Pediatric Inflammatory Bowel Disease

Máire A. Conrad, MD, MS[a], Joel R. Rosh, MD[b,*]

KEYWORDS

• Pediatrics • Adolescents • Inflammatory bowel disease • Crohn • Ulcerative colitis

KEY POINTS

- Inflammatory bowel disease (IBD) is a chronic immune-mediated condition of the gastrointestinal (GI) tract in which the goal of treatment is to induce and maintain durable remission.
- There is a wide spectrum of presenting symptoms in pediatric IBD, but esophagogastroduodenoscopy and colonoscopy are imperative to confirm the diagnosis.
- Treatment goals include achieving mucosal healing of the GI tract, reaching growth potential, limiting medication toxicities, and optimizing quality of life for all patients and families.

INTRODUCTION

IBD is a chronic immune-mediated condition of the GI tract in which the goal of treatment is to induce and maintain durable remission. Although classically divided into Crohn disease (CD) and ulcerative colitis (UC), IBD actually has a wide range of phenotypes with varied responses to therapy, which makes the natural history of this chronic disease difficult to predict. Pediatric IBD has several unique considerations in comparison to adult IBD, namely related to growth, development, pubertal maturation, bone health, and the psychological impact on the patient and family. Additionally, the longevity of disease burden and its consequent morbidity is significantly more in children than in adults diagnosed with IBD. The growing incidence and prevalence of IBD further highlight the importance of pediatric primary care providers being knowledgeable about and closely involved in the care of these patients.

Disclosure Statement: J.R. Rosh: Advisor/Consultant: Abbvie, Janssen; Grant/Research Support: Abbvie, Janssen.

[a] Division of Gastroenterology, Hepatology and Nutrition, The Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, 3401 Civic Center Boulevard, Philadelphia, PA 19104, USA; [b] Pediatric Gastroenterology, Clinical Development and Research Affairs, Goryeb Children's Hospital/Atlantic Health, Icahn School of Medicine at Mount Sinai, 100 Madison Avenue, Morristown, NJ 07962, USA
* Corresponding author.
E-mail address: joel.rosh@atlantichealth.org

Pediatr Clin N Am 64 (2017) 577–591
http://dx.doi.org/10.1016/j.pcl.2017.01.005 **pediatric.theclinics.com**

IBD can be categorized into CD, UC, and IBD-unspecified. CD may involve any portion of the GI tract, typically with serpiginous and aphthous ulcers often in patchy distribution, known as skip lesions. The pathognomonic feature of CD is noncaseating epithelioid granulomas, but the presence of granulomas is not essential for a diagnosis of CD. Most commonly, children have ileocolonic involvement and approximately one-third have upper tract involvement as well.[1,2] The inflammation in CD is typically transmural, which can lead to disease complications, including fistulae and subsequent intra-abdominal or perianal abscess formation. Perianal disease, including anal skin tags, fissures, fistulae, and abscesses, are associated only with Crohn disease. A subset of pediatric CD patients presents with stricturing disease at diagnosis, but the natural history of the disease shows that many patients progress from an inflammatory phenotype to stricturing disease over their lifetime.

UC is characterized by continuous mucosal inflammation of the colon starting from the rectum and extending proximally. UC is unique from CD because it does not have small bowel involvement other than the possibility of backwash ileitis (typically nonspecific inflammation in the terminal ileum in UC patients with pancolitis and no ileocecal valve changes) and does not have granulomas on histopathology.[3] Additionally, the depth of inflammation is much more superficial and largely limited to the mucosa in UC.

IBD-unspecified describes those patients with colonic disease but who otherwise have features that are not specific for CD or UC. The full range of clinical phenotypes and the complexity of IBD suggest a multifactorial pathophysiology. The etiology is not completely understood, but it is hypothesized to be the result of a dysregulated immune response to commensal and/or pathogenic organisms in genetically susceptible hosts.

Genome-wide association studies in adults and older children have identified approximately 200 IBD risk-associated loci. This highlights the polygenic nature of the disease, and many of the identified gene polymorphisms associated with CD and UC influence immune-mediated pathways, leading to dysregulation in autophagy, cell-mediated immune responses, or innate immune responses. This dysregulation allows for an altered intestinal microbial composition resulting in dysbiosis, which may induce intestinal inflammation.[4,5]

EPIDEMIOLOGY

The incidence of IBD in the general population is rising.[6,7] High suspicion and recognition by general practitioners are imperative because IBD is not uncommon in children, with up to 25% of patients with IBD diagnosed before age 20.[8] Environmental factors have been implicated in the rapid rise in IBD especially with the recognition that children who emigrate from underdeveloped countries where the incidence of IBD is low take on an increased risk of IBD when they are established in Western societies.[9,10] Additionally, the prevalence in children younger than age 20 with CD and UC is higher in the northeast United States than in Western US states.[11]

Although the average age of diagnosis of pediatric IBD is 10 years to 12 years, a growing subcohort of pediatric IBD includes very-early-onset IBD (VEO-IBD). VEO-IBD is diagnosed in children who present with symptoms by age 5 years and accounts for up to 15% of pediatric IBD cases. VEO-IBD may have a distinct phenotype that favors a colonic disease distribution, does not respond to conventional therapies, and can include primary immunodeficiencies with GI manifestations. Monogenic causes of VEO-IBD have been described and whole-exome sequencing has been innovative in identifying these rare novel variants.[12]

PRESENTATION

IBD can initially present with a heterogeneous constellation of symptoms, including but not limited to abdominal pain, diarrhea, rectal bleeding, weight loss or growth failure, constipation, fever, mouth sores, pallor, dizziness, and dehydration. In some rare cases, patients present with peritonitis, small bowel obstruction, appendicitis, or other surgical emergencies. IBD should be considered in previously healthy children who present with an acute intestinal surgical emergency, giving close attention to growth and chronic symptoms that may have been subtle prior to the acute onset of severe symptoms. In pediatrics, growth is one of the most critical factors and a slowed height velocity may precede apparent signs or symptoms of IBD, especially in cases of Crohn disease. Extraintestinal symptoms can involve dermatologic, musculoskeletal, hepatic, ophthalmologic, renal, pancreatic, or hematologic systems, as outlined in **Table 1**.

