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Author Disclosure
Drs Glick and Carvalho have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives

After completing this article, readers should be able to:

1. Develop a differential diagnosis and plan an initial evaluation for the child or adolescent who presents with bloody diarrhea and abdominal pain.
2. Recognize that growth failure and pubertal delay may be an initial presentation of Crohn disease.
3. List the extraintestinal manifestations of inflammatory bowel disease (IBD).
4. Discuss the genetic advances in understanding the pathogenesis of IBD.
5. Describe the current treatments for IBD and the common adverse effects.

Introduction

IBD is a complex, multifactorial disease characterized by chronic inflammation in the intestinal tract of a genetically predisposed host. The spectrum of IBD in children primarily includes ulcerative colitis (UC) and Crohn disease (CD). With pediatric patients now accounting for 20% to 25% of newly diagnosed cases, it is becoming increasingly important for pediatricians to recognize the symptoms of IBD. (1) In this review, we discuss the epidemiology, clinical presentation, diagnosis, and complications of IBD, with specific emphasis on growth failure and pubertal delay because these are unique manifestations in children. We also describe newer, less invasive diagnostic techniques and current trends in management and advances in the pharmacologic treatment of affected children.

Epidemiology and Demographics

The epidemiologic patterns of pediatric IBD have evolved over the past few decades, with significant increases in both incidence and prevalence. The current incidence is 5 to 11 per 100,000 children, with a recent statewide survey from Wisconsin reporting the annual rate of diagnosis as 4.56 per 100,000 for CD and 2.14 per 100,000 for UC. (2) Canadian studies have reported an acceleration in new diagnoses from 9.5 per 100,000 in 1994 to 11.4 per 100,000 in 2005. The most significant increases were among the younger age groups, with the incidence rising 5% annually in children younger than 4 years of age and 7.6% annually in children ages 5 to 9 years. (3)

The mean age at diagnosis of pediatric IBD in the United States is 12.5 years, (2) with 20% of children diagnosed before the age of 10 years and fewer than 5% diagnosed before age 5 years. Males seem overrepresented in new cases of pediatric CD, although an equal number of males and females receive a UC diagnosis. (4)

Many risk factors have been associated with IBD, including family history, ethnicity, and tobacco use. Up to 25% of children who develop IBD have a positive family history of IBD. (5) Children who have a first-degree relative affected by either UC or CD have a 10 to 13 times higher risk for developing IBD. (5) Monozygotic twin concordance is approximately 50% for CD and nearly 20% for UC. (6)

In the United States, population-based studies histori-

Abbreviations

5-ASA:	5-aminosalicylates
CD:	Crohn disease
EN:	erythema nodosum
ESR:	erythrocyte sedimentation rate
FC:	calprotectin
FL:	lactoferrin
IBD:	inflammatory bowel disease
IGF-1:	insulin-like growth factor-1
MRI:	magnetic resonance imaging
PG:	pyoderma gangrenosum
PSC:	primary sclerosing cholangitis
SNP:	single-nucleotide polymorphism
TNF:	tumor necrosis factor
UC:	ulcerative colitis
VCE:	video capsule endoscopy

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cally have shown a higher prevalence of IBD in patients of European or African descent than in patients of Hispanic or Asian descent. (7) Notably, Jewish ancestry (Ashkenazi more than Sephardic) is a significant risk factor for the development of IBD. However, more recent pediatric-specific population studies detected no differences in IBD frequency between ethnic groups. (2)

The prevalence of IBD is highest in the industrialized world, including North America, northern Europe, and the United Kingdom. However, with progressive modernization, the prevalence is now increasing in the developing world. Tobacco use is linked closely with an increased risk of IBD. In smokers, the probability of developing CD is twice as high as for nonsmokers. (7) Passive exposure to smoking may be influential as well. (8)

Genetics

A genetic predisposition to IBD has been hypothesized for decades because of the strong familial pattern of disease. Linkage analyses and genome-wide association studies have identified numerous IBD candidate genes. Many share a connection to the immune, inflammatory, or bacterial recognition pathways, which are fundamental mechanisms in the pathogenesis of IBD.

In 2001, the *NOD2/CARD15* gene, located on chromosome 16q in the IBD1 susceptibility locus, was associated with CD. Three high-risk single nucleotide polymorphisms (SNPs) are suggested to alter recognition of bacterial peptidoglycans in monocytes, macrophages, gut epithelial cells, and Paneth cells. *NOD2* mutations can impair the degradation of gut bacteria, leading to an accumulation of bacterial antigens and predisposing to mucosal T-cell activation.

Nearly 40% of white patients who have CD carry one of these *NOD2* SNPs compared with 20% of controls. (9) These allelic variants also have phenotypic implications for those who have CD, with earlier age of onset, stricturing disease, and ileal involvement occurring more frequently.

The *IBD5* locus on chromosome 5q31 is associated with a higher susceptibility toward CD. Patients who have CD and *IBD5* locus polymorphisms may have more perianal disease, colonic disease, and importantly in pediatric patients, decreased weight and height at diagnosis. (10) There also has been a weak association of the *IBD5* locus with UC.

