Inflammatory Bowel Disease

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Educational Gaps

Clinicians may be unaware of the recent advances in the field of inflammatory bowel disease as it relates to pathophysiology, diagnosis, and up-to-date treatment approaches.

Objectives

After reading the article, the reader should be able to:

1. Understand the current view of the pathophysiology of inflammatory bowel disease (IBD).
2. Know where IBD fits in the differential diagnosis of gastrointestinal symptoms.
3. Know how the history and physical examination contribute to the diagnosis and management of IBD.
4. Understand the role that laboratory and imaging studies play in diagnosing IBD.
5. Discuss current treatments used to treat IBD and their associated adverse effects.
6. Appreciate the benefits of a multidisciplinary approach in the management of chronic diseases.

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DEFINITION

Inflammatory bowel disease (IBD), classically divided into Crohn disease (CD) and ulcerative colitis (UC), is a chronic, debilitating condition characterized by relapsing and remitting episodes of gastrointestinal (GI) inflammation. UC affects the superficial mucosa, starting with the rectum, in a continuous pattern and is limited to the colon. CD is characterized by transmural inflammation that can affect any part of the GI tract from mouth to anus. Approximately 25% of patients with IBD are diagnosed during childhood or adolescence. Presenting symptoms often include, but are not limited to, abdominal pain, diarrhea, rectal bleeding, and weight loss. The clinical course can be highly variable, although it has been well established that pediatric patients frequently present with more extensive disease involvement. The purpose of this review is to provide clinicians with a practical, up-to-date overview of the pathogenesis, clinical presentation, diagnosis, and management of IBD.

EPIDEMIOLOGY

Epidemiologic studies estimate that 1.4 million people suffer from IBD in the United States. There are a variety of population-based cohorts of IBD throughout Europe and Canada, but most of the data available in the United States involve white, nondiverse populations. Although the content of epidemiologic studies varies, generally consistent results suggest that the prevalence of CD and UC in the US pediatric population is approximately 40 per 100,000 and 28 per 100,000, respectively. More than a decade has passed since the most recent population-based study of pediatric IBD reported the annual incidence in children to be 4.56 per 100,000 for CD and 2.14 per 100,000 for UC. Overall, these rates appear to be increasing. In addition, detection of very early-onset IBD (VEO IBD) appears to be increasing substantially in infants and children younger than age 5 years. How this disease phenotype in infants and younger children differs from more classic presentations is a focus of active investigation.

PATHOGENESIS

The exact cause of IBD is unknown. Pathogenesis has been attributed to a combination of causative factors, including genetic predisposition, alterations in the gut microbiome, defects in the innate and adaptive immune systems, and various environmental exposures. Genome-wide association studies have identified 163 susceptibility loci for IBD to date. These genetic polymorphisms are associated with a variety of molecular pathways critical to the innate and adaptive immune systems, such as autophagy (*ATG16L1*) and pathogen recognition (*NOD2*). Autophagy is a physiologic process that is responsible for recycling cellular debris. The *ATG16L1* gene encodes a protein integral to this process and polymorphisms have been implicated in IBD. The *NOD2* (nucleotide-binding oligomerization domain-containing protein 2) gene on chromosome 16 codes for an intracellular pattern recognition receptor that helps detect a specific protein, muramyl dipeptide, found in many bacteria. Patients positive for *NOD2* variants are at risk for an aggressive ileal phenotype and have a stronger family history of disease. Various genetic mutations that result in disruption in the balance of pro- and anti-inflammatory cytokines have also been attributed to IBD pathogenesis. More recently, mutations of the interleukin-10 receptor have been associated with a phenotype of VEO IBD in immunodeficient infants.

Genetic predisposition is insufficient to explain disease onset in most patients, and several putative environmental risk factors have been identified. In recent years, the study of environmental risk factors potentially related to IBD pathogenesis has focused on how these exposures perturb the steady state of the host microbiome. Defined as the collective genomes of all microbes (including bacteria, viruses, protozoa, and fungi) that normally and symbiotically inhabit the human GI tract, the microbiome is an exceptionally complex system. At steady state, a delicate balance exists between these commensal microorganisms and the innate and adaptive mucosal immune systems. Disruption of this balance, referred to as dysbiosis, has been implicated in a variety of immune-mediated disease processes, including IBD, diabetes, rheumatoid arthritis, and obesity. Researchers have established that patients with IBD have decreased microbial diversity. In addition, various taxa and species have been implicated as potential determinants of disease susceptibility. Although intriguing and the focus of much investigation, such microbiome-specific advances have yet to be translated and applied in a meaningful clinical context.

In general, IBD appears to be limited to westernized, industrial populations. In this light, the effects of environmental variables such as diet and hygiene on the microbial composition of the host GI tract are likely important determinants of disease susceptibility. In addition, cigarette smoking, prior appendectomy, vitamin D concentrations, stress, and depression have all been implicated as risk factors associated with both disease onset and relapse. Although identification and characterization of these exposures is integral to risk assessment of certain populations, the final common pathway appears to be a dysregulated immune response to the commensal microflora in a genetically susceptible host.

