Inflammatory Bowel Disease: An Update

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EDUCATION GAPS

Clinicians may be unaware of the most recent advances in our understanding of inflammatory bowel diseases and how this informs the diagnostic evaluation and approach to treatment. Furthermore, they need to understand how advances in precision medicine affect the care of all immune-mediated inflammatory diseases.

OBJECTIVES *After completing this article, readers should be able to:*

1. Understand how we currently view the pathophysiology of inflammatory bowel disease (IBD).
2. Appreciate the common and uncommon symptoms related to IBD.
3. Understand the importance of specific aspects of a child's history related to IBD.
4. Understand the importance of specific physical findings as they relate to IBD.
5. Understand the evaluation steps that help with the diagnosis and management of IBD.
6. Be able to guide patients regarding recent therapeutic advances in IBD.
7. Understand the roles of the members of a multidisciplinary treatment team.

INTRODUCTION

Inflammatory bowel disease (IBD) has historically been the term applied to Crohn disease (CD) and ulcerative colitis (UC). IBD-unclassified has been added and used to describe certain cases where the distinction between the 2 diagnoses is not clearly established. Although the terms *CD, UC, and IBD-unclassified* continue to be used ubiquitously, and will be used in this article, it is no longer adequate to consider them as specific diseases with clearly evident characteristics, treatments, clinical courses, and outcomes all based on predictable long-term descriptive data of historically similar patients. Instead, these should be considered immune-mediated inflammatory diseases (IMIDs) of the gastrointestinal (GI) tract worthy of highly individualized treatment and notable for unpredictable

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ABBREVIATIONS

CD	Crohn disease
GI	gastrointestinal
IBD	inflammatory bowel disease
IL	interleukin
IMID	immune-mediated inflammatory disease
JIA	juvenile idiopathic arthritis
MRE	magnetic resonance enterography
TNF-α	tumor necrosis factor α
UC	ulcerative colitis

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complications. With a wider array of therapeutic options and a more precise disease phenotype, recent personalized approaches have significantly altered the course and improved the outlook for patients previously forced to choose between the complications of their disease or the adverse effects of their therapies. This review summarizes our current understanding of the pathophysiology of IBD, the evolving epidemiology, basic aspects of history and symptoms, general diagnostic evaluation, and our current and rapidly evolving treatment approach, with progress in pharmacologic, dietary, and surgical interventions, acknowledging attendant risks and complications.

PATHOPHYSIOLOGY

IBD occurs in the genetically susceptible person when environmental factors trigger a dysregulated immune response. It is currently postulated that the environmental factors are associated with adverse alterations in the intestinal microbiome referred to as *dysbiosis*. The systemic response to intestinal dysbiosis includes the stimulation of various inflammatory cytokines that may be specific to IBD as well as associated with other IMIDs, such as psoriasis, psoriatic arthritis, juvenile idiopathic arthritis (JIA), and perhaps other autoimmune diseases as well.

Genetic Underpinnings

The contribution of genetic variation to IBD ranges from monogenic, in which a single gene variant causes the disease, to genetic susceptibility, in which 1 or more genetic variants confer risk of developing the disease. Most currently identified monogenic forms occur within the first 2 years after birth and are particularly severe. Children younger than 6 years with IBD are classified as having very early-onset IBD. Note that even in this young population, the rate of identified monogenic IBD remains low. (1) Through childhood and into adolescence the genetic architecture of IBD increasingly resembles that of adults, with susceptibility variants playing the largest role. The overall burden of genetic contribution among our youngest patients is, thus, higher than in adults. (2) Although this may explain the more complicated and aggressive phenotypes seen in very young children, (3)(4) it also affords an opportunity for discovery of molecular mechanisms that may help identify precise targets for novel medical therapies for patients of all ages. (5)(6)

The remarkable success of anti–tumor necrosis factor α (TNF-α) therapies for IBD has revealed the outsized role that T cells play in the development and perpetuation of intestinal inflammation. Genetic discovery, however, has led to the identification of molecular subtypes of IBD, such as the interleukin (IL)-10R pathway in regulatory T cells, (6) autoinflammatory pathways, and defects of the epithelial barrier. (7) These genetic perturbations may reveal the potential role of specific molecular pathways in those forms of IBD that do not have a discrete genetic etiology. Furthermore, the characterization of IMIDs, which include JIA and psoriasis, is shifting from organ-centered (eg, gut, joint, skin) to molecular-based, with emerging cytokine signatures (eg, TNF-α, IL-12, IL-23, IL-1) associated with phenotypic disease expression. (8)

Environmental Contributions Including Dietary Influences

Despite the dramatic influences noted in those rare occurrences of genetically acquired IBD and the identification of risk variants across large populations of people with IBD, (9) genetics alone can explain only a small portion of the incidence of IBD. (10) Environmental factors seem to be necessary to cause the disease even in the genetically susceptible host. In IBD, the most likely environmental candidate is diet. It has been noted that the rate of disease among immigrants who are being newly introduced to Westernized diets starts to emulate the rate of the new home country, with newly arrived children having similar rates as the existing pediatric population. (11) Diets high in animal fat and protein, as well as processed foods with additives, are associated with an increase in the risk of developing IBD, although identifying and isolating specific elements that increase risk has been challenging. (12) Regardless, a focus on Western diets, especially on the increasing use of additives such as emulsifiers, has emerged as a suspect cause. (13) This increased focus on diet is leading to increased interest in dietary manipulation as a potential therapy (see later herein).

Microbe-Host Interactions

The interface of the environment and mucosal immune system is hypothesized to have a critical mediator: the intestinal microbiome. Early and repeated antibiotic use is strongly correlated with increased risk of IBD and JIA. (14) One theory holds that antibiotic use leads to dysbiosis and a dysregulated immune response with the stimulation of various inflammatory cytokines.

