of colorectal cancer begins to increase 8–10 years after the onset of symptoms. The incidence of colorectal cancer is about 5–10% after 20 years and 12–20% after 30 years of disease.

Patients with UC should undergo surveillance colonoscopy, although the timing and the optimal number and location of biopsies that should be obtained are uncertain. Although specific recommendations regarding screening differ from various professional organizations, all agree that screening for cancer should occur in patients with UC who have not had a total colectomy. The timing of these screenings should be a collaborative decision between the patient and physician. The American Gastroenterological Association recommends that surveillance colonoscopy should begin 8 years after initial diagnosis of pancolitis, and 15 years after initial diagnosis of colitis involving the left colon. Colonoscopy should then be repeated every 1–2 years. The American College of Gastroenterology recommends annual surveillance colonoscopy beginning after 8–10 years of disease in patients who have not undergone colectomy. The American Society for Gastrointestinal Endoscopy recommends that patients with UC who have pancolitis begin surveillance colonoscopy after 8 years of disease. Four biopsies should be obtained every 10 cm from the cecum to the rectum. Suspicious lesions or masses should be biopsied. Colonoscopy should be repeated every 1–3 years. Colectomy is indicated if carcinoma, high-grade dysplasia, or dysplasia with lesions or a mass is found on surveillance.

Crohn's Disease

Clinical Manifestations of CD

In contrast to the common features found in patients with UC, the clinical manifestations of CD may vary greatly based on the extent of disease. Hallmark characteristics of CD include fatigue, prolonged diarrhea with abdominal pain, weight loss, and fever. Bleeding may or may not be present. Some patients may develop a fistula or abdominal abscesses.

Diarrhea may result from excessive fluid secretion and impaired fluid absorption, from bacterial overgrowth, or from bile salt malabsorption. Abdominal pain often is due to fibrotic strictures, which may lead to bowel obstruction.

Bleeding may be present in Crohn's colitis, but typically is observed less frequently than in UC. Diarrhea without bleeding, but with other features of IBD such as skin, eye, or joint problems, or a family history of IBD may aid in diagnosing CD.

Patients with CD are predisposed to sinus tract formation with potential bowel wall perforation resulting in acute peritonitis characterized by fever, abdominal pain and tenderness, and often a palpable mass. Fistula tracts can develop at various anatomical locations adjacent to the diseased bowel, and symptoms may vary accordingly. Patients with an enterocutaneous fistula have bowel contents draining to the skin surface. Enterointestinal fistulae may be asymptomatic or present as a palpable mass on physical examination. Enterovesical fistulae (bowel to bladder) lead to recurrent urinary tract infections often caused by multiple organisms and a complaint of pneumaturia, or the passage of air in urine. Passage of gas or feces through the vagina indicates presence of an enterovaginal fistula.

About 33% of patients with CD develop perianal disease. Signs and symptoms include perianal pain and drainage from large skin tags, anal fissures, perirectal abscesses, and anorectal fistulae.

Systemic symptoms in CD include fatigue, weight loss and fever. Weight loss often is related to decreased food intake because patients' symptoms are lessened when they do not eat. Weight loss also may result from malabsorption. Fever may be due to the inflammatory process or due to bowel infection.

Patients with mild to moderate CD are ambulatory and able to tolerate an oral diet without dehydration, toxicity, abdominal tenderness, mass, or obstruction. Patients with moderate to severe CD exhibit mild to moderate disease or present with prominent symptoms such as fever, weight loss, abdominal pain and tenderness, intermittent nausea or vomiting, or anemia. Patients with severe fulminant disease have persisting symptoms despite treatment with corticosteroids or exhibit high fever, persistent vomiting, intestinal obstruction, rebound tenderness, cachexia, or an abscess. Patients in remission become asymptomatic either spontaneously or after medical or surgical intervention. Patients requiring corticosteroids to remain asymptomatic are not considered to be in remission.

Complications of CD

Crohn's disease is associated with both local, extraintestinal, and malabsorption complications. Local

complications include intestinal obstruction, severe hemorrhage, acute perforation, the development of fistulae and abscesses and toxic megacolon. Patients with CD may exhibit extraintestinal manifestations related to inflammatory bowel disease activity as described in Table 1-2.

Malabsorption due to CD can have serious consequences, including weight loss, steatorrhea, calcium oxalate and uric acid stone formation, and vitamin B₁₂ deficiency. Bile acid malabsorption can occur in patients with distal ileal CD or who have had surgical resection of the distal ileum. Milder degrees of bile acid malabsorption may result in watery diarrhea, but more profound degrees of bile acid malabsorption impair micelle formation for fat absorption and can lead to development of steatorrhea. In addition, bile acid malabsorption often results in formation of gallstones because of build up of biliary sludge.

Steatorrhea can lead to severe malnutrition, clotting abnormalities, osteomalacia, osteoporosis, and hypocalcemia. Diarrhea and fat malabsorption due to steatorrhea may ultimately lead to weight loss and a decrease in absorption of key nutrients, such as fat-soluble vitamins. Calcium abnormalities lead to clotting disorders, osteomalacia, and osteoporosis. Primary bone density loss is related to corticosteroid use; however, alterations in calcium absorption also can occur in the setting of steatorrhea. Steatorrhea increases oxalate absorption and results in hyperoxaluria and can lead to calcium oxalate and uric acid kidney stone formation. Free calcium binds to fatty acids in the intestinal lumen, allowing free oxalate to be absorbed. Exposure to unabsorbed bile salts increases colonic permeability to small molecules such as oxalate. Volume depletion and metabolic acidosis can lead to a reduction in the urinary excretion of citrate, a process that normally inhibits oxalate stone formation. Dehydration and acidosis also increases uric acid kidney stone formation because acidic urine decreases uric acid solubility.

Vitamin B₁₂ is absorbed in the distal ileum; consequently, severe ileal disease or ileal resections can lead to vitamin B₁₂ malabsorption and deficiency, which may lead to pernicious anemia. Serum vitamin B₁₂ concentrations should be monitored in patients with ileal CD or in patients with a history of ileal resection.

Other nutrients commonly malabsorbed in patients with CD are folate, zinc, and iron. Folate deficiency may occur because of a decreased intake or because of treatment with sulfasalazine, which interferes with folate absorption. In general, other water-soluble vitamins are rarely deficient in CD. Zinc deficiency usually is caused by excessive wasting in diarrhea or by enteric fistulae. Iron deficiency frequently can be caused by a decreased intake, by rectal bleeding, and by decreased absorption in the gastrointestinal tract.

Patients with a long history of CD are at increased risk of colon cancer, and to a lesser extent small bowel cancer. In a population-based study from Sweden, the relative risk of colon cancer was 2.5 overall in patients with CD and 5.6 in those with only colonic disease. The relative risk was even greater in patients who were younger than 30 years of age at the time of diagnosis. Similar to UC, risk is related to the extent and duration of disease. Colorectal cancer in CD is observed in a similar time frame as that in UC. Despite the

increased relative risk of colon cancer in CD, the absolute number of patients at risk is relatively small because many patients with extensive colitis undergo colectomy early in the course of disease. Surveillance guidelines are similar for CD and UC. The American Gastroenterological Association concluded that the risk of colorectal cancer associated with UC and Crohn's colitis is similar for comparable extent, duration, and age of onset of inflammatory disease. As a result, the surveillance strategy previously discussed for UC also applies for Crohn's colitis. The American College of Gastroenterology recognizes the evidence of the carcinogenic potential of long-standing CD but does not provide specific guidelines for surveillance. The American Society for Gastrointestinal Endoscopy also recognizes that the risk of colorectal cancer is increased in Crohn's colitis. Surveillance colonoscopy and biopsy for dysplasia should be offered to patients with longstanding Crohn's colitis.

Diagnostic Approach and Tools

The clinical presentations of UC and CD are similar to many other diseases or conditions as listed in Table 1-3. Infection or adverse drug reactions must be ruled out both at diagnosis and during symptomatic periods. About 5–15% of patients are initially diagnosed with “indeterminate” colitis, because neither UC nor CD can be definitively diagnosed.

The diagnosis of IBD involves both subjective and objective parameters. Clinical history, family history, and patient physical examination often are as important as radiographic and endoscopic evaluations. A family history of IBD is associated with an earlier age of diagnosis in affected patients. Because of differences in treatment options, UC must be distinguished from Crohn's colitis.

Ulcerative colitis usually is diagnosed by characteristic clinical history, endoscopic mucosal findings, and histology from colonic biopsy. Presence of family history may aid in

Table 1-3. Differential Diagnosis for Ulcerative Colitis and Crohn's Disease

Mild disease
Lactose intolerance
Irritable bowel disease
Colonic disease
Radiation colitis
Ischemic colitis
Diverticular colitis
Infectious disease
<i>Salmonella</i>
<i>Shigella</i>
<i>Campylobacter</i>
<i>Aeromonas</i>
<i>Escherichia coli</i>
<i>Clostridium difficile</i> colitis
Cytomegalovirus
Tuberculosis
Amebiasis
Adverse drug reactions
Antibiotic drugs
Nonsteroidal anti-inflammatory drugs
Retinoic acid
Oral contraceptives
Penicillin-induced segmental hemorrhagic colitis

diagnosing UC. Flexible sigmoidoscopy often is necessary to determine the extent of disease present. A full colonoscopy usually is not necessary unless uncertainties remain regarding the underlying diagnosis.

Endoscopic findings in UC include mucosal erythema, petechiae, and possibly frank bleeding. More severe cases may be associated with ulcerations, exudates, and profuse bleeding. Colonic involvement is continuous in UC. Pseudopolyps may be present in diseased areas and indicate prior inflammation.

Characteristic histology can be identified through colonic biopsy and confirms the diagnosis of UC. Barium enema is rarely used as a diagnostic tool for UC because of its lack of specificity. Barium enema is contraindicated in severely ill patients who may be predisposed to ileus or toxic megacolon.

The diagnosis of CD usually is established with clinical and family history along with endoscopic and radiologic findings. Classic signs of CD seen on physical examination include perianal skin tags, sinus tracts, and a palpable, tender abdominal mass.

Colonoscopy is the major diagnostic tool used to establish the diagnosis of CD. Endoscopic features of CD usually demonstrate a “cobblestone” mucosal appearance. In contrast to the continuous inflammation of UC, areas of Crohn’s involvement are patchy and usually have intermittent areas of normal-appearing bowel. Pseudopolyps, as with UC, also may be present. Intestinal biopsy may be used to confirm the diagnosis of CD. Radiologic studies may be useful in documenting the diseased segments of the gastrointestinal tract not accessible by colonoscopy. Advances have been made in the development of diagnostic tools. A diagnostic imaging device in the form of a camera pill allows for the examination of the gastrointestinal tract without any adverse effects.

