Inflammatory Bowel Disease in Children and Adolescents

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, immune-mediated condition of the gastrointestinal tract classically labeled as either Crohn's disease (CD) or ulcerative colitis (UC). CD can affect any part of the GI tract from mouth to anus, whereas the inflammation of UC is limited to the colon. IBD can present at any age, from infants to the elderly. Approximately a third of patients are diagnosed during childhood or adolescence.[1] Disease phenotype and clinical course are highly variable, although it has been established that children present with more extensive, complicated disease. In addition to debilitating clinical symptoms, younger patients face the emotional challenges that come with adjusting to a lifelong illness. Caring for children with IBD involves several unique considerations including growth, puberty, bone health, and psychosocial factors that can impact the child and family unit.

EPIDEMIOLOGY

The worldwide incidence of IBD is increasing at an alarming rate, especially in industrialized nations.[2,3] A report from 195 countries found that the United States had the highest global prevalence with nearly a quarter of cases residing here in 2017.[2] A recent systematic review of 130 population-based studies from 48 countries reported a rising incidence and prevalence of pediatric IBD worldwide with a prevalence rate ranging from 28.3 to 63.6 cases per 100,000 in North America.[4] A dramatic rise in children under the age of 6, referred to as very early-onset (VEO) IBD, is also being observed.[5] Recent estimates suggest that VEO-IBD accounts for 15% of pediatric cases.[6] These patients are often very sick with severe disease phenotypes that may not respond to conventional therapies.

PATHOGENESIS

The immunopathogenesis of IBD has been attributed to a combination of causative factors including genetic predisposition, defects in the innate and adaptive immune system, alterations of the gut microbiome and various environmental exposures.[7,8] Genome-wide association studies (GWAS) have identified over 200 host susceptibility loci to date.[9] These genetic polymorphisms are associated with a variety of immune-mediated pathways within the mucosal immune system. Family history of IBD is noted in about 12% of patients and susceptibility risk is increased in those with an affected first-degree relative.[10] The concordance rate among monozygotic twins is reported to be approximately 15% and 35% for CD and UC, respectively.[11] Thus, genetic predisposition is insufficient to explain disease onset and several environmental risk factors have been identified.

Environmental risk in IBD seems to be driven by factors influencing the gut microbiome. At steady state the intestinal microbiota is comprised of trillions of bacteria, viruses, protozoa, and fungi. A number of chronic diseases have been associated with alterations in the delicate balance of this ecosystem, referred to as dysbiosis. Whether the dysbiosis observed in IBD is primary or secondary to the underlying intestinal inflammation is still not clear.

The adult microbiome is set during the first 3 years of life. Early life events such as birth method, breastfeeding, and exposure to antibiotics have been shown to impact microbiome development. A landmark study showed that the microbiome of healthy individuals living in industrialized nations (the United States) had a markedly less diverse microbiome compared to those residing in under-developed rural communities in Africa and Venezuela.[12] IBD is generally a disease of western civilization with increasing incidence noted in newly industrialized nations, suggesting that this baseline lack of microbial diversity driven by our environment is likely itself an important risk factor. One possible explanation of this phenomenon is termed the hygiene hypothesis. This presupposes that industrialization, improved hygiene and lack of enteric pathogen exposures may increase risk of developing certain immune-mediated conditions, including IBD.[13]

CLINICAL PRESENTATION

Children with IBD can present with a variety of signs and symptoms. The majority will present with a combination of gastrointestinal complaints including abdominal pain, nausea, vomiting, diarrhea or hematochezia. Patients with UC typically have blood in the stools at presentation. Significant proctitis or inflammation of the rectum is commonly seen in UC. This can result in debilitating symptoms such as urgency, tenesmus and nocturnal stooling. Younger children

with CD are more likely to have colonic involvement and the initial presentation can mimic UC. The majority of older children and adolescents with CD have inflammation to varying degrees in the terminal ileum and colon at presentation. These patients can present with a spectrum of symptoms related to the disease location.

Weight loss and delayed linear growth is especially concerning in pediatric IBD. Studies suggest that growth failure occurs in approximately 40% and 10% of children with CD and UC, respectively.[14,15] Increased metabolic demand, poor oral intake, malabsorption, corticosteroid therapy, and growth hormone resistance due to chronic inflammation are potential contributing factors. Review of an accurate growth chart is critical as children can present with an indolent decline in growth velocity and/or weight percentiles well before symptom onset. Co-morbid obesity should not dissuade further evaluation when clinically indicated. Recent reports suggest that approximately 30% of children with IBD are obese at the time of diagnosis.[16]

Up to 30% of children with IBD experience extra-intestinal manifestations (EIMs).[17] These are reviewed in a separate article.