The *IBD3* locus on chromosome 6 contains the major histocompatibility complex genes, which also may contribute toward IBD predisposition. The *DRB1*1502* gene has been associated with UC, and the *DRB1*07* gene has been associated with CD, particularly in patients who have ileal disease without a high-risk *NOD2* polymorphism. The *DRB1*0103* allele has been linked to UC and colonic CD. Patients who have UC and this variant seem to have a greater predisposition toward more extensive and severe colonic involvement. There also seems to be an association between *IBD3* locus variants and the extraintestinal manifestations of uveitis and peripheral arthropathy. (9)

The field of IBD genetics is continuously expanding, but genetic testing is currently limited to research. In the future, children who have IBD may undergo genetic testing to quantify disease risk in family members or to predict phenotypic expression.

Causes

The precise causes of IBD remain unknown, but the current understanding involves a genetic predisposition combined with a dysregulation between the immune system and the antigenic environment in the gastrointestinal tract, leading to inflammation and damage. (11) The major pathogenic mechanism underlying CD is an excessive Th1 immune response, whereby CD4+ T cells become upregulated and markedly resistant to apoptosis. (12) An excessive Th2 immune response has been implicated in patients who have UC. (13)

Defective gastrointestinal mucosal integrity may lead to enhanced uptake of luminal bacteria, causing the normally protective mucosal immune system to be overwhelmed. This derangement may be a result of tolerance to luminal antigens, a hyperreactive cell-mediated immune system, or specific gene mutations (such as *NOD2*).

It has been postulated that the unchecked intestinal immune response to ubiquitous bacterial and enteric antigens could lead to the pathologic gross tissue injury characteristic of IBD. Activated immune cells secrete a variety of soluble mediators of inflammation, including cytokines (tumor necrosis factor [TNF]-alpha, interferon-gamma, transforming growth factor-beta, and interleukin-2, -5, -6, -12, and -18), arachidonic acid metabolites, reactive oxygen intermediates, streptolysins, and growth factors. (12) Activated neutrophils and macrophages may also release metalloproteinases, which digest collagen in the lamina propria and basement membrane and are markedly elevated in the fistulous tracts of those who have CD.

The most persuasive argument for a pathogenic role of enteric flora comes from murine studies of IBD. (14)(15) The gut inflammation seen in mouse models of IBD depends on the presence of bacterial flora. No single infectious agent has been reproducibly associated with

IBD, but several bacterial species, including *Salmonella*, *Helicobacter*, toxigenic *Escherichia coli*, *Listeria*, and *Campylobacter*, have been suggested to play a role in pathogenesis. *Mycobacterium paratuberculosis* has been strongly suspected in IBD development. (16) Viral theories have been proposed, including the potential for measles virus to cause a granulomatous vasculitis. (17) Another antigenic hypothesis in the development of IBD includes the phenomenon of dysbiosis, which is an altered balance between protective bacteria, such as *Lactobacillus* and *Bifidobacterium*, and aggressive organisms, including *Bacteroides*, *Enterococcus*, and invasive *E coli*. (18)

Clinical Presentation

UC and CD can have varied yet overlapping presentations. The cardinal symptoms of UC are diarrhea, rectal bleeding, and abdominal pain. Most children present with an insidious history of diarrhea without systemic signs of fever or weight loss. One third present with moderate symptoms, including hematochezia, abdominal cramping associated with fecal urgency, malaise, low-grade or intermittent fevers, anorexia with weight loss, mild anemia, and hypoalbuminemia. Only 10% of patients present with severe colitis, characterized by five or more bloody stools per day; more profound anemia and hypoalbuminemia; fever; tachycardia; and a diffusely tender or distended abdomen. (19)(20) Children who have UC may develop symptoms of reflux or dyspepsia associated with inflammation of the upper gastrointestinal tract. (21)

The classic presentation of abdominal pain, diarrhea, and weight loss occurs in most children who have CD. Abdominal pain typically is crampy and can be diffuse or localized to the right lower quadrant. (22) Stools can appear nonbloody or melanotic or can contain frank red blood. Chronic perianal disease, including tags, fissures, fistulae, and abscesses, may be present. (23) Recurrent aphthous-stomatitis can also suggest the diagnosis. A decrease in height velocity may precede overt abdominal symptoms by 5 years, and growth failure may be the *only* sign of illness in 5% of children who receive the diagnosis of CD. (24) Poor appetite, fevers, and iron deficiency anemia are also commonly noted at initial presentation in children who have CD. Decreased bone density is seen in 25% of newly diagnosed children, even before initiation of corticosteroid therapy. (25)

Extraintestinal Manifestations

One third of patients who have IBD develop extraintestinal manifestations, which may predate the onset of intestinal symptoms (Table 1). (26) Arthralgias and arthritis are common extraintestinal manifestations of CD. (26) Arthropathy also occurs in 20% to 25% of patients who have UC and may be the presenting symptom. Large joints, such as the knee, ankle, hip, and wrist, typically are involved. A polyarticular arthropathy involves more than five joints; a pauciarticular form involves fewer joints and its disease course correlates with intestinal disease activity. (27) Ankylosing spondylitis associated with IBD runs a course independent of bowel disease activity and may progress to permanent deformity.