Differential diagnosis for CD is also described in Table 1-3. Findings favoring the diagnosis of CD include small bowel involvement, the absence of bleeding, sparing of the rectum, and presence of perianal disease or fistulae.

Measurements of serum antibodies may help distinguish UC from CD. In a study of children with IBD, patients who tested positive for pANCA and negative for anti-*Saccharomyces cerevisiae* antibodies were more likely to have UC than CD, with a sensitivity of 57% and a specificity of 97%. Children who were pANCA-negative but anti-*Saccharomyces cerevisiae* antibodies-positive were more likely to have CD with 49% sensitivity and 97% specificity.

Tools are available to assist clinicians in determining patient perception of IBD and for determining severity of disease for comparison of treatments in research studies. The Crohn’s Disease Activity Index was developed to aid in assessing severity of CD activity in adults. The Crohn’s Disease Activity Index evaluates eight variables such as number of stools per week, weight changes, patient

assessment of well-being, abdominal pain, and hematocrits. Scores of 150 and below are associated with quiescent disease, whereas values above 450 are associated with severe disease. Since the original study, researchers have associated scores of 200–250 with improved prognosis. In children and adolescents, the Pediatrics Crohn’s Disease Activity Index is used to assess disease severity. A score of 0 to 100 is assigned based on subjective patient historical information regarding abdominal pain, number of stools, and general well-being over the previous week. The index also assigns points based on laboratory assessment; weight changes; height velocity; and other physical examination findings. A score of 0–15 indicates minimal disease; 16–30, mild disease; and 31 or higher, moderate to severe disease. Children with severe CD will often have scores greater than 50. There is no universally accepted instrument for measuring disease activity in patients with UC. One commonly used instrument is the Disease Activity Index, which assesses stool frequency, presence of blood in the stool, a physician rating of disease activity, and sigmoidoscopic assessment. Remission is defined by a score of 0.

These instruments are specifically designed for clinicians’ assessment of disease; however, there also are patient-based questionnaires which allow practitioners to consider the patient’s own observations of disease impact.

Patient-based Questionnaires

Health-related quality of life assessment is an important measure of a patient’s own perception of his or her illness. The Inflammatory Bowel Disease Questionnaire is a widely used questionnaire for health-related quality of life assessment in patients with IBD. This questionnaire has been adapted to and validated in several languages and cultures. The original Inflammatory Bowel Disease Questionnaire contains 36 questions, but a shorter version and a pediatric version have been developed as well. This tool is useful both in clinical practice and in research.

Disease Progression Ulcerative Colitis

The progression of UC usually includes periods of intermittent exacerbations that alternate with periods of complete remission. For patients with proctitis and distal colitis, remission usually is achieved through medical treatment or may resolve spontaneously. Because of the potential for proximal progression of disease, patients should be monitored even after remission is achieved. For patients with more severe disease, medical therapy may be effective, but remission is difficult to achieve.

Surgical intervention with colectomy is considered curative for patients with UC, regardless of the severity of disease. Surgery is indicated for patients whose disease is refractory to conventional therapy or who experience massive hemorrhage or colonic perforation. Other potential surgical candidates include patients with toxic megacolon or

Ruemmele FM, Targan SR, Levy G, Dubinsky M, Braun J, Seidman EG. Diagnostic accuracy of serological assays in pediatric inflammatory bowel disease. *Gastroenterology* 1998;115:822–9.

Hyams JS, Ferry GD, Mandel FS, et al. Development and validation of a pediatric Crohn’s disease activity index. *J Pediatr Gastroenterol Nutr* 1991;12:439–47.

Table 1-4. Treatment Goals for Inflammatory Bowel Disease

Induce and maintain remission
Improve quality of life
<ul style="list-style-type: none"> • Alleviate or improve acute symptoms • Prevent or minimize psychosocial or emotional issues
Prevent or minimize risk of extraintestinal manifestations
Prevent or minimize risk of malnutrition or weight loss
Delay or prevent need for surgical intervention

carcinoma. About 30% of patients with UC eventually undergo colectomy.

Crohn's Disease

In general, patients with CD have alternating periods of exacerbations and remission. Although some patients experience prolonged remission, about 80% of patients with CD require surgical intervention.

For patients with IBD, the progression of disease can lead to many psychological and social issues. Patients may experience embarrassment with disease symptoms and may exhibit signs of anxiety and depression. Because of pain and embarrassment, possible slow response to therapy, or the inability to perform normal daily functions, patients and their caregivers often become desperate and may turn to expensive, unproven methods of therapy. Clinicians, including pharmacists, should intervene to educate patients and their caregivers on the nature and progression of disease and available treatment options. Appropriate education helps encourage patients to seek appropriate methods of treatment and prevents patients from having unrealistic expectations regarding their disease or treatment options.

Therapeutic Goals and Outcomes

Therapeutic goals for treating patients with IBD include lifestyle adjustments and pharmacotherapy management. The multifaceted nature of IBD, with potential for both local and extraintestinal manifestations and numerous psychosocial issues and economic burdens, necessitates a critical listing of desired outcomes. Outcome measurements include the use of tools to determine improvement in symptoms or a more general assessment of success by using data such as the number of hospitalizations or lengths of stay. Table 1-4 lists common therapeutic goals for patients with IBD. These goals may be altered or expanded to meet patient-specific needs. Barriers to these goals include a patient's inability to afford appropriate therapy, patient noncompliance, a lack of understanding regarding the nature of the disease, or unrealistic patient expectations regarding treatment effectiveness.

Quality Patient Care

Pharmacotherapy

Therapeutic options for UC and CD include similar drugs; however, desired outcomes and therapeutic goals may differ, depending on the severity and location of disease as illustrated in Figure 1-1. Many of the therapeutic agents used to treat IBD have contributed to a better understanding

of the complex pathogenesis of these disorders. The standard classes of drugs used to treat IBD, the rationale for their use, and their potential adverse effects are listed in Table 1-5.

Anti-inflammatory drugs (i.e., aminosalicylates and corticosteroids), antibiotic drugs, and immunomodulators are considered conventional therapy for IBD. Several preparations of mesalamine, or 5-aminosalicylate, are available but differ by delivery mode. Sulfasalazine, the prototype of the anti-inflammatory drugs, contains both mesalamine and sulfapyridine moieties. The drug must be cleaved by colonic bacteria to deliver active mesalamine to the inflammation site; therefore, its site of action is primarily the colon, although studies show effectiveness in the distal ileum. Adverse effects occur in up to 45% of patients treated with sulfasalazine and are mostly attributed to the sulfapyridine component of the drug. Patients with a sulfonamide allergy should not be treated with sulfasalazine. Dose-related adverse effects include nausea, vomiting, diarrhea, anorexia, arthralgias, and headache. Other adverse effects include rash, fever, and hepatotoxicity. Rare but serious reactions include bone marrow suppression, thrombocytopenia, pancreatitis, and hepatitis. Sulfasalazine doses should be increased in a stepwise fashion over several months to improve the patient's tolerance to the dose-related side effects.

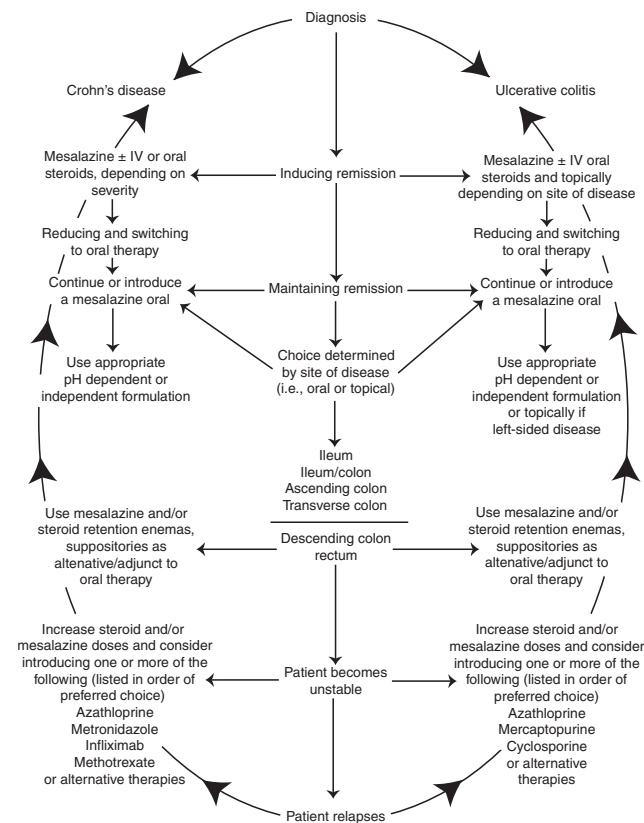


Figure 1-1. Treatment algorithm for ulcerative colitis and Crohn's disease. IV = intravenous.

Adapted with permission from Elsevier. Evans BK. Inflammatory bowel disease. In: Walker R, Edwards C, eds. Clinical Pharmacy and Therapeutics, 3rd ed. London: Elsevier, 2002:174.

Table 1-5. Drugs Used to Treat Inflammatory Bowel Disease

Drug Classifications/Examples	Usual Dose	Route	Possible Mechanism of Action	Potential Adverse Effects
Anti-inflammatory Drugs				
5-Aminosalicylates				
Sulfasalazine (Azulfidine)	2–4 g/day	Oral	Act on epithelial cells to moderate release of lipid mediators, cytokines and reactive oxygen species	Headache, nausea, rash, hemolytic anemia, hepatotoxicity, and decreased sperm count
Mesalamine (controlled release) (Pentasa) (Asacol)	3–4 g/day 2.4–4.8 g/day	Oral		
Olsalazine (Dipentum)	2–3 g/day			
Balsalazide (Colazal)	6.75 g/day			
Topical mesalamine (Rowasa)	2–4 g/day (enema) 1 g/day (suppository)	Rectal		Rectal injury
Corticosteroids				
			Inhibit several inflammatory pathways, Suppress IL transcription Suppress arachidonic acid metabolism Stimulate apoptosis of lymphocytes within the lamina propria of the gut	
Prednisone	20–60 mg/day initially, then taper	Oral		Adrenal suppression, growth failure, osteopenia, osteoporosis, edema, hirsutism, and hyperglycemia
Methylprednisolone	60 mg 3 times/day	Intravenous		Psychosis, cataracts, altered body shape, and impaired wound healing
Topical hydrocortisone (Cortenema)	100–200 mg/day	Rectal		Rectal injury Fewer systemic effects
Antibiotic Drugs				
			Treatment of undetermined pathogen Treatment of bacterial overgrowth Treatment of bowel microperforation	Inhibitory effect on normal bowel flora may lead to <i>Clostridium difficile</i> colitis or development of resistant microorganisms
Ciprofloxacin	500 mg 2 times/day	Oral		Nausea, diarrhea, rash, arthralgias, Achilles' tendon rupture, dizziness, fatigue, seizures, Stephens-Johnson syndrome, paresthesias, photosensitivity, metallic taste, disulfiram-like reaction, glossitis, paresthesias, peripheral neuropathy (irreversible)
	400 mg 2 times/day	Intravenous		
Metronidazole	10–20 mg/kg/day	Oral		
		Intravenous		
Immunomodulators				
Azathioprine	2.5 mg/kg/day	Oral	Inhibit proliferation of T and B lymphocytes	Nausea, vomiting, malaise Bone marrow depression (2%), liver dysfunction (0.3%), lymphoma, pancreatitis (3–5%), and allergic reactions
Mercaptopurine	2 mg/kg/day	Oral	Precise mechanism in IBD unknown	