One of the main distinctions between pediatric IBD and adult IBD is the impact of the disease on growth and development. Growth retardation and pubertal delay are common at the time of diagnosis of CD and less commonly associated with UC.[13] Growth failure may be attributed to poor caloric intake as well as the direct effects of inflammation causing growth hormone resistance.[13] Diagnosing and intervening with appropriate medical or surgical therapy before a child has completed puberty are integral for optimizing a patient's final adult height. Delayed puberty, including absence of breast development, testicular enlargement, or delayed menarche, can lead to growth retardation in itself as well as decreased bone mineralization. It can also lead to psychological sequelae as a child recognizes differences in his/her own sexual maturation compared with other children of similar age.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of IBD can vary widely based on the presenting symptoms and disease location in both adults and children (**Table 2**). The most common

Table 1
Extraintestinal manifestations of inflammatory bowel disease

Dermatologic	Pyoderma gangrenosum Erythema nodosum Alopecia Bowel-associated dermatosis-arthritis syndrome
Rheumatologic	Arthritis Enthesitis Sacroiliitis Ankylosing spondylitis
Ophthalmologic	Uveitis Episcleritis Iritis
Hepatic/pancreas/biliary	Primary sclerosing cholangitis Autoimmune hepatitis Pancreatitis Cholelithiasis
Musculoskeletal	Osteopenia Osteoporosis
Hematologic	Anemia — iron deficiency or chronic disease Venous thrombosis
Urologic	Nephrolithiasis

Table 2
Differential diagnosis of inflammatory bowel disease

Infectious	*C difficile* Salmonella Shigella Campylobacter Yersinia Giardia Cryptosporidium Enteroviruses Other bacterial, viral, or parasitic infections
Inflammatory	Appendicitis Celiac disease Microscopic colitis
Malabsorptive	Lactose intolerance Fructose intolerance Small intestinal bacterial overgrowth
Allergy/immunology	Eosinophilic GI diseases Food protein–induced enterocolitis Primary immunodeficiency Acquired immunodeficiency Autoimmune enteropathy
Rheumatology	Henoch-Schönlein purpura Behçet syndrome Sarcoidosis Systemic lupus erythematosus
Oncologic	Lymphoma Neuroblastoma Sarcoma
Other	Irritable bowel syndrome Eating disorders Laxative abuse Lymphoma Radiation enteritis Ischemia

symptoms include diarrhea with or without blood, abdominal pain, and poor growth. An acute onset of symptoms, such as abdominal pain, diarrhea, and low-grade fever, suggests infectious gastroenteritis or colitis or acute appendicitis in the differential diagnosis. Celiac disease can present with diarrhea, abdominal pain, weight loss, poor growth, and low bone mineral density but is not associated with bloody diarrhea. Eosinophilic GI disorders are less common but can present similarly and typically are only delineated from other diagnoses by endoscopy. Lactose intolerance with chronic abdominal pain and frequent diarrhea should also be considered but should resolve with dietary changes and not affect growth. Eating disorders, including anorexia nervosa, should be considered in children with weight loss, abdominal pain, and vomiting as well as laxative abuse in children with diarrhea. Additional rare considerations include oncologic etiologies, sarcoidosis, and ischemic colitis. Finally, functional disorders, including irritable bowel syndrome, are likely the most common cause of chronic and recurrent abdominal pain, diarrhea, and/or constipation in children.

Primary immunodeficiencies should be considered in children with a significant infectious history prior to diagnosis as well as in all children who are presenting with symptoms before age 5. The intestinal mucosa is in close proximity to gut-associated lymphoid

tissue and is the site of host-microbe interactions, which are critical to the appropriate development of the immune system. Primary immunodeficiencies, including chronic granulomatous disease, common variable immunodeficiency, Wiskott-Aldrich syndrome, Hermansky-Pudlak syndrome, B-cell defects and T-cell defects, phagocyte defects, and antibody-mediated defects, can initially present with an IBD phenotype.[14]

DIAGNOSTIC EVALUATION

The diagnostic evaluation in a patient suspected of having IBD begins with a thorough history to characterize abdominal pain and diarrhea as well as identify red flags, including blood in stool, nocturnal awakenings to defecate, tenesmus, defecation urgency, fevers, weight loss, mouth ulcers, joint swelling, redness, warmth, and pain (**Table 3**).

First and foremost, a detailed review of the World Health Organization growth chart to determine if there is a decreased height velocity or change in growth percentiles for age must be performed in every patient in whom there is suspicion for IBD. The physical examination should assess the abdomen for focal tenderness, peritoneal signs, and palpable masses that could be related to stricturing or penetrating disease. A perianal examination and rectal examination should not be overlooked due to the frequency of perianal abscesses and fistulae that are present at the time of diagnosis.[15] Some patients have no discomfort associated with perianal lesions and others are reticent to disclose these details to a physician. Rectal strictures may form if there has been longstanding local inflammation. Additional physical examination findings may be shallow, whitish ulcers in the oropharynx, a flow murmur due to anemia, hepatomegaly, joint swelling, redness or effusions, or limited lumbar spine range of motion. Rashes associated with IBD are typically on the lower extremities, including erythema nodosum, depicted as deep erythematous painful nodules, and pyoderma gangrenosum, characterized by ulceration, necrosis, and vasculitis. Clubbing of digits can be seen in CD as well.

