

Inflammatory Bowel Disease

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Objectives After completing this article, readers should be able to:

1. Develop a differential diagnosis for the child or adolescent presenting with bloody diarrhea.
2. Recognize that growth failure may be the initial presentation of Crohn disease and understand the pathogenesis of this disease complication.
3. Describe the manifestations of severe colitis and start appropriate intervention.
4. Understand the limitations of corticosteroid therapy for inflammatory bowel disease in children and recognize the need for alternative maintenance therapies.

Introduction

Inflammatory bowel disease (IBD) is the generic term used to describe two idiopathic disorders associated with gastrointestinal inflammation: Crohn disease (CD) and ulcerative colitis (UC). These disorders need to be distinguished from other conditions that may display similar clinical and laboratory findings, such as infection, allergy, and neoplasm. Because IBD also may be associated with a large array of extraintestinal manifestations, knowledge of the clinical spectrum of these disorders is important to the clinician who may encounter associated problems such as growth delay, arthritis, hepatitis, and anemia. Once IBD is diagnosed, newer medical and surgical treatments allow most affected children to lead relatively normal lives.

Definitions

The definitions of UC and CD are based on the location and characteristics of the inflammatory process within the gastrointestinal tract. In UC, relatively generalized inflammation is confined to the mucosa, starting in the rectum and involving a variable extent of colon proximally. Crypt abscesses are common. Rarely, patients may have discontinuous inflammation at diagnosis or even relative rectal sparing. Over the course of the illness, however, the inflammation becomes more confluent. Inflammation limited to the rectum, observed in 10% of pediatric patients, is termed ulcerative proctitis. In about 30% of cases, the disease is limited to the left side of the colon; in 40% to 50% of cases, there is pancolitis.

The inflammation associated with CD may involve any portion of the alimentary tract, from mouth to anus. The earliest abnormality seen commonly is a superficial oral ulcer overlying a lymphoid follicle (aphthous lesion). Mucosal inflammation may become more generalized or remain patchy and may extend gradually into the submucosa, muscularis, and serosa. Transmural inflammation can result in fistula formation. Granulomas, believed to be pathognomonic for CD, are found only in a minority of patients. Radiologically evident inflammation is limited to the small bowel (usually the terminal ileum) in about 30% of cases, involves the ileum and colon in 60% of cases, and is limited to the colon in 10% to 20% of cases. Gastroduodenal inflammation is evident in about 30% to 40% of all patients. The advent of fiberoptic endoscopy and video capsule endoscopy has shown that disease frequently is present throughout the gastrointestinal system in many patients despite limited disease noted radiographically.

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Epidemiology and Genetics

IBD affects males and females equally. Recent observations suggest that previous data showing a greater incidence of disease in Caucasians than in non-Caucasians may no longer be the case. Diseases associated with a higher frequency of IBD include Turner syndrome, Hermansky-Pudlak syndrome, glycogen storage disease type IB, and inborn errors of leukocyte adhesion.

The single greatest risk factor for the development of IBD is having a first-degree relative who has the disease, with the estimated risk being 30 to 100 times greater than in the general population. At the time CD is diagnosed, the likelihood of finding IBD in a first-degree relative of the proband is 10% to 25%. For a first-degree relative of a proband who has CD, the age-adjusted risk of developing IBD during a lifetime is about 4%. The risk for relatives of probands who have UC is somewhat less than 4%. Genetic linkage analyses, through genome-wide screens, have identified a number of susceptibility loci designated IBD1 through IBD6 on chromosomes 16, 12, 6, 14, 5, and 19, respectively. The IBD1 locus has shown the greatest association and is termed NOD2/CARD15. Three primary polymorphisms have been described (R702W, G908R, 1007fs). Although having one copy of the risk allele confers a small increased risk of developing CD (two- to fourfold), having two copies (homozygote or compound heterozygote) increases the risk by 20- to 40-fold. Current evidence suggests that these genetic variants alter nuclear factor-kappa beta activation in response to bacterial lipopolysaccharide and peptidoglycan.

