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Inflammatory Bowel Disease in Children and Adolescents

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Abstract

The inflammatory bowel diseases (IBDs), including ulcerative colitis and Crohn disease, are chronic inflammatory disorders of the gastrointestinal tract most often diagnosed in adolescence and young adulthood, with a rising incidence in pediatric populations. These disorders are common enough in children that most pediatricians and other pediatric clinicians will encounter children with IBD in their general practice. Inflammatory bowel disease is caused by a dysregulated mucosal immune response to the intestinal microflora in genetically predisposed hosts. Although children can present with the classic symptoms of weight loss, abdominal pain, and bloody diarrhea, many present with nonclassic symptoms of isolated poor growth, anemia, or other extraintestinal manifestations. Once IBD is diagnosed, the goals of therapy consist of eliminating symptoms, normalizing quality of life, restoring growth, and preventing complications while minimizing the adverse effects of medications. Unique considerations when treating children and adolescents with IBD include attention to the effects of the disease on growth and development, bone health, and psychosocial functioning. The purpose of this review is to provide a contemporary overview of the epidemiologic features, pathogenesis, diagnosis, and management of IBD in children and adolescents.

Epidemiologic Features

The inflammatory bowel diseases (IBDs), including ulcerative colitis (UC) and Crohn disease (CD), are chronic inflammatory disorders of the gastrointestinal tract that begin most commonly during adolescence and young adulthood. Approximately 25% of patients with IBD present before age 20 years.[1] Among children with IBD, 4% present before age 5 years

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and 18% before age 10 years, with the peak onset in adolescence.[2] The incidence of pediatric IBD is approximately 10 per 100 000 children in the United States and Canada and is rising.[2-4] With a prevalence of 100 to 200 per 100 000 children in the United States (and an estimated total of 70 000), most pediatricians will treat children with IBD in their practices.[2,5]

Pathogenesis

In patients with IBD, host genetic, environmental, and microbial influences converge and result in a dysregulated mucosal immune response against the commensal intestinal microbiota.[6] Recent technologic advances have led to an explosion of discovery of the genetic and microbial influences on IBD.[7] Genome-wide association studies have identified common variants in more than 150 genes that confer risk for IBD.[8] Risk variants can be grouped into biological pathways that shed light on IBD pathogenesis, including innate and adaptive immunity and epithelial function.[7] No difference exists in the common risk genes between pediatric-and adult-onset IBD; however, early-onset IBD may be associated with a higher burden of common risk variants and rarer variants with high penetrance.[9]

Three important observations underscore the importance of the environment on the development of IBD. First, the concordance rate for CD in monozygotic twins is only 50% and even less for UC.[10] Second, the rising incidence of IBD during the past 60 years is too fast to be explained by changes in our genetic makeup.[4,11] Third, IBD is less common in developing countries, but, as countries become more developed, the incidence of IBD also rises.[11] Furthermore, children of those who immigrate from developing countries to Western countries exhibit an incidence of IBD similar to that of Western populations.[12] Therefore, early-life environmental factors associated with a Western lifestyle may predispose to IBD. In fact, cesarean delivery, lack of exposure to breast milk, dietary fat intake, and early exposure to antibiotics have all been implicated as risk factors for IBD.[13-16]

Most humans live in harmony each day with the 10 trillion bacteria and fungi that constitute our intestinal microbiome, a relationship that is quite remarkable when one considers that only a single layer of intestinal epithelial cells separates these organisms from patrolling mucosal immune cells. Thus, investigators have an intense interest in understanding how the gut microbiome contributes to IBD. Animal studies[17] have demonstrated the fundamental role of the microbiome in the development of IBD because intestinal inflammation does not develop in most rodent models of IBD raised in germ-free conditions. Children and adults with IBD are known to exhibit a dysbiosis with an overall restriction in the diversity of intestinal bacterial species and overrepresentation and underrepresentation of specific taxa.[7,18]