The laboratory evaluation for a patient suspected of having IBD is outlined in **Table 4**. Normal laboratory results do not exclude the possibility for IBD. IBD serologies, including anti–*Saccharomyces cerevisiae* and perinuclear antinuclear cytoplasmic antibody, have been identified as immunologic markers found in some individuals with IBD. The diagnostic role of serology has undergone much study and debate in pediatrics and has been found considerably less sensitive than C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) for the presence of IBD.[16–19] The high cost and poor overall predictive value make this a less useful addition to the diagnostic work-up for IBD.

Table 3
Red flags in history and physical examination of patients suspected of having inflammatory bowel disease

History	Physical Examination
Blood in stool	Fevers
Nocturnal awakenings to defecate	Weight loss, decreased height velocity
Tenesmus	Abdominal tenderness, peritoneal signs, palpable mass
Defecation urgency	Perianal fistulae, abscesses, rectal stricture
Fevers	Mouth ulcers
	Cardiac flow murmur
	Hepatomegaly
	Joint swelling, erythema, warmth, or effusion
	Skin rashes, including nodules and ulcerations

Table 4
Laboratory evaluation in patients suspected of having inflammatory bowel disease

Initial Laboratory Considerations	Abnormalities Seen with Inflammatory Bowel Disease
Complete blood cell count with differential	Leukocytosis, microcytic anemia, thrombocytosis
Electrolytes	Acidosis and elevated BUN:Cr due to GI losses
Liver function tests	Hypoalbuminemia, elevated AST, ALT, GGT
CRP	Elevated marker of inflammation
ESR	Elevated marker of inflammation
Stool tests	
Stool culture	Rule out infectious enteritis causes, including salmonella, shigella, yersinia, and campylobacter
Rapid giardia and cryptosporidium antigen	Rule out parasitic infections
Stool *C difficile* toxin	Rule out *C difficile*
Stool calprotectin	Elevated marker of inflammation

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; GGT, gamma-glutamyl transferase.

Infectious stool studies must be performed to rule out other causes of chronic diarrhea or bloody diarrhea before proceeding with endoscopy, which is the diagnostic gold standard. *Clostridium difficile* testing; stool culture for *Salmonella*, *Shigella*, and *Campylobacter*; and ova and parasite testing, including *Giardia* and *Cryptosporidia* antigens, are particularly important. If one of these are detected, the patient should be treated or observed appropriately and further evaluation considered if symptoms persist.

In addition to ruling out infection by stool studies, fecal calprotectin has been used to screen for active inflammation. Calprotectin is a calcium-binding and zinc-binding neutrophilic cytosolic protein that can be detected in stool as an indicator of gut inflammation. Testing for fecal calprotectin has been established as a useful screening tool prior to considering endoscopy.[20,21] Additionally, it correlates closely with endoscopic activity of IBD, and there is growing evidence for serial monitoring as a marker of disease activity and treatment response.[22] Importantly, although fecal calprotectin has a high sensitivity, it is not specific to IBD, especially in children. Other causes of gut inflammation can lead to elevated calprotectin, including nonsteroidal anti-inflammatory drug use, infectious enterocolitis, inflammatory polyps including juvenile polyps, and oncologic processes. Therefore, calprotectin cannot take the place of endoscopic evaluation.

Children and adolescents with suspicion for IBD should be referred for evaluation by a pediatric gastroenterologist. On review of this evaluation, esophagogastroduodenoscopy and colonoscopy should both be performed for appropriate and complete evaluation. In pediatrics, biopsies during these procedures are essential to ensure the diagnosis and that histology is consistent with the chronic inflammation that is characteristic of IBD.

Diagnosis of IBD in very young children who developed symptoms before the age of 5 or those with a suspicious history, including recurrent infections, should have an immunologic evaluation to rule out primary immunodeficiencies, including chronic granulomatous disease and common variable immunodeficiency, among others. This may include dihydrorhodamine flow cytometry assay; measuring immunoglobulin (Ig) A, IgG, IgE, and IgM; and vaccine titers to diphtheria, tetanus, and pneumococcus to assess appropriate specific antibody response in children who have been vaccinated.[23]

A complete evaluation for IBD includes small bowel imaging to assess the intestine that is not evaluable by conventional endoscopy.[24] Upper GI study with small bowel follow-through has been a common method of evaluation for many years but does provide significant exposure to ionizing radiation and has low sensitivity and specificity. More recently, magnetic resonance enterography of the abdomen/pelvis has been growing in popularity because it prevents this radiation exposure. It requires a child to drink contrast and lie still for a prolonged period of time, which may be difficult for certain ages.[25]

MANAGEMENT

Once a diagnosis has been confirmed, the goal of treatment of pediatric IBD is to induce and maintain clinical remission, achieve normal growth, provide the best quality of life, promote psychological health, and minimize toxicity as much as possible. Additionally, the gold standard of optimal therapy is to achieve mucosal healing endoscopically to change the natural history and prevent complications of progressive bowel destruction, including hospitalization, surgery, and increased risk for colorectal cancer.[26] There are not yet tools to predict which therapy can meet this goal in individual patients, but there is ongoing research to identify genetic, serologic, and microbiome markers for this purpose. In observational adult studies of predicting outcomes in IBD, young age at onset of disease is repeatedly considered high risk for poor prognosis, which reinforces the need for a highly effective treatment approach in children. Treatment of IBD should be handled by a child and family focused multidisciplinary team of practitioners, including a pediatric gastroenterologist, pediatric surgeon, nurse, dietician, psychologist, and social worker to provide holistic care.