However, it is possible that these children have an underlying predisposition toward infection along with an existing immune dysregulation (ie, antibiotics reflect infection risk rather than contributing to pathogenesis). It is likely that a combination of intestinal dysbiosis and immune dysregulation leads to the development of IBD, with a spectrum of

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weighted contribution. In a few children, such as those with monogenic etiologies, alteration of the underlying immune system is likely sufficient to lead to IBD, whereas in others, environmental factors leading to intestinal dysbiosis are probably necessary. Recently, there have been examples of underlying genetic changes combining with an altered microbial composition to increase the risk of developing pediatric CD. (15)

Inflammatory Progression and Bowel Damage

Inflammation in IBD can lead to irreversible bowel damage despite medical therapy. Although CD and UC are likely not the distinct entities previously thought, there are particular clinical features that tend to distinguish them. In CD, any part of the GI tract can be affected, from the oral cavity to the anus. CD may extend from the inner mucosa to include the surrounding intestinal serosa, and it is this extension that is used to classify its behavior. Initially it is *inflammatory*, but due to its transmural nature, it may proceed to become *stricturing* (associated with fibrosis) and ultimately *penetrating* (ie, abscess or fistula). Twenty-five percent of patients with CD may have their disease present with or extend to include perianal disease. Perianal disease can involve fistula formation initiating anywhere in the bowel wall and then progressing to invade the perianal area and surrounding tissues (Fig 1).

In UC the disease is primarily limited to the colon, and unlike CD, which is transmural, UC is considered to be a mucosal disease. The intestinal inflammation characteristically is continuous, with most distal bowel always affected, and a range of involvement from isolated ulcerative proctitis to pancolitis. Although inflammation in the ileum (by extension from the cecum) and inflammation in the stomach may occasionally be noted, the significance of such findings is a cause of diagnostic debate. UC may progress to a medically refractory state in which a colectomy is the only option to address uncontrollable inflammation.

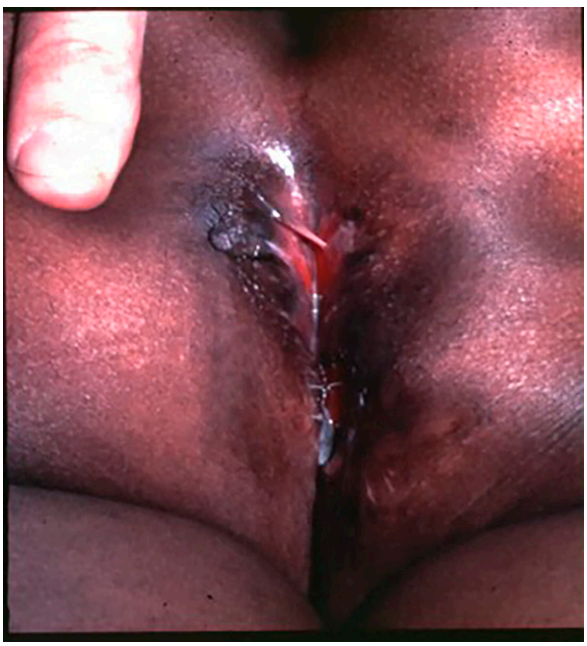

Figure 1. Perianal fistula.

Patients diagnosed as having IBD-unclassified generally have most features consistent with UC but with some additional element potentially consistent with CD, such as mild inflammation of the terminal ileum or apparent sparing of the rectum.

EPIDEMIOLOGY

Worldwide the incidence and prevalence of IBD in children and adults is increasing, and this seems to correlate with industrialization. Western, industrialized countries display the highest rates historically, and industrializing countries are seeing the most rapid increases during the past 30 years. Furthermore, as noted previously, populations that immigrate to areas of the world that are more industrialized exhibit an increase in IBD, both in the group that migrates and, to a greater extent, their progeny. The incidence of pediatric CD in the United States (1.3–15.3 per 100,000 person-years) is similar to that in Canada (4.3–11.2) and Western Europe (2.1–15.3). Pediatric UC also has a similar incidence in the United States (0.5–4.0 per 100,000 person-years), Canada (1.2–5.7), and Western Europe (1.5–8.4). (16) A model for the evolution of IBD epidemiology proposes 4 stages: 1) emergence, 2) acceleration in incidence, 3) compounding prevalence, and 4) prevalence equilibrium, in which stable incidence is balanced with low mortality. (17) Adult populations in some industrialized countries seem to be in the compounding prevalence stage; however, the pediatric population seems to still be in an acceleration phase. (16) In many areas of the world, such as in parts of Asia and Central and South America, the IBD populations are in emergence and are progressing into acceleration in incidence as industrialization progresses.

DIAGNOSIS

Clinical Presentation

The hallmark symptoms of IBD in children are abdominal pain and fatigue, and the characteristic signs include diarrhea, hematochezia, weight loss, and growth and pubertal delay (Table 1). Any of these should raise suspicion for IBD, but none is necessary or sufficient. Although these

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Table 1. Evaluation for IBD

HISTORY AND PHYSICAL EXAMINATION	LABORATORY EVALUATION	DEFINITIVE DIAGNOSIS	THERAPY
			See Table 4
Growth delay (review old growth curves)	CBC with differential	Magnetic resonance enterography	
Weight loss	Erythrocyte sedimentation rate	Magnetic resonance imaging of the pelvis	
Abdominal pain	C-reactive protein	Ileocolonoscopy with biopsy	
Diarrhea with or without blood or tenesmus	Liver function tests (albumin)	Upper endoscopy with biopsy	
Family history of IBD or other IMIDs	Iron deficiency panel		
Arthralgias or arthritis	Stool pathogen testing		
Fever	Stool occult blood		
Fatigue	Stool calprotectin		
Oral ulcers	Vitamin D		
Unexplained rash			
Loss of interest in school, hobbies, friends, etc			
Focus on location of toilets			

CBC=complete blood cell, IBD=inflammatory bowel disease, IMID=immune-mediated inflammatory disease.

are more specific to the nature of IBD as a disorder of intestinal mucosal immunity, IBD also produces a state of systemic inflammation that may cause fever and fatigue, as well as extraintestinal manifestations involving the joints (arthralgia, arthritis), eyes (uveitis, episcleritis), and skin (psoriasiform rash, erythema nodosum, pyoderma gangrenosum) (Table 2). Onset can be sudden or insidious, the course may be persistent or intermittent. It may spontaneously remit and recur, with variable severity. The progression of these clinical features may provide insight into the underlying phenotype of IBD. For example, diffuse, severe, unremitting, and progressive bloody diarrhea over 4 weeks suggests colonic inflammation (which may be UC or CD). Subtle or significant decline in growth velocity noticed during annual health supervision visits paired with pubertal delay would be consistent with CD.