A perinuclear antineutrophil antibody (pANCA) is found in approximately 70% of individuals who have UC (compared with 6% of those who have CD) and is believed to represent a marker of a genetically controlled immunoregulatory disturbance. The presence of pANCA is concordant within families. Anti-*Saccharomyces cerevisiae* antibody (ASCA) is detected in about 50% to 60% of patients who have CD. The presence of ASCA antibody in patients who have CD correlates with the presence of small bowel involvement as well as fibrostenosing and perforating disease.

Pathogenesis

The cause(s) of IBD is (are) not known. Whether UC and CD are two distinct diseases that have similar clinical manifestations or diseases that have different histopathologic and geographic localization and are causally linked also is unknown. Genetic susceptibility has been suggested by the predisposition to IBD in certain ethnic groups and by familial occurrence.

Most investigations have focused on possible infectious causes as well as on immunologic disturbances. To date, no specific infectious agent has been reproducibly associated with IBD. Several bacterial species, including *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia*, can cause acute intestinal inflammation, but the course of infection is self-limited, and histopathologic examination of affected tissue usually can differentiate infection from chronic IBD. No convincing data prove that *Mycobacterium paratuberculosis* has a role in the pathogenesis of CD, despite suggestions that it did a number of years ago. It has been hotly debated whether measles virus infection can result in a granulomatous vasculitis of mesenteric vessels that causes microvascular thrombosis and tissue ischemia and may be important in the pathogenesis of CD. Interestingly, IBD occurs less frequently among persons who have inherited disorders of coagulation such as hemophilia and von Willebrand disease.

Abnormalities in gastrointestinal immunoregulation appear to be important contributors to the pathogenesis of IBD. The gut is under constant immunologic stimulation from microbial agents and dietary antigens. It also is rich in immunologically active cells, which work with the barrier function provided by epithelial cells to keep the noxious external world at bay. Accordingly, the gut is in a state of constant “physiologic inflammation,” with a modest number of immune cells (lymphocytes, macrophages, plasma cells) present in the lamina propria. It is believed that this “physiologic inflammation” becomes uncontrolled in CD, resulting in pathologic inflammation, increased numbers of immune cells, and eventual tissue damage. Activated immune cells secrete a variety of soluble mediators of inflammation, including cytokines, arachidonic acid metabolites, reactive oxygen intermediates, and growth factors. Cytokines such as interleukin (IL)-1, IL-6, and IL-8 promote inflammation by increasing the expression of vascular adhesion molecules, which attract inflammatory cells, increase eicosanoid production, induce nitric oxide synthase, and induce collagen production. This cascade leads to tissue destruction and remodeling, with consequent fibrosis. Electrolyte secretion is stimulated by these mediators, which contributes further to diarrhea. Other causes of diarrhea in CD include malabsorption in the small intestine; loss of bile salts from the terminal ileum into the colon, affecting colonic electrolyte absorption; and bacterial overgrowth in the small bowel with bile salt deconjugation. Diffuse mucosal disease leads to exudation of serum proteins (protein-losing enteropathy) and bleeding.

Clinical Aspects

Gastrointestinal

Virtually all patients who have UC present with bloody diarrhea, except those who have proctitis, in whom the stools may be formed. Abdominal pain in patients who have UC usually is limited to times of defecation. Abdominal pain is a more prominent problem among those who have CD. The pain is usually more severe, occurs at any time of the day, and may awaken the child from sleep. It is most common in the right lower quadrant in those who have ileal or ileocecal disease and is periumbilical in those who have colonic or generalized small bowel disease. Epigastric pain simulating ulcer is observed in those who have gastroduodenal involvement. Diarrhea, occasionally bloody, is seen in about 50% of patients who have CD. Nausea and vomiting may be present with either UC or CD, particularly when the disease is severe. Perirectal inflammation with fissures and fistulas occurs in about 25% of CD patients and may be an early sign of the disorder. Oral canker sores (aphthous lesions) are noted in many patients who have CD. Fever occurs in UC only in the presence of fulminant disease. Fever may be insidious in CD, occur in the absence of severe gastrointestinal symptoms, and be diagnosed initially as a fever of unknown origin.