There are a few approaches to initiating and optimizing treatment of IBD. In Crohn disease, the oldest treatment paradigm includes step-up therapy. This non–evidence-based approach traditionally started with locally active agents, including 5-aminosalicylate (5-ASA) preparations or antibiotics, followed by prednisone or budesonide to control symptoms due to ongoing inflammation, and then escalated to immunomodulators, biologics, and, finally, after failing all medical therapies, surgery. This approach has been shown to potentially provide symptomatic management without necessarily achieving mucosal healing and changing the natural history of Crohn disease. The top-down approach to therapy, which initiates treatment with immune-modifying therapy, has demonstrated a definitively positive impact on clinical outcomes in children and adolescents, in particular those who have moderate to severe disease, likely due to the true and rapid induction of mucosal healing.[27] Future and ongoing studies intended to identify clinical markers useful in risk stratification will help provide the most personalized therapeutic plans for patients.

In UC, the mucosal confinement of the inflammatory process leads to a somewhat different treatment paradigm. 5-ASA medications, including mesalamine, balsalazide, and sulfasalazine, are locally acting anti-inflammatory agents, which topically treat the intestinal mucosa. They are well established, effective, and safe medications for adults with mild to moderate UC and can provide long-term steroid-free remission in up to 40% of pediatric UC patients.[28–31] These agents can be administered orally or rectally and overall are well tolerated with few dose-related adverse effects. Although these have a clear role in the maintenance of remission in pediatric UC, a majority of patients require an initial course of corticosteroids to induce that remission.

Intestinal dysbiosis is a major tenet of the pathophysiology of IBD, and, as a result, antibiotics have been a longstanding therapeutic approach.[32] Adult studies have shown metronidazole and rifaximin lead to clinical improvement in Crohn disease.[33–35]

Metronidazole and ciprofloxacin are typically first-line medical treatment of perianal fistulae but had the best efficacy in combination with anti–tumor necrosis factor (TNF)-α agents.[36] More recent studies have looked at combinations of antibiotics, including an 8-week trial of azithromycin and metronidazole in pediatric CD with improvement in clinical activity index and CRP.[37] Recent evidence has also emerged for using triple antibiotics (amoxicillin, doxycycline, and metronidazole) as salvage therapy for acute severe UC.[38] Alternatively, there have been several studies linking antibiotic exposure with developing IBD and there is clear dysbiosis shown with the use of antibiotics in intestinal microbiome studies.[39–42] The risks and benefits of prolonged antibiotic exposure must be weighed depending on individual cases.

Along with pharmacologic treatment approaches, dietary therapies for IBD continue to be explored. Enteral nutrition (EN) therapy, in which 100% of total calories are delivered by commercial formula and whole table foods are excluded from the diet, is the only nutritional therapy to date proved to induce remission and decrease steroid exposure in children and adolescents. There is evidence to support that 80% to 90% of calories from EN may be as effective.[43] EN provides additional support for the role of diet and the gut microbiota in the pathogenesis of IBD.

The appeal of EN compared with pharmacologic agents is that there are no serious associated side effects. Although proved an effective therapy in CD, the mechanism of action of nutritional therapy has not been fully characterized. A recent study of pediatric CD patients on exclusive EN (EEN) (90% of total caloric intake by dietary formula) compared with partial EN (53% by formula) showed EEN was superior at improving symptoms and quality of life as well as inducing mucosal healing, suggesting that the thorough elimination of solid table foods may be the key to why EN is therapeutic.[44] In addition, the alteration of the gut microbiota may be another possible mechanism of action. In the same study of pediatric CD patients, effective EEN therapy changed the microbiota within 1 week and reduced the dysbiosis seen initially.[40] Additionally, EN to induce remission has been shown to have an increased benefit to improving growth velocity over corticosteroids over 6 months.

Immunomodulators, including thiopurine analogs (azathioprine and 6-mercaptopurine), were one of the first classes of medications shown to effectively maintain remission in refractory, steroid-dependent Crohn disease.[45] Despite the efficacy of these medications, the long-term safety profile has come into question with the observation of a slightly increased risk of non-Hodgkin lymphoma as well as the observation of a small cohort of predominately male patients who develop an almost uniformly fatal form of hepatosplenic T-cell lymphoma. Alternatively, methotrexate has also been shown an effective immunomodulator in this setting.[46] Methotrexate has not been as extensively studied in IBD, but there are no reports of associated hepatosplenic T-cell lymphoma to date.[47]

Corticosteroids have been considered effective first-line therapy to induce remission in IBD among all age groups for more than 50 years. Unfortunately, the side effects of systemic steroids, including growth failure, bone demineralization, secondary adrenal insufficiency, acne, and increased infectious complications and emotional labiality make them an unfavorable therapeutic option. Avoiding ongoing use of systemic corticosteroids is now emphasized in adult and pediatric IBD. Nonsystemic corticosteroids, such as budesonide, have offered targeted therapy for IBD with high first-pass hepatic metabolism, resulting in less systemic glucocorticoid exposure than prednisone. In a pediatric randomized controlled trial, budesonide was just as effective as prednisone at inducing remission in CD by 12 weeks with less severe cosmetic side effects.[48] Neither budesonide nor prednisone is particularly effective at maintaining remission, although this has largely been studied in adults.[49,50]