Disease Classification

Inflammatory bowel disease is classified into UC and CD. Ulcerative colitis is characterized by diffuse, continuous inflammation of the colon extending from the rectum proximally. Patients with UC and diffuse pancolitis can exhibit mild inflammation of the ileum termed *backwash ileitis*.[19] In addition, 40% to 70% of patients with UC exhibit mild inflammation in the upper gastrointestinal tract.[19]

Crohn disease can involve any area in the gastrointestinal tract from the mouth to the anus but most commonly involves the terminal ileum and colon and can present with an inflammatory, penetrating, stricturing, or combination phenotype. Endoscopic features that distinguish CD from UC include discontinuous inflammation and discrete aphthous or linear ulceration (Figure).[19] In addition, 20% of children with CD will have perianal involvement, including skin tags, fissures, fistulas, and/or abscesses.[20]

Histologic features common to CD and UC include evidence of active inflammation (ie, neutrophils) and chronicity (ie, crypt loss or branching, mucin depletion, and/or lamina propria lymphocytosis). Although the inflammation and injury in UC is limited to the mucosa, CD can be a transmural process. Noncaseating granulomas are observed in as many as 60% of pediatric patients with CD and, in the right clinicopathologic setting, can distinguish CD from UC.[21]

Crohn disease involving the colon only is more common in children than adults, which makes it difficult to distinguish CD and UC in some patients. The term *IBD unspecified* (previously called *indeterminate colitis*) is reserved for patients who cannot be classified definitively as having UC or CD.[19]

Diagnosis

Clinical Presentation

The presentation of IBD in children and adolescents can be variable.[20,22,23] The reported incidence of presenting signs and symptoms is detailed in the Table. Pediatricians and other primary care clinicians should become familiar with the atypical presentations of IBD because 22% of children present with growth failure, anemia, perianal disease, or other extraintestinal manifestations as the only predominant initial feature.[24] Extraintestinal manifestations associated with IBD are detailed in Box 1. A detailed family history should be obtained because 20% of children with IBD have an affected relative.[3]

Physical Examination

A careful physical examination may provide clues to underlying pathologic features. Assessment of growth curves is critical; although some patients may present with acute weight loss, others will present with a more insidious chronic flattening of their weight and height curves (eFigure in the Supplement). Conversely, the possibility of IBD in obese patients should not be dismissed because 25% of children with IBD are obese.[25] Abdominal examination may reveal focal tenderness or fullness relating to the distribution of their disease. Rebound tenderness and guarding may indicate perforation or abscess that should be evaluated promptly with imaging. The perianal region should be examined for tags, fissures, fistulas, or abscesses. Digital rectal examination may provide information regarding anal strictures, fluctuance from an abscess, or occult blood. Other potential findings of the physical examination may include oral aphthous ulcers, clubbing, signs of delayed puberty, and skin lesions, such as erythema nodosum and pyoderma gangrenosum.

Laboratory Examinations

Common abnormal laboratory findings in children with IBD at diagnosis include anemia, thrombocytosis, hypoalbuminemia, and elevated levels of inflammatory markers.[26] The recommended initial laboratory evaluation in a patient with suspected IBD is detailed in Box 2. A normal laboratory evaluation result does not exclude a diagnosis of IBD because approximately 10% to 20% of children with IBD will have normal laboratory results.[26] Stool should be examined for occult blood, bacterial pathogens (including *Clostridium difficile*), ova, and parasites. Fecal calprotectin, a neutrophil-derived protein with elevated concentrations in the setting of intestinal inflammation, is emerging as a useful biomarker, with 98% sensitivity and 68% specificity in children with suspected IBD.[27]

An IBD diagnostic panel, including serologic and genetic markers, is commercially available, but a sizeable number of children with IBD will have negative test results for these markers, resulting in a modest sensitivity of 65% to 75%.[28] Such panels may be more valuable as prognostic tools for predicting an aggressive disease course.[29] The development of noninvasive peripheral biomarkers of active intestinal inflammation is an area of great interest. One such promising test, the polymorphonuclear CD64 index, capitalizes on inflammation-induced expression of Fcγ receptor I (CD64 markers) on neutrophils and has a high sensitivity and specificity for CD in children.[30]