CLINICAL ASPECTS

The differential diagnosis of conditions that can mimic IBD is presented in Table 1.

History

The clinical presentation of IBD often involves some combination of luminal GI symptoms in conjunction with fatigue, weight loss, and linear growth failure, but children can present with any number of signs and symptoms. Accordingly, a thorough history and complete physical examination are of paramount importance in the initial evaluation of a child with suspected IBD. Most commonly, patients present with numerous complaints related to the GI tract that include, but are not limited to, long-standing bloody (or nonbloody) diarrhea, nausea, vomiting, and abdominal pain of varying quality and location. Classically, patients who have colitis

TABLE 1. **Differential Diagnostic Considerations with Inflammatory Bowel Disease**

MORE LIKELY TO PRESENT WITH CHRONIC COMPLAINTS	MORE LIKELY TO PRESENT MORE ACUTELY
• Growth failure - endocrinopathy	• Appendicitis
• Irritable bowel syndrome	• Mesenteric adenitis
• Lactose intolerance	• Fissure-in-ano
• Ovarian cyst	• Hemorrhoids
• Celiac disease	• Colonic polyps
• Acid-peptic disease	• Meckel diverticulum
• Anorexia nervosa	• Acute infections such as:
• Arthritides	*Clostridium difficile*
• Hepatitis	*Salmonella/Shigella/ Campylobacter* species
• Excess laxative intake	– *Yersinia* species
• Lymphoma	– *Giardia* species
• Constipation	– *Entamoeba histolytica*
• Sorbitol ingestion	• Parasitic infections
• Infections (*Giardia* species)	• Perianal streptococcal dermatitis
	• Henoch-Schönlein purpura

report infraumbilical cramping (often in the left lower quadrant) in conjunction with complaints of urgency and tenesmus (the sensation of constantly needing to pass a bowel movement despite an empty or near-empty colon). Patients with CD can present with a variety of multisystemic complaints. Because children with newly diagnosed CD have some degree of inflammation in the terminal ileum, they often report right lower quadrant pain.

Presenting symptoms generally relate to the GI system, but up to 25% of children also experience various extra-intestinal manifestations (EIMs) of IBD. Most of these EIMs occur during the first year and tend to be associated with more severe disease. However, certain EIMs, such as erythema nodosum and primary sclerosing cholangitis, can flare independently of luminal symptoms.

In addition to an exhaustive history of the present illness, a thorough social and family history is important in the initial evaluation. Approximately 20% of newly diagnosed patients report a first-degree relative with IBD. Family history of other immune-related conditions such as psoriasis or rheumatoid arthritis increases the likelihood of IBD, based on the various human leukocyte antigen (HLA) associations. Social histories in children and adolescents may document decline in school performance or loss of interest in various extracurricular activities, which could be attributed to the child's fear or embarrassment surrounding the use of public restrooms.

Physical Examination

Although children who have IBD can appear pale and fatigued, the presentation is often insidious. Review of an accurate growth chart is mandatory and can provide an invaluable suggestion that a more systemic process such as IBD is present. Patients with both CD and UC may exhibit varying degrees of weight and/or growth delay. Growth delay, especially in children with CD, remains an area of great concern and active investigation. Table 2 presents a review of IBD-related findings and EIMs that have been described for various organ systems.

Laboratory Tests

There are no pathognomic laboratory tests for IBD. Initial evaluation often focuses on a broad approach assessing for nonspecific signs of inflammation and chronic disease. A complete blood cell count may reveal leukocytosis, chronic anemia, and thrombocytosis. Serum hemoglobin results should be correlated with certain red blood cell indices such as mean corpuscular volume to assess for chronicity. Although children with IBD often have elevated inflammatory markers such as the erythrocyte sedimentation rate and C-reactive protein, this is not always the case. Another objective marker of longstanding intestinal inflammation is serum albumin, which can be low in children with more aggressive or extensive disease. The reason for this observation is related to a combination of poor oral intake and chronic intestinal inflammation resulting in malabsorption and fecal losses. Serum transaminases and gamma glutamyltranspeptidase should be measured to assess for comorbid hepatic processes such as primary sclerosing cholangitis and autoimmune hepatitis. Although laboratory tests can be helpful in guiding further evaluation and assessing clinical response to therapy, up to 20% of children with IBD can present with normal laboratory values. Thus, a seemingly unrevealing set of blood test results should not deter further evaluation when clinically indicated.