Erythema nodosum (EN) and pyoderma gangrenosum (PG), although rare, are the most frequent cutaneous manifestations in IBD. EN occurs more commonly with CD; is characterized by tender, warm, red nodules or plaques; and typically is localized to the extensor surfaces of the lower extremities. PG occurs in fewer than 5% of UC patients and often is associated with more extensive colonic involvement. The lesions may appear initially as discrete pustules with surrounding erythema and subsequently extend peripherally, developing into an ulceration that has a well-defined border and a deep erythematous-to-violaceous color. PG tends to develop

Table 1. Extraintestinal Manifestations of Inflammatory Bowel Disease

System	Extraintestinal manifestations
Skeletal	Arthritis, arthralgia, ankylosing spondylitis, digital clubbing (hypertrophic osteoarthropathy), osteopenia, osteoporosis, aseptic necrosis
Cutaneous	Erythema nodosum, pyoderma gangrenosum, aphthous ulcers, vesiculopustular eruption, necrotizing vasculitis, metastatic Crohn disease
Ocular	Uveitis, episcleritis, corneal ulceration, retinal vascular disease
Hepatic	Primary sclerosing cholangitis, bile duct carcinoma, autoimmune chronic active hepatitis, fatty liver disease, cholelithiasis
Endocrine	Growth failure, pubertal delay
Hematologic	Autoimmune hemolytic anemia, thrombocytopenic purpura, thrombocytosis, thrombophlebitis, thromboembolism, arteritis
Renal	Nephrolithiasis (classically oxalate stones)
Cardiac	Pericarditis, myocarditis, heart block
Pancreatic	Acute pancreatitis (Crohn disease > ulcerative colitis)
Neurologic	Peripheral neuropathy, myelopathy, myasthenia gravis

around sites of trauma and surgical scars. Although the emergence of EN usually follows intestinal disease activity, PG runs an independent course, often necessitating potent therapy.

Transient transaminase elevation occurs in some children who have IBD and may be related to medications or disease activity. Persistent elevations suggest the presence of primary sclerosing cholangitis (PSC) or autoimmune hepatitis. PSC is more commonly associated with UC and can predate the onset of intestinal symptoms in 50% of patients. (28) Typical symptoms include chronic fatigue, anorexia, pruritus, and jaundice, although children may be asymptomatic. Elevated gamma-glutamyltranspeptidase and alkaline phosphatase values along with results of cholangiography and liver biopsy help confirm the diagnosis. (29)

Nutritional Considerations

Growth failure occurs in 15% to 40% of children who have IBD and is more frequent in CD than UC. The Z-score (or standard deviation score) is used as an objective measurement of growth. The mean height Z-score at diagnosis of pediatric CD is −0.54, and a delay in diagnosis or presence of jejunal disease is negatively correlated with the Z-score. (4) Poor weight gain also may precede a diagnosis of IBD. Mean weight Z-score at diagnosis of pediatric CD is −1.06, with almost 30% of patients having weight Z-scores below the 3rd percentile. In comparison, mean weight Z-score at diagnosis of UC is −0.32, with only 9% of patients falling below the 3rd percentile for age. (4)

The cause of growth failure in IBD is multifactorial. Patients often experience abdominal pain and diarrhea related to eating, leading to food avoidance behaviors and a decrease in total energy intake. Elevated concentrations of proinflammatory cytokines contribute to anorexia and can cause growth hormone resistance, with inhibition of insulin-like growth factor-1 (IGF-1) production. (30) In CD, active inflammation in the small intestine can decrease the absorptive surface area, resulting in a protein-losing enteropathy. Fat malabsorption contributes to the general energy-deficient state and may cause deficiencies in fat-soluble vitamins. Disease complications such as the presence of internal fistulae, surgical bowel resections, or diverting ostomies can decrease nutrient absorption further.

Differential Diagnosis

The differential diagnosis for a child or adolescent presenting with abdominal pain and bloody diarrhea is broad. Infectious enterocolitis, pseudomembranous colitis, lymphocytic colitis, eosinophilic enterocolitis, Henoch-Schönlein purpura, and hemolytic-uremic syndrome should be considered in addition to IBD. Intestinal malignancies such as non-Hodgkin lymphoma also should be considered. The periodic fevers syndromes, including TRAPS (TNF receptor-associated periodic syndrome) and PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis), are rare but have some clinical overlap with IBD. Rheumatologic disorders, such as juvenile idiopathic arthritis, ankylosing spondylitis, and systemic lupus erythematosus, share many characteristics with pediatric IBD, specifically, weight loss, malaise, recurrent fevers, and joint involvement. Finally, intestinal tuberculosis and CD have similar clinical, radiographic, and endoscopic features and can be remarkably hard to differentiate. Intestinal tuberculosis typically involves the ileocolonic region, and the ulcerative form is most common. A patient who has risk factors for tuberculosis should have a tuberculin skin test placed.