Endoscopy

Prompt referral to a pediatric gastroenterologist for endoscopic evaluation is appropriate when a primary care clinician suspects IBD in a child based on clinical and laboratory findings. Esophagogastroduodenoscopy and ileocolonoscopy with biopsy remain the criterion standard for the diagnosis and classification of IBD in children.[19] Gross and histopathologic findings are crucial for determining disease severity and extent and for distinguishing UC from CD. Video capsule endoscopy may be indicated to evaluate the proximal small intestine when a high suspicion for CD exists and the diagnosis cannot be confirmed by results of conventional endoscopy and imaging.

Imaging

Small-bowel imaging is essential for mapping disease location, assessing severity, and identifying complications, such as fistulas, abscesses, and intestinal strictures.[31] Imaging should be performed after endoscopic diagnosis because imaging is not as sensitive for colonic and mild small-bowel disease, and specialized imaging protocols are used to evaluate IBD. Cross-sectional enterography, including computed tomographic enterography and magnetic resonance enterography, has replaced fluoroscopic small-bowel follow-through as the modality of choice. Both modes of enterography permit assessment of the lumen, the mucosa, the bowel wall, and intra-abdominal complications. Pelvic magnetic resonance imaging and rectal endoscopic ultrasonography in centers with expertise are the preferred modalities for evaluating perianal abscesses and fistulas.[32]

Treatment

Overall Treatment Goals and Strategy

The goals of treatment of IBD in children have changed dramatically in the past 15 years. When treatment options were limited, the primary goal was the reduction of symptoms. Now, with biologics targeting tumor necrosis factor (TNF) that can heal the mucosa and augment growth, we have the opportunity to modify the natural history of the disease. Therefore, the current goals of treatment are to (1) eliminate symptoms and restore quality of life, (2) restore normal growth, and (3) eliminate complications.

Therapies for IBD may be broadly classified according to their ability to induce remission of active disease and maintain remission in patients with quiescent disease. Some therapies are effective only for remission induction or maintenance, whereas others are appropriate for both indications.

Corticosteroids

Corticosteroids are effective for the induction of clinical remission in CD and UC in children; however, approximately half of the patients will become dependent on corticosteroids or require surgery.[33] Fewer than one-third of patients with CD in clinical remission with corticosteroid treatment will achieve mucosal healing.[34] Corticosteroids are not appropriate as maintenance therapy owing to the panoply of well-established adverse effects with long-term use. Budesonide is a high-potency corticosteroid that undergoes extensive first-pass metabolism in the liver, limiting the systemic bioavailability and adverse effects. Controlled-release budesonide formulations are effective for induction of remission in UC and CD; however, they are not effective as maintenance therapy.[35,36] Although budesonide formulations are appealing owing to their reduced adverse effect profile, they are not as effective as conventional corticosteroids and are reserved for mild to moderately active disease.

Enteral Nutrition Therapy

Treatment with exclusive enteral nutrition (EEN), defined as the provision of essentially 100% of caloric needs by liquid formula, is as effective as corticosteroid therapy for inducing clinical remission in children with CD.[37] Duration of EEN therapy typically is 8 to 12 weeks. Advantages of this approach compared with corticosteroids include support of growth by EEN, avoidance of corticosteroid-associated adverse effects, and more effective healing of the mucosa.[37] The primary disadvantage of EEN is the strict liquid formula diet, which requires many patients to place a nasogastric tube each evening (or keep it in all day) for nocturnal continuous feeding. Exclusive enteral nutrition is widely used as first-line induction therapy in Europe and is gaining increasing traction in the United States. Inflammation and symptoms will return with discontinuation of EEN therapy; therefore, EEN is often used in combination with maintenance medical therapy. Some success has been reported using various partial enteral nutrition regimens as maintenance therapy, such as overnight feedings with a normal daytime diet or nasogastric feeding for 1 of every 4 months.[38]