EVALUATION

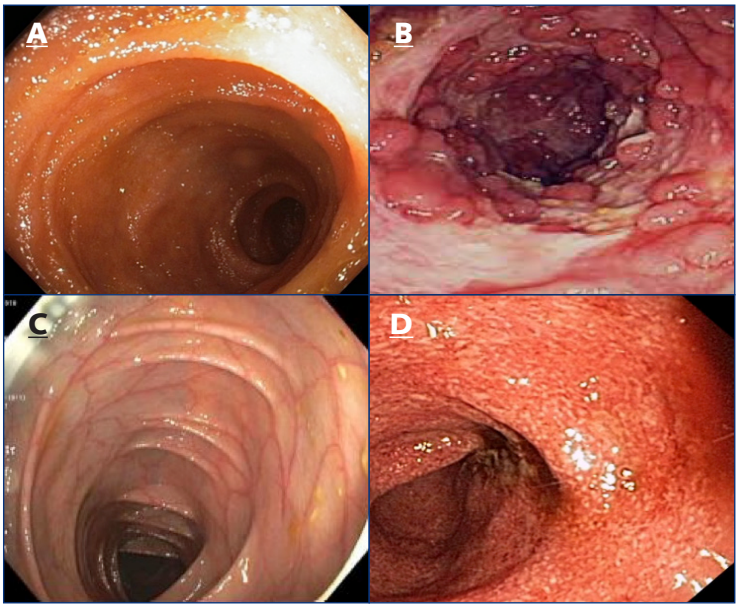
The diagnosis of IBD is based on a combination of clinical, serologic, endoscopic, pathologic and radiographic data. Initial evaluation should involve a thorough history, physical exam and review of outpatient growth charts. Pubertal assessment via Tanner staging should be completed, when appropriate. A supervised perianal inspection should also be performed to assess for possible perianal skin tags, fistulae or abscesses. Digital rectal exam is rarely required in children with suspected IBD.

Table 1. Laboratory Evaluation of IBD

Blood	Anemia, low mean corpuscular volume, leukocytosis, thrombocytosis Hypoalbuminemia: chronic malnutrition, intestinal inflammation, malabsorption Iron deficiency: chronic inflammation, malnutrition Elevated ESR and CRP Elevated Liver enzymes Genetic test: r/o monogenic IBD in VEO-IBD Immune deficiency work up: r/o immunodeficiency condition in VEO-IBD Antibody test: pANCA, ASCA, Anti-Cbir, Anti-Ompc1 -No initial diagnostic role -Could predict disease behavior and disease severity Serum trough and antibody level (Biologics): help optimize treatment
Stool	Salmonella, Shigella, Campylobacter, Yersinia, Escherichia coli 0157:H7 Clostridium Difficile: frequent monitoring and aggressive treatment indicated Fecal calprotectin &lactoferrin

pANCA: Antineutrophil Cytoplasmic Antibodies
ASCA: Anti-Saccharomyces Cerevisiae (ASCA) Antibodies

Figure 1: Endoscopic views of healthy tissue compared with inflammatory bowel disease. **A.** Normal terminal ileum. **B.** Crohn disease with patchy inflammation, cobble stoning, deep ulcers, exudates, altered vascular pattern and friability. **C.** Normal colonic mucosa with intact architecture and vascular patter. **D.** Ulcerative colitis with continuous, uniform inflammation.



Laboratory tests to assess for signs of inflammation and disease chronicity are often the first step in evaluation (**Table 1**). Up to 20% of children can present with normal laboratory values.[18] Thus, normal blood work should not deter further evaluation when clinically indicated. Esophagogastroduodenoscopy (EGD) and Ileo-colonoscopy with biopsies provide detailed evaluation of mucosal inflammation and distribution (**Figure 1**). In certain cases, advanced endoscopic techniques such as single- and double-balloon and spiral enteroscopy can assess the mid-small bowel, which is otherwise inaccessible via standard endoscopic approaches. These advanced procedures are rarely indicated in pediatric patients. Video capsule endoscopy (VCE) is another way to evaluate the small bowel and can be completed in most children, when indicated. Magnetic resonance enterography (MRE) and computerized tomography enterography (CTE) are the preferred imaging modalities to assess for small bowel involvement in CD. These cross-sectional images also assess for complicated disease behavior such as intestinal strictures, fistulae and abscesses. An MRE is preferred due to lack of radiation exposure, although these are long study protocols which younger children may not be able to tolerate. A bone age study, via radiograph of the hand, is frequently utilized in children to assess the degree of growth impairment. Bone mineral density analysis via dual-energy x-ray