Diagnosis

A new diagnosis of IBD often is suggested by the clinical history and findings on physical examination (Fig. 1). The history should focus on the nature and duration of symptoms; location and quality of abdominal symptoms; frequency and consistency of bowel movements; presence of blood in stools; urgency, tenesmus, and nighttime awakening for bowel movements; and perianal, systemic (weight loss, fevers, fatigue), and extraintestinal symptoms (aphthous ulcers, skin lesions, joint pains, eye symptoms). A family history of IBD is of critical importance.

The physical examination should include measurements of height and weight as well as Sexual Maturity Rating staging. A complete evaluation includes examining the mouth for aphthous lesions and performing a thorough abdominal examination. Physical findings may include abdominal tenderness, right lower quadrant mass or fullness, pallor, and digital clubbing. A benign abdominal examination does not exclude the diagnosis of IBD. A rectal examination is mandatory, and the perianal area must be checked for skin tags, fistulae, and fissures.

Nutritional assessment should include measurements of growth velocity, height and weight Z-scores, and a comparison of absolute height with predicted mid-parental height. A bone age radiograph can be obtained if there is concern for significant growth delay. A dietary history should be obtained, with calculation of protein, carbohydrate, fat, vitamin, and mineral intake and comparison to recommended daily values. Serum concentra-

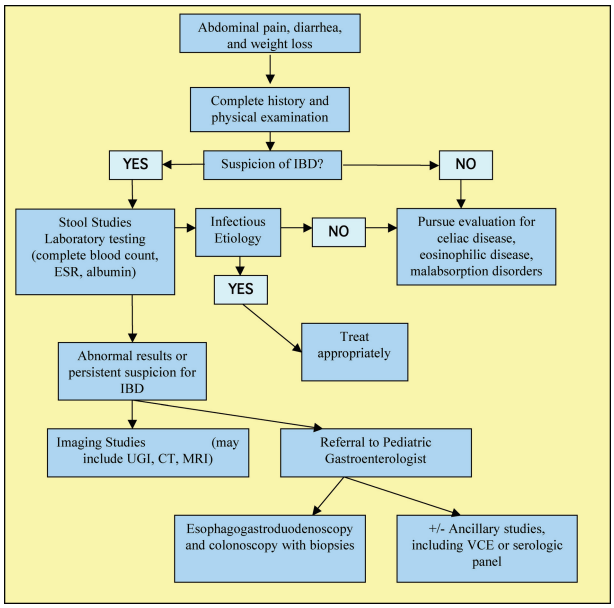

Figure 1. Evaluation of a patient suspected of having inflammatory bowel disease (IBD). ESR=erythrocyte sedimentation rate, UGI=upper gastrointestinal, VCE=video capsule endoscopy

tions of total protein, albumin, vitamin D, and iron should be measured. Depending on disease location, vitamin B_{12}, folic acid, and micronutrients such as zinc also should be assessed.

Measurements of hemoglobin, platelet count, erythrocyte sedimentation rate (ESR), and albumin classically show abnormalities in children who have new-onset IBD. Anemia is present in approximately 70% of patients, and ESR is elevated in nearly 75% of children who have moderate-to-severe disease. Only 4% of children who have moderate or severe IBD have normal test results at the time of diagnosis compared with 21% of patients who have mild CD and about 50% of those who have mild UC. (31) Thus, normal values in these domains should not delay further diagnostic evaluation if a high degree of suspicion for IBD exists.

An infectious cause should be excluded before diagnosing IBD. Screening stool studies should include: culture for *Salmonella*, *Shigella*, *E coli, Campylobacter*, and *Yersinia;* examination for *Giardia* and *Cryptosporidium*; and an assay for *Clostridium difficile* cytotoxin. If there is a history of immigration or overseas travel, stool should be checked for *Entamoeba histolytica*.

Fecal markers, such as calprotectin (FC) and lactoferrin (FL), are released by neutrophils that have migrated into the intestinal wall and can be measured quantitatively in stool samples. (32) These markers are used as noninvasive markers of gut inflammation. Although conditions other than IBD, such as infections, can cause inflammation and thus elevate these markers, measurement of FC and FL has a role in differentiating children who have IBD from those who have noninflammatory gastrointestinal conditions, such as irritable bowel syndrome. (33)

The use of IBD serologic panels for population screening or as an isolated diagnostic tool is not recommended. False-positive results can create unwarranted anxiety and lead to excessive invasive testing. It should be noted that nearly one third of patients who have a positive serologic panel do not have IBD. Serologic panels are most useful in children who have indeterminate colitis to differentiate CD from UC (Table 2). (34) Higher serologic antibody titers and a greater number of positive markers are associated with a more aggressive disease course. (35)(36) Notably, anti-*Saccharomyces cerevisiae*-positive CD patients are more likely to have perianal disease and ileal stricturing disease requiring resection. (37)

Imaging studies play an important role in the diagnosis of IBD. With CD, a barium upper gastrointestinal radiographic series may demonstrate stenosis, abnormal separation of bowel loops, and fistula formation. Computed tomography scan can assess for intestinal wall thickening and is important in the assessment of urgent complications of IBD, such as abscess formation and fistulizing or stricturing disease. Magnetic resonance imaging (MRI) is beginning to play a larger role in children who have IBD because there is no radiation exposure. MRI has greater than 90% sensitivity and specificity for detecting CD of the small intestine and has the potential to distinguish colonic CD from UC because mucosal and full-thickness bowel wall inflammation enhance differently. (38)(39)

Endoscopy, including esophagogastroduodenoscopy and colonoscopy with biopsy sampling, is the gold standard for diagnosing IBD. Inflammation of the upper gastrointestinal tract can be seen in both UC and CD, although the presence of noncaseating granulomas in the stomach (versus nonspecific gastritis) is diagnostic of CD.

