



Pediatric Inflammatory Bowel Disease

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Received date: 31 January 2021; **Accepted date:** 22 February 2021; **Published date:** 01 March 2021

Citation: Rotondo-Trivette S, Michail S. Pediatric Inflammatory Bowel Disease. *Asp J Pediatrics Child Health*. 2021 Mar 01;3(1):11-17.

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Abstract

Inflammatory bowel disease is an important pediatric disease, with as many as 25% of cases presenting during childhood. In this article, we review the types, etiology epidemiology, presentation, diagnosis, and management of pediatric inflammatory bowel disease. We also highlight the unique aspects of pediatric-onset inflammatory bowel disease versus adult-onset and future directions in this field, such as the use of genetic studies and ultrasound for the management of pediatric patients with inflammatory bowel disease.

Keywords

Inflammatory Bowel Disease, Pediatric Disease, Crohn's Disease, Ulcerative Colitis, Indeterminate Colitis

Key Points

1. Pediatric-onset inflammatory bowel disease is unique from adult-onset, and has several different categories based on age of diagnosis.
2. Pediatric patients with inflammatory bowel disease may struggle with growth delays and psychosocial impacts of their disease; multidisciplinary management with dietitians and mental health professionals may be warranted.
3. HLA typing and the use of ultrasound in pediatric inflammatory bowel disease may mitigate the risk of treatment failure and exposure to invasive procedures over the course of a child's disease.

Background

Inflammatory bowel disease (IBD) includes Crohn's disease (CD), ulcerative colitis (UC), and indeterminate colitis (IC) [1,2]. These diseases are chronic, relapsing inflammatory disorders of unknown pathogenesis [1,2]. Approximately 25% of IBD patients are diagnosed before the age of 18 [3], and the prevalence of pediatric IBD increased by 133% from 2007 to 2016 [4].

There is growing evidence that pediatric-onset IBD may represent a distinct disease with differences in disease type, disease location, disease behavior, gender preponderance, and genetically attributable risk compared with its adult counterpart. In this article, we will review the etiology and epidemiology as well as the diagnosis and management of pediatric IBD while highlighting the differences from adult IBD.

Crohn's Disease:

CD can affect any part of the GI tract, but most commonly affects the ileum and colon in children. CD may have discontinuous inflammation and appear in patches. The inflammation may extend through the entire bowel wall, leading to several complications such as fistulas, abscesses, and strictures [2].

Ulcerative Colitis:

UC affects the colon and rectum exclusively. Inflammation starts at the rectum and progresses proximally in a continuous fashion. Children most often present with pancolitis, affecting the entire colon, but may also present with left-sided only or proctocolitis limited to the rectum. This inflammation is limited to the mucosal layer of the colon, so patients are much less likely to develop fistulas and strictures as seen in CD [2].

Indeterminate Colitis, also known as IBD-Unspecified:

Due to CD often presenting as isolated colitis in children, it is often difficult to assign a diagnosis of CD or UC at the time of initial presentation. These children may be placed in the category of IC until other features develop that can distinguish between the two. However, it is important not to overuse this category and to correctly diagnosis the type of IBD for treatment and prognosis purposes [3].

Etiology

While the exact etiology of IBD remains unknown, recent advances continue to support a hypothesis that involves environmental triggers in genetically susceptible individuals causing immune dysregulation. CD appears to be more influenced by genetics than UC. CD has a higher monozygotic twin concordance rate as well as a higher risk of passing the disease to offspring [5]. In a subset of patients with very-early onset IBD, an IBD-like syndrome may be caused by a monogenic disorder [6]. Nearly 60 monogenic IBD forms have been reported [6]. These genes most often involve defects in epithelial barrier function, immune regulation and immune system cell function [6].

Epidemiology

Pediatric IBD is defined by onset at less than 18

years of age. As highlighted in **Table-1**, pediatric IBD can be further broken down by age of onset. Neonatal and infantile IBD are rare and may represent a distinct disease process that is beyond the scope of this article. Additionally, as seen in **Fig-1**, very early onset IBD accounts for nearly 20% of pediatric IBD patients [6]. In contrast to adults, CD is approximately two times more common in this age group than UC and boys appear to be affected more than girls [3]. Interestingly, in the United States, the Northeast has the highest prevalence of pediatric IBD while the West has the lowest [3].