Aminosalicylates

Aminosalicylates exert a topical anti-inflammatory effect on the intestinal mucosa. They can be administered orally informulations that release the active moiety 5-aminosalicylic acid (5-ASA) in the ileum and colon or topically via enema or suppository. Sulfasalazine has been used for more than 40 years to treat IBD, but many patients cannot tolerate sulfa-related adverse effects (ie, nausea, headache, fever, and rash). Therefore, newer sulfa-free 5-ASA drugs (mesalamine, balsalazide disodium, and osalazine sodium) have been developed that deliver high concentrations of 5-ASA to the intestinal mucosa with fewer adverse effects. The 5-ASA drugs are effective for the induction and maintenance of remission in adults with mildly to moderately active UC, but few clinical trials have been conducted in children.[39] Balsalazide, the only 5-ASA agent with an indication from the US Food and Drug Administration in children, induces a clinical response at 8 weeks in 45% of children with mildly to moderately active UC and remission in 12%.[40] A large observational study showed that 30% of children with UC will maintain remission with administration of 5-ASA drugs alone.[41] Although 5-ASA drugs are still commonly prescribed for CD, systematic reviews do not support their efficacy.[42] Rare adverse effects of 5-ASA include paradoxical exacerbation of colitis, interstitial nephritis, pericarditis, and pneumonitis.

Immunomodulators

Thiopurine drugs, including azathioprine sodium and its active metabolite mercaptopurine (6-MP), have been used for the treatment of IBD for more than 30 years. Given their delayed onset of effect of several weeks, thiopurines are mainly effective as maintenance therapies. A landmark multicenter, randomized clinical trial demonstrated that early (within the first 8 weeks of adiagnosis) introduction of 6-MP reduces corticosteroid exposure and improves the maintenance of clinical remission in children with CD.[43] In a similar fashion, observational studies support the use of thiopurines in children with UC refractory to 5-ASAdrugs.[44] Adverse effects associated with thiopurines include myelosuppression, elevated transaminase levels, and pancreatitis. A small increased risk for lymphoma associated with thiopurines has been noted, with an absolute risk of 4.5 per 10 000 patient-years in children receiving thiopurines compared with 0.6 per 10 000 patient-years in the general pediatric population.[45]

Methotrexate sodium is another immunomodulator being used with increased frequency given concerns regarding the modest risk for lymphoma with thiopurines. Large retrospective cohort studies support the use of methotrexate as effective in maintaining clinical remission in about one-third of children with CD.[46] Methotrexate may also be used for maintenance of remission in pediatric UC. Adverse effects of methotrexate include nausea, hepatotoxicity, and myelosuppression. Patients should take a daily folic acid supplement when receiving methotrexate.

Anti-TNF Therapy

The introduction of therapeutic monoclonal antibodies directed against TNF, a major proinflammatory pathogenic cytokine in CD and UC, has revolutionized the treatment of IBD. These anti-TNF biologics are administered by infusion (infliximab) or subcutaneous injection (adalimumab, certolizumab pegol, and golimumab). Infliximab, the first anti-TNF

drug introduced in 1998, has been studied in well-designed trials in children and has been indicated by the US Food and Drug Administration for the treatment of moderately to severely active CD and UC in children. In children with CD, 88% respond to infliximab with 56% in remission at 1 year.[47] For UC, 73% respond with 39% in remission at 1 year.[48] Adalimumab also has demonstrated efficacy for the treatment of moderately to severely active CD in children and is approved by the US Food and Drug Administration for this indication.[49] Anti-TNF drugs are typically used in children with IBD refractory to corticosteroids or in those who are corticosteroid dependent despite immunomodulator therapy. They are sometimes used in conjunction with immunomodulators, and, in adults, the combination of infliximab and azathioprine is more effective than either agent alone.[50]

Anti-TNF agents are superior to thiopurines for inducing complete mucosal healing of the intestine and are the only class of drugs with demonstrated ability to heal perianal fistulas completely in CD.[51] Furthermore, infliximab has been shown to improve linear growth in children with associated growth failure.[47] For these reasons, anti-TNF agents may be prescribed as first-line therapy for CD in children with severe deep mucosal ulcerations, perianal fistulas, and/or significant growth failure.