Endoscopic features of UC include the characteristic *continuous* inflammation beginning in the rectum and extending a variable distance proximally into the large intestine. A sharp demarcation may exist between normal and diseased colon. The mucosal surface may be erythematous and granular, and there can be a loss of the normal vascular pattern with remarkable friability in areas of endoscope contact (Fig. 2). There may be small erosions, patches of exudates, and pseudopolyps. "Patchy"

Table 2. **Detection of Commercially Available Serologic Markers**

Serologic Marker	Crohn Disease	Ulcerative Colitis	Controls
ASCA (anti-*Saccharomyces cerevisiae* antibody) immunoglobulin A and G	40% to 56%	0% to 7%	<5%
ANCA (anti-neutrophil cytoplasmic antibody) histamine 1 protein, DNAase-specific	18% to 24%	60% to 80%	<5%
Anti Omp C (outer membrane protein of *Escherichia coli*)	25%	6%	3%

colitis and relative rectal sparing can be consistent with early disease or partially treated UC. Biopsies may reveal crypt distortion with branching, shortening, or atrophy; there may also be crypt abscesses. Inflammatory changes are limited to the mucosal layer.

Endoscopic features of CD include the characteristic skip lesions, in which areas of inflamed mucosa are interspersed with normal-appearing gut. "Cobblestoning" involves linear ulceration, with adjacent swelling giving tissue a cobblestone pattern (Fig. 3). Aphthae, exudates, and stricturing may be present anywhere from the mouth to the anus, but the rectum typically is spared from gross inflammation. The terminal ileum is classically abnormal on gross inspection, and the ileocecal valve may be stenotic. The characteristic finding on biopsy is noncaseating granulomas. Inflammation can extend through the full thickness of the bowel wall.

Wireless video capsule endoscopy (VCE) is an exciting modality that can detect small bowel lesions in areas not accessible to traditional endoscopy. VCE is also

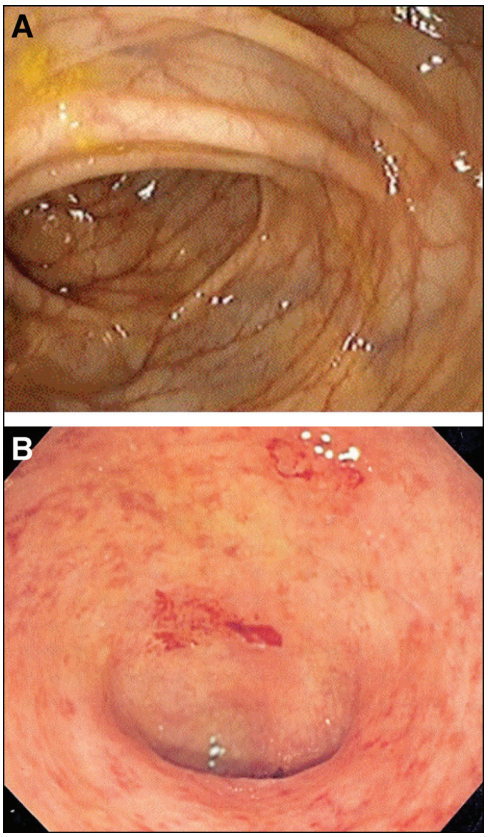

Figure 2. A. Normal colonic mucosa and vascularity. B. Colon in a child who has ulcerative colitis, showing continuous inflammation, swelling, loss of vascular markings, and bleeding.

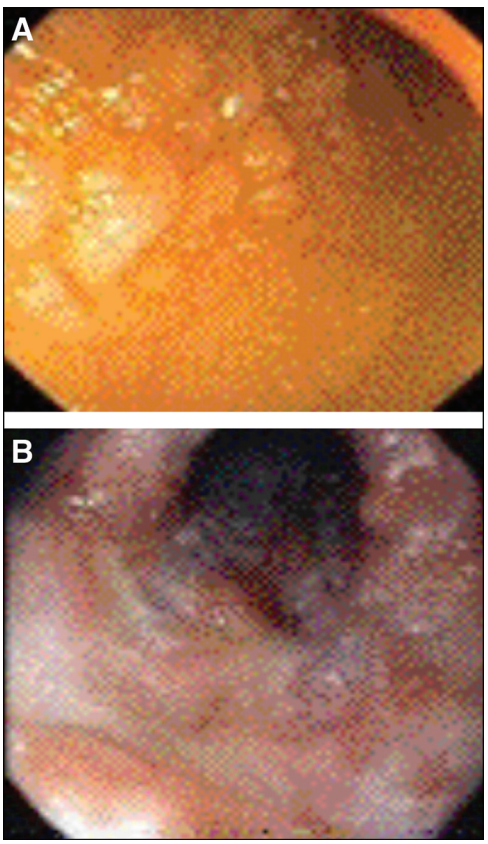

Figure 3. A. Normal terminal ileum with lymphoid nodularity. B. Terminal ileum in a child who has Crohn disease, showing inflammation, cobblestoning, exudates, and bleeding.

helpful in identifying disease recurrence, evaluating anastomotic sites, and detecting luminal complications such as malignancy. The drawbacks of VCE are difficulty with capsule ingestion in young children and risk of capsule retention.