Table 1-5. Drugs Used to Treat Inflammatory Bowel Disease (Continued)

Drug Classifications/Examples	Usual Dose	Route	Possible Mechanism of Action	Potential Adverse Effects
Methotrexate	25 mg weekly	Intramuscular Oral	Metabolites inhibit dihydrofolate reductase Possible inhibition of cytokine synthesis	Nausea, vomiting, diarrhea, hepatotoxicity, pneumonitis, and stomatitis
Cyclosporine	2–4 mg/kg/day	Intravenous	Prevents clonal expansion of T-cell subsets	Tremor, paresthesias, malaise, headache, abnormal LFTs, hirsutism, gingival hyperplasia, renal impairment, infection, and neurotoxicity
Biological Agents				
Infliximab	5 mg/kg/dose 5 mg/kg/dose at 0, 2, and 6 weeks for fistulizing disease 10 mg/kg/dose every 8 weeks for maintenance	Intravenous	Monoclonal antibody to TNF- α , apoptosis of inflammatory cells	Infusion-related reactions, fever, rash, myalgia, headache, infection, exacerbation of heart failure, activation of tuberculosis, and hepatotoxicity

IBD = inflammatory bowel disease; IL = interleukin; LFT = liver function test; TNF- α = tumor necrosis factor-alpha.

Other mesalamine-containing products do not have the sulfapyridine moiety and are therefore associated with fewer adverse effects. The formulation of these products differs, allowing for variations in the delivery site. An ethylcellulose-coated, delayed-release gelatin capsule formulation is designed to release mesalamine into the small intestine (jejunum and ileum) and the colon. A delayed-release tablet coated with an acrylic-based resin, which dissolves at a pH of 7, releases mesalamine only into the terminal ileum and beyond. A rectal formulation (suspension and suppository) allows delivery of active mesalamine to the rectum and distal colon. Olsalazine contains two mesalamine molecules linked by an azo bond and delivers both active molecules to the terminal ileum and colon. However, up to 25% of patients treated with olsalazine experience watery diarrhea that may require drug discontinuation. Balsalazide contains mesalamine attached to an inactive moiety, which is cleaved by bacterial azoreductase to deliver mesalamine to the colon.

Corticosteroid therapy works rapidly to reduce inflammation; however, these drugs are ineffective for maintaining remission and often are associated with significant adverse effects. Short-term effects include adrenal suppression, fluid retention, hypertension, hyperglycemia, and acne. Longer term effects include osteoporosis, muscle wasting, and psychoses. Patients taking corticosteroids are more prone to infection. The National Institutes of Health has published a consensus statement regarding the prevention, diagnosis, and therapy of osteoporosis in patients receiving corticosteroids. Patients treated with a daily dose of at least 5 mg of prednisone for more than 2 months should be considered for measurement of bone mineral density using dual x-ray absorptiometry. Calcium supplementation of 1000–1500 mg/day and vitamin D 800 units/day should be considered for patients requiring chronic corticosteroid therapy. In addition, treatment with bisphosphonate therapy

should be considered in patients with IBD using corticosteroids for more than 3 consecutive months. In controlled trials, alendronate, risedronate, and etidronate were effective in preventing corticosteroid-induced osteoporosis in non-IBD populations.

Immunomodulators such as azathioprine and its metabolite, mercaptopurine, may be useful for maintaining remission in both UC and CD. These drugs have a delayed onset of action, which may be as long as 3 months to 1 year. Doses used in IBD are lower than those used in organ transplant recipients. Adverse effects include allergic reactions, nausea, leukopenia, and pancreatitis. Potential toxicities of azathioprine and mercaptopurine often are attributed to their metabolites. Two enzymes are responsible for the production of these metabolites: thiopurine methyltransferase and hypoxanthine phosphoribosyl transferase. The accumulation of metabolites depends on the genetic polymorphism of these individual enzymes. Bone marrow suppression and hepatitis are related primarily to the activity of thiopurine methyltransferase. Genetic testing for thiopurine methyltransferase polymorphisms and direct measurements of metabolites have been suggested to optimize efficacy and minimize toxicity of these drugs. Whether these measurements will improve outcomes in patients with IBD has not been clearly established. Mesalamine is a relatively potent inhibitor of thiopurine methyltransferase and thus increases accumulation of the active metabolites of mercaptopurine increasing the risk of myelosuppression.

Tumor necrosis factor- α plays a pivotal role in the pathogenesis of mucosal inflammation in CD. Overwhelming success using infliximab, the chimeric monoclonal antibody to TNF- α , has profoundly changed the management of refractory and fistulizing CD. More than 66% of patients with CD treated with infliximab achieve remission. Maintenance therapy with infliximab has been widely accepted because of its corticosteroid-sparing

efficacy. Infliximab at doses greater than 5 mg/kg is contraindicated in patients with moderate to severe (New York Heart Association Class III/IV) heart failure due to higher rates of cardiovascular events and mortality. The Food and Drug Administration has issued several warnings regarding the adverse effects associated with infliximab, the most serious concerns relate to the reactivation of latent tuberculosis, development of sepsis and other infections, hepatic toxicity, and hematologic toxicities, including leukopenia, neutropenia, and pancytopenia. Patients should not receive infliximab who have not been screened for tuberculosis; however, patients who have initially been tuberculin skin test-negative also have development active tuberculosis while receiving infliximab. Patient monitoring during infliximab therapy should include complete blood cell counts and liver function tests, as well as clinical signs of toxicity, including pallor, easy bruising, fatigue, right upper quadrant pain, dark urine, or jaundice. In addition, an increased number of lymphomas were reported in a group of patients with CD who were treated with infliximab. Whether this is a true effect of infliximab or that patients with CD have an increased risk of lymphoma needs further study. Infusion reactions such as rash, hypotension, and shortness of breath occur, and drugs for treatment of hypersensitivity reactions should be available during infliximab infusions. Development of antichimeric antibodies may increase the risk of infusion reactions with each subsequent infliximab administration. Other adverse effects observed with the use of infliximab include neurologic disorders (e.g., multiple sclerosis, optic neuritis, and myelitis) and systemic vasculitis.

Treatment of UC

Development of a treatment plan for UC requires an understanding of the site and severity of disease. In addition, the presence of systemic or extraintestinal manifestations influences the treatment for the individual with UC. Goals of treatment are directed at inducing and maintaining remission of symptoms and inflammation to improve quality of life. In 2004, the American Gastroenterological Association published practice guidelines for adults with UC. These guidelines were developed using evidence-based research, and recommendations for patient management are classified by strength of the evidence.

Proctitis

Proctitis typically is treated topically with administration of mesalamine suppositories or corticosteroid foams. Local mesalamine therapy is preferred because of proven effectiveness as maintenance therapy. Remission rates are as high as 90%, and remission is maintained longer than 1 year in 75% of these patients. Anal irritation or discomfort may limit the effectiveness of or compliance with local therapies. Oral therapy with sulfasalazine or mesalamine also may be given. Relief of symptoms typically takes 3–4 weeks of therapy. Once remission is achieved, the dose can be tapered or discontinued. Because mesalamine oral agents are associated with adverse effects that mimic the symptoms

caused by the disease itself, episodes of diarrhea that occur at the time of initiation or dosage changes of mesalamine may require discontinuation of the drug until the cause of diarrhea is determined.

Left-sided Colitis

Left-sided colitis may respond to topical agents, depending on the severity of disease. Mild to moderate disease can be treated with mesalamine or hydrocortisone enemas. Because topical corticosteroids may produce systemic adverse effects, topical administration of mesalamine is considered first-line therapy. Mesalamine enema 4 g/night is given with response anticipated in 4–6 weeks. If response does not occur in this time, a morning dose is added or a hydrocortisone enema may be added. Mesalamine enemas cost considerably more than oral mesalamine agents; however, because the enemas are administered topically, they lack systemic effects and are associated with fewer adverse effects than the oral drugs.

If local administration of mesalamine is not effective, oral agents may be used. Combination therapy with topical and oral mesalamine may be more effective than either modality alone. Sulfasalazine, mesalamine, olsalazine, and balsalazide have been effective in UC. Doses of these drugs should be optimized and titrated to clinical effect before concluding lack of response or treatment failure. Sulfasalazine can be titrated up to 6 g/day, mesalamine to 4.8 g/day and olsalazine to 3 g/day, all in divided dosages. The oral drugs may require up to 6 weeks of treatment to achieve maximum benefit. Once remission is achieved, the regimen can be reduced to maintenance doses of sulfasalazine 2 g/day, mesalamine 1.2–2.4 g/day, or olsalazine 1 g/day. A Cochrane review of mesalamine products and sulfasalazine for maintenance of remission in patients with UC found both therapies effective, but suggested that sulfasalazine was significantly more effective than the newer drugs. The newer mesalamine agents have markedly fewer adverse effects in comparison with sulfasalazine. Patients who experience exacerbations of disease while receiving maintenance doses may require higher doses of maintenance therapy to prevent recurrence. Folic acid supplementation is necessary for patients taking sulfasalazine because it inhibits folate absorption. For mesalamine treatment failure and more serious cases, corticosteroids should be considered. Prednisone 40–60 mg/day orally usually is an appropriate starting dose, depending on severity of disease and symptoms. This dose generally is effective within 2 weeks, and subsequently the dose should be tapered by 5 mg/week. Often, it is prudent to initiate maintenance therapy during corticosteroid therapy. Although corticosteroids are effective at inducing remission, they are not effective in maintaining remission. Maintenance therapy with mesalamine products can be initiated concurrently during the taper of corticosteroids, and the therapeutic end point for corticosteroid use is remission.

Sutherland L, Roth D, Beck P, May G, Makiyama K. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2004;(4):CD000544.