Table 2. Extraintestinal Manifestations and Associations

Extraintestinal manifestations of IBD
Arthralgias
Arthritis
Erythema nodosum
Primary sclerosing cholangitis
Pancreatitis
Chronic active hepatitis
Iritis/uveitis
Ankylosing spondylitis
Psoriasis
Pyoderma gangrenosum
Associations with IBD
Mental health (including depression and anxiety)
Venous thromboembolic complications
Pulmonary
Neurologic
Bone
Mucocutaneous
Cardiovascular
Cancer

IBD=inflammatory bowel disease.

On physical examination, tachycardia may be evident, resulting from dehydration or anemia. Growth parameters may indicate weight loss or deceleration and short stature. Uveitis or episcleritis may be present during ophthalmic examination, and psoriatic lesions may be present anywhere on the child's body. Oral manifestations such as aphthous ulcers and cheilitis are common. Cardiopulmonary examination may reflect systemic disease (such as flow murmur from chronic anemia). A full careful abdominal examination is requisite and should focus on differential diagnoses. Inspection for abdominal distention is important in suspected partial small-bowel obstruction. Palpation for localized tenderness can indicate affected bowel segments, eg, right lower quadrant and terminal ileal disease, or epigastric/periumbilical and left lower quadrant for colitis.

Palpation and percussion to assess for hepatomegaly and hepatobiliary disease is important. Isolated flank tenderness may be a sign of kidney stones. Sexual maturity rating should be performed to determine pubertal delay. A targeted joint examination to distinguish arthralgia and arthritis should be performed. A full skin examination may detect dermatologic manifestations, notably psoriasis. Examination of the anterior legs may reveal erythema nodosum or pyoderma gangrenosum. Finally, a careful perianal

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inspection is important, especially in adolescents, who may avoid discussing relevant findings. A full digital rectal examination may be necessary depending on findings and history. If it is clear that the child is about to undergo a colonoscopy, the digital rectal examination may be postponed until it can be performed under anesthesia. An appropriate chaperone should be present in the examination room for examination of the genitalia and perianal areas.

Differential Diagnosis and Overlapping Etiologies

When IBD is part of the differential diagnosis, it is important that the diagnostic evaluation be performed expeditiously. Bowel inflammation should be considered as a serious matter requiring prompt evaluation and treatment.

Fulminant colitis has an extended differential diagnosis that requires urgent evaluation and appropriate treatment. Patients presenting with fulminant colitis are or are about to become very ill and may have all or many of the following symptoms: fever, chills, nausea and/or vomiting, abdominal distention, and abdominal tenderness. Their evaluation likely will reveal leukocytosis, anemia, dehydration, and electrolyte imbalance. The process may rapidly advance and can be fatal. Patients are at risk for perforation, and surgical consultation should be obtained at the time of admission or as early as feasible. The differential diagnosis includes colonic perforation, hemolytic uremic syndrome, Hirschsprung enterocolitis, and infections (including *Clostridioides difficile*, toxigenic *Escherichia coli*, enteroinvasive *E coli*, *Salmonella*, *Shigella*, *Campylobacter*, and cytomegalovirus). Acute severe colitis may increase the risk of thromboembolic events, and preventive anticoagulation is widely used in hospitalized patients with severe colitis.

The other acute presentation requiring emergency evaluation is the child with right lower quadrant pain. The history may suggest acute onset or relatively acute onset. Acute appendicitis, as well as appendiceal perforation, will be part of the differential diagnosis.

Physical examination may be positive for right lower quadrant pain or may reveal a mass. The mass may be an abscess, resulting from either a ruptured appendix or perforating CD, or adherent loops of inflamed bowel. Emergency imaging and appropriate medical and surgical consultation generally clarify the disease process.

Apart from the previously mentioned emergency situations, the evaluation for IBD should advance expeditiously, with laboratory, imaging, and endoscopic and colonoscopic evaluations being accomplished, ideally, within a 2-week period.

Diagnostic Evaluation and Disease Characterization

In a child with suspected IBD, the initial evaluation includes blood work and stool testing. A complete blood cell count with differential (anemia, leukocytosis, thrombocytosis), basic metabolic panel, hepatic function panel (hypoalbuminemia), C-reactive protein level, and erythrocyte sedimentation rate is standard (Table 1). Additional blood work based on the differential count should also be sent. Additional studies may clarify the presence or absence of celiac disease (IgA–tissue transglutaminase and serum IgA), as well as thyroid disease (thyrotropin, free thyroxine). Stool testing for infectious gastroenteritides (GI polymerase chain reaction panel or stool culture, ova and parasites, *C difficile* toxin) as well as for a specific marker of inflammation, fecal calprotectin, should also be performed. If the differential diagnosis includes a reasonable probability of IBD, tuberculosis should be excluded with an appropriate blood test or tuberculin skin test. Excluding latent tuberculosis will also facilitate the initiation of any therapy that is associated with reduced immune function.

The gold standard procedure to diagnose IBD is an ileocolonoscopy with biopsy and an upper endoscopy with biopsy. The ileocolonoscopy will provide an endoscopic characterization of the colon and terminal ileum, which often is sufficient to distinguish CD from UC. Ulcerations, congestion, erythema, exudates, and/or stenosis in the terminal ileum are consistent with CD, as are deep and discontinuous ulcerations in the colon (Figs 2 and 3). Continuous erythema, congestion, ulcerations, and exudates in the colon beginning distally from the rectum are consistent with UC (Figs 4 and 5), and there is

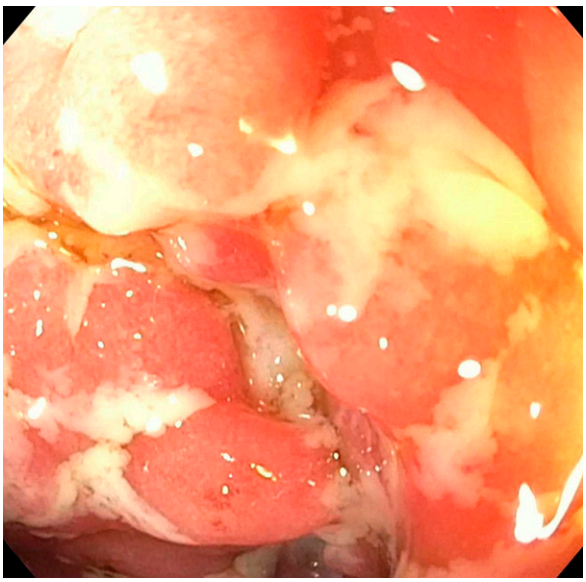

Figure 2. Deep ulceration in the terminal ileum, Crohn disease.