An infectious disease evaluation should be completed as part of the initial evaluation of any patient presenting with chronic diarrhea. A stool culture negative for *Salmonella, Shigella, Campylobacter,* and *Yersinia* species as well as *Escherichia coli* 0157:H7 and *Clostridium difficile* should be documented. In addition, screening for *Giardia* and *Cryptosporidium* species and *Entamoeba histolytica* should be

TABLE 2. **Comorbid Signs and Symptoms of Inflammatory Bowel Disease by Organ System**

SYSTEM	CLINICAL SIGNS/SYMPTOMS
Eye	• Uveitis, episcleritis, keratitis, iritis, cataracts (due to corticosteroids) • Annual assessment by ophthalmologist recommended
Oral cavity	• Oral aphthae and aphthous stomatitis: can be difficult to differentiate in patients with orthodontic hardware
Gastrointestinal	• Abdominal pain of varying quality and location, diarrhea, rectal bleeding, urgency and tenesmus (attributed to proctitis), dyspepsia, odynophagia, nausea, vomiting
Hepatobiliary	• Primary sclerosing cholangitis, autoimmune hepatitis, hepatitis as adverse effect of certain medications (6-mercaptopurine and methotrexate), Budd-Chiari syndrome
Genitourinary and perineum	• Perianal/perineal fistulas, fissures, abscesses, and skin tags • Penetrating fistulae (eg, rectovaginal, enterovesical) can result in hematuria, pneumaturia, fecaluria • Inflammatory disease in pelvis can result in hydronephrosis
Skin	• Erythema nodosum, pyoderma gangrenosum, Stevens-Johnson syndrome (reported from sulfasalazine), striae, and acne (attributed to corticosteroid exposure) • Psoriasis as adverse effect of certain biologic therapies • Increased risk of skin cancer attributed to certain immune-suppressing agents • Annual assessment by dermatologist recommended
Rheumatologic	• Arthritis and arthralgias (often of large joints), ankylosing spondylitis, sacroiliitis
Hematologic	• Microcytic iron deficiency anemia, macrocytosis due to folate or vitamin B_{12} deficiency, thrombocytosis
Vascular	• Hypercoagulability, thrombosis, phlebitis
Bone	• Osteopenia, osteoporosis. Aseptic necrosis of femoral head (due to corticosteroids)
Psychiatric	• Depression, anxiety, social phobia, poor sleep, poor energy
Others	• Anorexia, weight loss, fever, growth failure

considered for select patients. Patients with an established IBD diagnosis should be evaluated for an intercurrent infectious process before attributing active symptoms to a flare of disease. *C difficile* has become increasingly problematic in patients with IBD. Susceptibility to this pathogen is likely due to various alterations in the mucosal immune system and a dysbiosis that is generally favorable to the organism. Frequent monitoring and aggressive treatment may be warranted in select patients.

Certain commercial tests that assess for the presence of antimicrobial antibodies such as antineutrophil cytoplasmic antibodies and anti-*Saccharomyces cerevisiae* antibodies are available. Some data suggest that these tests may accurately reflect disease behavior and severity, but they have no role in the initial diagnostic evaluation of a child with suspected IBD. More recently, commercial assays for serum trough levels and detection of antibodies against certain biologic agents (such as infliximab and adalimumab) have become available. These tests have proven to be invaluable in helping guide treatment and dosage adjustments, thus maximizing the therapeutic durability of such agents. Currently very expensive and often not covered by insurance, these assays are destined to become standard of care for patients receiving certain biologic therapies in the near future.

Recently, the neutrophil-associated proteins calprotectin and lactoferrin have been identified as convenient, noninvasive tests for determining luminal inflammation from stool samples. Fecal calprotectin assays are becoming increasingly available in the United States. These tests can be helpful in triaging patients with nonspecific GI complaints and may serve a role in differentiating inflammatory conditions from more functional disorders such as irritable bowel syndrome. Normal values should not delay evaluation if the clinician has an otherwise high index of suspicion for IBD. For patients who have established diagnoses of IBD, these tests can be helpful in differentiating disease flares from other noninflammatory processes. The role of these tests in assessing interval response to certain treatments is promising, although further work is needed to validate this practice.

Endoscopic Approach

Any patient with a suspected diagnosis of IBD should be referred to a pediatric gastroenterologist for endoscopic

evaluation. Ileocolonoscopy with biopsies can provide valuable information about the degree and distribution of inflammation in patients with IBD (Figure). Most patients with UC have continuous inflammation in the rectum that extends proximally in a continuous pattern. Although most patients with inflammation in the terminal ileum ultimately may be diagnosed with CD, a select number of patients with pancolitis also have gross or histologic evidence of ileal inflammation that is sometimes referred to as "backwash ileitis." In such cases, the constellation of findings can be unclear and a third entity termed "IBD unclassified" may be described. This designation is reserved to classify a colonic phenotype of IBD in which the clinical and pathologic characteristics do not allow clear classification as either UC or CD. In most cases, clinicians perform upper endoscopy (esophagogastroduodenoscopy) at the same time as colonoscopy. Although nonspecific upper GI tract inflammation has been described in patients with UC, assessment of the esophagus, stomach, and proximal duodenum can provide valuable information regarding disease distribution in patients with CD.

In recent years, more advanced endoscopic techniques, such as single- and double-balloon and spiral enteroscopy, have been used to visualize and potentially biopsy the mid-small bowel, which is otherwise inaccessible via standard endoscopic and colonoscopic approaches. These procedures are primarily accomplished by endoscopists with advanced training and are rarely employed in pediatric patients.