Pancolitis

Initial therapy for pancolitis in patients with mild to moderate symptoms includes the combination of oral mesalamine or sulfasalazine and topical therapy with either mesalamine or corticosteroid enemas. The addition of oral corticosteroids, such as prednisone 40–60 mg/day, should be considered in patients when treatment fails with mesalamine therapy. Corticosteroids should be maintained until response, then tapered while maintenance doses of oral mesalamine are continued. Concurrent use of topical mesalamine may decrease the risk of recurrence. Patients with pancolitis also may develop iron deficiency anemia because of chronic blood loss. Iron replacement may be indicated. The persistence of diarrhea may require treatment with antidiarrheal drugs; however, these drugs should be used with caution and avoided in acutely ill patients, such as those with active pancolitis or bloody diarrhea, because of the risk of developing toxic megacolon. Loperamide is the antidiarrheal drug of choice because of its effectiveness and safety profile.

Fulminant Colitis

Patients with severe or fulminant colitis are at risk for toxic megacolon and bowel perforation. These patients most often require hospitalization. Abdominal radiographs should be obtained on admission, and decompression with a nasogastric tube or rectal tube often is required. Therapy for severe UC includes bowel rest and parenteral corticosteroids. Methylprednisolone, up to 20 mg given intravenously every 8 hours, is associated with fewer electrolyte disturbances such as sodium retention and potassium loss than is hydrocortisone.

Patients should respond to intravenous corticosteroids within 72 hours; if symptoms persist, the addition of mesalamine or corticosteroid enemas may be beneficial as adjunctive therapy. The role of antibiotic drugs in patients with severe UC continues to be evaluated. Controlled trials have not demonstrated therapeutic benefit from the use of oral vancomycin, intravenous metronidazole, or ciprofloxacin, when added to intravenous corticosteroids to treat severe UC. However, treatment regimens for severe colitis typically include broad-spectrum antibiotic drugs for patients with worsening symptoms despite intensive medical therapy.

Patients with severe disease refractory to corticosteroids may benefit from intravenous cyclosporine as a continuous infusion of 2–4 mg/kg/day. Lower doses also are effective with less toxicity, specifically with lower incidence of hypertension. One trial of 30 patients demonstrated evidence that monotherapy with cyclosporine in patients never treated with corticosteroids may be as effective as intravenous corticosteroid monotherapy for inducing remission (64% vs. 53%). Another study showed that cyclosporine use allowed avoidance of colectomy for up to 5 years in 62% of patients with severe, corticosteroid-

refractory UC. Forty-two patients with severe UC that was unresponsive to intravenous corticosteroids were treated with intravenous cyclosporine (4 mg/kg/day). Thirty-six patients (86%) responded to treatment, and oral cyclosporine (8 mg/kg/day) was continued in 31 patients for an overall mean of 20 weeks. Ten patients whose severe UC initially responded to cyclosporine had colectomies after a mean of 6 months. Of the initial responders, 25 (69%) also received mercaptopurine or azathioprine, and the cyclosporine and corticosteroid doses were tapered. For patients receiving cyclosporine without an immunomodulator, 45% required colectomy compared with 20% in patients receiving cyclosporine and azathioprine or mercaptopurine. The results showed 62% of all patients, 72% of initial cyclosporine responders, and 80% of patients whose severe UC initially responded to cyclosporine who received azathioprine or mercaptopurine avoided colectomy. All colectomies occurred within 18 months of cyclosporine initiation. Serum cyclosporine concentrations should be monitored during therapy to avoid toxicity; however, specific acceptable ranges are laboratory-dependent. Surgery is advised if cyclosporine therapy is ineffective in 7–10 days.

Surgical Intervention

Patients whose UC is unresponsive to medical therapy or who develop toxic megacolon should be considered for surgical intervention with total colectomy. Partial resections are not recommended for patients with UC because of the increased risk of cancer development.

Refractory UC

Patients with persistent symptoms despite therapeutic doses of mesalamine, topical therapy, or corticosteroid therapy may require additional drugs to control their symptoms. Azathioprine or mercaptopurine may be considered in patients with refractory UC before proceeding with surgical intervention. In one study of 34 corticosteroid-dependent patients with UC treated with azathioprine, therapeutic success of glucocorticoid withdrawal within 12 months was 70%, and of those, 73% continued without corticosteroid requirements within another year. The mean time to corticosteroid withdrawal was 4.6 months. Complete blood cell counts and liver function tests should be monitored every 2 weeks initially, then monthly. Because of the curative nature of colectomy and because of the toxic potential of these drugs, the risks and benefits must be weighed by both the health care team and the patient. Pharmacists can play a vital role by counseling the patient on the use of these drugs and discussing the anticipated course of the disease.

Alternative Therapies for UC

Nicotine

Epidemiologic studies have shown a protective effect of

D'Haens G, Lemmens L, Geboes K, et al. Intravenous cyclosporine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. *Gastroenterology* 2001;120:1323–9.

Cohen RD, Stein R, Hanauer SB. Intravenous cyclosporin in ulcerative colitis: a five-year experience. *Am J Gastroenterol* 1999;94:1587–92.

Lopez-Sanroman A, Bermejo F, Carrera E, Garcia-Plaza A. Efficacy and safety of thiopurinic immunomodulators (azathioprine and mercaptopurine) in steroid-dependent ulcerative colitis. *Aliment Pharmacol Ther* 2004;20:161–6.

cigarette smoking on UC activity. Trials using transdermal nicotine have shown effectiveness in active, mild UC. Trials using a transdermal nicotine patch in combination with mesalamine showed higher rates of remission than with mesalamine alone. Adverse effects were more prominent in nonsmokers. Transdermal nicotine is not effective for maintaining remission in UC.

Infliximab

Because of its overwhelming beneficial results in CD treatment, infliximab has been suggested for use in refractory UC; however, results from open-label and controlled, clinical trials in humans have been mixed. The largest study of infliximab in UC focused on patients with corticosteroid-refractory disease. Forty-two patients were randomly assigned to receive infliximab (5 mg/kg) or placebo at baseline and again at 2 weeks. During follow-up, disease activity, quality of life, and safety were assessed. After 6 weeks, remission rate in the infliximab group was similar compared with placebo (36% vs. 30%). The median change in quality of life as measured by the Inflammatory Bowel Disease Questionnaire was similar in both groups from week 0–6.

Although there currently are no reports comparing infliximab with intravenous cyclosporine, in placebo-controlled trials in patients with corticosteroid-refractory UC, response rates with infliximab are inferior to response rates reported with intravenous cyclosporine therapy (about 30% vs. 60–80%). Reports of successful infliximab therapy in UC are mostly open-label trials. Clinical trials are in progress to delineate the possible role for infliximab therapy in UC.

Treatment of CD

Differences in treating UC and CD relate to differences in the nature of disease, the presenting symptoms, and the presence of additional complications often associated with CD. Development of a treatment plan for CD requires an understanding of the site and severity of disease. In addition, the presence of systemic or extraintestinal manifestations may add to the treatment goals for the individual with CD. Goals of treatment are directed at inducing and maintaining remission of symptoms and inflammation to improve quality of life. Perhaps because of the complexity of disease and the relative explosion of newer treatment options, consensus and evidence-based guidelines or algorithms have not been endorsed in the United States. Algorithms have been proposed and are anticipated when consensus is reached. The IBD Section of the British Society of Gastroenterology recently published guidelines for managing IBD in adults. Guidelines for managing CD are being developed by the American Gastroenterological Association.

Crohn's Ileitis

Patients presenting with Crohn's ileitis should initially be treated with oral mesalamine agents. Sulfasalazine has been

established to be significantly superior to placebo for left-colon CD. No other drugs have been consistently superior to placebo or controls for induction of remission in mildly to moderately active CD.

Decisions regarding progressive addition of antibiotic drugs, corticosteroids or immunosuppressive drugs depend on the severity of disease and nature of patient response. Antibiotic drugs often are warranted in periods of presumed infection as indicated by fever and elevated white blood cell count. Corticosteroids should be added to the regimen if oral mesalamine agents fail to induce remission. An immunomodulator often is added as maintenance therapy early in the course of disease because of its delayed onset of action. Multiple drug therapy is warranted at initial presentation, if symptoms are severe. Lactose malabsorption is present in 35% of patients with CD due to lactase deficiency, and symptoms may be difficult to distinguish from active CD. Symptoms include diarrhea, abdominal pain, and flatulence after ingestion of milk or milk-containing products. Treatment can include reduction of dietary lactose intake, substitution of alternative energy and nutrient sources, and administration of commercially available lactase. Calcium supplementation should be considered to prevent bone loss in patients requiring lactose-restricted diets. Calcium carbonate typically is recommended because it is the cheapest form available. One tablet containing 200 mg of elemental calcium, provides 20% of the recommended daily allowance for calcium. Because sulfasalazine requires colonic bacteria for release of the mesalamine moiety, it is minimally effective for Crohn's ileitis. Delayed-release products containing mesalamine are the first-line drugs of choice. Appropriate use of these products improved Crohn's Disease Activity Index scores and resulted in higher rates of remission compared with placebo. Clinical response typically is achieved in 4 weeks. Comparison of mesalamine in an acrylic-based resin-coated tablet at a dose of 4 g/day and methylprednisolone 40 mg/day showed similar rates of remission. Initial dosages of these drugs usually are 2 g/day in divided dosages, but can be titrated to 4.8 g/day, based on patient response.

For patients with Crohn's ileitis who do not tolerate or respond to mesalamine products, a trial of antibiotic drugs may be warranted. Most experience in treating CD with antibiotic drugs is with metronidazole. Several trials have demonstrated benefit of using ciprofloxacin 500 mg 2 times/day and metronidazole 250 mg 4 times/day, alone or in combination, for treating active CD. Duration of therapy may vary based on response; however, response often requires up to 6 months of therapy.

Similar rates of remission have been achieved with the use of ciprofloxacin 500 mg 2 times/day and mesalamine in an ethylcellulose-coated gelatin capsule 2 g 2 times/day. Benefit from ciprofloxacin lasted for at least 6 months. For patients who respond favorably to ciprofloxacin, the regimen can be tapered to a maintenance dose of 500 mg/day after 6 weeks. Other broad-spectrum

Probert CS, Hearing SD, Schreiber S, et al. Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomised controlled trial. *Gut* 2003;52:998–1002.

Carter MJ, Lobo AJ, Travis SP. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2004;53(suppl 5):V1–V16.

antibiotic drugs effective in CD of the small bowel include tetracycline, cephalexin, and clarithromycin. Some patients may benefit from alternating antibiotic drugs over several weeks of treatment.