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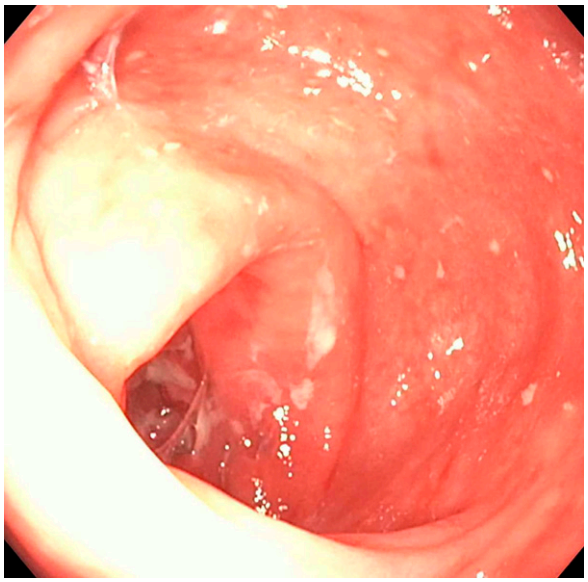

Figure 3. Confluent and aphthous ulceration in the colon, Crohn disease.

occasionally sharp demarcation of inflamed from noninflamed bowel (Fig 6). Biopsies of targeted affected areas are important, but so are random biopsies of healthy-appearing bowel, which are performed for histologic evaluation.

This is most true of the rectum and the terminal ileum. Tissue samples that demonstrate both active inflammation and features of chronicity are consistent with the diagnosis of IBD when characteristic endoscopic lesions are present. The upper endoscopy is performed in children to evaluate for upper GI tract disease that may be more suggestive of CD and to assess for alternate diagnoses, such as celiac and eosinophilic GI disease.

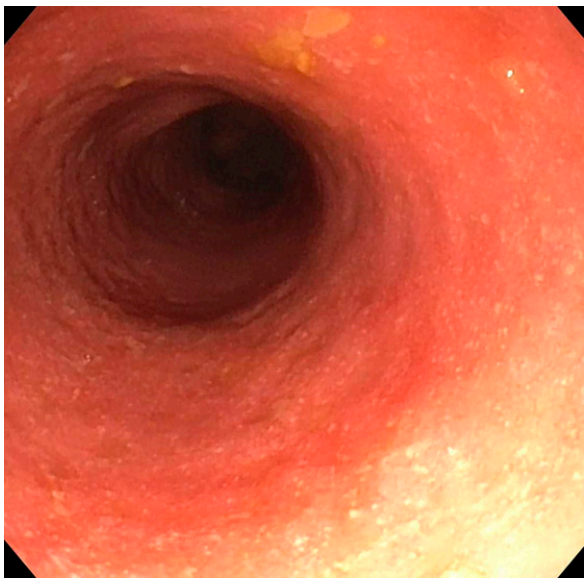

Figure 4. Continuous and diffuse superficial ulceration in the colon, ulcerative colitis.

To complete the characterization of IBD, imaging is performed with 2 primary goals: 1) to assess for bowel involvement beyond the reach of upper endoscopy and ileocolonoscopy and 2) to determine whether penetrating or stricturing disease is present (Table 3). Magnetic resonance enterography (MRE) includes imaging of the abdomen and pelvis. It is a lengthy study that also necessitates venous injection and oral ingestion of a large volume of contrast material. It is the most comprehensive and reliable imaging modality in IBD. It has limitations in its use for young children (<6 years of age) owing to their inability to remain still for the long duration of the study. Abdominal computed tomography is to be avoided, when possible, given its high radiation exposure, although it is fast and accessible and is important if an urgent determination of intra-abdominal pathology is needed. Intestinal ultrasonography may provide helpful information when standard methods of imaging are unavailable. Ultrasonography does not provide the extent of evaluation of MRE.

Other evaluation includes a radiograph of the hand for bone age determination. This may help characterize the nature of any existing growth delay and may provide a sense of urgency should the growth potential as determined by the bone age be very limited. Bone densitometry provides an assessment of bone health but is not uniformly performed.

Beyond the previously described evaluation, collaboration between specialties is important for a thorough evaluation of the patient suspected of having IBD. Involvement of skin, eye, or joints may be assessed via referrals to dermatology, ophthalmology, or rheumatology, respectively, and immunology consultation is often sought if there is a suspected underlying immune defect, especially in children diagnosed before 6 years of age. Evaluation by endocrinology should occur in the setting of unexplained or significant IBD-related growth failure.

TREATMENT

Goals of Care and Treatment Targets

The natural goal of any treatment for a child with IBD is to help regain their health. Although this may be obvious, it can be elusive. Standards to help refine a clinical end point have evolved from "physician global assessments" to clinical indices to patient-reported outcomes, with ever-increasing focus on the experience of the disease and its effect on the patient. Two indices in children, the Pediatric Crohn Disease Activity Index

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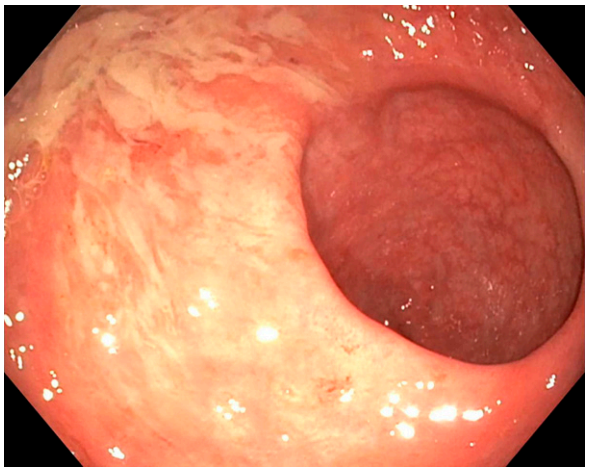

Figure 5. Ulceration and erythema with change to normal mucosa in the colon, ulcerative colitis.

and the Pediatric Ulcerative Colitis Activity Index, have played an important role in clinical trials and advancing the care of children with IBD. The former (18) includes elements of history (eg, abdominal pain, stool frequency), physical examination and growth, and laboratory values (hematocrit, albumin, erythrocyte sedimentation rate), and the latter (19) contains only subjective symptoms (number of stools, degree of blood in stool, stool consistency, etc). Newer patient-reported outcomes for CD and UC are on the horizon. The importance of these is to assist in recognizing "clinical remission," an end point that conveys that the child feels completely well.