Biologic agents, including anti-TNF antibodies and antiintegrin antibodies, have greatly improved the ability to treat moderate to severe CD and UC. The safety and efficacy of anti–TNF-α antibodies are well established, even demonstrating a significant response to a single infusion.[51] In children, infliximab is efficacious in inducing and maintaining remission in pediatric CD and UC.[52,53] Adalimumab has had similar success in pediatric Crohn disease, but studies of adalimumab for pediatric UC are ongoing.[54,55] Furthermore, studies have shown that early use of anti-TNF therapy is more effective in children than immunomodulators in inducing remission.[27,56] One of the profound outcomes from infliximab and adalimumab therapy in pediatrics has been the increase in height particularly in children diagnosed with CD early in puberty or before puberty.[56]

Vedolizumab is a humanized anti-$\alpha 4\beta 7$ integrin, IgG1 monoclonal antibody, which down-regulates intestinal inflammation by inhibiting T-cell migration in the GI tract. Vedolizumab has been shown to have modest improvement in clinical response and remission in both adult UC and CD patients. In children, observational studies of vedolizumab have demonstrated similar efficacy and safety.[57,58]

Therapeutic drug monitoring available for infliximab and adalimumab has helped optimize medication dosing for individual patients, which can help achieve improved clinical, biochemical, and endoscopic outcomes, increase the rate of remission, and decrease the incidence of antibody formation resulting in loss of response to these drugs.[59–61] Low or undetectable serum trough concentrations of infliximab are associated with worse clinical outcomes and worse disease activity as measured by CRP and antibodies to infliximab increase the clearance of the drug, which can lead to low trough levels.[62]

Despite medical advances, surgical intervention is still sometimes warranted in refractory pediatric IBD. In UC, total colectomy with end ileostomy can be curative for failure of medical management, resulting in transfusion dependent anemia and other sequelae of inadequate disease control. In 1 or 2 subsequent surgeries, takedown of the ileostomy and ileal pouch anal anastomosis can be performed.[63] For severe colitis in patients with CD or indeterminate colitis, diverting ileostomy has become a preferable option to resection or colectomy due to the high risk of complications long term in this subpopulation. This diverts the fecal stream away from the inflamed colonic mucosa, allowing for potential healing. Finally, CD patients may require intestinal resections, most commonly ileocecectomy. Surgical resection in childhood and adolescence is an increased risk for postoperative recurrence during adulthood and requires continued medical therapy and careful endoscopic surveillance postoperatively.

HEALTH MAINTENANCE

Health maintenance is critically important in the developing and growing child or adolescent with IBD. Monitoring growth is crucial to detecting subtle changes that may be indicative of ongoing disease activity. Detecting poor linear growth early is crucial to adequate therapy and disease control to ensure that patients with IBD meet their growth potential. Patients are at risk of malnutrition as well as obesity, which should be addressed during regular nutrition assessments.[64,65] Small intestinal disease or history of small intestinal resection increases risk for malabsorption and resulting malnutrition.

On diagnosis, the immunization status of each patient should be reviewed and kept up to date.[66,67] Vaccines should not be delayed in IBD patients, except that live vaccines should be avoided in patients treated with immune-modifying agents, including corticosteroids, thiopurines, methotrexate, and biologics. Patients with IBD on aminosalicylate monotherapy are not immunosuppressed. Ideally, vaccines should be administered

when off of immune-modifying agents; therefore, catch-up immunizations should be administered at the time of diagnosis prior to initiating these therapies. Four weeks after varicella vaccine is given and 6 weeks after measles-mumps-rubella live vaccines are given are the acceptable time periods before starting immunosuppression.[68,69] The risks and benefits of holding immunizations versus postponing therapy for IBD should be discussed between pediatrician and gastroenterologist to determine the appropriate timing.

In addition to reviewing immunization status, tuberculosis exposure and hepatitis B status should be assessed. Purified protein derivative tuberculin or interferon assay testing should be completed prior to starting biologics. Hepatitis B surface antigen and antibody should be checked to ensure no active disease and appropriate immunization status. If hepatitis B surface antibody is negative, repeat hepatitis B vaccine series should be given, especially in those receiving anti-TNF therapy.

Due to their immunosuppressed status, IBD patients' treating pediatric gastroenterologists should be contacted during an infectious illness, especially if a patient is receiving biologics, immunomodulators, or high-dose corticosteroids. In particular, active or recent Epstein-Barr virus (EBV) should be discussed due to the possible complications, including lymphoma and hemophagocytic lymphohistiocytosis (HLH), especially in those on thiopurines. IBD patients with EBV should be monitored closely for evidence of laboratory test abnormalities, including cytopenia, hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia, which require emergent evaluation for HLH.[70] In uncomplicated EBV, a gastroenterologist may consider discontinuing immunosuppression until EBV serology is consistent with past infection (viral capsid antigen–IgG positive).[67]

A nutritional assessment should be obtained at each routine pediatric visit to ensure patients are meeting caloric requirements appropriate for age. Extra consideration is recommended for children with active inflammatory disease because they likely have higher caloric needs. Nutritional deficiencies, including iron, vitamin D, and zinc, may be apparent. Vitamin B_{12} deficiency should also be considered in children who have had surgical resections, particularly of the terminal ileum. A pediatric dietician with experience in IBD can provide additional recommendations for children with ongoing malnutrition or poor growth. Supplemental oral and, if needed, enteral nasogastric tube feeds may be required to provide adequate caloric intake for the malnourished patient.