Corticosteroids may be used when mesalamine or antibiotic drug therapies fail. The National Cooperative Crohn's Disease Study found oral prednisone more effective than placebo in achieving remission. Dosages used in the study were 0.25 mg/kg/day for mild disease, 0.5 mg/kg/day for moderate disease, and 0.75 mg/kg/day for severe disease. The majority of adult patients treated with oral prednisone doses of 40–60 mg/day usually respond within 10–14 days. When response is achieved, the dose should be tapered gradually by 5 mg/week, with a goal to discontinue corticosteroids within a few months.

Once patients respond adequately to initial therapies of mesalamine, antibiotic drugs, or corticosteroids, maintenance therapy should be initiated to prevent disease recurrence. A meta-analysis demonstrated that agents containing mesalamine reduced relapse rates significantly in patients with inactive CD. Rates of relapse prevention were 91% at 6 months, 84% at 1 year, and 72% at 2 years in contrast to 77%, 60%, and 52%, respectively, in the placebo or no treatment groups.

Peritonitis

Patients who develop fever, chills, right lower quadrant pain, and leukocytosis may have microperforations with localized peritonitis. The management of peritonitis includes broad-spectrum antibiotic drugs and bowel rest. Recently published evidence-based guidelines from the Infectious Diseases Society of America aid the practitioner in selecting an appropriate regimen, therapy duration, and monitoring parameters. Intravenous antibiotic drug therapy includes a variety of drugs alone or in combination, depending on the severity of infection. Response to therapy typically is observed within 72 hours, and the intravenous antibiotic drug therapy should continue until clinical signs of infection resolve, including normalization of temperature and white blood cell count and return of gastrointestinal function. If there is an inadequate response to therapy after 5–7 days, appropriate diagnostic investigation with computed tomography or ultrasound imaging should be performed. Antimicrobial drug therapy should be continued against organisms initially identified. The use of corticosteroids in these patients is controversial. Treatment failure with medical therapy may prompt consideration for surgical intervention.

Treatment options vary for patients who experience abscesses, depending on location and nature of the abscess and the patient's surgical history. These options include one or more of the following: antibiotic drug therapy possibly along with corticosteroids, percutaneous drainage, or resection of the involved area of the intestine. Abscesses can

be detected and drained percutaneously when guided by computed tomography imaging. Appropriate antibiotic drug therapy is required after drainage.

Patients with obstructive symptoms caused by stenosis or intestinal adhesions from previous surgeries usually are managed with bowel rest and decompression by nasogastric suction.

Ileocolitis

Patients with active ileocolitis or colonic CD should initially be treated with sulfasalazine 1 g/day titrated up to 6 g/day or mesalamine 2 g/day titrated up to 4.8 g/day. Patients who are unresponsive to one of these drugs after 3–4 weeks may benefit from antibiotic drug therapy. Some studies suggest that metronidazole is equal to, or slightly more effective than, sulfasalazine for inducing remission. Oral metronidazole doses of 10 mg/kg/day usually are effective, but may be titrated to 20 mg/kg/day. In patients with more severe disease or who do not respond to initial therapies, corticosteroids such as prednisone 40–60 mg/day orally may be considered. The combination of sulfasalazine and prednisone has been more effective than either drug alone. When remission is achieved, corticosteroid doses should be tapered, and maintenance therapy with an oral mesalamine agent should be continued.

Refractory Disease

Many patients with CD remain symptomatic despite optimized doses of mesalamine, antibiotic drugs, and corticosteroids. Others experience disease flares when corticosteroid doses are reduced or discontinued. More aggressive pharmacotherapy or surgical intervention may be considered in these patients. Surgical intervention may provide temporary alleviation of symptoms; however, the rate of recurrence is high and multiple surgeries are associated with a risk of short bowel syndrome, a condition characterized by a significantly shortened gastrointestinal tract with resulting malabsorption of fluids and nutrients. Patients with short bowel syndrome often require lifelong parenteral nutrition and have a high potential for developing hepatobiliary complications.

Immunosuppressive drugs have been used successfully to induce remission in refractory CD. The most common drugs used are azathioprine and mercaptopurine at an initial dose of 50 mg/day. The dose can be titrated to 2 mg/kg for mercaptopurine and 2.5 mg/kg/day for azathioprine, based on clinical response. Response to therapy typically is seen in 3–6 months. Patients often need corticosteroids continued during the initial treatment with the immunosuppressive drugs, but the dose can be tapered after 1–2 months of azathioprine or mercaptopurine. The response rate for these immunosuppressive drugs is 60–70%. Meta-analysis showed a higher likelihood of remission with azathioprine treatment than with placebo (71% vs. 53%). In addition, the

Messori A, Brignola C, Trallori G, et al. Effectiveness of 5-aminosalicylic acid for maintaining remission in patients with Crohn's disease: a meta-analysis. *Am J Gastroenterol* 1994;89:692–8.

Solomkin JS, Mazuski JE, Baron EJ, et al. Guidelines for the selection of anti-infective agents for complicated intra-abdominal infections. *Clin Infect Dis* 2003;37:997–1005.

Pearson DC, May GR, Fick G, Sutherland LR. Azathioprine for maintaining remission of Crohn's disease. *Cochrane Database Syst Rev* 2000;(2):CD000067.

group treated with azathioprine demonstrated a greater ability to taper corticosteroids (83% vs. 53%) and a higher likelihood of withdrawal from therapy because of adverse effects (6.2% vs. 1.2%). Patients who are successfully treated with azathioprine or mercaptopurine should be continued on these drugs to prevent relapse. The optimal therapy duration has not been determined. Methotrexate may be used as alternative therapy in patients whose disease does not respond or in those who do not tolerate azathioprine or mercaptopurine. The initial dosing of methotrexate is 25 mg/week, usually administered intramuscularly. Response should be observed within 3 months. Once a response is achieved, the patient can be changed to an oral regimen. Folic acid 1 mg/day is recommended to minimize the hematologic adverse effects of methotrexate. Patients who have continued disease despite treatment with mesalamine agents, antibiotic drugs, and immunomodulators may require chronic low-dose corticosteroid therapy. Patients who require long-term corticosteroids should be monitored for cataracts and should receive a treatment regimen to minimize bone loss.

Fistulae

The presence of fistulae can be debilitating for patients with CD. Patients often experience pain, embarrassment, and frustration because of the inability to perform normal daily activities; they often become reclusive to minimize social interactions.

Conventional treatment of fistulae includes immunosuppressive drugs such as azathioprine or mercaptopurine. After 6 months of treatment with mercaptopurine, fistula closure was observed in 39% and improvement was seen in an additional 26%. However, exacerbation was common on discontinuation of therapy. Antibiotic drug therapy may be necessary when infection accompanies the fistula drainage, such as with enterovesicular fistulae, while surgical intervention often is required; however, surgery may not permanently eradicate fistulizing disease. The development and success of infliximab has revolutionized treatment of fistulae for patients with CD, and anti-TNF therapies are becoming a mainstay of therapy for these patients.

Infliximab is effective in patients with refractory, fistulizing CD and should be considered in patients whose fistulae do not respond to conventional therapy. In a study of 94 such patients, three consecutive infliximab doses of 5 or 10 mg/kg were given at 0, 2, and 6 weeks or placebo. After 26 weeks of follow-up, 68% in the 10 mg/kg arm, 56% in the 5 mg/kg arm, and 26% of the placebo arm experienced a reduction in the number of draining fistulae and avoided the need for additional increases in other pharmacological agents. Median time to response was 2 weeks, and duration of response was 12 weeks.

In a study of 306 patients with fistulizing CD, patients whose disease initially responded to infliximab at weeks 0, 2, and 6 and continued to demonstrate response at weeks 10 and 14 were randomized to receive 5 mg/kg of infliximab or

placebo at 8-week intervals. Those treated with infliximab had a higher likelihood of sustained response over 54 weeks compared with placebo. At 54 weeks, 36% of patients in the treatment group and 19% of patients in the placebo group had a complete absence of draining fistulae ($p=0.009$).

Patients may develop antibodies against infliximab, increasing the risk of infusion reactions and perhaps shortening the duration of response. Antibodies to infliximab were less likely to develop in patients who were treated while receiving concomitant therapy with corticosteroids, azathioprine, or mercaptopurine, possibly because of the impaired humoral response caused by these immunosuppressive drugs, and response to infliximab may be prolonged. The exact role for concomitant use of infliximab and immunomodulators has not been determined, although many practitioners continue immunomodulators while treating patients with infliximab.

Comparative studies with infliximab have not been conducted, but patients who are not able to receive infliximab could potentially be considered for treatment with cyclosporine. Some patients may not be candidates to receive infliximab because of a history of heart disease, tuberculosis, pneumonia, or hepatic disease. An alternative treatment for refractory, fistulizing CD is continuous intravenous infusion of cyclosporine. Initial dosing at 4 mg/kg/day intravenously can be switched to doses of 6–8 mg/kg/day orally after initial response. Although some patients have experienced fistula closure, long-term efficacy has not been demonstrated with cyclosporine.

Fibrin glue is another treatment option for mild, low-output fistulae in patients with CD. Fibrin tissue glue is a biological product that can stimulate wound healing and is not associated with significant risks. Fibrin glue cannot be used for patients with high-output fistulae. Further study is required to evaluate its overall effectiveness.

Postoperative Recurrence

Patients with CD who have a surgical partial resection with anastomosis have a 10–15% clinical recurrence rate, with endoscopic recurrence in as many as 80%. The recurrence rate is lower for patients with colonic disease who undergo a total colectomy with ileostomy. Because of the potential for intestinal contents triggering postoperative recurrence in patients with anastomosis, prophylactic maintenance therapy should be initiated after surgical intervention. Recurrence prevention or delay has been demonstrated with metronidazole and oral slow-release mesalamine agents. Patients who have had two or more resections may be considered for prevention therapy with azathioprine or mercaptopurine.

Adjunctive Therapies for IBD

Patients who have an incomplete response to first-line therapy may benefit from adjunctive therapy, such as antidiarrheal drugs, psychotropic drugs, fish oil, or probiotics. A general understanding of the rationale and use of various adjunctive diet therapies may aid the pharmacist or

Korelitz BI, Present DH. Favorable effect of 6-mercaptopurine on fistulae of Crohn's disease. *Dig Dis Sci* 1985;30:58–64.

Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004;350:876–85.

in providing appropriate counseling for patients and their caregivers.