absorptiometry scan (DEXA) should be considered in children at risk for low bone mineral density, especially in those with prolonged corticosteroid (CS) exposures. The workup for younger children with VEO-IBD involves genetic testing to rule out monogenic causes and underlying immunodeficiency syndromes that can result in an IBD-like phenotype. Thus, all children under the age of 2 with suspected IBD should have genetic testing prior to starting immune-modulating medications. Such genetic testing is commercially available as a monogenic IBD gene panel which is offered by laboratories such as Invitae and the Mayo Clinic. Additionally, genetic testing is available through VEO-IBD research consortia at centers across the country.

DISEASE CLASSIFICATION

IBD is classified into CD, UC and IBD- unclassified (IBD-U). IBD-U is typically reserved for patients with colonic inflammation that may not completely meet diagnostic criteria for either CD or UC. Disease phenotype and behavior is classified in adults according to the Montreal Classification schema.[19] This does not take into account important pediatric-specific factors. Thus, the Paris Classification is used in children.[20] This tool includes more detailed description of disease phenotype and behavior while incorporating assessment of patient age and growth. Side-by-side comparison of the Montreal and Paris Classifications for CD and UC are presented in **Tables 2**,**3**.

Table 2. Montreal and Paris classification of CD

CHARACTERISTICS	MONTREAL	PARIS
Age At Diagnosis	A1: <17 yrs. A2: 17-40 yrs. A3: >40 yrs.	A1a: 0 to<10 yrs. A1b: 10 to <17 yrs. A2: 17 to 40yr A3: >40 yrs.
Location	L1: Terminal ileal +/- limited cecal disease L2: Colonic L3: Ileocolonic L4: Isolated track disease	L1: Distal 1/3 ileal +/- limited cecal disease L2: Colonic L3: Ileocolonic L4a: Upper disease proximal to LoT L4b: Upper disease distal to LoT and proximal to distal 1/3 ileum
Behavior	B1: Non-stricturing and Non-penetrating B2: Stricturing B3: Penetrating P: perianal disease modifier	B1: Non-stricturing and Non-penetrating B2: Stricturing B3: Penetrating B2/B3: Both penetrating and structuring disease P: perianal disease modifier
Growth	NA	G0: No evidence of growth delay G1: Growth delay

*LoT: Ligament of Treiz

MANAGEMENT

Goals of therapy in children include controlling active symptoms, achieving mucosal healing, optimizing quality of life and minimizing adverse effects of medications, many of which suppress the immune system. The focus in a newly diagnosed patient is to induce remission and thereby improve clinical symptoms. Systemic corticosteroids (CS) have been a mainstay induction therapy for the last 50 years. While CS are effective at quickly improving symptoms, they are associated with a myriad of adverse physical and emotional side effects. Thus, long-term use can be problematic and steroid-sparing strategies are increasingly used in children with IBD. Other therapies used for induction of remission include biologic agents, high dose mesalamine in mild-to-moderate UC and exclusive enteral nutrition (EEN) in small bowel CD.

Table 3. Montreal and Paris classification of UC

CHARACTERISTICS	MONTREAL	PARIS
Extent	E1: Ulcerative proctitis E2: Left Sided UC (distal to splenic flexure) E3: Extensive (proximal to splenic flexure)	E1: Ulcerative proctitis E2: Left-Sided UC (distal to splenic flexure) E3: Extensive (distal to hepatic flexure) E4: Pancolitis (proximal to hepatic flexure)
Severity	S0: Clinical remission S1: Mild UC S2: Moderate UC S3: Severe UC	S0: Never severe S1: Ever severe

*Extent defined by maximal macroscopic inflammation
*Severe defined by Pediatric Ulcerative Colitis Activity Index (PUCAI) ≥ 65