Extraintestinal

The more common extraintestinal manifestations of IBD are shown in Table 1. Extraintestinal manifestations are noted in approximately 25% to 35% of patients and can be classified into several groups: 1) those directly related to disease activity, which usually respond to therapy directed against bowel diseases (eg, fever, anemia); 2) those whose course is unrelated to bowel disease activity (eg, sclerosing cholangitis); 3) those that result from the presence of diseased bowel (eg, ureteral obstruction); and 4) those that arise from therapy (eg, drug-induced pancreatitis).

Growth failure occurs in up to 20% to 30% of children who have CD and up to 10% of those who have UC. In the latter group, growth failure almost always is due to the prolonged use of high-dose corticosteroids. In CD, the pathogenesis of growth impairment is multifactorial and includes chronic undernutrition, corticosteroid ad-

Table 1. Extraintestinal Manifestations of Inflammatory Bowel Disease

Site	Manifestation
Skin	Erythema nodosum, pyoderma gangrenosum, metastatic Crohn disease
Liver	Steatosis, nonspecific elevation of aminotransferases, chronic hepatitis, sclerosing cholangitis, cholelithiasis, acalculous cholecystitis, Budd-Chiari syndrome
Bone	Osteopenia, aseptic necrosis
Joints	Arthralgias, arthritis, ankylosing spondylitis, sacroiliitis
Eye	Uveitis, episcleritis, keratitis
Urologic	Nephrolithiasis, obstructive hydronephrosis, enterovesical fistula, nephritis, amyloidosis
Hematologic	Anemia (iron, folate, vitamin B ₁₂ , autoimmune hemolytic), thrombocytosis, thrombocytopenia
Vascular	Hypercoagulability (thrombosis, thrombophlebitis, portal vein thrombosis)
Pancreas	Pancreatitis
Other	Growth delay, pubertal delay, increased risk of colonic malignancy with chronic colonic inflammation

ministration, and the effects of proinflammatory cytokines released from diseased bowel, which circulate and affect bone metabolism (Fig. 1). Growth failure and delayed pubertal development may constitute the primary presentation in some children who have CD.

Two forms of arthritis are noted in patients who have IBD. The peripheral form (10% of patients) commonly affects the larger joints (knees, ankles, wrists, elbows) and usually is related to active colonic disease. The axial form, ankylosing spondylitis/sacroiliitis, is rare in children. Although abnormal concentrations of

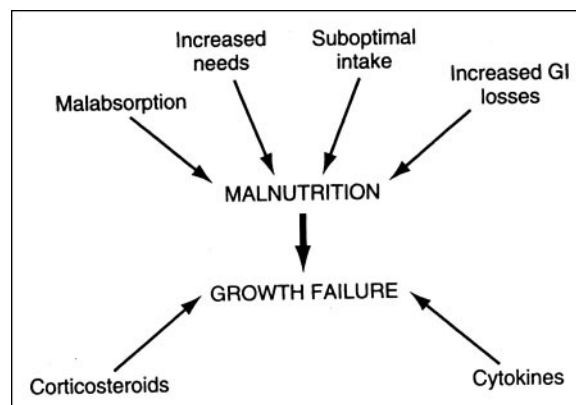


Figure 1. Pathogenesis of growth failure in children and adolescents who have inflammatory bowel disease. Adapted from Hyams JS. Crohn's disease. In: Wyllie R, Hyams JS, eds. *Pediatric Gastrointestinal Disease: Pathophysiology, Diagnosis, Management*. 2nd ed. Philadelphia, Pa: WB Saunders; 1999:408.

serum aminotransferases are found in up to 15% of patients during their disease course, serious liver disease such as sclerosing cholangitis (3% of UC patients) and chronic active hepatitis (<1% of patients) is uncommon. Persistent elevation of serum gamma-glutamyltransferase (GGT) concentrations suggests the presence of sclerosing cholangitis.

Diagnosis

A detailed clinical history, including family history, and physical examination have no substitute for diagnosing IBD. Not only can the diagnosis usually be suspected, but there are good clues suggesting whether the patient has UC or CD. Laboratory studies are used to confirm the diagnosis.