Although clinical remission is paramount, it is a subjective outcome and is insufficient for determining true disease control. If left as the sole target, it may not capture the full extent of ongoing disease activity, potentially resulting in disease progression and irreversible bowel damage. With the development of effective treatments during the past 25 years, the current target for children is now "mucosal healing," a concept that continues to evolve but essentially entails resolution of intestinal inflammation as determined by objective assessment. (20) Currently, the mainstay method of disease assessment is endoscopic evaluation, with endoscopic remission an acceptable treatment target. Absence of histologic inflammation is referred to as "deep remission." Laboratory tests such as the serum inflammatory markers C-reactive protein and erythrocyte sedimentation rate and the stool inflammatory marker calprotectin are important intermediary targets but are insufficient to document true healing. The target of remission on imaging, such as demonstrated by MRE, is emerging and, in clinical practice, most often individualized (eg, in a child with transmural inflammation at diagnosis, resolution of the transmural inflammation is an important goal of therapy). Restoring a normal growth trajectory as well as progression through puberty are critical and time-sensitive treatment targets for children with growth or pubertal delay.

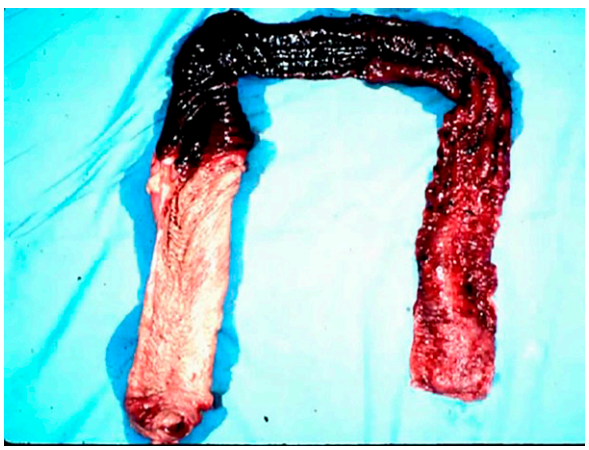

Figure 6. Colectomy specimen with line of demarcation in the ascending colon, ulcerative colitis.

For the family and for the child with newly diagnosed IBD, an explanation of treatment targets and outcomes is very important. Parents and patients should understand the nature and extent of their disease as well as remission targets: clinical, biomarker, endoscopic, and radiographic. Achieving clinical remission may improve quality of life, but the impact of a diagnosis of a lifetime chronic disease is emotionally consequential. Realistic treatment options for IBD include injections, infusions, potential hospitalization, invasive procedures, and surgery, all with known and unknown adverse effects that may affect the quality of life of patients differently. Nonetheless, a normal quality of life is an attainable central goal for most patients with IBD. To achieve this, recognizing the added layers of chronic disease to the general risk of mental health disorders in children and adolescents, dedicated psychosocial care, by a qualified behavioral psychologist or a trained social worker, is a key component of comprehensive care for children with IBD. Ideally, a pediatric psychologist, trained and experienced with children with IBD, would be available. Pediatric psychology is an area of expertise that is distinct from a child behavioral psychologist not specifically aligned with an active IBD-centered practice. An appreciation of the symptoms and subtleties related to the clinical course of IBD is ideal and may often be a key contribution of the treatment team's clinical social worker. The role of the clinical social worker may include evaluation and support for patient and family behavioral issues, assistance with school authorities, and insurance issues,

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Table 3. Intestinal Complications of Inflammatory Bowel Disease

COMPLICATION	CROHN DISEASE	ULCERATIVE COLITIS
Stricture	May represent progression from inflammatory Crohn disease	Rare
Fistula or abscess	May represent progression from inflammatory or stricturing Crohn disease	No
Bowel perforation	Generally, not a free perforation, but rather progression through bowel wall with formation of abscess or fistula	May occur, especially with fulminant colitis; generally, results in free perforation with peritonitis
Severe bleeding or hematochezia	Occurs and may be associated with area of deep ulceration	Most frequently associated with severe and extensive ulcerative colitis
Toxic megacolon	Unlikely	Known (but rare) complication

and it may extend almost indefinitely to support the child and family.

With attention centered on the implications of a new diagnosis of a serious chronic disease, it is important not to overlook ensuring vaccine protection for our children with IBD. At the time of the diagnosis of IBD, a review of vaccine status should be conducted and immunizations should be brought up to date as quickly as possible. This is not always practical, especially if immunosuppressive medication is imminent. Current recommendations suggest that children with IBD should be immunized according to the same immunization schedule followed by well children, including for influenza and SARS-CoV-2. (21) However, if they are taking an immunosuppressive agent, they should avoid live virus vaccines. More evidence relating to the specific recommendations concerning efficacy, immunogenicity, and safety would be welcome. (22)

Shared decision-making is a cornerstone of pediatric medicine, and the advances in treatment options for IBD have provided increasing opportunities for the medical team to support children and families in making decisions that align with their values and preferences. (23) The overall process thus entails free exchange of information, ascertaining values and preferences from the patient and family and expertise provided by the medical team, combined with weighing the benefits and risks of all the acceptable approaches. As the treatment plan is carried out, the child, family, and medical team can feel confident together in their mutual decision, appreciate that periodic reassessment is always advisable, and be prepared to make alterations in the plan as needed.

Medications

For many years, the field of IBD was without reliable clinical trials to examine the efficacy of various medications. Clinical drug treatment trials have resulted in some progress of our understanding of which drugs to use and how to use them appropriately. However, children are largely excluded from these trials, and treatment strategies may reflect approaches to adult disease, in addition to limited study and anecdotal experience in children. Descriptions of some of the most commonly used medications are listed in Table 4.