Antidiarrheal Drugs

Caution should be exercised in treating diarrhea because the etiologies can be due to IBD itself, concurrent infectious or viral infections, and lactose intolerance. Eliminating milk products or adding lactase may help if the patient has lactose intolerance. Antidiarrheal drugs such as loperamide may be administered safely to most patients with IBD. Oral doses can be titrated to achieve the desired effect, but should not exceed 16 mg/day. Potential adverse effects include constipation with overdose, central nervous system depression, and hypersensitivity reactions. Drugs that slow gastrointestinal motility should be avoided in patients who are acutely ill, as their use might precipitate development of toxic megacolon. Patients with ileal disease or with a history of ileal resection may have bile salt diarrhea and may benefit from cholestyramine or colestipol as binding agents. Dosages of cholestyramine are initiated at 4 g/day and may be titrated to 12 g/day in divided dosages. The primary concern is the potential for intestinal obstruction. Patients who are taking warfarin should not take cholestyramine at the same time because cholestyramine will bind to warfarin, decreasing its absorption, and resulting in decreased anticoagulant effects. Prothrombin time and international normalized ratio monitoring is necessary in patients receiving both drugs. Cholestyramine also can reduce the absorption of other drugs; therefore, other drugs should be administered 1 hour before or 4–6 hours after giving cholestyramine. Drugs with possible interactions with cholestyramine include hydroxymethylglutaryl coenzyme A reductase inhibitors, thiazide diuretics, β -blockers, corticosteroids, thyroid hormones, digoxin, valproic acid, nonsteroidal anti-inflammatory drugs, loop diuretics, sulfonyleureas, and troglitazone. Patient compliance with cholestyramine often is problematic because of complaints of unpleasant taste and dyspepsia.

Psychotropic Drugs

Psychosocial stresses are problematic in patients with IBD. Limited evidence suggests that stress may worsen UC. Some patients may benefit from mild anxiolytic drugs such as benzodiazepines. In addition, antidepressant drugs may be indicated. Few scientific data exist for treating patients with IBD with these drugs. Controlled-release formulations may be inadequately absorbed in patients with severe disease or who have had significant portions of their bowel removed.

Fish Oil

Eicosapentaenoic acid derives from fish oil, contains n-3 fatty acids, and inhibits leukotriene activity. Eicosapentaenoic acid is effective as adjunctive therapy for UC. One trial of 18 patients with active UC showed that 4 months of fish oil was associated with decreased leukotriene B₄ concentrations in rectal dialysates, improved the histology index, weight gain, and reduced the

corticosteroid dose required. Higher rates of remission have been shown with fish oil than placebo in patients with relapsed CD. The dose of fish oil typically prescribed is 15–18 capsules/day (0.18 g eicosapentaenoic acid/capsule). Compliance is limited with this therapy because of the large number of capsules required and the resulting fishy mouth odor. However, benefit may be seen in 6–8 weeks. The routine use of fish oil as adjunctive therapy typically has not been accepted as standard practice; however, it is not a harmful intervention and decisions on whether to add fish oil to the treatment regimen should be discussed with the patient.

Probiotics

Probiotics is a term for live microorganisms, bacteria and yeasts, that may beneficially affect the host upon ingestion by improving the balance of the intestinal microflora. Because of the possible role of bacteria in the pathogenesis of IBD, probiotics have been suggested as therapeutic agents. Probiotics offer potential benefits by aiding in lactose digestion and absorption, decreasing the incidence of diarrhea, and modulating gastrointestinal immunity through increased immunoglobulin A production and effects on cytokine secretion. Probiotic preparations are available in capsules and as additives of lactobacilli or bifidobacteria in yogurt or milk. Two trials have shown the oral probiotic preparation of *Escherichia coli* Nissle 1917 to be as effective as mesalamine for maintaining remission in UC. There is little evidence of any risk associated with probiotics. These agents might be recommended for patients with lactose intolerance or diarrhea.

Nutritional Considerations

Malnutrition is commonly observed in IBD as a result of decreased intake, malabsorption, or increased energy expenditure due to hypermetabolism. Nutrition intervention should be aimed at meeting patients' nutrition requirements and preventing nutrient deficiencies.

Patients with IBD often have difficulty maintaining their ideal body weight. Up to 70% of patients with CD and up to 62% of patients with UC have weights below the ideal range. Pubertal delay is observed in up to 30% of pediatric patients with IBD.

Malnutrition can lead to decreased bone mineral density in patients with IBD. Corticosteroid therapy may increase the risk of osteopenia and osteomalacia. Supplementation with calcium and vitamin D may be indicated.

Patients with IBD benefit from adjunctive therapies that include diet modification or the addition of alternative drugs. Patients should be cautioned against the unproven claims of nutritional products that are not Food and Drug Administration-regulated. Many patients search the Internet, grasping for any possible intervention or product that may be helpful. Potential harm can occur when patients alter compliance with their prescribed medical therapy in favor of products with unproven efficacy. In addition, many products are expensive and may add significant cost to the patient's already burdened economic state.

Aslan A, Triadafilopoulos G. Fish oil fatty acid supplementation in active ulcerative colitis: a double-blind, placebo-controlled, crossover study. *Am J Gastroenterol* 1992;87:432–7.

Diet is an important consideration for patients with IBD. Patients should be advised to avoid foods that they associate with exacerbating symptoms; however, patients should maintain a well-balanced diet. Because diarrhea may be precipitated by bulky fiber, patients may be advised to adhere to a low-residue diet, which provides a low amount of indigestible foods and ultimately decreases the fecal output after digestion. Table 1-6 lists some foods that patients should avoid if they are placed on a low-residue or low-fiber diet. In addition, patients may benefit from avoiding spicy foods, high-fat foods, caffeine, carbonated beverages, and alcohol. Fermentable fiber, which is more soluble, may be helpful in maintaining remission because of the lack of bulk produced. Multivitamin use should be considered, especially when dietary restrictions are present. Parenteral nutrition is not used for therapeutic benefit in patients with IBD; however, in patients who are already malnourished or who are likely to be unable to eat for 7–10 days, parenteral nutrition may be a temporary intervention to prevent further decline in nutrition status. Parenteral nutrition may be indicated in patients with severe malnutrition awaiting surgery or as a beneficial adjunctive therapy in patients with severe fistulizing disease. Enteral nutrition is preferred over parenteral nutrition and may be beneficial in patients who have experienced weight loss or loss of appetite. Elemental enteral formulas are absorbed in the proximal gastrointestinal tract and may provide a means for better nutrient absorption and less output than other formulas in some patients with diarrhea or fistulae. Some enteral formulas are marketed specifically for use in IBD. These formulas are supplemented with probiotics but are expensive. Often, a general probiotic supplement is well tolerated and will not add significant cost to the patient's therapeutic regimen.

Issues in Special Patient Populations

Reproductive Health

Men and women with mild IBD have the same fertility rate as the general population. Risks of complications during pregnancy are similar to that of the general population as well. However, infertility in patients with IBD can occur in certain scenarios. Sulfasalazine use can decrease sperm count, a finding not seen with other mesalamine agents. This effect typically is reversible about 2 months after discontinuing the drug. Azathioprine may be used safely in men and women trying to conceive. Decreased fertility has been reported in women who have undergone surgery with colectomy. Impotence is an uncommon complication after proctocolectomy.

Patients with IBD who desire children may consider genetic counseling before conception because of the higher rate of IBD development in first-degree relatives.

Nutrition is particularly important during the first trimester of pregnancy. Women with IBD who become pregnant should have a nutritional assessment with intervention if desired weight gain is not achieved. Women with perianal CD typically are encouraged to have an abdominal delivery to avoid further trauma to the perianal area. Flexible sigmoidoscopy can be used safely during pregnancy, but colonoscopy should be avoided if possible. Treatment options typically are the same as with

Table 1-6. Foods to Avoid for a Low-residue or Low-fiber Diet

Whole grain flour
Cracked wheat
Bran
Oatmeal
Raw or dried fruits
Raw or dried vegetables
Seeds
Nuts
Coconut
Berries
Popcorn
Pickles

nonpregnant patients with the exception of drugs that are contraindicated in pregnancy. Long-term metronidazole use is mutagenic in bacteria and carcinogenic in rodents. Methotrexate is a potential abortifacient associated with skeletal abnormalities if used during pregnancy. Insufficient data exist for use of infliximab in pregnancy. Antidiarrheal drugs such as loperamide or diphenoxylate with atropine should be avoided. Exposure to diphenoxylate with atropine during the first trimester has the potential for causing fetal malformation. The benefit of continued use of corticosteroids, azathioprine, or mercaptopurine in more severe cases may outweigh the risks and should be discussed with the patient.

Pediatric and Adolescent Patients

Pediatric and adolescent patients are treated with similar regimens as adults, with age and weight appropriate dosages. Growth should be monitored closely and nutrition requirements and deficiencies should be addressed proactively. For pediatric and adolescent patients with IBD, enteral nutrition often is considered primary therapy. Corticosteroids should be used judiciously because of potential adverse effects, especially decreased growth and bone loss. Psychological support often is recommended because of effects of IBD on growth, body image, and appearance.

Investigational and Alternative Therapies for IBD

Investigational and alternative treatments are available for patients with IBD who are refractory to conventional therapy. Some drugs offer advantages over conventional therapy, but the risk-benefit ratio should be carefully evaluated. For example, budesonide is an alternative to prednisone and has significantly fewer systemic effects; however, it is not as effective as conventional corticosteroids in inducing remission. The therapies discussed in this section are not as well understood or as widely studied as the conventional drugs previously discussed; however, the goals of these therapies are to improve IBD treatment. Adverse effects associated with these drugs may not be well described or fully understood. Further investigation is required before these drugs can be routinely incorporated into conventional treatment regimens.

Budesonide

Budesonide is a corticosteroid that possesses a strong affinity for the glucocorticoid receptor but has low systemic effects because of extensive first-pass hepatic metabolism; thus, its toxicity profile and hypothalamic-pituitary-adrenal axis suppression effects are minimized. European trials of rectally administered budesonide have demonstrated benefit, but currently this form of the drug is not available in the United States. Oral budesonide is considered an alternative to prednisone and may be particularly useful to avoid the long-term effects of prednisone in pediatric patients. A meta-analysis of six trials concluded that oral budesonide was significantly less effective than conventional corticosteroids in inducing remission in active CD, but the risks of adverse effects were significantly reduced with budesonide. Budesonide was not effective in preventing relapse after remission was achieved.

Anti-integrin Antibodies

α -4 integrins are involved in leukocyte migration across vascular endothelium. Natalizumab, an antibody against α -4 integrin, recently was evaluated in a controlled trial of 248 patients with moderate to severe CD. Groups that received two natalizumab infusions (6 mg/kg or 3 mg/kg) had significantly higher remission rates compared with placebo. The highest remission rate was 44% at week 6 in the group that received two infusions of 3 mg/kg. All doses were well tolerated. Natalizumab was voluntarily removed from the market in February 2005, after two case reports, including one fatality, of progressive multifocal leukoencephalopathy in patients taking natalizumab concurrently with interferon-beta-1a for treating multiple sclerosis. Other clinical trials using natalizumab were halted pending further investigation.