The differential diagnosis for a child whose IBD presents as acute colitis includes infection, hemolytic-uremic syndrome, Henoch-Schönlein purpura, and ischemic colitis. Enteric pathogens must be excluded by appropriate stool culture and examination for *Salmonella*, *Shigella*, *Campylobacter*, *Escherichia coli* 0157:H7, *Yersinia*, *Aeromonas*, and *Clostridium difficile*. When isolated terminal ileal infection is present radiographically, tuberculosis should be considered. Anemia is common and usually due to iron deficiency. Thrombocytosis reflects both the inflammatory state (IL-6 stimulates thrombopoiesis) and gastrointestinal bleeding. The erythrocyte sedimentation rate is elevated in 80% of patients who have CD and in about 40% of those who have UC. C-reactive protein may be especially sensitive in screening for active bowel inflammation. Albumin concentrations often are low, reflecting enteric protein loss and poor nutrition. Serum aminotransferases and GGT should be measured to evaluate possible hepatic involvement. Commercial testing for pANCA and ASCA can be performed, but rarely is needed to diagnose IBD; they may be more helpful in differentiating UC from CD in indeterminate cases.

Colonic inflammation is diagnosed via endoscopic visualization (Fig. 2) and confirmed on histologic examination of biopsied tissue. Barium enema has virtually no role in the diagnosis of colonic inflammation. Radiographic evaluation of the small bowel, with particular attention to the terminal ileum, is mandatory when looking for evidence of CD (Fig. 3). Intra-abdominal complications of CD such as abscess are demonstrated best with computed tomography. In more than 90% of patients, the clinician can differentiate UC from CD reliably with these examinations. Video capsule endoscopy can be performed in children old enough to swallow the video capsule and may show disease in the small bowel that is not evident by contrast radiography.

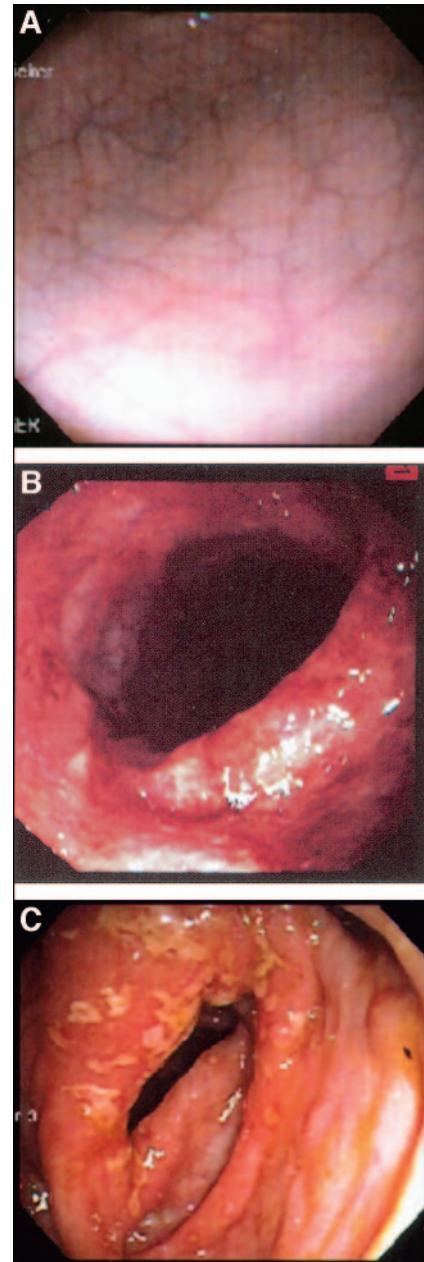


Figure 2. Endoscopic findings in inflammatory bowel disease. A) Normal colonic mucosa. B) Severe ulcerative colitis. Note marked erythema, granularity, spontaneous bleeding, and loss of vascular pattern. C) Severe Crohn disease of cecum with deep ulceration.

Management

Therapy is intended to decrease bowel inflammation, with the goals of eventual healing, addressing complications, and preventing recurrent or worsening disease.



Figure 3. Radiographic findings of extensive distal small bowel disease in a 14-year-old girl who has Crohn disease.