Bone health can be adversely affected in patients with IBD due to inflammation, malnutrition, corticosteroid use, and low physical activity. Up to 40% of children newly diagnosed with IBD have been reported to have deficit in bone mass, which can have an impact long term on risk of fractures and overall linear growth. Bone mineral density is measured by dual energy x-ray absorptiometry scan, whose result is expressed as a *z* score, which measures the difference in bone mineral density from the normal mean for gender and age. Vitamin D deficiency (mild–moderate 25-hydroxy vitamin D level, 10–24 ng/mL, and severe level, <10 ng/mL) is prevalent among children with IBD, especially in those with severe disease and upper GI tract involvement.[71,72] Aside from the benefits for bone health, vitamin D and its receptors may inhibit colitis by protecting the mucosal epithelial barrier.[73–75] The 25-hydroxyvitamin D level should be monitored every 6 months to 12 months, depending on if a patient is deficient or not. Supplementation with cholecalciferol to maintain a 25-hydroxyvitamin D level greater than 30 ng/mL is suggested.[66]

The toll of a chronic disease on both physical and mental health can be extensive and lead to depression, anxiety, social isolation, and altered self-image.[76,77] In pediatrics, this burden extends to the entire family of a patient with a chronic disease. For patients

with IBD, the relapsing and remitting nature of the disease can have a great impact on quality of life and the ability to fully participate in school. Regular assessment of major psychosocial stressors, school performance, and attendance as well as depression and suicide screening should be performed at all office visits. Up to 25% of adolescent patients with IBD may have symptoms of depression that often are undetected.[76] Psychological support is highly encouraged for families affected by pediatric IBD, especially for the patients, to provide strategies for coping with a chronic disease long term, and cognitive behavioral therapy is a useful tool in treating depression and anxiety. Pediatric IBD support groups are also effective venues for helping patients discover other children coping with similar scenarios and stressors.

This article outlines the unique features and considerations necessary for the appropriate care of pediatric IBD. Many medical advances in the past 10 years to 20 years have optimized the ability to care for these patients. Heightened awareness on the part of primary care providers as to the presentation of pediatric IBD allows for early diagnosis and the best prognosis. Each child and family requires the collaborative care of the primary care provider team as well as the pediatric gastroenterology team to ensure the best long-term outcomes and quality of life for the patient.

REFERENCES

1. Lemberg DA, Day AS. Crohn disease and ulcerative colitis in children: an update for 2014. J Paediatr Child Health 2015;51(3):266–70.
2. Castellaneta SP, Afzal NA, Greenberg M, et al. Diagnostic role of upper gastrointestinal endoscopy in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2004;39(3):257–61.
3. North American Society for Pediatric Gastroenterology Hepatology, Nutrition, Colitis Foundation of America, Bousvaros A, et al. Differentiating ulcerative colitis from Crohn disease in children and young adults: report of a working group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Crohn's and Colitis Foundation of America. J Pediatr Gastroenterol Nutr 2007;44(5):653–74.
4. Haberman Y, Tickle TL, Dexheimer PJ, et al. Pediatric Crohn disease patients exhibit specific ileal transcriptome and microbiome signature. J Clin Invest 2014; 124(8):3617–33.
5. Sartor RB. Therapeutic manipulation of the enteric microflora in inflammatory bowel diseases: antibiotics, probiotics, and prebiotics. Gastroenterology 2004; 126(6):1620–33.
6. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012;142(1):46–54.e42 [quiz: e30].
7. Eszter Muller K, Laszlo Lakatos P, Papp M, et al. Incidence and Paris classification of pediatric inflammatory bowel disease. Gastroenterol Res Pract 2014;2014: 904307.
8. Turunen P, Kolho KL, Auvinen A, et al. Incidence of inflammatory bowel disease in Finnish children, 1987-2003. Inflamm Bowel Dis 2006;12(8):677–83.
9. Barreiro-de Acosta M, Alvarez Castro A, Souto R, et al. Emigration to western industrialized countries: a risk factor for developing inflammatory bowel disease. J Crohns Colitis 2011;5(6):566–9.
10. Benchimol EI, Mack DR, Guttmann A, et al. Inflammatory bowel disease in immigrants to Canada and their children: a population-based cohort study. Am J Gastroenterol 2015;110(4):553–63.