Biologic Therapy

The use of biologic therapies has transformed management of pediatric IBD over the last 20 years. Infliximab (IFX) and adalimumab (ADA) are monoclonal antibodies against the inflammatory cytokine TNF-α. They are FDA-approved for both induction and maintenance of remission in moderate-to-severe pediatric CD and UC. These medications are superior to thiopurines for achieving mucosal healing (i.e., deep remission), can heal perianal fistulae in CD and improve linear growth in children.[21,22] Several studies have shown that early use of anti-TNF therapy is associated with improvement in clinical outcomes, increased rates of sustained clinical remission, improved rates of mucosal healing

and decreased surgical rates.[22,23] Adverse effects include increased risk of infection related to degree of immunosuppression, infusion reaction (IFX) or reaction at the site of injection (ADA), and hematologic or hepatic toxicity. However, the risk of serious infection with anti-TNF therapy has been shown to be less than in patients with prolonged corticosteroid exposure.[24] Anti-TNF medications were previously associated with increased malignancy risk, though a recent prospective study reported no difference in risk of malignancy associated with exposure to infliximab.[24,25] The pharmacokinetics and pharmacodynamics of these biologic medications differ between children and adults. Children often require higher doses and/or more frequent doses to achieve therapeutic drug levels and maintain a durable treatment response. This can be especially challenging when seeking insurance approval for certain medications and doses.

Several newer biologic agents and small molecules have shown promising results in treatment of IBD but are still not FDA-approved for use in children. These include vedolizumab (α4β7 integrin inhibitor), ustekinumab (anti-interleukin 12/23), rizankinumab (anti-interleukin 23), tofacitinib, upadacitinib (both janus kinase (JAK) inhibitors) and ozanimod (sphingosine-1 phosphate inhibitor).

5-Aminosalicylates and Immunomodulators

Other options for therapy in pediatric IBD include 5-aminosalicylate (5-ASA) medications such as mesalamine and sulfasalazine, immunomodulators (6-mercaptopurine, azathioprine, and methotrexate), antibiotics, and dietary therapy. 5-ASA medications are indicated for treatment of mild-to-moderate ulcerative colitis and can be used as adjunctive therapy in patients with Crohn's disease, though often this drug class is not effective in maintaining remission long term. The PROTECT study demonstrated a minority of study participants with UC achieving corticosteroid-free remission at 52 weeks with mesalamine alone. Milder presentation, higher baseline hemoglobin, and clinical remission at week 4 were factors associated with corticosteroid-free remission at week 52 with mesalamine alone.[26]

Immunomodulators are typically not effective in inducing remission alone but can be used as adjunctive maintenance therapies along with biologics. 6-mercaptopurine (6-MP) is a thiopurine analog that has been shown to maintain corticosteroid-free remission in pediatric IBD.[27] Methotrexate inhibits production of dihydrofolate reductase and can also be effective in maintenance of remission in CD.[28] Both drugs are immunosuppressive and can be associated with hepatotoxicity. Methotrexate is a known teratogen and counselling on safe sexual practices with double contraception is important when using this medication is females of child-bearing age. Prolonged exposure to 6-MP has been associated with an increased risk of lymphoma. Additionally, primary Epstein–Barr virus (EBV) infection in children with IBD receiving 6-MP therapy has been associated with increased risk for severe EBV infections and potential complications like malignancies or hemophagocytic lymphohistiocytosis, and warrants cautious use of 6-MP in EBV naïve patient population.[29,30] T-cell lymphoma is a rare but fatal disease that has been reported in a small number of mostly male patients exposed to both 6-MP and infliximab. Because of this, many practitioners are transitioning to the use of methotrexate rather than 6-MP for concomitant therapy with biologic medications to prevent immunogenicity, especially in males.[28]

Surgery

Surgery remains an integral part of the comprehensive management of children with IBD. Those with moderate-to-severe, treatment-refractory UC may require total colectomy with ileal pouch anal anastomosis (IPAA). IPAA entails resecting diseased colon and constructing a pouch from the distal ileum and anastomosing it to the cuff of rectum to preserve continuity and avoid a permanent ileostomy. Those with CD are at risk for debilitating complications, such as perianal fistulae, abscesses, intestinal strictures, fistulae and perforation. Patients with stricturing CD may require a limited ileocecectomy. Penetrating CD can present with fistulae extending from the bowel to multiple extraluminal locations such as bladder (entero-vesical), vagina (entero-vaginal) and abdominal wall (entero-cutaneous). Many of these complications require surgical intervention and justify aggressive early use of biologic medications, especially in those who present with severe disease phenotypes. Recent population-based data suggest a general decline in surgical rates over time, likely attributed to increased, early use of biologic agents and successful achievement of mucosal healing.