Pharmacologic Therapy

Medications used to treat IBD can be divided into six categories: aminosalicylates, corticosteroids, immunomod-

ulators, antibiotics, probiotics, and biologic agents (Table 2). Patients who have severe colitis (more than five bloody stools per day, fever, hypoalbuminemia, anemia) require hospitalization, bowel rest with parenteral nutrition support, intravenous corticosteroids, and very careful monitoring. The past several years have seen increasing use of immunomodulators such as 6-mercaptopurine to decrease the amount of corticosteroids used to treat severe diseases. The biologic agent infliximab, a chimeric antitumor necrosis factor- α antibody, is being used increasingly for patients who have severe CD, particularly those who are corticosteroid-refractory or -dependent.

Initial therapy depends on the severity of the presenting disease. Mild colonic inflammation from either UC or CD usually is treated first with 5-aminosalicylates (5-ASA). Severe symptoms in either disorder are addressed most commonly with oral or intravenous corticosteroids. For either disorder, the goal is to use corticosteroids for as short a period as possible and then change to a maintenance therapy. For some patients, such therapy might involve the use of a 5-ASA agent. For others, an immunomodulator such as azathioprine or 6-mercaptopurine may be required. For refractory patients who have CD, infliximab may need to be added as a maintenance agent.

Patients who have severe colitis (fever, hypoalbuminemia, anemia) from either UC or CD require hospitalization, intravenous fluid and nutrition support, and intravenous corticosteroids. Infliximab has been used in the treatment of severe CD, but experience with its use in fulminant UC is limited. Lack of improvement despite 7 to

Table 2. Pharmacologic Therapy of Inflammatory Bowel Disease

Medication Class	Indications	Complications
Aminosalicylates (eg, mesalamine, sulfasalazine)	Mild-to-moderate UC, mild Crohn colitis, or mild distal small bowel disease (mesalamine)	Rash, headache, bloody stools, pancreatitis
Corticosteroids (eg, prednisone, budesonide)	Budesonide: Mild-to-moderate distal small bowel and proximal colon disease (CD). Prednisone: Moderate-to-severe UC or CD	Cushingoid facies, growth suppression, osteopenia, hypertension, acne
Immunomodulators (eg, azathioprine, 6-mercaptopurine, methotrexate)	Severe small or large bowel disease, steroid-dependent or refractory disease, severe fistula, growth failure (CD or UC)	Bone marrow suppression, pancreatitis, hepatitis, infection
Antibiotics (eg, metronidazole, ciprofloxacin)	Perirectal fistula, abscess, pouchitis (CD)	Neuropathy, dysgeusia, nausea, fungal overgrowth
Probiotics (eg, <i>Lactobacillus</i> GG, <i>Saccharomyces boulardii</i>)	Adjunctive therapy, recurrent pouchitis	None
Biologic therapy (eg, infliximab)	Steroid-dependent or refractory CD, perirectal fistulae, maintenance of remission	Hypersensitivity reactions, infection, autoimmune disease

10 days of intensive medical therapy should prompt consideration of surgery.

Nutrition Therapy

This type of therapy may be either primary or adjunctive in CD and is only adjunctive in UC. Early and continued assessment of a patient's nutritional status is important. Elemental or polymeric formulas provided as the sole source of nutrition may effect remission in up to 80% of those who have CD. Oral supplements and even nasogastric or gastrostomy feedings may be critically important in addressing chronic undernutrition and growth failure. Growth failure often can be reversed with the administration of adequate calories if disease activity is controlled and daily corticosteroid use avoided.

Surgical Therapy

The goals of surgical therapy differ for UC and CD, although the indications often are similar. Uncontrolled gastrointestinal bleeding, bowel perforation, obstruction, unacceptable medication toxicity, and intractability to other therapy can prompt surgery in either disorder. At times, surgical resection is used to treat growth failure, especially if it allows the discontinuation of corticosteroids. Perirectal disease may necessitate surgery in some who have CD. Carcinoma may occur in either condition and require operative intervention.

The surgical procedure of choice in UC is ileal pouch-anal anastomosis. This curative procedure can be performed either as a primary operation or in a staged approach, depending on the condition of the patient. Excellent long-term results have been demonstrated, although inflammation of a surgically created pouch reservoir (pouchitis) develops in up to 40% of children. In CD, surgery is not curative because recurrent disease at the surgical site is very common. Segmental bowel resection is the most common procedure and usually involves the diseased terminal ileum and adjacent inflamed colon. Short segments of bowel that have been narrowed from fibrosis and are not actively inflamed can be treated with strictureplasty, in which a longitudinal incision is made in the fibrotic segment and closed transversely.