Medical treatment has 2 phases: initial induction of disease remission and then maintenance of that remission. Maintenance of remission requires periodic monitoring to ensure that disease remission is durable. Corticosteroids are used to treat inflammation indiscriminately in pediatric medicine, yet they remain an important medication for induction in UC and, to a lesser degree, CD. Corticosteroids do not achieve bowel healing but can improve the control of inflammation. In UC, the oldest targeted class of medications, the 5-aminosalicylic acids, are oral medications that are effective and safe for mild to moderate forms of UC as both induction and maintenance agents. The class of medications known as immunomodulators have been diminished in their usefulness owing to the superior efficacy and safety profile of anti-TNF-α therapies. 6-Mercaptopurine and azathioprine are maintenance medications for CD and UC that are no longer recommended due to their increased cancer risk. Methotrexate, the other main immunomodulator, is another maintenance agent, and its major role today is to suppress drug antibody formation. Biological medications have become the mainstay treatment for CD and severe UC. The anti-TNFs infliximab and adalimumab are effective for both induction and maintenance. The newer agents anti–IL-12/23 (ustekinumab) and anti-integrin (vedolizumab) for CD and UC are not yet first-line therapies in children, but early experience shows promise. Recently, the small molecule JAK inhibitors are showing increasing success in adult IBD, but safety considerations remain an incomplete area of study that may limit wide adoption in children. Last, antibiotics have had a pivotal role in the management of IBD, spanning treatment of intra-abdominal abscesses, concurrent infectious gastroenteritides, modulation of dysbiosis, and as short-term adjunctive therapy.

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Table 4. Pharmacologic Treatment for Inflammatory Bowel Disease

TREATMENT	DESCRIPTION	STATUS
Aminosalicylates		
Sulfasalazine	Developed in the 1940s with the intent to combine a sulfa antibiotic with an anti-inflammatory agent (5-ASA).	Widely used as only therapy (along with corticosteroids for much of latter part of last century). Severe life-threatening adverse effects such as Stevens-Johnson syndrome and subacute hepatic failure led to the development of 5-ASAs without the sulfa component. Because it is available as a liquid, it may still occasionally be used in children unable to swallow pills.
Mesalamine	The most widely used form of 5-ASA; it is available as tablets, delayed-release tablets, rectal enemas, foams, and suppositories.	Oral form is initial therapy for mild UC, enemas used for recalcitrant distal colonic disease. (Use in CD colitis is generally discouraged, with successful outcomes based on anecdotal reports.)
Corticosteroids		
Budesonide	Oral or rectal corticosteroid with significant first-pass metabolism by liver, limiting systemic corticosteroid adverse effects.	Sometimes used as initial therapy for mild ileocecal CD. An enema form is available for left-sided UC. For these indications, it is preferable to other corticosteroids but should be considered for short-term use only. Depending on its effectiveness, it is a bridge to a more long-term treatment regimen.
Prednisone, methylprednisolone, methylprednisone	Oral and intravenous corticosteroids that are effective anti-inflammatory agents for short-term induction of remission in moderate to severe CD and UC. Serious adverse effects limit their use. "Corticosteroid-free" remission is a common end point of drug trials.	Used to induce rapid remission in moderate UC. Lack of effect within 5 d is considered a sign of the need for rescue therapy with anti–TNF-α therapy.
Immunomodulators		
Azathioprine/6-mercaptopurine	Effective at maintaining remission in both CD and UC, now increasingly used only for a limited time to suppress antibody formation to biological agents.	Known carcinogens, widely used before adoption of anti–TNF-α therapy for maintenance therapy. Because of effectiveness, some doctors and patients continue to use. Methotrexate is a known teratogen with special additional concerns, including hepatotoxicity. They are all being replaced by biological agents.
Methotrexate	An antimetabolite that has replaced azathioprine and 6-mercaptopurine for maintenance, but is a well-known teratogen with a limited safety profile.	
Antibiotics		
Metronidazole Ciprofloxacin	Used for perirectal disease, abscess, and fistula formation. Use for small-bowel CD and acute UC or CD colitis is controversial.	Some anecdotal evidence of successful use in treating small-bowel CD and acute UC and CD colitis. No satisfactory clinical trial evidence of effectiveness.
Rifaximin		
Biological agents		
Infliximab (and biosimilars)	Target TNF-α.First-line therapy for moderate to severe forms of CD and UC.	Most effective and with the best safety profile. First agents that have the capacity to alter course of aggressive disease. No live virus vaccines while on anti–TNF-α therapy.
Adalimumab		
Vedolizumab	Targets $\alpha 4\beta 7$ integrins.	Agents currently under investigation for use in patients aged <18 y. Approved for adult use.

Continued

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Table 4. Pharmacologic Treatment for Inflammatory Bowel Disease (Continued)

TREATMENT	DESCRIPTION	STATUS
Ustekinumab	Targets p40 subunit of IL-12 and IL-23.	
Small molecule agents		
Tofacitinib	Janus kinase inhibitor.	Agents currently under investigation for use in patients aged <18 y. Approved for adult use.
Ozanimod	S1P receptor modulator.	
Calcineurin inhibitors (tacrolimus, cyclosporine)	Unapproved agents occasionally used in very special situations as a "rescue" therapy to avoid colectomy.	Unapproved agents with known serious adverse effects.
Thalidomide	Rarely used	Known teratogen with other major side effects
Probiotics	Widely used.	Inadequate evidence to define a therapeutic role.
Dietary therapy	See text	
	Specific carbohydrate diet	Appropriate for specific therapeutic situations with highly motivated patients and family.
	Crohn disease exclusion diet	
	Mediterranean diet	

5-ASA=5-aminosalicylate, CD=Crohn disease, IL=interleukin, TNF-α=tumor necrosis factor α, UC=ulcerative colitis.