Thalidomide

Thalidomide decreases production of proinflammatory cytokines, including TNF- α and interleukin-12 production by macrophages, monocytes, and microglial cells. Thalidomide was taken off the market decades ago secondary to its significant adverse effect profile, including teratogenic effects. However, recently, it reappeared as an effective therapy for many neoplastic, infectious, and inflammatory conditions. In two open-label trials, thalidomide appeared to be effective for inducing remission in some patients with active CD. Therapy for 12 weeks controlled active inflammation and induced fistula healing in patients with refractory CD. In a series of cases, thalidomide has been reported as an alternative strategy for patients who previously responded to anti-TNF therapy. However, the adverse effect profile may preclude long-term treatment in some patients and may limit its use for maintenance therapy. Toxicity of thalidomide include drowsiness, peripheral neuropathy, edema, and dermatitis.

Further study is needed before broad application is recommended.

Additional Anti-TNF Antibody Therapies

Two anti-TNF antibody therapies labeled for use to treat rheumatoid arthritis, etanercept and adalimumab, have been evaluated in clinical trials of patients with CD. Etanercept was not effective. Adalimumab, a recombinant human immunoglobulin G1 monoclonal antibody specific for human TNF, has been evaluated and appeared beneficial in an open-label trial of patients with CD who were no longer responsive or were intolerant to infliximab. Other humanized anti-TNF antibodies such as CDP571 and CDP870 also have been evaluated for treating CD. Safety and efficacy of these drugs have been evaluated in patients with moderate to severe CD, and their role and advantages over infliximab have not been determined. Potential advantages of humanized forms of anti-TNF antibody treatments include fewer infusion-related reactions and possible prolonged response; however, further research is required.

Growth Hormone

Crohn's disease often is associated with increased intestinal permeability. Regulatory peptides such as growth hormone or insulin-like growth factor-I are involved in control of intestinal permeability. In an open-label trial, recombinant growth hormone treatment in corticosteroid-dependent children with IBD was associated with positive changes in body composition, bone metabolism, and linear growth, without carbohydrate intolerance. Researchers concluded that treatment with growth hormone has beneficial effects in prednisone-dependent growing children. A controlled trial using growth hormone in CD showed a potential benefit on body composition in adults. These studies demonstrate a potential role for growth hormone in patients who may be at risk for growth failure due to disease and corticosteroid dependence; however, more research is needed before broad application can be recommended.

Antimycobacterial Therapy

Because of the observed link between CD and mycobacteria, antituberculous therapy has been investigated. A meta-analysis of seven trials aimed at treating *Mycobacterium* species in patients with CD indicated beneficial results of antituberculous therapy. Treatment regimens typically included clarithromycin and antileprotic drugs such as clofazimine or dapsone. Larger trials are being conducted to further understand the mechanism and benefit of these drugs. Investigational and alternative therapies may eventually lead to a better understanding of the pathogenesis of IBD and combination therapies to slow disease progression. Pharmacists should

Papi C, Luchetti R, Gili L, Montanti S, Koch M, Capurso L. Budesonide in the treatment of Crohn's disease: a meta-analysis. *Aliment Pharmacol Ther* 2000;14:1419-28.

Ghosh S, Goldin E, Gordon FH, et al. Natalizumab for active Crohn's disease. *N Engl J Med* 2003;348:24-32.

Kane S, Stone LJ, Ehrenpreis E. Thalidomide as "salvage" therapy for patients with delayed hypersensitivity response to infliximab: a case series. *J Clin Gastroenterol* 2002;35:149-50.

familiarize themselves with both conventional and alternative modalities to help optimize pharmacotherapeutic outcomes.

Monitoring

Pharmacists should monitor patients for drug effectiveness and safety. Response to therapy include improvement or resolution in symptoms such as diarrhea, abdominal pain, and fever. Pharmacists should have an understanding of potential adverse effects and should proactively seek ways to prevent or minimize these effects.

Laboratory tests to routinely monitor include complete blood cell count, electrolyte profile, and liver function tests. During periods of exacerbation, a sedimentation rate or C-reactive protein value may be beneficial to assess inflammatory activity.

Identifying those patients with IBD in remission who are at risk of early relapse is difficult, but, if possible, will allow optimization of therapy for those at highest risk of relapse. Calprotectin is a calcium-binding protein secreted primarily by neutrophils. Elevated fecal calprotectin concentrations have been observed in patients with IBD and gastrointestinal tract infections. Elevated fecal calprotectin concentrations correlate well with the more expensive and invasive indium 111-labeled leukocyte excretion. Recently, a fecal calprotectin concentration greater than 150 mcg/g stool was predictive of relapse within the next year, with the test having greater specificity for patients with UC than for those with CD (i.e., 82% vs. 43%, respectively). Other serum markers may prove to be useful in monitoring of patients with IBD. Further studies of the role of calprotectin or other markers of inflammation are needed before their use can be incorporated into routine clinical practice.

Patients taking corticosteroids to treat their IBD are at risk for many adverse effects, including osteoporosis and osteopenia (in children). The American College of Gastroenterology and American Gastroenterological Association have both published guidelines for diagnosing and managing osteoporosis in IBD. Bone testing using dual x-ray absorptiometry should be considered in patients with IBD who have many risk factors for osteoporosis such as smoking, low body mass index, sedentary lifestyle, hypogonadism, family history of osteoporosis, nutritional deficiencies, or age older than 60 years. Bisphosphonates should be prescribed for patients with IBD who have a T score on dual x-ray absorptiometry below -2.5. For patients taking long-term corticosteroids or with other important risk factors such as previous fractures, treatment with bisphosphonates should be considered at T scores below -1.0. For the patient with significant bone loss, referral to a specialist should be considered.

Patients taking immunomodulator therapy should be monitored for decreases in white blood cell counts, and therapy should be held and dosing reduced if the white blood cell count falls below 3000 cells/mm³. Patients also should be monitored for signs of infection or for classic signs of lymphoma (i.e., lymphadenopathy, night sweats, decreased appetite, and weight loss). In general, a complete

blood cell count should be obtained initially every 2 weeks for 2 months, then monthly for about 3 months, then every other month thereafter. In addition, patients can be monitored for metabolite concentrations to minimize risk of toxicity. The exact role for these measurements has not been fully identified.

Patients who receive cyclosporine therapy should be monitored for changes in kidney function that might warrant dosage adjustment. Monitoring serum cyclosporine concentrations may be useful to minimize adverse effects; however, in general, doses are lower and length of therapy shorter than for treating other disease states; therefore, monitoring may not be warranted.

Patients should be evaluated for heart failure and should be screened for tuberculosis before infliximab therapy is initiated. During therapy, patients should be monitored for signs of infusion-related reactions, infection, or hepatotoxicity. Monitoring efficacy and safety is an important responsibility for pharmacists, and proper administration of these drugs is another important consideration.

System Support for Drug Use Process

The ideal drug support system includes continuity of care from acute care to ambulatory care and provides for long-term care of patients with IBD. Patients dislike seeing different clinicians at each visit and want a system that allows a choice about appropriate long-term follow up. In addition, state-of-the-art informatics, appropriate personnel, and a health care system that allows rapid access for appointments, patient information, and physical and emotional support for patients with IBD will aid the drug support system. Patient information, history, and response to previous therapy should be easily accessible to all members of the health care team. Ideally, patients with IBD should be managed by a multidisciplinary team that includes physicians, nurses, enterostomal therapists, psychologists, and pharmacists. A system that offers assistance with matters related to insurance, medical assistance, and employment would be helpful. A robust informatics system helps provide accurate and efficient care.

Documentation

Pharmacists in community and inpatient settings should maintain care plans for patients with IBD and should record response to various therapies so that problems can be anticipated or prevented during future admissions or therapy attempts. Documentation of treatment successes and failures within the care plan and in an information database helps improve individual patient's care and the overall system by identifying areas for changes in patient management. Suggested documentation on a patient's care plan includes patient history, allergies, treatment goals, patient symptoms, pharmacotherapy selections and doses, time for observed effectiveness, adverse effects, and length of hospitalizations. In addition, laboratory monitoring of complete blood cell counts, liver function tests, and electrolytes, and for some patients, serum concentrations of drugs, such as

Costa F, Mumolo MG, Ceccarelli L, et al. Calprotectin is a stronger predictive marker of relapse in ulcerative colitis than in Crohn's disease. *Gut* 2005;54:364-8.

Table 1-7. Web Site Resources for Patients with Inflammatory Bowel Disease

Organization	Web Site	Patients Who May Benefit
Crohn's & Colitis Foundation of America	www.ccfa.org	Patients with IBD looking for helpful tips, information about disease, treatment and support groups
United Ostomy Association	www.uoa.org	Patients who have had surgical intervention with resulting ostomy
Oley Foundation	www.oley.org	Patients with UC or CD who require parenteral or enteral nutrition support
Centocor, Inc.	www.crohnsresource.com	Patients with IBD looking for information, helpful tips and clinical research reports
Centocor, Inc.	www.remicare.com	Patients who are treated with infliximab who want to keep up with latest research and developments with treatment
American Society for Gastrointestinal Endoscopy	www.asge.org	Patients with IBD who need screening recommendations for cancer

CD = Crohn's disease; IBD = inflammatory bowel disease; UC = ulcerative colitis.
All Web sites accessed on June 13, 2005.

cyclosporine, should be documented. Nutrition parameters also should be a part of the patient care plan. Changes in weight can be documented to aid nutrition screening and determining if an intervention is necessary. Adverse drug events should be documented and reported to the Food and Drug Administration according to the health care facility protocols or guidelines.

Patient Education

Pharmacists play a vital role in providing appropriate patient education. Early in the diagnosis phase and throughout the disease course, patients with IBD can be overwhelmed by the complexity of the disease process, the painful and frustrating symptomatology and debilitating nature of the disease, the economic impact, and the psychosocial issues that are caused by these disorders. Pharmacists should be equipped with the knowledge and ability to assist patients and their caregivers to deal with the multifaceted nature of these diseases. The first step in providing assistance is to demonstrate compassion and empathy. As pharmacists build rapport with patients, patients are more willing to accept the information and counsel provided. In addition to providing important information regarding pharmacotherapy, pharmacists are in a position to educate patients about the disease process, the potential course of disease, and lifestyle changes that may improve patient quality of life.