Treatment

Medical Management

Immense progress has been made in the medical management of pediatric IBD over the past decade. The primary goals of therapy are induction and maintenance of remission, prevention of disease complications (such as fistula, stricture, abscess, and cancer), control of postoperative disease recurrence, maintenance of normal growth and development, and maximization of quality of life.

Medications are selected based on the disease location and severity, the potential for adverse effects, and anticipated compliance. Current IBD medications include corticosteroids, 5-aminosalicylates (5-ASA), immunomodulators, biologic agents, antibiotics, and probiotics (Fig. 4).

Moderate-to-severe symptoms initially are addressed most commonly with oral or intravenous corticosteroids, which inhibit the inflammatory cascade. The goal is to use corticosteroids for as short a period as possible, then change to nonsteroidal maintenance therapy. Budesonide, an oral corticosteroid, is frequently employed in the treatment of mild-to-moderate CD because it is released in the distal small bowel and proximal colon, common sites of inflammation. Acute response to corticosteroids is excellent, with 80% of IBD patients showing improvement, although corticosteroid dependency occurs in up to 50% of UC patients and 30% of CD patients. (40)(41)

For adult patients who have mild-to-moderate UC, 5-ASA medications (sulfasalazine, mesalamine, balsalazide) are effective in inducing and maintaining remission in 90% of cases. (42) Experience in children suggests similar response rates. The exact mechanism of action remains unknown but may involve decreased leukotriene production or scavenging of reactive oxygen species. A new, once-daily 5-ASA medication, mesalamine delayed-release tablets, has shown comparable efficacy with the benefit of better compliance. However, the use of 5-ASA medications in CD has become controversial because a meta-analysis demonstrated no superiority to placebo in maintaining remission. (43)

The use of immunomodulators in children who have IBD has become the standard of care. Fifty percent of newly diagnosed children who have UC and 75% of those who have CD are given immunomodulators within 2 years of diagnosis. Immunomodulators such as azathioprine and 6-mercaptopurine, which interfere with purine biosynthesis, have demonstrated good tolerance and can maintain remission in 75% of patients after discontinuation of corticosteroids. (44)(45) Because azathioprine (which is metabolized to 6-mercaptopurine) and 6-mercaptopurine require 3 to 6 months to take effect, these medications often are started soon after diagnosis.

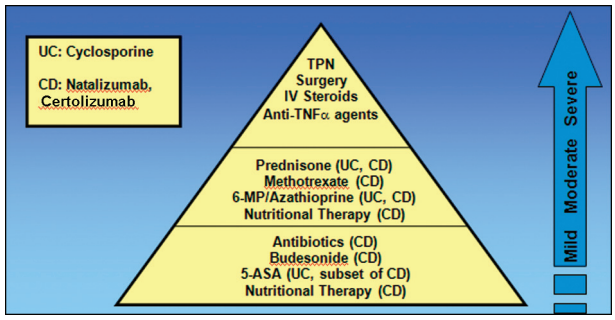

Figure 4. Treatment pyramid for ulcerative colitis (UC) and Crohn disease (CD) in children. TPN=total parenteral nutrition, TNF-α=tumor necrosis factor-alpha, 6-MP=6-mercaptopurine, 5-ASA=5-aminosalicylates, IV=intravenous

Methotrexate is used in children who have CD and may be particularly useful when remission is not achieved with azathioprine or 6-mercaptopurine or in patients who experience intolerable adverse effects from those medications. (46) Methotrexate inhibits dihydrofolate reductase, an enzyme necessary for folic acid metabolism and thymidine synthesis. The drug is effective at providing short-term symptom control, long-term remission, and steroid withdrawal. (47) Methotrexate usually is delivered as a weekly subcutaneous injection, and folic acid supplementation is recommended. Other immunomodulators used infrequently in IBD treatment include tacrolimus and mycophenolate mofetil.

For moderate-to-severe disease, biologic therapy is useful for induction and maintenance of remission. Infliximab is a chimeric monoclonal antibody directed against the cytokine TNF-alpha that acts by inducing apoptosis of active T lymphocytes. A response rate of up to 90% is achieved in patients who have moderate-to-severe CD, even when disease is refractory to corticosteroids and immunomodulators. (48) Those children who have refractory UC previously were treated with cyclosporine, but infliximab has become the treatment of choice because cyclosporine therapy has a high likelihood of eventual treatment failure and the need for colectomy in children.