Nutrition

Nutrition is critical to the maintenance and treatment of children with IBD. Specific dietary therapies can be used as primary and adjunctive treatments and are discussed in a separate article.

HEALTH MAINTENANCE

Routine health maintenance visits are integral to the care of children and adolescents with IBD. Assessing growth and pubertal development on a regular basis is important, regardless of disease activity. Some patients with sub-clinical inflammation will still experience poor growth. Thorough physical exam, review of growth charts, routine lab work and trending of the fecal calprotectin (a stool inflammatory marker) are important to routine care. Each patient's immunization status needs to be reviewed at diagnosis. While vaccines should not be delayed in IBD, live virus vaccines need to be avoided in patients treated with immune suppressing

medications such as corticosteroids, immune modulators (such as methotrexate or 6-mercaptopurine) and biologics. Vaccination guidelines are reviewed in a separate article and updated guidelines can be downloaded from the Crohn's and Colitis Foundation website or the Cornerstones Health website. Screening for tuberculosis exposure or latent infection and Hepatitis B immune status need to be obtained prior to initiation of biologic agents.

Longstanding inflammation increases the risk of malignant transformation and cancer, especially in UC. A meta-analysis reported the incidence of colorectal cancer (CRC) among patients with IBD to be 1%, 2%, and 5% after 10, 20, and > 20 years of disease duration, respectively.[31] Significantly higher risk was seen in patients with longer disease duration, extensive disease, and in patients diagnosed at a young age.[32] Surveillance colonoscopy is thus recommended 8-10 years from diagnosis and then every 1-5 years depending on risk factors for neoplasia which include extent and duration of disease, inflammation burden over time and at last colonoscopy, male gender, family history of colorectal cancer under the age of 50, and primary sclerosing cholangitis (PSC) (AGA guidelines). Patients with both IBD and PSC are considered high risk and start surveillance at diagnosis and then annually.

PSYCHOLOGICAL CONSIDERATION

Children with IBD are at higher risk for anxiety and depression.[33] Routine assessment of psychosocial stressors at home and at school should be performed at each visit. Involving a child psychologist early on can help screen for those most at risk while providing coping strategies for adjusting to a chronic illness. Support groups can also provide a valuable resource for patients and families struggling to adjust to a new diagnosis of IBD.

A MULTIDISCIPLINARY TEAM APPROACH

A multidisciplinary care team often includes pediatric GI providers, nurse specialists, social workers, nutritionists, administrative support, clinical research coordinators, and behavioral psychologists. Optimal care involves close collaboration with other clinical specialties including, but not limited to, dermatology, rheumatology, immunology, ophthalmology, pharmacy, psychology, psychiatry, nutrition, radiology, anesthesia and pediatric surgery. Care coordination between outpatient, inpatient and infusion services is integral for patients on biologic medications. A dedicated GI or IBD social worker can serve as a liaison for patients and families serving as a constant, supportive presence. Coordination with schools and colleges is also important to ensure adequate accommodations are available relative to bathroom access and academic support.

TRANSITION OF CARE TO ADULT GASTROENTEROLOGY

Assuring a seamless transition of care for young adults with IBD from pediatric to adult gastroenterology practices is critical and often challenging. Advanced planning and effective communication among the key stakeholders in the patient's care is essential to a successful transition. The timeline is unique for every patient and should be based on a combination of factors including transition readiness, developmental maturity and emotional maturity, which does not always correlate with chronological age. For example, a patient with developmental or cognitive delays may benefit from a later transition to adult GI providers. In general, discussion of transition of care begins in early adolescence as the patient takes a more active role in discussion of their health care needs and management decisions. Once the decision to transition has been completed, a formal sign out between the pediatric and adult gastroenterologist should be completed to ensure adequate communication of salient clinical details. While there is no standard approach, a number of transition models, instruments and checklists are currently available to help support patients through this important phase.

CONCLUSIONS

IBD is a chronic, debilitating condition with rapidly increasing disease burden in the pediatric population worldwide. The presentation of IBD in children and adolescents is variable and primary care clinicians should be familiar with atypical clinical presentations to avoid delays in diagnosis. Treatment focuses on controlling active symptoms and preventing long-term complications with a focus on preserving age-appropriate quality of life. Successful management of children with IBD involves a multidisciplinary team approach. Close attention to emotional health is as important as medical management in this especially vulnerable patient population.

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