Another approach to assessing the mid-small bowel is via video capsule endoscopy. This test occasionally provides valuable diagnostic information in helping detect evidence of luminal inflammation and signs of previous or active GI bleeding. Smaller children may have difficulty swallowing the capsule, necessitating deployment under direct endoscopic visualization. Any patient for whom there is concern about a luminal narrowing or stricture should be given a self-dissolving dummy capsule before swallowing the actual device to identify and thereby avoid obstructive complications. Although helpful in providing real-time images, data obtained from video capsule endoscopy are limited to gross information about the mucosa because biopsies for histologic assessment are not possible.

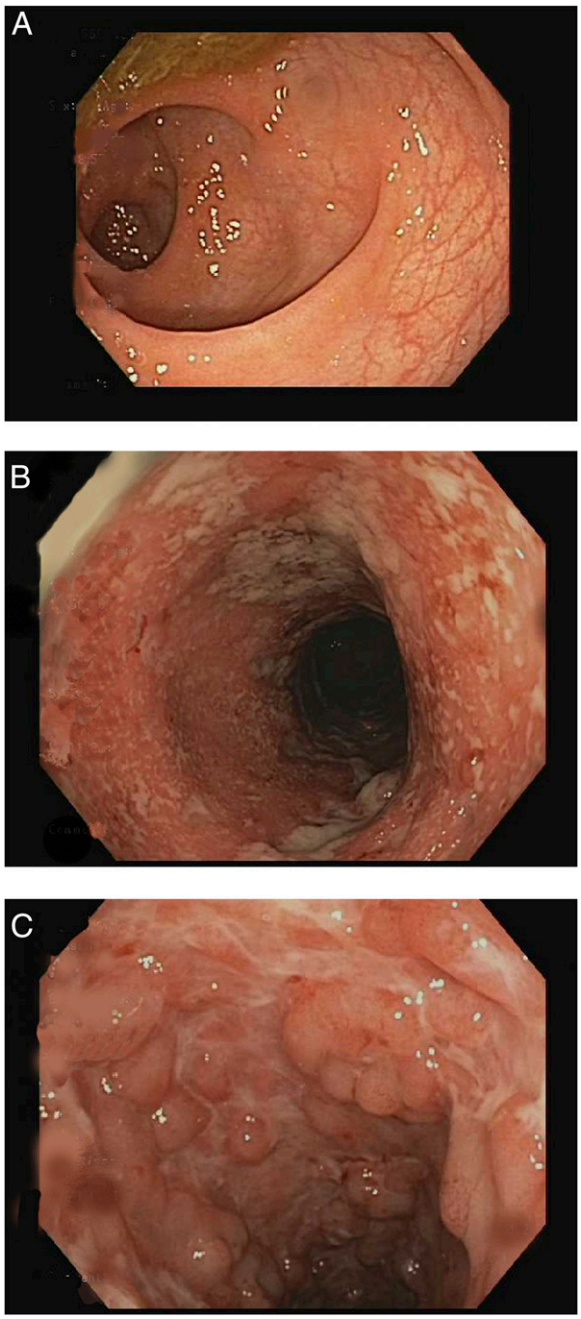

Figure. Endoscopic views of healthy tissue compared with inflammatory bowel disease. A. Normal colonic mucosa with a visible fine vascular pattern. B. Ulcerative colitis with continuous inflammation, loss of vascular pattern, exudates, edema, and bleeding. C. Crohn disease with patchy inflammation, cobblestoning, deep ulcers, exudates, altered vascular pattern, edema, and bleeding.

Histologic Features

Histologic evaluation of mucosal biopsies obtained during both upper endoscopy and colonoscopy provides another important layer of diagnostic information. Characteristic histologic features of UC include crypt architectural distortion, branching, crypt abscesses, and a lymphoplasmacytic infiltrate. Paneth cell metaplasia in the left side of the colon is another marker of a chronic inflammatory process and can be seen in either CD or UC. A variety of chronic histopathologic changes can be seen in patients with CD, but identification of a noncaseating granuloma is often considered diagnostic.

Radiologic Findings

Although upper endoscopy allows direct visualization of the proximal small bowel and colonoscopy allows visualization of the colon and terminal ileum, assessing the remainder of the small intestine is difficult without the previously described more advanced endoscopic approaches. Thus, imaging modalities such as magnetic resonance-enterography (MRE) represent an important addition to the evaluation of any patient with a suspected diagnosis of IBD. Not only does MRE allow detailed cross-sectional imaging of the small bowel, but it can detect specific luminal and extraluminal complications, such as strictures, fistulae, and abscesses. In addition, the dedicated pelvic imaging of patients with perianal CD obtained from MRE can provide invaluable information about the presence and extent of perianal fistulae and abscesses. Because involvement of the external anal sphincter ultimately affects fecal continence, detailed information about the degree and location of perianal disease offers vital information in the risk stratification of any patient with CD. Although MRE is considered preferable to computed tomography (CT) scan based on the lack of radiation exposure, MRE can be problematic in younger patients. In addition to the need to drink a large volume of oral contrast, the MRE takes significantly longer than a CT scan and younger children may require sedation. Any patient presenting with signs concerning for an acute abdominal process should not wait for MRE if a CT scan can be obtained in a more timely fashion.