Adverse effects of anti-TNF biologics include infusion or injection site reactions and a psoriasis-like rash. Anti-TNF drugs increase the risk for infection, in particular fungal, viral, and mycobacterial infections. All patients must be screened for latent tuberculosis infection before initiation of anti-TNF therapy.

Any risk for lymphoma associated with anti-TNF therapy alone has been difficult to discern because, in adults, anti-TNF agents are commonly prescribed in conjunction with thiopurines or in patients with previous exposure to thiopurines. A recent systematic review in children with IBD treated with anti-TNF biologics identified 2 cases of lymphoma during 9516 patient-years of follow-up. This risk of 2.1 per 10 000 patient-years in patients treated with anti-TNF drugs was statistically similar to the 0.6 per 10 000 patient-years in the general pediatric population.[45]

Since 1996, reports of a rare and particularly lethal form of hepatosplenic T-cell lymphoma in patients treated with anti-TNF drugs and thiopurines have accumulated. From 1996 through 2010, 36 cases of hepatosplenic T-cell lymphoma were reported in patients with IBD. All had received combination therapy with an anti-TNF drug and thiopurine or treatment with thiopurine alone, and none received anti-TNF drugs alone. Most of the patients had received thiopurines for at least 2 years and were males younger than 35 years.[52] Therefore, the risks of combination therapy with an anti-TNF drug and thiopurine, particularly in young men, must be weighed carefully against the anticipated benefits.

Surgery

Surgery is an important therapeutic option in the comprehensive management of UC and CD in children. Total colectomy with ileal pouch anal anastomosis is indicated in children with UC refractory to medical therapy. In this procedure, the diseased colon is removed, and a pouch reservoir is constructed from the distal ileum and anastomosed to a short cuff of remaining rectum to preserve continuity and avoid a permanent ileostomy. Children have

excellent long-term outcomes after this procedure, with a quality of life similar to that of the general population.[53]

Owing to the transmural nature of the inflammation in CD, complications such as fistulas, intra-abdominal abscesses, and bowel strictures can arise that require surgery. Surgery may also be indicated in CD when disease is refractory to medical therapy. Among children with CD, 14% require intra-abdominal surgery within 5 years of diagnosis.[54]

Long-term Sequelae

Micronutrient Deficiencies

Disease factors that include chronic blood loss, intestinal malabsorption, decreased intake, and chronic inflammation place patients with IBD at risk for deficiencies of various micronutrients, such as iron, folate, vitamin B_{12}, and vitamin D. Vitamin D deficiency (25-hydroxyvitamin D level, <15 ng/mL [to convert to nanomoles per liter, multiply by 2.496]) occurs in 35% of children with IBD, and 60% exhibit suboptimal levels (25-hydroxyvitamin D level, <30 ng/mL).[55] Although the role of vitamin D for supporting intestinal calcium absorption and bone health is well established, mounting evidence suggests that vitamin D also maintains intestinal immunehomeostasis and epithelial integrity.[56] Children with low vitamin D levels are more likely to have disease recurrence, and maintaining serum vitamin D levels greater than 30 ng/mL increases the likelihood of maintaining clinical remission.[57]

Growth and Bone Health

Growth failure occurs in approximately 40% and 10% of children with CD and UC, respectively.[58] The cause of growth failure in pediatric IBD is multifactorial and includes decreased intake, increased metabolic demand, malabsorption, cytokine-induced growth hormone resistance, and corticosteroids. Nineteen percent of children with CD achieve an adult height 8 cm shorter than expected.[59] Thus, close monitoring of linear growth is imperative, and treatment should be directed at restoring normal growth.