IBD Type	Age Group
Neonatal IBD	< 28 days old
Infantile IBD	< 2 years old
Very-early onset IBD	< 6 years old
Childhood onset IBD	6 - 10 years old
Adolescent onset IBD	10 - 17 years old

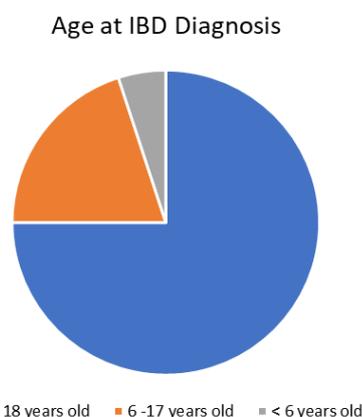


Fig-1:

The proportion of individuals with IBD diagnosed in adults (>18 years old) and children (<18 years old), with very early onset IBD (<6 years old) separated out.

Presentation

Identifying IBD in children can be difficult. Children commonly present with long standing, nonspecific symptoms such as intermittent abdominal pain, nausea, vomiting, fevers, fatigue, or growth restriction [7]. However, some children may present similarly to adults with symptoms dependent on the location of their disease, such as severe bloody diarrhea and significant abdominal pain [3,7]. Some children may also present with extra-intestinal manifestations of

IBD, such as oral ulcers, uveitis, pyoderma gangrenosum, or arthritis [3,7].

Interestingly, the initially presentation of IBD in children differs significantly from adults. In pediatric CD, most patients have ileocolonic or colonic disease and have non-stricturing, non-penetrating disease at presentation [3]. Adults more often present with terminal ileal disease without colonic involvement and already have structuring and penetrating disease at diagnosis [3]. Additionally, pediatric UC presents more often with pancolitis versus left-sided colitis/proctitis and time to first surgery is significantly shorter in children than adults [3].

Growth is the most significant difference in presentation between adult and pediatric IBD [3]. Poor growth prior to diagnosis has been documented in multiple studies examining growth in pediatric IBD [3]. Furthermore, puberty has been shown to be delayed and some patients have decreased final adult height [3,7].

Diagnosis

The diagnosis of IBD cannot be confirmed without endoscopic and histological evidence. While children with persistent bloody diarrhea or perianal disease should proceed directly to endoscopy, children with non-bloody diarrhea or other non-specific symptoms should be screened prior to proceeding to endoscopy in order to avoid unnecessary procedures [8]. **Table-2** describes the screening tests, which includes symptoms, blood markers, and fecal calprotectin.

Table-2: Screening for IBD prior to endoscopy in patients without bloody diarrhea or perianal disease
Symptoms (persistent or recurrent non-bloody diarrhea, abdominal pain, unintended weight loss)
Extraintestinal manifestations (arthritis, dermatological manifestations, uveitis)
Family history of IBD
Elevated CRP
Anemia
Elevated fecal calprotectin

A child with a suspected diagnosis of IBD will often undergo a combined upper endoscopy, colonoscopy, and terminal ileoscopy as the initial diagnostic procedure [9]. During the colonoscopy, it is suggested that random biopsies be obtained from the terminal ileum and each segment of the colon (cecum, ascending, transverse, descending, sigmoid, rectum) [9]. Biopsies from each location should be placed in separate specimen containers, with the location of the biopsy clearly labeled. Endoscopic evidence of UC would be diffuse continuous mucosal inflammation involving the rectum and extending to a point more proximal in the colon [9]. CD can be difficult to diagnosis in the absence of straightforward evidence of small bowel involvement or severe perianal disease. Often, the differentiation of CD from UC is based on observations by the endoscopist showing focal discontinuous inflammation, deep fissuring ulcers, and aphthous lesions superimposed on a background of normal colonic mucosa [9].