For patients who respond to infliximab, scheduled

maintenance infusions are continued every 6 to 12 weeks. Gut mucosal healing has been demonstrated following infliximab therapy. Infliximab also plays an important role in treating fistulizing CD, which typically is more resistant to conventional therapies, and extraintestinal manifestations of IBD. PG, vasculitis, uveitis, EN, and arthritis have responded to this therapy.

Infliximab is the only immunomodulator approved by the United States Food and Drug Administration for children who have CD. However, two other anti-TNF agents, adalimumab and certolizumab, appear efficacious. Response rates are similar to infliximab, but because these antibodies are more fully humanized, allergic reactions may be less common. Adalimumab has shown efficacy in children who are intolerant or become unresponsive to infliximab. (49)

Natalizumab (anti-alpha 4 integrin) inhibits the adhesion, migration, and activation of monocytes, macrophages, and lymphocytes in a variety of tissues and has demonstrated clinical efficacy in treating children who have CD. (50) Three cases of progressive multifocal leukoencephalopathy associated with the human JC virus were described following trials in adults, which has created concern about its routine use.

Nutritional therapy may be a primary or adjunctive treatment in CD. Exclusive enteral nutrition from elemental or polymeric formulas has been associated with short-term remission in up to 80% of children, equal to the response rate from corticosteroids. (51) The mechanism involves adequate suppression of bowel inflammation and the induction of mucosal healing. (51) Improved growth and development, without the adverse effects of corticosteroids, makes enteral nutrition an excellent choice for first-line therapy in children who have active CD. However, after induction, long-term medications, such as immunomodulators, are necessary to maintain remission. Supplements such as iron, folic acid, calcium, and vitamin D are required in certain situations.

Antibiotics have specific indications in IBD treatment. Metronidazole is used to treat perirectal fistulas, although recurrence rates are high and toxicity (eg, paresthesias) often limit long-term use. (52) Ciprofloxacin is also useful in fistula treatment. Both antibiotics are prescribed for treatment of pouchitis following colectomy or ileoanal pouch procedures in UC patients. (53) Rifaximin, a nonabsorbed oral antibiotic, has shown benefit in symptom reduction of abdominal pain and diarrhea in children who have IBD. (54)

Probiotics have not been shown reproducibly to alter the natural history of CD, but for children who have newly diagnosed UC, probiotics are beneficial for maintaining remission when added to standard treatment regimens. (55) Probiotics are also helpful in the prevention and treatment of pouchitis. (56)(57) Safety in IBD patients is well established.

Significant adverse effects exist for all of the previously described medications (Table 3). A favorable risk-benefit ratio is the goal when considering any therapy. Infliximab is contraindicated in patients who have active tuberculosis, opportunistic infection, history of demyelinating disease, malignancy, congestive heart failure, or concurrent serious infection. Immunity to varicella should be ascertained before use of anti-TNF therapy. Recently, an aggressive malignancy, hepatosplenic T-cell lymphoma, has been described in young patients (mostly male) who were treated with a combination of infliximab and either azathioprine or 6-mercaptopurine. (58)

Surgical Management

Despite improvements in medical strategies, surgery maintains an important therapeutic role. Indications for surgery include uncontrolled gastrointestinal bleeding, bowel perforation, obstruction, intractable disease de-

Table 3. Adverse Effects of Medications Commonly Used to Treat Inflammatory Bowel Disease

Medication Class	Important Adverse Effects
Corticosteroids	Cushingoid facies, growth suppression, osteopenia, hypertension, hyperglycemia, acne, cataracts, hypothalamic–pituitary–adrenal axis suppression
5-Aminosalicylates	Hypersensitivity reaction, disease exacerbation, headache, diarrhea, rash, pneumonitis, interstitial nephritis
6-Mercaptopurine, azathioprine	Bone marrow suppression, pancreatitis, hepatitis, rash, vasculitis; increased risk of lymphoma
Methotrexate	Hepatitis, liver fibrosis, rash, folic acid deficiency, nausea, vomiting, hair loss
Anti–tumor necrosis factor	Resurgence of tuberculosis, histoplasmosis, varicella, malignancies (including lymphoma), fatal lymphoproliferative syndromes, anaphylaxis, serum sickness syndrome, lupuslike syndrome, increased risk of serious infections
Anti-integrin	Progressive multifocal leukomalacia

spite standard therapy, and dysplasia. At times, surgical resection is used to treat growth failure, especially if it allows the discontinuation of corticosteroids.

The surgical procedure of choice in UC is resection of the entire colon with 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. Long-term results are excellent, and continence can be achieved in 89% of patients after 2 years with creation of a J-pouch reservoir. (59) The major complication occurring after ileoanal pull-through is inflammation of the pouch (pouchitis), which occurs in 10% to 40% of children. (60)(61)

In CD, segmental bowel resection is the most common surgery and typically involves removing the diseased terminal ileum and adjacent inflamed colon. Short segments of bowel that are narrowed from fibrosis can be treated with stricturoplasty. Perirectal disease also may necessitate surgery.

Adjunctive Therapies

Oral nutrition supplements and either nasogastric or gastrostomy feedings may be critically important in addressing chronic undernutrition in children who have IBD. The administration of adequate calories with the addition of these supplements can help to reverse growth failure.