Obtaining a single radiograph of the hand to assess a child's bone age can provide important information about the degree of comorbid growth impairment. Any child with impaired growth and/or delayed puberty attributable to IBD should be considered a candidate for a more aggressive therapeutic approach. Furthermore, bone mineral density analysis via dual-energy x-ray absorptiometry should be considered in patients at risk for low bone mineral density, especially if they are exposed to corticosteroids (CS) for a prolonged period of time.

Medical Therapy

Treatment of IBD is a balance between controlling active symptoms and preventing long-term complications of aggressive disease while being mindful of potential adverse effects of medication. This is especially challenging in the pediatric and adolescent population because both the disease and its treatments can negatively affect growth, development, puberty, and emotional health. Most of the medications used in IBD management suppress the immune system and all are associated with a variety of adverse effects, some of which are especially concerning in the pediatric population. Table 3 presents a comprehensive list of medications used to manage IBD in pediatrics.

Although 5-aminosalicylate medications such as mesalamine and sulfasalazine can be used for the treatment of mild-to-moderate UC and have a supplementary role in patients with CD, they are often not sufficient to maintain long-term remission. Mainstays of treatment for the past 50 years, systemic CS remain a first-line option for the induction of remission in patients with active disease. These agents are often effective, but a substantial number of patients develop CS dependence, with their disease flaring when doses are decreased or CS therapy is discontinued. The well-established negative physical and emotional adverse effects associated with prolonged CS exposure present a substantial problem in children. To avoid these adverse effects, therapeutic regimens that rely on enteral nutrition can be used to induce remission.

Immune-modulating therapies such as 6-mercaptopurine (6-MP) and methotrexate (MTX) have been used to maintain corticosteroid-free remission and prevent immunogenicity to certain biologic agents. 6-MP is a thiopurine analog that has been established as a corticosteroid-sparing agent in children with IBD. MTX inhibits production of dihydrofolate reductase, which is critical to purine and pyrimidine biosynthesis. Although effective, these medications are not without risk. Both 6-MP and MTX result in immune suppression and have been associated with hepatotoxicity. MTX is a teratogen that must be used with caution in any potentially sexually active female. Prolonged exposure to 6-MP has been associated with a relative increased risk of lymphoma. In addition, the development of hepatosplenic T-cell lymphoma, a rare yet universally fatal tumor, has been reported in a very small number (approximately 60 worldwide) of mostly male patients exposed to both 6-MP and infliximab. Although the risk of developing hepatosplenic T-cell lymphoma is exceptionally low, some practitioners choose to substitute MTX for 6-MP, especially in male patients who require an immunomodulator.

The use of monoclonal antibody-based medications, termed biologics, which target the inflammatory cytokine tumor necrosis factor-α (TNF-α), has dramatically increased in the past 10 years. Infliximab and adalimumab, the two most commonly prescribed biologics, are approved by the US Food and Drug Administration for the treatment of moderate-to-severe CD and UC in children. One advantage of these medications is that they can effectively be used for both induction and maintenance of remission in patients with active disease. Infliximab is administered

TABLE 3. **Medications Used to Treat Inflammatory Bowel Disease**

MEDICATION CLASS	TYPICAL USE	COMMENTS
Aminosalicylates: - Sulfasalazine - Mesalamine	Mild-to-moderate UC or colonic CD, distal terminal ileitis	Potential adverse effects: Rash due to sulfa component (rarely Stevens-Johnson syndrome), headache, diarrhea, pancreatitis
Corticosteroids: - Prednisone/Prednisolone - Methylprednisolone sodium succinate (IV) - Budesonide	To induce remission; not indicated for maintenance therapy due to serious adverse effects with prolonged use.	Increasing use of budesonide (a topical preparation) as adjuvant therapy, risk of overuse and adrenal suppression must be considered Corticosteroid-free remission is the goal of modern pediatric IBD studies
Immunomodulators: - Azathioprine - 6-Mercaptopurine - Methotrexate	To maintain corticosteroid-free remission Combination therapy with biologic agents to decrease immunogenicity (ie, decreased development of antidrug antibodies)	6-mercaptopurine has been established therapy for years; recently under scrutiny due to reported association with increased risk of secondary cancers Methotrexate use has increased as concerns are raised about 6-mercaptopurine; known teratogen and can be hepatotoxic Both drugs associated with immunosuppression, pancreatitis, hepatotoxicity
Antibiotics: - Metronidazole - Ciprofloxacin - Rifaximin	Controversial use in complex and/or small bowel disease Often used in patients with active perianal disease	As interest in microbiome increases, both a causative and a therapeutic role become of great interest, but these roles remain speculative; potential role in postsurgical prophylaxis
Biologic Agents: - Infliximab - Adalimumab - Certolizumab - Vedolizumab - Natalizumab	"Rescue" therapy for severe, corticosteroid-dependent, or corticosteroid-refractory disease Anti-TNF-α agents considered standard of care, first-line therapy in select clinical scenarios	Revolutionized management and outcomes Durability of treatment can be negatively affected by development of antidrug antibodies Infliximab, adalimumab, and certolizumab are anti-TNF-α agents Vedolizumab is a newer biologic agent that blocks $\alpha 4\beta 7$-integrin Natalizumab is an $\alpha 4$—integrin inhibitor, associated with progressive multifocal leukoencephalopathy in patients positive for the JC virus
Other agents: - Calcineurin inhibitors (tacrolimus) - Thalidomide - Probiotics - *Lactobacillus* GG - *Saccharomyces boulardii*	"Rescue" therapy for severe, corticosteroid-dependent, or corticosteroid-refractory disease Often used as bridging therapy to colectomy in patients with refractory colitis Recurrent pouchitis in patients postcolectomy Role as maintenance therapy not established	Adverse effects reported with prolonged use Thalidomide is a well-known teratogen Appear to be safe, but effectiveness and role remain unclear