Histological evidence is also important as it can distinguish CD and UC from other causes of colitis, such as acute self-limited colitis (ASLC) that may look similar to the endoscopist. The histological features present in UC but rarely seen in ASLC are crypt architectural distortion (including irregular crypt shape or placement, branching, atrophy, or surface villiform change), basal lymphoplasmacytosis, and Paneth cell metaplasia in the left colon [9]. Alternatively, a CD diagnosis can almost certainly be made if there are multiple non-caseating granulomas present on biopsy [9].

Management

IBD is a complicated disease that can affect many aspects of a patient's life. Therefore, the management of this disease must be multifactorial. The main stay of treatment involves medications to induce remission as well as medications for maintenance of remission. These medications may be used along or in combination. Unfortunately, many of the medications that are routinely used for management of adult IBD have not been well studied in children.

Induction:

Corticosteroids are the mainstay of induction

therapy in IBD. However, their use must be minimized in children due to their adverse effects on growth and bone development [3]. Several other countries have adopted the use of exclusive enteral nutrition for first line induction therapy of CD [3]. It appears to have similar effectiveness as corticosteroids without the adverse effects. However, it requires patients to exclusively consume formula for 6 to 8 weeks, which may not be tolerable for certain patients [3]. Additionally, there is not good evidence for its use in induction of remission in UC. As more evidence comes out and more tolerable formulas developed, perhaps exclusive enteral nutrition will become more popular in the United States for induction of remission in children with IBD.

Maintenance:

Maintenance of remission can be achieved using several different categories of medication in combination or alone. Treatment strategies should be individualized as much as possible to patient preference and lifestyle in order to optimize medication compliance.

The first class of medications are 5-aminosalicylates, including mesalamine and sulfasalazine. These medications have not undergone randomized controlled trials for induction or maintenance of pediatric IBD; however they are widely used because they are well tolerated in children [3]. They appear to be most effective as maintenance therapy in mild to moderate UC, while there is no data to support their use in CD [3].

The next class of medications are thiopurines, or so-called “immunomodulators”. These medications include azathioprine, 6-mercaptopurine, and methotrexate. These medications have been shown to be effective in maintaining remission in approximately 40-60% of both CD and UC patients, but real-life studies indicate that a substantial proportion of children with IBD will eventually fail this treatment [10]. Additionally, there is increasing concern about the risk of leukemia and lymphoma that accompany these medications especially in children [3,10].

Lastly, there are biologics which have been shown to

be effective in both inducing and maintaining remission of pediatric IBD [3,11]. Infliximab, an anti-TNF, has been shown to be effective in inducing and maintaining remission of CD and UC in pediatric patients [11]. However, this medication is not without risk. The main adverse effects include increased susceptibility to infection, development of antibodies to infliximab, and acute infusion reactions [11]. Interestingly, children with very early onset IBD are more likely to fail treatment with infliximab due to adverse events. Regardless of age, it is known that approximately 50% of patients will lose their response to infliximab within 5 years [11]. Adalimumab, a fully humanized anti-TNF, was developed with this in mind. However, it lacks placebo control trials in pediatric IBD. Retrospective studies suggest that adalimumab should be considered as second-line therapy for pediatric patients that fail infliximab [11]. Other biologics such as golimumab, vedolizumab, and ustekinumab are also available but are rarely used in children due to the lack of evidence supporting their use [11].

It is important to note that as several biologics have reached the end of their exclusivity, biosimilars have become available on the market. Biosimilars have the same active ingredients, but with a slightly different formulation of inactive ingredients [12]. Biosimilars can alleviate some of the costliness associated with biologics and make these medications more accessible to the patients that need them.

Multidisciplinary Approach:

A pediatric IBD patient’s care should involve at minimum involve a pediatric gastroenterologist and a registered dietitian. Surgeons and psychiatrists should also be included on a case by case basis (**Fig-2**). Registered dietitians are essential with respect to growth. They can provide nutritional assessments and continued management in order to ensure patients are consuming appropriate calories for growth and correcting any nutritional deficiencies [7]. Additionally, it is important to note that youth with IBD are at increased risk for anxiety and depression. Pediatric IBD patients should be screened frequently for these disorders, as well as for impairments in social functioning, and referred appropriately [13]. A surgeon

should be consulted for those who fail medical management or have disease-related complications that require it, such as dysplasia, perforations, and obstructions [14,15].