Intricately linked to growth deficits are significant abnormalities in bone metabolism in children with IBD. Although many disease factors, including malnutrition, delayed puberty, decreased physical activity, malabsorption, and corticosteroid use, have a negative effect on bone metabolism, chronic inflammation itself may exert the most profound effects.[60] Because most adult bone mass is achieved by 16 and 18 years of age in boys and girls, respectively, without appropriate monitoring and treatment, children with IBD may not achieve optimal adult bone mass, which places them at risk for fracture as they age. Vertebral compression fractures have been reported in children with IBD and low levels of bone mineral density.[61] Dual-energy x-ray absorptiometry of the total body is recommended in children with IBD and growth impairment, delayed puberty, prolonged corticosteroid use, or severe inflammation.[62] A dietary intake of 1000 to 1600 mg of elemental calcium and 800 to 1000 IU of vitamin D is recommended for children and adolescents with IBD.[62]

Colon Cancer

Owing to chronic inflammation, patients with UC and CD involving the colon have an increased risk for colon cancer. The cumulative incidence of colon cancer in patients with UC from population-based studies is 13 per 1000 patients.[63] The risk increases with time from diagnosis, and higher-risk groups include those younger at diagnosis, with pancolitis, or with associated primary sclerosing cholangitis. Therefore, beginning 7 to 10 years after the diagnosis, children with UC and Crohn colitis should undergo colonoscopy with surveillance biopsy every 1 to 2 years.

Psychosocial Function

Children with IBD have higher rates of depressive and anxiety disorders compared with children with other chronic conditions.[64] Depressive and anxiety symptoms correlate with disease activity, and factors such as the effect of proinflammatory cytokines on the brain, sleep disturbance, and corticosteroids may contribute.[65] Cognitive behavioral therapy is effective, and, at times, pharmacotherapy may be helpful as an adjunct to therapy.[65] Clinicians should be alert for symptoms of depression and anxiety and refer patients for treatment when indicated.

Symptoms such as abdominal pain, fatigue, and diarrhea also affect the patients' quality of life and social functioning.[64,65] Pediatricians and other primary care clinicians should support families in establishing a formal plan at school (eg, a 504 plan at US public schools for students with disabilities) to ensure appropriate accommodations are made for IBD symptoms (eg, unfettered access to restrooms and extended time to complete assignments after periods of absence).[65]

The Future of Pediatric IBD

The care of children with IBD is being advanced by new drug development and large collaborative research efforts. Vedolizumab, a monoclonal antibody against $\alpha 4\beta 7$ integrin that inhibits lymphocyte migration to the intestine, is the most recently approved treatment for CD and UC in adults and is starting to be used in older children with disease refractory to anti-TNF agents.[66,67] The established collaborative research networks have led to increased remission rates through quality improvement,[68] the discovery of new pediatric IBD riskgenes,[69] and insights into the microbiome and molecular pathogenesis of pediatric IBD.[18,70] Thus, we hope that the translation of recent discoveries will lead to a day when most children with IBD achieve a sustained remission, enjoy a healthy childhood, and are free to pursue their goals unhindered by disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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At a Glance

- Inflammatory bowel disease (IBD) consists of chronic intestinal inflammation caused by the interaction of genetics, environmental factors, and the microbiome.
- In approximately 25% of patients, IBD is diagnosed before age 20 years.
- The presentation of IBD in pediatric patients is variable, and primary care clinicians should be familiar with atypical presentations, such as unexplained poor growth or anemia.
- The goals of IBD treatment are to eliminate symptoms, restore normal growth, and prevent surgical complications.