CD=Crohn disease, IBD=inflammatory bowel disease, IV=intravenous, TNF=tumor necrosis factor, UC=ulcerative colitis.

via infusion, typically every 8 weeks, and adalimumab is administered via subcutaneous injection, which can be administered by a patient at home every 2 weeks. These medications are also potent immunosuppressive agents and have been rarely associated with secondary malignancies such as lymphoma. A recent systematic review demonstrated that the risk of lymphoma was no greater than that previously reported for other IBD therapies and the rate of serious infection was significantly lower among pediatric patients treated with anti-TNF agents than those treated with CS. More population-based research is needed, but preliminary longitudinal follow-up evaluations from multiple studies have demonstrated or suggested improved clinical outcomes, accelerated growth in children, and decreased surgery rates with greater use of biologic therapy, especially early in the disease course.

The use of any immunosuppressive agent requires judicious monitoring for infectious complications. Documenting that the child is negative for tuberculosis via either Mantoux tuberculin skin test, QuantiFERON-TB Gold, or a screening chest radiograph is required before initiating therapy with a biologic agent such infliximab or adalimumab. In addition, immunosuppressed patients on either biologic or immune-modulating agents should not receive live virus

vaccines. These include, but are not limited to, live attenuated intranasal influenza, varicella-zoster, measles-mumps-rubella, yellow fever, smallpox, and the oral polio vaccines. Routine immunization is especially important in this vulnerable population, but the nature of any vaccine should be verified before its administration.

Multiple studies have demonstrated the clinical efficacy of exclusive enteral nutrition (EEN) with a polymeric formula for the induction and maintenance of remission in patients with CD. Few patients can drink the prescribed volume of formula each day, so most require administration via nasogastric or rarely, gastrostomy tube. The mechanism of action is likely multifactorial and has been attributed to a combination of enhanced mucosal barrier function, reduction in proinflammatory cytokines, alterations in the intestinal microflora, and overall improvement in nutritional state. This practice is substantially more common in Europe and Canada and is likely underutilized in the United States. A meta-analysis of pediatric studies indicated that EEN was as effective as systemic CS for inducing remission in pediatric patients with active CD. Although effective, the long-term use of EEN can be challenging.

Natural History

IBD phenotype and disease behavior can vary substantially in pediatric patients. Those who have moderate-to-severe UC may require colectomy and those who have CD are at risk for an array of debilitating complications. Perianal CD disease can be especially troublesome in children. This can be characterized by the presence of large perianal skin tags, fistulae, and in some cases, development of perianal and perirectal abscesses. Because many children do not report perianal symptoms, a thorough perianal inspection should be performed in any child being evaluated for chronic GI complaints. In addition, patients with CD can present with or develop penetrating fistulizing disease over time. Such fistulae can extend from the intestinal (or colonic) lumen to an array of extraluminal locations, such as the bladder (enterovesical), vagina (enterovaginal), and abdominal wall (enterocutaneous). Furthermore, patients with CD often develop inflammatory or fibrotic strictures, which can present with signs of acute intestinal obstruction. As a result of these complications, a substantial number of children with IBD ultimately require surgical resection for obstructive disease. Previous reports on pediatric CD estimate that approximately 18% and 28% of patients require surgery at 5 and 10 years from original IBD diagnosis, respectively. Similarly, a recent meta-analysis estimated the 10-year risk of colectomy in children with UC to be 22%. More recent population-based data suggest an overall decrease in surgical rates over time. The contribution of increased early use of biologic agents such as infliximab and adalimumab to these decreased rates is yet to be determined.