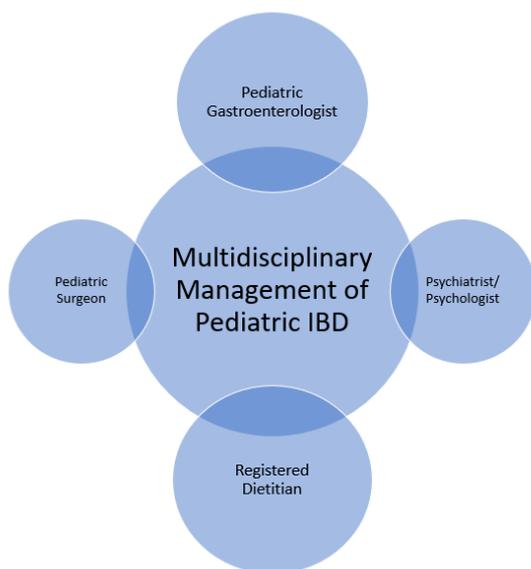


Fig-2:

Pediatric Gastroenterologist should be at the head of the team, well supported by a registered dietitian. Pediatric surgeons and mental health professionals should be referred to as necessary.

Prognosis

It is important to note that despite treatment, pediatric CD often progresses to stricturing and penetrating disease. Approximately 30% of pediatric CD patients will undergo surgery and 40% of pediatric UC patients will undergo colectomy within 10 years of diagnosis [3,15]. Understanding that surgery may be necessary at some point early in the disease course may help patients with accepting this outcome when the time comes. While still rare, IBD patients are also at increased risk for malignancies, such as adenocarcinoma, lymphoma, and skin cancers, compared to their healthy peers. Mortality due to IBD in childhood is even more rare and is most often the result of infection [16,17].

Future Directions

While IBD therapy and management has come a long way, children still face significant burdens associated with the treatment and surveillance of this disease. Children with IBD are likely to go through a

series of expensive medications and undergo several invasive procedures throughout their lifetime. While it is important to balance the risk of uncontrolled disease against the risk of adverse effects, finding inexpensive, safe, and effective treatment and monitoring strategies should be a priority. However, there are several strategies being investigated that may help clinicians better utilize what is currently available to them.

Genetics:

As stated previously, approximately 50% of patients will lose their response to infliximab within 5 years [11]. One reason a biologic may fail is due to the development of antibodies to the medication. Recent studies suggest that certain HLA types may be associated with an increased risk of developing antibodies to biologics, especially infliximab and adalimumab [18,19]. In the future, HLA typing may be able to help predict which children are at risk for developing antibodies and so that we may treat these patients with the addition of an immunomodulator in order to mitigate that risk and prolong the efficacy of the biologic [20].

Our increased understanding of genetics has also allowed for increased understanding of monogenic IBD. For example, in Japan, a targeted sequence panel for 20 genes associated with monogenic IBD has been approved [6]. An expanded panel including the 60 currently identified genes associated with monogenic IBD could improve the diagnostic strategies currently available for very early onset IBD and identify patients that may benefit from hematopoietic stem cell transplantation or other, more targeted therapies, early on [6].

Ultrasound:

Lastly, the use of ultrasound in IBD is becoming more common. Ultrasound is widely available, non-invasive, inexpensive, and has been shown to be effective identifying abscesses, fistulas, stenosis and obstructions [21]. It is also able to characterize the extent of inflammation by measuring the bowel wall thickness, locating the disease, and identifying involvement of the mesentery [21]. The use of ultrasound in the evaluation of pediatric IBD appears to be effective and would save significant time and

money, as well as decrease the exposure of children to invasive procedures and radiation. Its use is likely to become more common as point of care ultrasound gains increasing popularity.

Conflict of Interests

All authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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