Drugs used to treat IBD can include local, oral, and intravenous administration routes. Some drugs are self-administered by the patient; others are administered in the hospital or ambulatory care settings by a nurse. Appropriate administration techniques are important to stress to patients, their caregivers, and other health care providers. For example, patients should receive instruction on the proper technique for administering an enema. Written materials are available from the Crohn's & Colitis Foundation of America. These pamphlets include information on CD and UC, information for patients facing surgery, recommended diet management, and explanations of treatment modalities. Information is also available on the Crohn's & Colitis Foundation of America Web site at

www.ccfa.org. Other patient information is available on various Web sites listed in Table 1-7.

Patient Support

Patients with IBD often find their symptoms to be embarrassing or humiliating. Patients often avoid public places because of the fear of a sudden onset of uncontrolled symptoms. Patient knowledge of the nearest restroom can be extremely important. Clinicians should be well aware of these issues and should treat patients with sensitivity. Because of the chronic nature of IBD, patients often have many unpredictable impacts on quality of life. The required lifestyle adjustments for patients diagnosed with IBD can have profound psychosocial and economic impacts on the patients and their families. Patients may have difficulty maintaining employment or finding insurance coverage. For pediatric and adolescent patients, growth failure or lack of sexual development due to the disease, or its treatment, may trigger significant psychological problems. Patients with IBD and their caregivers must be educated effectively and must actively participate in treatment decisions to ensure optimal management of the disease. Pharmacists should be equipped with the knowledge and ability to assist patients and their caregivers to deal with the multifaceted nature of these diseases. Family support and professional counseling may be beneficial for patients who have difficulty accepting their disease and its impact on their quality of life. Patient support and advocacy groups have helpful Web sites with resources for both clinicians and patients, which are listed in Table 1-7.

Economics

Patients with IBD often face significant economic impact from the disease. Few studies have examined the economic impact of IBD. Newer therapies, although expensive, may help to reduce overall patient costs by reducing hospitalizations and complications because of these diseases. The cost of biological therapies is high. Infliximab and other anti-TNF antibodies are expensive. In addition, intravenous administration is associated with the additional cost of infusion units and specialized nurses. One way to

control costs is to reserve biological therapy for cases of treatment failure with immunosuppressive therapy. In Europe, this restriction is the standard practice, and, in most European countries, reimbursement for intravenous biological therapy requires conventional treatment failure. In the United States, anti-TNF strategies are used much more liberally.

One method to reduce cost of biological therapies is to use episodic therapy rather than systematic maintenance therapy after induction of response or remission. The Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen showed that the differences in response and remission rates at the end of 54 weeks were not significantly different for patients treated episodically with infliximab 5 mg/kg compared with patients treated systematically with 5 mg/kg or 10 mg/kg every 8 weeks. In a 1-year study period, the total amount of drug administered was on average 4 times higher for the 5 mg/kg maintenance dosing and 6–7 times higher for the 10 mg/kg maintenance dosing compared with episodic therapy.

For episodic therapy, the average raw cost has been estimated to be \$3,900 (in U.S. dollars) over 1 year for a patient weighing 50 kg and \$6,000 (in U.S. dollars) for a patient weighing 80 kg. For the lower dose systematic regimen, costs have been estimated to range from \$11,800 to \$18,400 (in U.S. dollars), and for the higher dose systematic regimen a range of \$23,120 to \$36,380 (in U.S. dollars). The average cost to patients or insurers is about 1.5–2.0 times the average wholesale cost.

The assessment of cost also must include other medical costs and the indirect costs attributed to disease impact on patient ability to be a productive member of society. In moderate to severe CD, the largest driver of direct cost is hospitalizations and surgeries. Studies have shown that 56% of medical costs for patients with CD are derived from hospitalizations, compared with only 4% from drugs. Mean reimbursements for a CD hospitalization in the United States totals almost \$22,000. Retrospective analysis of infliximab showed a 66% reduction in emergency department visits, a 43% reduction in endoscopies, a 12% reduction in radiology studies, and a 16% reduction in outpatient visits after patients began infliximab maintenance therapy. Such reductions in health care resource use can be expected to result in a substantial cost-savings that offsets the cost of maintenance infliximab therapy. Data extrapolated over a patient's lifetime may indicate a substantial amount of the cost of biologic therapies can be balanced by savings in other direct medical costs. Additional savings may be derived from indirect costs such as work attendance and productivity. Further analyses are warranted to assess the true cost, or savings, brought about by biologic therapies in CD.

Uninsured patients or patients who are economically unable to pay for newer therapies may apply for assistance from the manufacturer of these therapies. Pharmacists should assist patients in this process. Information regarding the Remicade Patient Assistance Program from Centocor, Inc. can be found by calling (866) 489–5957.

Quality Improvement

Outcome measurements for patients with IBD include response to therapy, morbidity and mortality, cost or other economic issues, and number and length of hospitalizations. Other performance indicators include time missed from work, progression to diagnosis of cancer, and need for psychological intervention. Audits should be performed periodically for adverse drug reactions associated with drugs used to treat IBD. Response to therapy can be measured using previously validated scoring mechanisms such as the Inflammatory Bowel Disease Questionnaire and the Crohn's Disease Activity Index. Clinicians should maintain a database for comparing these scores and should track the progress each patient makes with various treatment regimens. Informatics systems can aid the clinician in tracking economic issues and hospitalization statistics and outcomes.

Conclusion

Inflammatory bowel disease management is complex and encompasses not only pharmacotherapy, but also lifestyle management. Pharmacists play a unique role to impact the lives of patients with IBD by showing a genuine interest in assisting in disease management and improving the quality of life of those patients. Pharmacists provide a vital role in communicating information to both patients and other health care professionals. Counseling provided by pharmacists can reassure patients and their families of potential benefit of therapy, help prevent adverse effects associated with pharmacotherapy, and direct patients toward appropriate decision-making. Patients and their families appreciate the genuine compassion and trust shown by caring pharmacists who provide quality pharmaceutical care.

Annotated Bibliography

1. Sands BE. From symptom to diagnosis: clinical distinctions among various forms of intestinal inflammation. *Gastroenterology* 2004;126:1518–32.

This review is one of a series of articles in this issue of the journal devoted to the many aspects of inflammatory bowel disease (IBD). Topics include valuable insights into the clinical aspects of IBD genetics, pharmacogenomics and genotype/phenotype correlations, clinical epidemiology, differential diagnosis, diagnostic imaging, dysplasia screening, and therapeutics. This comprehensive review describes the clinical presentation of patients with IBD and suggests ways to differentiate among Crohn's disease (CD), ulcerative colitis (UC), and other forms of intestinal inflammation. The tables in this article are concise and complete. The author describes various physical, radiographic, and endoscopic findings that differentiate other intestinal inflammation syndromes that can resemble IBD. The author also discusses newer genetic findings in IBD in a complete manner. This citation provides a useful, current tool for understanding the differences between UC and CD. Other articles in this journal issue also may benefit the reader.

Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;359:1541–9.

2. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2004;99:1371–85.

These recent practice guidelines for adults with UC were developed using evidenced-based medicine; specific recommendations are classified by strength of scientific support. The committee responsible for developing these guidelines included physicians, scientists, and other experts. These guidelines address recommendations for a variety of aspects of UC, including diagnosis and assessment, approach to general management, management of mild to moderate distal colitis, maintenance of remission in distal disease, management of mild to moderate extensive colitis with active disease, maintenance of remission in patients with mild to moderate extensive colitis, management of severe colitis, surgery, pouchitis, and cancer surveillance. These guidelines should be considered by gastroenterologists the gold standard for managing UC. The American Gastroenterological Association is in the process of developing similar guidelines for CD. Current British guidelines for IBD are available and beneficial for providing basic information, but there are major differences in prescribing habits in the United States, such as a higher threshold for demonstrating conventional treatment failure before approving treatment with biological therapy.

3. Nayar M, Rhodes JM. Management of inflammatory bowel disease. *Postgrad Med J* 2004;80:206–13.

This review article provides a concise but complete description of the diagnosis, pathogenesis, disease course, and treatment of IBD. Tools for diagnosis such as endoscopy are discussed, and mechanisms to distinguish UC from CD are discussed. The pathogenesis of IBD includes genetic and environmental factors. Approach to pharmacotherapy and surgical intervention are described according to location and severity of disease. The authors include a review of newer therapies for treating IBD. Special populations and presentations of disease are discussed. This citation is a valuable quick reference to understanding the differences in presentation, diagnosis, and current treatment options for patients with UC and CD. This is a comprehensive review, covering many aspects of IBD.

4. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999;340:1398–405.

This landmark study provides the basis for infliximab use for treating fistulizing CD. Infliximab was evaluated to determine its effectiveness as a treatment for enterocutaneous fistula. In this multicenter, randomized, double-blind, placebo-controlled trial, 94 adult patients with draining abdominal or perianal fistulae secondary to CD and of at least 3 months duration were randomly assigned to one of three treatment groups and received one of the following: placebo (31 patients), 5 mg of infliximab per kilogram of body weight (31 patients), or 10 mg/kg of infliximab (32 patients) administered intravenously at weeks 0, 2, and 6. The primary end point was a reduction of 50% or more from baseline in the number of draining fistulae observed at two or more consecutive study visits. A secondary end point was closure of all fistulae. Results of the study demonstrated that 68% of patients receiving 5 mg/kg of infliximab and 56% of patients receiving 10 mg/kg, and 26% of patients in the placebo group achieved the primary end point ($p=0.002$ and $p=0.02$, respectively). In addition, 55% of patients receiving 5 mg/kg of infliximab, 38% of those receiving 10 mg/kg, 13%

of patients assigned to placebo demonstrated closure of all fistulae ($p=0.001$ and $p=0.04$, respectively). The median length of time during which fistulae remained closed was 3 months. More than 60% of patients in all three comparison groups experienced adverse events. This well-designed study established the current infliximab dosing schedule for treating patients with refractory, fistulizing CD.

5. Kim SC, Ferry GD. Inflammatory bowel diseases in pediatric and adolescent patients: clinical, therapeutic, and psychosocial considerations. *Gastroenterology* 2004;126:1550–60.

This review is a part of a series of articles in this journal devoted to IBD. Inflammatory bowel disease primarily affects young adults, but in 15–25% of cases, the disease starts in childhood. Important issues that are specific to pediatric patients include growth velocity impairment, derangements in and treatment of abnormal bone mineralization, and transitional care issues; the lack of large randomized, controlled therapeutic trials in pediatric patients is also a concern. The authors review the epidemiology of IBD in pediatric patients including incidence and prevalence worldwide, clinical issues, diagnostic and therapeutic interventions, and psychosocial issues unique to pediatric patients. The authors also highlight future research directions and suggest opportunities for practitioners to perform research using existing pediatric research databases. This reference is a good review of important issues that relate specifically to the pediatric IBD populations.