Box 1

Extraintestinal Manifestations of Inflammatory Bowel Disease in Children and Adolescents

Dermatologic

Erythema nodosum

Pyoderma gangrenosum

Musculoskeletal

Arthritis

Growth failure

Osteopenia

Osteoporosis

Ankylosing spondylitis

Hepatic

Primary sclerosing cholangitis

Autoimmune hepatitis

Ocular

Episcleritis

Uveitis

Iritis

Renal

Nephrolithiasis

Pancreatic

Pancreatitis

Hematologic

Anemia

Venous thromboembolism

Box 2

Suggested Initial Laboratory Evaluation for Suspected Inflammatory Bowel Disease in Children and Adolescents

Blood Laboratory Tests

Complete blood cell count (CBC) with differential

Inflammatory markers (C-reactive protein level, erythrocyte sedimentation rate)

Liver profile (levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, and γ-glutamyl transferase)

Albumin level

Stool Examination

Salmonella, *Shigella*, *Campylobacter*, and *Yersinia* species, *Escherichia coli* O157, and *Clostridium difficile*

Ova and parasites

Occult blood

Fecal calprotectin or fecal lactoferrin

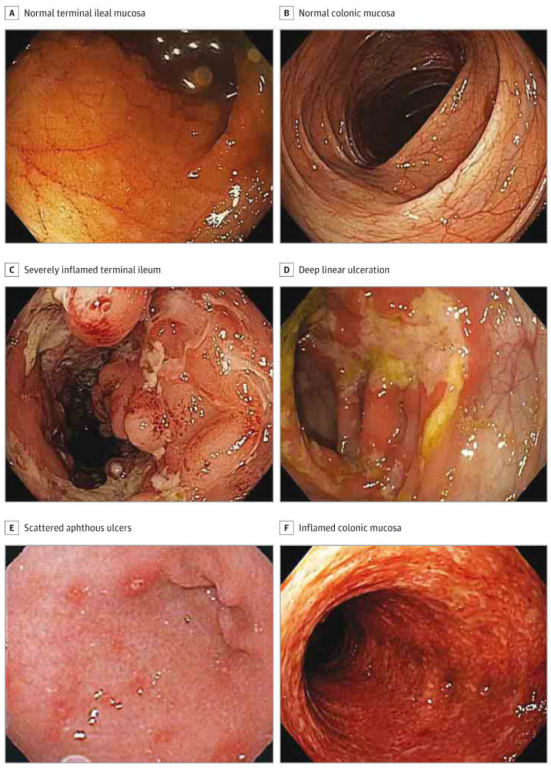

Figure. Representative Endoscopic Images of Normal and Inflamed Gastrointestinal Mucosa From Pediatric Patients With and Without Inflammatory Bowel Disease

A, A vascular pattern, villous epithelium, and normal lymphoid nodularity are visible. B, A thin transparent glistening mucosa and delicate vascular network are visible. C, Terminal ileum in a child with Crohn disease (CD) shows mucosal thickening and erythema, complete loss of vascular pattern, pseudopolyps surrounded by deep ulceration, and luminal narrowing. D, Linear ulcer directly adjacent to normal colon mucosa in a young child with CD. E, Tissue in the stomach antrum of a 10-year-old child with CD. F, An adolescent with ulcerative colitis has diffuse erythema, loss of vascular pattern, and granular-appearing superficial ulceration.

Table

Clinical Presentation of IBD in Children and Adolescents

	Classification of IBD, % of Patients[a]	
Presenting Symptom	**Crohn Disease**	**Ulcerative Colitis**
General		
Weight loss	55-80	31-38
Fever	38	NA
Anorexia	2-25	6
Growth retardation	3-4	0
Lethargy	13-27	2-12
Gastrointestinal tract		
Abdominal pain	67-86	43-62
Diarrhea	30-78	74-98
Rectal bleeding	22-49	83-84
Nausea/vomiting	6	<1
Constipation	1	0
Perianal disease	6-15	0
Mouth ulcers	5-28	13

Abbreviations: IBD, inflammatory bowel disease; NA, not applicable.

[a]Ranges are derived from data reported by Kugathasan et al,[20] Griffiths,[24] and Sawczenko and Sandhu.[22]