Complementary and alternative medicine approaches are used by up to 40% of patients who have IBD. To prevent medication interactions and limit undue adverse effects, these therapies are not routinely recommended without physician consultation.

The need for family education and reassurance cannot be overemphasized. Adolescents who have IBD may have a particularly difficult time because of issues related to growth failure, body image (eg, cushingoid features and acne from corticosteroids), and social invalidism from abdominal pain and diarrhea. Pubertal delay may also cause significant anxiety. Recent trials with growth hormone and IGF-1 have shown some promise in improving growth.

In general, patient and family counseling and peer support groups are very helpful.

Prognosis and Disease Complications

Disease symptoms recur in up to one third of patients at 1 year and more than one half at 2 years after initiation of therapy. Factors that predispose to a relapse of CD include the number of previous strictures and the presence of FC or FL in the stool. (62)(63)(64) In UC, a significant number of patients remain corticosteroid-dependent after 1 year, and 5% may require colectomy. (40)

Toxic megacolon, although rare in children, occurs in approximately 5% of adults who have severe UC and may be triggered by hypokalemia or opiate use. Colonic perforation may occur and colectomy may become necessary. (65) 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. Anecdotal experience supports the use of infliximab in reducing colectomy rates among patients who have severe colitis.

The risk of colorectal cancer depends on the extent and duration of the disease. (66) The cumulative incidence of colorectal cancer in patients who have pancolitis is 5% to 10% after 20 years and 12% to 20% after 30 years of disease. Screening is recommended beginning 8 years after diagnosis.

Patients who experience early-onset CD have a lower final adult height compared with predicted mid-parental height, with an average height reduction of 2.4 cm. Population studies have not shown a difference in final adult height in pediatric patients who have UC. (67) Osteopenia and osteoporosis can occur because of vitamin D deficiency, corticosteroid use, and high concentrations of circulating inflammatory cytokines, which inhibit IGF-1. Abnormally low bone mineral density is found in nearly 50% of patients who have IBD. Maintaining disease remission, avoiding corticosteroids, exercising, and ensuring adequate calcium and vitamin D intake are imperative to optimize bone development and mineralization in the growing child, particularly during puberty. Dual-energy radiograph absorptiometry scans should be performed in children who experience growth failure and prolonged steroid use. (25)(68)(69)

Issues for the General Pediatrician

Children and adolescents who have IBD should avoid the use of nonsteroidal anti-inflammatory drugs (including ibuprofen) because their routine use can trigger a disease flare, enteropathy, or gastritis. Cautious use of acetaminophen is suggested for treatment of minor pain and fever. The casual use of antibiotics should be limited in children who have IBD to prevent the risk of *C difficile* colitis, which has been associated with increased morbidity. Children taking immunosuppressive medications and biologic therapy should be restricted from live vaccine administration. With administration of inactivated vaccines, seroconversion is not always obtained if immunosuppressive therapy is being used concomitantly. Mea-

surement of growth velocity, evaluation of pubertal Sexual Maturity Rating staging, and annual-to-biannual eye examinations are recommended, even for asymptomatic children who have IBD.

Summary

- Recent major advances have been made in the diagnosis and treatment of pediatric IBD, and understanding of its pathophysiology continues to evolve.
- The long-term outcome for children who have IBD continues to improve with better appreciation of genotype-phenotype correlations, earlier diagnosis, and more effective treatments.
- Although the incidence of pediatric IBD appears to be rising, the future for affected children and adolescents appears promising.

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PIR Quiz

Quiz also available online at http://pedsinreview.aappublications.org.

6. Which of the following symptoms or signs is seen in children who have Crohn disease, but not in children who have ulcerative colitis?

   A. Anemia.
   B. Arthritis.
   C. Loose stools.
   D. Perianal fistula.
   E. Weight loss.

7. Which of the following infections can mimic the intestinal inflammation of Crohn disease?

   A. Epstein-Barr virus.
   B. Herpes simplex virus-1.
   C. Measles virus.
   D. Rotavirus.
   E. Tuberculosis.

8. Which of the following tests is the "gold standard" for diagnosis of IBD?

   A. Abdominal computed tomography scan.
   B. Endoscopy and colonoscopy with biopsy.
   C. Fecal lactoferrin.
   D. Serologic panel.
   E. Wireless capsule endoscopy.

9. A 15-year-old boy received the diagnosis of Crohn disease of the colon 6 months ago. He has had active disease despite 5 months of 6-mercaptopurine therapy and two courses of corticosteroid therapy. Of the following, which medication is *most* likely to induce remission?

   A. Azathioprine.
   B. Infliximab.
   C. Mesalamine.
   D. Metronidazole.
   E. Rifaximin.

10. An adolescent girl who has ulcerative colitis has been successfully maintained on 6-mercaptopurine for 2 years and presents today for a health supervision visit. She asks which immunizations she can have in the future. Which of the following vaccines is contraindicated?

    A. Human papillomavirus vaccine.
    B. Influenza vaccine.
    C. Measles, mumps, and rubella vaccine.
    D. Pneumococcal vaccine.
    E. Tetanus toxoid.

Inflammatory Bowel Disease

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