In an effort to prevent the development of complications, the practitioner should objectively assess clinical response to certain therapies. The current consensus is that patients should be restaged with repeat endoscopic evaluation to assess mucosal healing (also referred to as "deep remission") at 1 year after the initial diagnosis and before consideration of any escalation of therapy. Even among clinically asymptomatic patients, varying degrees of active inflammation can be detected on repeat endoscopy. Although not immediately apparent, the presence of persistent inflammation does put the patient at risk for specific complications, such as development of fibrotic strictures, and malignant transformation over longer periods of time. How noninvasive fecal tests (ie, calprotectin and lactoferrin) will fare as surrogate markers of mucosal healing is yet to be determined. Malignancy generally is believed to be associated with long-standing inflammation. Therefore, the more extensive the involvement of disease and the longer its duration, the greater the risk for cancer. Annual cancer surveillance colonoscopy is recommended for those who have IBD after the first decade of disease.

Nutritional Considerations

Growth failure is one of the more feared complications of IBD in children. The cause is multifactorial. Patients with active symptoms frequently experience poor appetite and resulting inadequate energy intake. From a physiologic standpoint, this is likely attributable to elevated concentrations of proinflammatory cytokines. In addition, patients with CD often have varying degrees of inflammation in the small intestine, which can result in protein-losing enteropathy and fat malabsorption. A complete nutritional assessment of patients at diagnosis and regularly thereafter is extremely important.

Monitoring of certain micronutrients should be considered in specific high-risk patients. All patients should be screened for vitamin D deficiency via serum measurement of 25-hydroxyvitamin D. Not only do patients with IBD have a relative increased risk of vitamin D insufficiency or deficiency, but vitamin D has been shown to have immune-regulatory properties affecting both the innate and adaptive immune systems. Iron studies in patients with anemia should be followed as indicated. Patients with terminal ileal disease or postileal resection require regular

monitoring of fat-soluble vitamins (A, D, E, and K) and vitamin B_{12}. Select patients may require monthly supplementation with vitamin B_{12} injections. Both MTX and sulfasalazine can negatively affect folate absorption. Patients taking these medications should be regularly screened for folate deficiency and receive concomitant supplementation. Serum zinc concentrations should be checked in patients with extensive disease. This value can vary with serum albumin. A low alkaline phosphatase value may suggest comorbid zinc deficiency for which supplementation may be indicated.

In general, IBD patients should be instructed to eat well-balanced diets. Patients with documented inflammatory or fibrotic strictures may benefit from a "low-residue" diet. This involves eliminating certain foods high in indigestible fiber or seeds because of the risk of perpetuating an acute obstructive process. Regardless of phenotype, some patients ingesting nondigestible or difficult-to-digest carbohydrates (such as lactose) might focus on reducing or eliminating these agents. Some success with this approach has been suggested with the so-called FODMAP diet (Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols). "FODMAPS" are intended to represent short-chain carbohydrates that are not adequately absorbed in the proximal GI tract and, therefore, are subjected to fermentation by normal intestinal bacteria. The results of fermentation generally include hydrogen and methane gas and short-chain fatty acids. Symptoms result from these metabolic products or from changes in microbiota associated with the diet. Although patients with active inflammation may have difficulty with some of these foods, tolerance may return once mucosal healing is achieved. In all circumstances in which any altered diet is considered, a registered dietitian nutritionist should be involved to assure nutritional adequacy of the new diet.

Systematic reviews of the literature suggest that a good strategy might be to have each patient maintain a food and symptom diary and base dietary alterations on these results. An individualized nutrition plan may be warranted for certain children with IBD. Although hearing that a sick child is eating just like his or her healthy friends can be reassuring, the amounts of calcium, vitamin D, and zinc that are part of the typical American diet may not be adequate to provide optimal nutritional support to a chronically ill patient with IBD.

A Multidisciplinary Team Approach. A multidisciplinary team approach is important to provide optimal care to children with IBD and their families. In addition to knowledgeable pediatric GI practitioners, this team is often composed of nurse specialists, social workers, nutritionists, clinical research coordinators, and behavioral psychologists. The members of the team provide and help coordinate care on both inpatient and outpatient units, including the medication infusion units when applicable. Substantial advances in therapy have been made, but medications approved for adults are often delayed for use in pediatric patients. The practical effect of this reality is an increased burden on the clinicians and family to obtain approval from insurance companies before initiating certain therapies that are deemed clinically indicated. Nurse specialists, social workers, and case managers are absolutely essential to help patients and clinicians navigate the associated gauntlet of paperwork and administrative obstacles.

Behavioral Considerations

When considering any chronic illness that affects children, the importance of psychological and behavioral health cannot be overstated. Some psychological and emotional stressors are related to the disease itself; others are inherent to childhood and adolescence. Regardless, emotional and behavioral factors play a significant role in disease management and outcomes. The symptoms of IBD can be exquisitely debilitating and have the potential to adversely affect the child's or adolescent's quality of life. Several reports suggest that adolescents with IBD are more prone to endorse symptoms of depression. Screening for such behavioral sequelae of disease is a critical aspect of the regular health supervision of any child with IBD. In addition, recent work has highlighted the serious issue of medication adherence in children with IBD and other chronic diseases. Detailed prospective studies have shown that a substantial number of pediatric patients with IBD are poorly adherent to oral medication regimens. Accordingly, poor medication adherence must be considered in certain patients not responding to orally administered agents. The explanation for poor adherence in this patient population is likely multifactorial. Therefore, having a child psychologist help comanage these medically and behaviorally complex patients should be considered standard of care.