Dietary Approaches

The role of therapeutic dietary interventions is currently of increasing interest. Dietary interventions have long had a central role in the management of IBD in children. At the most basic level, children with IBD are at risk for malnutrition and, therefore, may require nutritional repletion. When corticosteroids and 5-aminosalicylic acids were the only medical options, the administration of defined formula diets became a cornerstone for treating nutritional deficiencies in many patients with IBD and often for helping to manage symptoms associated with consuming regular diets. The association of formula-only diets and bowel healing opened the field of dietary manipulation as a primary treatment approach. (24) The concept of exclusive enteral nutrition emerged and became a primary treatment modality for pediatric CD in Europe (25) and has had moderate adoption in the United States. (26) The actual mechanisms that are responsible for reported therapeutic responses are uncertain, although early studies have pointed toward alteration in the intestinal microbiome. (27)

The limited feasibility of a formula-only diet has led to modified enteral regimens combining diet with partial enteral nutrition and to the exploration of elimination diets as possible treatment options. The specific carbohydrate diet and the CD exclusion diet, as well as the Mediterranean diet, all contain elements of reducing food additives, reducing animal products, and limiting refined grains while increasing fruits and vegetables. The potential therapeutic role of diet remains to be clearly delineated. (28)(29)(30) Pursuing a dietary approach in circumstances where medical therapy is the optimal choice remains a challenge, partially owing to limitations in sound clinical research on dietary therapy. The risk of disease progression while awaiting any therapy to gain maximum effectiveness must be carefully assessed by both the treatment team and the child and family. The pursuit of dietary therapy necessitates a knowledgeable and dedicated team, including a dedicated IBD dietitian. Similar to the IBD behavioral health professional, the IBD dietitian must be familiar with the signs, symptoms, complications, and treatments related to IBD. The internet, as well as well-meaning acquaintances, expose parents to substantial alternative nutritional regimens. These may include unknown supplements and potentially harmful concoctions. Parents may conceal these from their treating physicians but often will discuss with an IBD registered dietitian whom they trust.

Microbial Therapy

Due to the long-recognized contribution of altered microbial composition to the development and persistence of IBD, modification of the intestinal microbiome continues to be an anticipated therapeutic approach. Fecal microbial transplant, in which donor stool is administered to the intestinal lumen of the patient, has become a well-established treatment for recurrent *C difficile* in adults and children, even in those with IBD. (31) The use of fecal microbial transplant specifically for IBD in the absence of *C difficile*, however, remains under investigation, with some trials in adults with UC showing promise.

Surgery

Surgery has a critical role in the management of IBD in 3 key areas: 1) emergency/urgent complications (eg, perforation), 2) irreversible bowel damage (eg, fibrotic stricture), and 3) unrelenting severe disease refractory to medical therapy.

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Crohn Disease. In CD, operative intervention is generally warranted for intestinal obstruction (most often as a result of disease progression to stricture formation) and perforation, often resulting in destructive fistulae (Fig 1). When there is distal disease not responding to medical therapy, diversion of the fecal stream with creation of a temporary or permanent ostomy may be a successful therapeutic approach. Surgical removal of resistant disease may be effective treatment for inadequately controlled bleeding or growth failure with or without pubertal delay.

Multicenter cohort studies have estimated the risk of surgery in children with CD to be 9% at 5 years and 26% at 10 years, with most surgeries occurring within the first 3 years of diagnosis. (32)(33) Patients who were diagnosed at an older age, had more severe disease, had stricturing disease, or had penetrating disease were all predisposed to surgery, and the severity at diagnosis was an independent predictor of early surgery. Altogether, surgery is hard to prevent once severe disease is present. A critical factor in preventing bowel complications of CD is starting effective treatment early, before the accumulation of significant bowel damage.

When surgery becomes an option for children with CD, the potential for postoperative recurrence should be discussed early with the child and family. Although most surgical interventions will entail resecting the involved bowel, surgery is not a cure for CD. Before the widespread use of biologicals, recurrence rates of symptomatic CD after an initial operation have been reported to occur in 17% at 1 year, 38% at 3 years, and 60% at 5 years. Adult data suggest that postoperative use of biologicals may significantly decrease the risk of recurrence of disease, but this remains to be clarified in children.

The unique phenotype of perianal fistulizing disease in CD sometimes requires surgical intervention. Perianal abscesses may require surgical drainage and may benefit from the placement of a seton—a loop of flexible tubing through the fistula and 2 external openings—to maintain patency and facilitate drainage.

Ulcerative Colitis. Surgery in UC typically involves a colectomy—removal of the diseased organ. In contrast to CD, in UC, the entire burden of disease is resected, which some may deem as curative. Although the potential surgical "cure" can seem attractive, the postcolectomy course can be very traumatic, especially with the patient with newly diagnosed UC who had been completely well weeks or months before presentation.

In the pediatric age range, approximately 10% to 15% of children with UC will present with acute fulminant disease. These patients are generally toxic-appearing and very ill. While aggressive medical management proceeds, surgical consultation is necessary urgently. Before the widespread use of anti–TNF-α medications, prospective multicenter studies showed the risk of colectomy to be as high as 19% within the first year of diagnosis for children who presented with severe disease at diagnosis. (34) These disappointing numbers provided the impetus for the early use of high-dose intravenous anti–TNF-α therapy; however, even during the anti–TNF-α era, although rates of colectomy seem to be lower, an estimated 13% to 14% of children with UC will require colectomy within 5 years of diagnosis. (35)(36)

If surgery is required in an emergency setting, especially if the child is taking high-dose corticosteroids and immunosuppressive agents, surgeons will likely prefer removal of the colon with retention of the distal rectal stump (Hartmann pouch) and diverting end ileostomy. A completion proctectomy is performed at a second surgery. For some patients, the return to a "normal" life with an ileostomy is welcome relief from a life-threatening acute disease experience. For others, living with an ostomy appliance is a dreadful and psychologically draining experience. Professional consultation with a knowledgeable pediatric behavioral health provider can be critical to the successful return of the child (and the family) to a normal life. For nonemergency surgical intervention in UC, a complete proctocolectomy may be performed at the initial surgery.

Reconstructive surgery yielding rectal fecal continence is an elective procedure, with the timing determined by full recovery several months or even years after colectomy. The current state-of-the-art restorative procedure is the construction of an ileal pouch (J-pouch)–anal anastomosis. The term *J pouch* refers to the final shape of the surgical construction of the pouch from the remaining small bowel, which is anastomosed to the remnant cuff of rectal tissue or into the anal canal. In most circumstances, restorative surgery in pediatric UC occurs in stages, with the final stage including taking down the ileostomy. The goal is to restore or maintain rectal continence with an acceptable bowel habit and a stool frequency of 3 to 6 bowel movements per 24 hours. Permanent ileostomies are generally considered as operations of last resort, and direct (straight) ileoanal anastomosis is seldom performed now.