11. Kappelman MD, Moore KR, Allen JK, et al. Recent trends in the prevalence of Crohn's disease and ulcerative colitis in a commercially insured US population. Dig Dis Sci 2013;58(2):519–25.
12. Kelsen JR, Dawany N, Moran CJ, et al. Exome sequencing analysis reveals variants in primary immunodeficiency genes in patients with very early onset inflammatory bowel disease. Gastroenterology 2015;149(6):1415–24.
13. Sanderson IR. Growth problems in children with IBD. Nat Rev Gastroenterol Hepatol 2014;11(10):601–10.
14. Snapper SB. Very-early-onset inflammatory bowel disease. Gastroenterol Hepatol (N Y) 2015;11(8):554–6.
15. Keljo DJ, Markowitz J, Langton C, et al. Course and treatment of perianal disease in children newly diagnosed with Crohn's disease. Inflamm Bowel Dis 2009;15(3):383–7.
16. Benor S, Russell GH, Silver M, et al. Shortcomings of the inflammatory bowel disease Serology 7 panel. Pediatrics 2010;125(6):1230–6.
17. Olives JP, Breton A, Hugot JP, et al. Antineutrophil cytoplasmic antibodies in children with inflammatory bowel disease: prevalence and diagnostic value. J Pediatr Gastroenterol Nutr 1997;25(2):142–8.
18. Ruemmele FM, Targan SR, Levy G, et al. Diagnostic accuracy of serological assays in pediatric inflammatory bowel disease. Gastroenterology 1998;115(4):822–9.
19. Khan K, Schwarzenberg SJ, Sharp H, et al. Role of serology and routine laboratory tests in childhood inflammatory bowel disease. Inflamm Bowel Dis 2002;8(5):325–9.
20. van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. BMJ 2010;341:c3369.
21. Henderson P, Anderson NH, Wilson DC. The diagnostic accuracy of fecal calprotectin during the investigation of suspected pediatric inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol 2014;109(5):637–45.
22. Sipponen T, Kolho KL. Fecal calprotectin in diagnosis and clinical assessment of inflammatory bowel disease. Scand J Gastroenterol 2015;50(1):74–80.
23. Uhlig HH, Schwerd T, Koletzko S, et al. The diagnostic approach to monogenic very early onset inflammatory bowel disease. Gastroenterology 2014;147(5):990–1007.e3.
24. Levine A, Koletzko S, Turner D, et al. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. J Pediatr Gastroenterol Nutr 2014;58(6):795–806.
25. Anupindi SA, Grossman AB, Nimkin K, et al. Imaging in the evaluation of the young patient with inflammatory bowel disease: what the gastroenterologist needs to know. J Pediatr Gastroenterol Nutr 2014;59(4):429–39.
26. Schnitzler F, Fidder H, Ferrante M, et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflamm Bowel Dis 2009;15(9):1295–301.
27. Walters TD, Kim MO, Denson LA, et al. Increased effectiveness of early therapy with anti-tumor necrosis factor-alpha vs an immunomodulator in children with Crohn's disease. Gastroenterology 2014;146(2):383–91.
28. Sutherland L, Macdonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev 2006;(2):CD000543.

29. Sutherland L, Macdonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev 2006;(2):CD000544.
30. Sandborn WJ. Oral 5-ASA therapy in ulcerative colitis: what are the implications of the new formulations? J Clin Gastroenterol 2008;42(4):338–44.
31. Zeisler B, Lerer T, Markowitz J, et al. Outcome following aminosalicylate therapy in children newly diagnosed as having ulcerative colitis. J Pediatr Gastroenterol Nutr 2013;56(1):12–8.
32. Wang SL, Wang ZR, Yang CQ. Meta-analysis of broad-spectrum antibiotic therapy in patients with active inflammatory bowel disease. Exp Ther Med 2012; 4(6):1051–6.
33. Scott FI, Osterman MT. Medical management of crohn disease. Clin Colon Rectal Surg 2013;26(2):67–74.
34. Prantera C, Lochs H, Grimaldi M, et al. Rifaximin-extended intestinal release induces remission in patients with moderately active Crohn's disease. Gastroenterology 2012;142(3):473–81.e4.
35. Su JW, Ma JJ, Zhang HJ. Use of antibiotics in patients with Crohn's disease: a systematic review and meta-analysis. J Dig Dis 2015;16(2):58–66.
36. Schwartz DA, Ghazi LJ, Regueiro M. Guidelines for medical treatment of Crohn's perianal fistulas: critical evaluation of therapeutic trials. Inflamm Bowel Dis 2015; 21(4):737–52.
37. Levine A, Turner D. Combined azithromycin and metronidazole therapy is effective in inducing remission in pediatric Crohn's disease. J Crohns Colitis 2011;5(3): 222–6.
38. Turner D, Levine A, Kolho KL, et al. Combination of oral antibiotics may be effective in severe pediatric ulcerative colitis: a preliminary report. J Crohns Colitis 2014;8(11):1464–70.
39. Margolis DJ, Fanelli M, Hoffstad O, et al. Potential association between the oral tetracycline class of antimicrobials used to treat acne and inflammatory bowel disease. Am J Gastroenterol 2010;105(12):2610–6.
40. Lewis JD, Chen EZ, Baldassano RN, et al. Inflammation, antibiotics, and diet as environmental stressors of the gut microbiome in pediatric Crohn's disease. Cell Host Microbe 2015;18(4):489–500.
41. Card T, Logan RF, Rodrigues LC, et al. Antibiotic use and the development of Crohn's disease. Gut 2004;53(2):246–50.
42. Shaw SY, Blanchard JF, Bernstein CN. Association between early childhood otitis media and pediatric inflammatory bowel disease: an exploratory population-based analysis. J Pediatr 2013;162(3):510–4.
43. Gupta K, Noble A, Kachelries KE, et al. A novel enteral nutrition protocol for the treatment of pediatric Crohn's disease. Inflamm Bowel Dis 2013;19(7):1374–8.
44. Lee D, Baldassano RN, Otley AR, et al. Comparative effectiveness of nutritional and biological therapy in North American children with active Crohn's disease. Inflamm Bowel Dis 2015;21(8):1786–93.
45. Markowitz J, Grancher K, Kohn N, et al. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. Gastroenterology 2000;119(4):895–902.
46. Turner D, Grossman AB, Rosh J, et al. Methotrexate following unsuccessful thiopurine therapy in pediatric Crohn's disease. Am J Gastroenterol 2007;102(12): 2804–12 [quiz: 2803–13].
47. Sunseri W, Hyams JS, Lerer T, et al. Retrospective cohort study of methotrexate use in the treatment of pediatric Crohn's disease. Inflamm Bowel Dis 2014;20(8): 1341–5.