CONCLUSIONS

IBD is a chronic, debilitating condition that negatively affects children and adolescents on multiple levels. In addition to struggling with daily symptoms such as abdominal pain, diarrhea, rectal bleeding, and fatigue, children with IBD often require admission to the hospital and, in some cases, surgery. Active disease and recurrent

hospitalizations can result in missed school and negatively affect academic performance. In addition, struggling with active GI symptoms in public represents a significant stressor, especially for children. Treatment focuses on controlling active symptoms and preventing long-term complications of aggressive disease. Certain medications are associated with serious adverse effects that also must be addressed. Thus, successful IBD management in the pediatric population is a considerable challenge that must take into account numerous complex and often interrelated medical and psychosocial variables. A multidisciplinary team approach is integral to providing optimal care.

Summary

- On the basis of level A research, the pathogenesis of inflammatory bowel disease (IBD) is attributed to a combination of genetic and environmental factors. (1)
- On the basis of level A research, various putative environmental exposures attributed to increased IBD susceptibility result in alterations in the microbiome, which is referred to as dysbiosis. (2)
- On the basis of level A research, the worldwide incidence and prevalence of IBD is increasing. (3)
- On the basis of level A research, biologic agents such as infliximab and adalimumab are effective therapies for pediatric patients with moderate-to-severe disease. (4)(5)(6)
- On the basis of level A research, a multidisciplinary team approach that takes into account numerous biopsychosocial variables and that addresses issues related to medication adherence is important for successful management of IBD. (7)

CME Quiz, References, and Suggested Readings for this article are at http://pedsinreview.aappublications.org/content/37/8/337.

Parent Resources from the AAP at HealthyChildren.org

Inflammatory Bowel Disease

- https://www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/Irritable-Bowel-Syndrome-IBS-and-Inflammatory-Bowel-Disease-IBD.aspx (English only)

PIR Quiz

There are two ways to access the journal CME quizzes:
1. Individual CME quizzes are available via a handy blue CME link under the article title in the Table of Contents of any issue.
2. To access all CME articles, click "Journal CME" from Gateway's orange main menu or go directly to: http://www.aappublications.org/content/journal-cme.

1. A 12-year-old boy recently was diagnosed with Crohn disease. His 30-year-old paternal uncle lives in Europe and has a long history of inflammatory bowel disease. The parents ask if their son's diagnosis could be related to the uncle's condition. Which of the following is the most appropriate answer?
    A. Likely because approximately 20% of newly diagnosed patients report a first-degree relative with inflammatory bowel disease.
    B. Unlikely because the uncle is the mother's brother.
    C. Likely because the first-degree relative is male.
    D. Unknown because the uncle's *ATG16L1* gene status has not been established.
    E. Unknown because the uncle's diet is undetermined.
2. A 14-year-old girl presents with a 3-month history of fatigue, frequent diarrhea, and weight loss. She has not achieved menarche. Review of her linear growth chart reveals declining growth rate over the past 2 years. Further questioning of the patient's history would most likely reveal which of the following?
    A. Hair loss.
    B. Intolerance to cold.
    C. Rapid heart rate.
    D. Right lower quadrant abdominal pain.
    E. Headache.
3. Physical examination of the 14-year-old girl in the previous question reveals erythema nodosum over the anterior tibias and stage 2 Sexual Maturity (Tanner) Rating. Which of the following is the next best step in evaluation?
    A. Endoscopy.
    B. Complete blood cell count.
    C. *ATG16L1* gene analysis.
    D. Blood culture.
    E. Screen for antineutrophil cytoplasmic antibodies.
4. The 14-year-old patient in the previous question has microcytic anemia, leukocytosis, and thrombosis. Her erythrocyte sedimentation rate is 70 mm/h, serum albumin is 3.2 g/dL (32 g/L), and stool calprotectin test result is positive. A gastroenterologist schedules an endoscopy. If the patient has Crohn disease, which of the following is most likely to be found upon endoscopy?
    A. Inflammation in the terminal ileum.
    B. Esophageal varices.
    C. Continuous inflammation limited to the rectum.
    D. Gastric ulcerations.
    E. Crypt abscesses in the descending colon.
5. A 17-year-old sexually active girl with newly diagnosed mild ulcerative colitis is placed on sulfasalazine to induce remission. One week later, the patient develops skin erythema, conjunctivitis, and mucositis. The sulfasalazine is discontinued. Which of the following is the most appropriate next step in therapy?
    A. Observation.
    B. Prescribe infliximab therapy.
    C. Prescribe prednisone therapy.
    D. Begin a FODMAP diet.
    E. Prescribe methotrexate therapy.

REQUIREMENTS: Learners can take *Pediatrics in Review* quizzes and claim credit online only at: http://pedsinreview.org.

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