Psychological Therapy

The need for family education and reassurance cannot be overemphasized. Adolescents who have IBD may have a particularly difficult time because of issues of growth and pubertal delay, body image (eg, cushingoid features, acne from corticosteroids), and social invalidism from abdominal pain and diarrhea. Counseling and peer support groups are very helpful.

Prognosis

IBD typically is marked by periods of exacerbation and remission. Most children (70%) who have UC enter remission within 3 months of initial therapy, and approximately 50% remain in remission over the next year. Colectomy within 5 years is required in up to 26% of children presenting with severe disease compared with less than 10% of those who have mild disease. Children who present with proctitis have up to a 70% likelihood of developing more extensive disease over time.

Only 1% of patients who have well-documented CD do not have at least one relapse after diagnosis and initial therapy. Those who have ileocolitis tend to respond more poorly to medical therapy and have a greater need for surgery than do those who have only small bowel disease. Approximately 70% of children who have CD require surgery within 10 to 20 years of the original diagnosis.

The risk of developing cancer in chronically diseased bowel is significant, and patients who have long-standing colonic CD appear to be at similar risk as those who have UC. The two most critical risk factors for the development of adenocarcinoma in diseased colon are duration of colitis (especially >10 y) and extent of colitis (pancolitis >left sided colitis> proctitis). The presence of sclerosing cholangitis in UC patients is another major risk factor. Patients who have had colonic disease for more than 8 to 10 years should undergo annual to biannual screening colonoscopies for any evidence of dysplasia. The finding of dysplasia prompts colectomy. Multifocal or synchronous tumors are present in 10% to 20% of patients who have UC.

Suggested Reading

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

1. A symptom or finding that is likely at initial presentation with Crohn disease in contrast to ulcerative colitis is:
 - A. Aphthous ulcers.
 - B. Arthritis.
 - C. Bloody diarrhea.
 - D. Growth delay.
 - E. Uveitis.
2. A 3-year-old boy who has lived on a farm all of his life has experienced weight loss, fever, episodes of vomiting, and diarrhea for the past 3 months. Radiographic evaluation reveals a narrowing of his distal ileum, suggesting the diagnosis of Crohn disease. Infection with which pathogen would *most* likely cause a similar presentation?
 - A. *Entamoeba histolytica*.
 - B. *Giardia lamblia*.
 - C. *Mycobacterium tuberculosis*.
 - D. *Salmonella typhi*.
 - E. *Yersinia enterocolitica*.
3. A 7-year-old girl has had a low-grade fever, diarrhea, anorexia, and failure to grow for the past 6 months. Her physical examination reveals aphthous ulcers, swollen knees, and rectal skin tags. The radiographic procedure that is *most* helpful in confirming that this child has Crohn disease is:
 - A. Abdominal computed tomography.
 - B. Abdominal magnetic resonance imaging with contrast.
 - C. Abdominal ultrasonography.
 - D. Barium enema.
 - E. Upper gastrointestinal series with small bowel follow-through.
4. A 5-year-old girl has a history of weight loss, loose stools, and poor growth for the past 4 months. In the last 6 days, her parents have noted eight to nine large, loose, bloody stools each day as well as fever elevations as high as 103.1°F (39.5°C). Physical examination demonstrates pallor, oral sores, abdominal distention, and rectal fissures. Initial laboratory evaluations reveal a hemoglobin of 8 g/dL (80 g/L) and a serum albumin concentration of 1.5 g/dL (15 g/L). You promptly consult a gastrointestinal specialist, who concurs with your suspected diagnosis of inflammatory bowel disease. The *best* course of treatment at this time in this patient is:
 - A. Hospital admission and intravenous corticosteroids.
 - B. Hospital admission and intravenous infliximab.
 - C. Outpatient care and oral methotrexate.
 - D. Outpatient care and oral metronidazole.
 - E. Outpatient care and oral sulfasalazine.