48. Levine A, Weizman Z, Broide E, et al. A comparison of budesonide and prednisone for the treatment of active pediatric Crohn disease. J Pediatr Gastroenterol Nutr 2003;36(2):248–52.
49. Ford AC, Bernstein CN, Khan KJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol 2011;106(4):590–9 [quiz: 600].
50. Simms L, Steinhart AH. Budesonide for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2001;(1):CD002913.
51. Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's disease cA2 study group. N Engl J Med 1997;337(15):1029–35.
52. Hyams J, Damaraju L, Blank M, et al. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. Clin Gastroenterol Hepatol 2012;10(4):391–9.e1.
53. Hyams J, Walters TD, Crandall W, et al. Safety and efficacy of maintenance infliximab therapy for moderate-to-severe Crohn's disease in children: REACH open-label extension. Curr Med Res Opin 2011;27(3):651–62.
54. Rosh JR, Lerer T, Markowitz J, et al. Retrospective evaluation of the safety and effect of adalimumab therapy (RESEAT) in pediatric Crohn's disease. Am J Gastroenterol 2009;104(12):3042–9.
55. Hyams JS, Griffiths A, Markowitz J, et al. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. Gastroenterology 2012;143(2):365–74.e2.
56. Walters TD, Gilman AR, Griffiths AM. Linear growth improves during infliximab therapy in children with chronically active severe Crohn's disease. Inflamm Bowel Dis 2007;13(4):424–30.
57. Singh N, Rabizadeh S, Jossen J, et al. Multi-center experience of vedolizumab effectiveness in pediatric inflammatory bowel disease. Inflamm Bowel Dis 2016;22(9):2121–6.
58. Conrad MA, Stein RE, Maxwell EC, et al. vedolizumab therapy in severe pediatric inflammatory bowel disease. Inflamm Bowel Dis 2016;22(10):2425–31.
59. Maser EA, Villela R, Silverberg MS, et al. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. Clin Gastroenterol Hepatol 2006;4(10):1248–54.
60. Seow CH, Newman A, Irwin SP, et al. Trough serum infliximab: a predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis. Gut 2010;59(1):49–54.
61. Adedokun OJ, Sandborn WJ, Feagan BG, et al. Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis. Gastroenterology 2014;147(6):1296–307.e5.
62. Vande Casteele N, Khanna R, Levesque BG, et al. The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn's disease. Gut 2015;64(10):1539–45.
63. Baillie CT, Smith JA. Surgical strategies in paediatric inflammatory bowel disease. World J Gastroenterol 2015;21(20):6101–16.
64. Long MD, Crandall WV, Leibowitz IH, et al. Prevalence and epidemiology of overweight and obesity in children with inflammatory bowel disease. Inflamm Bowel Dis 2011;17(10):2162–8.
65. Kugathasan S, Nebel J, Skelton JA, et al. Body mass index in children with newly diagnosed inflammatory bowel disease: observations from two multicenter North American inception cohorts. J Pediatr 2007;151(5):523–7.

66. Breglio KJ, Rosh JR. Health maintenance and vaccination strategies in pediatric inflammatory bowel disease. Inflamm Bowel Dis 2013;19(8):1740–4.
67. Rufo PA, Denson LA, Sylvester FA, et al. Health supervision in the management of children and adolescents with IBD: NASPGHAN recommendations. J Pediatr Gastroenterol Nutr 2012;55(1):93–108.
68. Wasan SK, Baker SE, Skolnik PR, et al. A practical guide to vaccinating the inflammatory bowel disease patient. Am J Gastroenterol 2010;105(6):1231–8.
69. Lu Y, Bousvaros A. Immunizations in children with inflammatory bowel disease treated with immunosuppressive therapy. Gastroenterol Hepatol (N Y) 2014; 10(6):355–63.
70. Imashuku S. Systemic type Epstein-Barr virus-related lymphoproliferative diseases in children and young adults: challenges for pediatric hemato-oncologists and infectious disease specialists. Pediatr Hematol Oncol 2007;24(8):563–8.
71. Pappa HM, Gordon CM, Saslowsky TM, et al. Vitamin D status in children and young adults with inflammatory bowel disease. Pediatrics 2006;118(5):1950–61.
72. Kabbani TA, Koutroubakis IE, Schoen RE, et al. Association of vitamin D level with clinical status in inflammatory bowel disease: a 5-year longitudinal study. Am J Gastroenterol 2016;111(5):712–9.
73. Liu W, Chen Y, Golan MA, et al. Intestinal epithelial vitamin D receptor signaling inhibits experimental colitis. J Clin Invest 2013;123(9):3983–96.
74. Meckel K, Li YC, Lim J, et al. Serum 25-hydroxy vitamin D concentration is inversely associated with mucosal inflammation in patients with ulcerative colitis. Am J Clin Nutr 2016;104(1):113–20.
75. Stio M, Retico L, Annese V, et al. Vitamin D regulates the tight-junction protein expression in active ulcerative colitis. Scand J Gastroenterol 2016;51(10):1193–9.
76. Szigethy E, Levy-Warren A, Whitton S, et al. Depressive symptoms and inflammatory bowel disease in children and adolescents: a cross-sectional study. J Pediatr Gastroenterol Nutr 2004;39(4):395–403.
77. Szigethy E, McLafferty L, Goyal A. Inflammatory bowel disease. Child Adolesc Psychiatr Clin N Am 2010;19(2):301–18, ix.