Ileal Pouch Disorders. Although the ileal pouch has revolutionized the quality of life for patients who require colectomy, several disorders of the pouch may develop. (37) The most common disorder, pouchitis, is an inflammatory condition suspected to result from proinflammatory cytokines, mucosal ischemia, fecal stasis, and bacterial overgrowth. Rates

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of pouchitis in children range from 31.5% to 67%, and it tends to develop within the first 6 months of initial reconstructive surgery. (38)(39)(40) First-line therapy for pouchitis is antibiotics (ciprofloxacin or metronidazole). Therapies for chronic pouchitis include long-term antibiotics, probiotics, and, increasingly, biologicals. Endoscopic intervention may be warranted for mechanical problems such as the development of a stricture. Such interventions must be handled by endoscopists familiar with the complications, treatment, and anatomy of the surgical pouch, especially in children. Removal of the pouch and creation of an ileostomy is a last resort. Limited long-term data suggest that pouch loss may occur at higher rates in children than in adults. (41)

CANCER RISK

Patients with extensive and long-term colitis have an increased risk of colorectal carcinoma. Although there is some uncertainty about the precise risk, there is widespread agreement that after 8 to 10 years of colonic disease, patients should begin yearly surveillance colonoscopy. Colon cancer is rare in the pediatric population, but after 8 years of disease, colonoscopic surveillance is indicated.

CONCLUDING OBSERVATIONS

Our newest and most effective treatments for IBD are expensive. Financial constraints placed on the treatment decision-making process by the health-care industry (mainly insurers) discriminate against our children and add to the burden and responsibilities of those treating these children. (42) The focus on early suspicion, diagnosis, and optimally effective treatment of children with IBD is critical. Waiting for disease progression and imminent complications before using our best treatments is unacceptable. The diligence and persistence of the IBD community, including patients, families, clinicians, and researchers, will continue to advance the care of IBD in research breakthroughs and patient-centered care provision.

Summary

- Based on strong evidence, inflammatory bowel disease (IBD) should be considered as an immune-mediated inflammatory disease probably triggered by environmental stimuli.
- Based on strong evidence, inflammation in IBD can lead to irreversible bowel damage if not successfully controlled.
- Current evidence does not allow us to reliably predict who is most likely to have a mild versus a severe IBD course.
- Based on strong evidence, clinical remission is a subjective outcome that is less useful than documented mucosal healing.
- Based on consensus, most children with IBD can be expected to do well and to lead normal lives. Of the remaining, most can look forward to a relatively normal life thanks to recent tremendous advances in pharmacotherapeutics.

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PIR QUIZ

1. A 13-year-old boy is admitted to the hospital with a 6-week history of abdominal pain and bloody stools. Ileocolonoscopy is notable for pancolitis with a normal terminal ileum. Therapy with intravenous corticosteroids is begun for new-onset ulcerative colitis. He goes on to develop an increasing white blood cell count, worsening microcytic anemia, and mild acidosis. He continues to have unformed, bloody stools multiple times per day and overnight as well, with a Pediatric Ulcerative Colitis Activity Index score in the severe range despite therapy. Which of the following is the most appropriate next step in management?

   A. Begin oral 5-aminosalicylic acid therapy.
   B. Consult pediatric surgery.
   C. Initiate a gluten-free diet.
   D. Order intestinal ultrasonography.
   E. Seek a donor for fecal microbial transplant.

2. An 18-year-old man presents with a 7-month history of weight loss, right lower quadrant pain, and oral ulcers. Laboratory examination is notable for microcytic anemia, hypoalbuminemia, and elevated serum inflammatory markers. Upper endoscopy findings are normal. Ileocolonoscopy shows a friable, ulcerated, and edematous terminal ileum. Biopsies of the area show chronic and active inflammation with rare granulomas. Treatment with adalimumab is planned. Which of the following diagnostic studies is the most comprehensive to allow further evaluation of the small bowel?

   A. Abdominal computed tomography.
   B. Capsule endoscopy.
   C. Intestinal ultrasonography.
   D. Magnetic resonance enterography.
   E. Upper gastrointestinal and small-bowel follow-through fluoroscopic series.

3. You are seeing a young man who just turned 18 years old. He has a history of fistulizing and perianal Crohn disease diagnosed 3 years ago, and he is currently treated with infusions of infliximab every 5 weeks. He has no symptoms, and his gastroenterologist considers him to be in deep remission based on his laboratory studies and most recent endoscopies with biopsies. The patient is previously unvaccinated by parental choice. Now that he is 18 years old, he wishes to become fully vaccinated. Which of the following vaccines should be avoided in this patient?

   A. Human papillomavirus virus.
   B. Inactivated influenza.
   C. Meningococcal.
   D. Tetanus.
   E. Varicella.

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4. A 15-year-old girl with Crohn disease undergoes removal of 9 cm of her terminal ileum along with her cecum due to a narrowing that did not respond to medical therapy and led to intestinal obstruction with recurrent distention and emesis. The surgeon was able to perform a primary anastomosis, and she did not need an ileostomy. She is brought to the office today for follow-up and feels totally well. She is eating a regular diet without abdominal pain or distention and is stooling 2 to 3 times per day without blood in her stools. In discussing with her parents the postoperative future of her disease, which of the following is the most appropriate advice to provide the family at this time about her clinical condition?

   A. She is an ideal candidate for fecal microbiota transplant.
   B. She is cured of her Crohn disease.
   C. She needs to avoid biological therapies.
   D. She remains at risk for recurrence of her disease.
   E. She should observe a low-protein diet for the next 6 months.

5. An 18-year-old woman previously diagnosed as having ulcerative pancolitis at 8 years of age is seen in the clinic for follow-up. She was induced into remission at diagnosis with oral corticosteroids and transitioned to 5-aminosalicylic acid therapy for 3 years before having a flare of her disease, which led her to be transitioned to infliximab infusions. She has done well since and is receiving intravenous infliximab infusions every 7 weeks. She consumes a regular diet by mouth and stools twice per day without pain or blood. Her physical examination findings are normal. Blood cell counts, electrolyte levels, liver indices, and serum inflammatory markers obtained before each of her recent infusions have been normal. Given the duration of her diagnosis and her risk of colon cancer, which of the following yearly screening tests are recommended for this patient?

   A. Abdominal computed tomography with intravenous, oral, and rectal contrast.
   B. Colonoscopic surveillance.
   C. Fecal immunochemical test.
   D. Fecal leukocyte assay.
   E. Fecal occult blood testing.

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