

Pediatric Inflammatory Bowel Disease: Highlighting Pediatric Differences in IBD

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- Crohn disease • Ulcerative colitis
- Inflammatory bowel disease • Pediatric
- Evidence-based treatment algorithms

Inflammatory bowel disease (IBD) includes Crohn disease (CD) and ulcerative colitis (UC), and is often diagnosed in late childhood and early adulthood. IBD is thought to develop as a result of dysregulation of the immune response to normal gut flora in a genetically susceptible host. Approximately 25% of incident cases of IBD occur during childhood and the rest occur throughout adulthood, peaking in the second and third decades of life. What determines the age of onset remains unexplained. Studying early-onset presentation and epidemiology of complex predominately adult diseases such as IBD is particularly necessary, as the early onset may represent the “pure” form of the disease process and hence may hold secrets of the initiating events of IBD pathogenesis. Basic, translational, and clinical scientists continue to focus on pediatric IBD, because it may shed light not only on the cause but also the prevention of this lifelong disease. Over the last decade, data from pediatric IBD studies have demonstrated many similarities and differences between pediatric and adult onset, which continue to add pieces to an increasingly complex IBD puzzle. The mechanism responsible for these similarities and differences remains unanswered.

The purpose of this article is to discuss clinically relevant epidemiology and treatment aspects of pediatric IBD, with a special focus on similarities and differences in pediatric and adult IBD. Epidemiologic similarities and differences may ultimately provide the link to a better understanding of the pathogenesis of IBD. This article also highlights evidence-based treatment algorithms, with special focus on pediatric studies and care for children.

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EPIDEMIOLOGY

Gender Differences

The male to female ratio of IBD differs in multiple studies when comparing pediatric IBD to adult IBD. Whereas in adult IBD there is an equal ratio of male to female disease or perhaps more women with disease, prepubertal males seem to be more affected by pediatric CD. Van Limbergen and colleagues¹ demonstrated that in pediatric CD there is a strong trend toward males, with a male to female ratio of 1.5:1. Vernier-Massouille and colleagues² also confirmed a male predilection, with a similar ratio of 1.4:1 in children younger than 15 years. This figure directly compares with a ratio nearing 1:1 in patients older than 15 years in the same population. Other adult epidemiologic studies similarly have shown a gender ratio of approximately 1:1. A summary of recent epidemiologic studies demonstrating a male preponderance in pediatric CD is provided in **Table 1**.

Pediatric UC does not demonstrate the male predominance seen in pediatric CD. In fact, similar to adult UC, males and females are equally affected in pediatric UC in multiple studies. **Table 2** demonstrates the equal distribution of males and females in pediatric UC.

Very early onset IBD (age <5–8 years) has been recently suggested as perhaps a different spectrum of IBD. Multiple epidemiologic studies have demonstrated a male preponderance of very early onset IBD. It is unclear whether this male preponderance is only seen in CD or in both CD and UC, as many of the studies do not provide specific gender information based on specific diagnosis.³

Together, these gender differences generate more questions than they answer. The effect of puberty and sex hormones on disease pathogenesis continues to be unanswered. Further study will continue to explore these interesting epidemiologic findings and may ultimately provide important information as to the cause of pediatric IBD.

Crohn Disease:Ulcerative Colitis Ratio

The ratio of CD:UC significantly differs in children and adults. Van Limbergen and colleagues¹ demonstrated a significant predilection for CD in children, with a ratio of 2.8:1. Adult IBD demonstrated a ratio of 0.85:1. Other epidemiologic studies that have been performed using various methods (ie, population based, insurance claims,

	CD			
	Male	Female	Male:Female Ratio	
Van Limbergen et al ¹	164	112	1.464285714	Childhood Adult
	216	380	0.568421053	
Kugathasan et al ⁵⁰	80	49	1.632653061	Childhood
Vernier-Massouille et al ²	256	216	1.185185185	Childhood
Kappelman et al ⁵¹ (per 100,000)	47	38	1.236842105	Childhood Adult
	183	216	0.847222222	
Herrinton et al ⁵² (per 100,000)	40	27	1.481481481	Childhood Adult
	184	188	0.978723404	
Sawczenko et al ⁵³ (per 100 diagnoses)	62	38	1.631578947	Childhood
Newby et al ⁵⁴	83	33	2.515151515	Childhood

Table 2
Equal distribution of males and females in pediatric and adult UC

	UC			
	Male	Female	Male:Female Ratio	
Van Limbergen et al ¹	48	51	0.941176471	Childhood
	342	359	0.95264624	Adult
Kugathasan et al ⁵⁰	33	27	1.222222222	Childhood
Kappelman et al ⁵¹ (per 100,000)	29	26	1.115384615	Childhood
	238	237	1.004219409	Adult
Herrinton et al ⁵² (per 100,000)	28	29	0.965517241	Childhood
	312	283	1.102473498	Adult
Sawczenko et al ⁵³ (per 100 diagnoses)	51	49	1.040816327	Childhood
	—	—	—	—
Newby et al ⁵⁴	45	29	1.551724138	Childhood

and so forth) have suggested a similar higher ratio of CD than UC in children. This directly differs from adult studies that have demonstrated more UC than CD diagnoses. **Table 3** illustrates recent studies that reveal this significant difference in CD:UC ratios in children and adults.

There is clearly a significantly higher CD:UC ratio in children than in adults. Similar to gender differences, this observation clearly requires further investigation, with few data available to suggest a mechanism for this significant difference between pediatric and adult IBD.

Disease Location

Disease location at presentation differs in pediatric IBD compared with adult IBD. In pediatric CD a majority of patients have ileocolonic disease or colonic disease, whereas adults more often present with terminal ileal disease without colonic involvement. During follow-up of pediatric CD, Vernier-Massouille and colleagues² and Van

Table 3
CD preponderance in pediatric IBD and UC preponderance in adult IBD

	CD	UC	CD:UC Ratio	
Van Limbergen et al ¹	276	99	2.79	Childhood
	596	701	0.85	Adult
Kugathasan et al ⁵⁰	129	60	2.15	Childhood
Vernier-Massouille et al ²	472	151	3.13	Childhood
Kappelman et al ⁵¹ (per 100,000 prevalence)	1118	722	1.55	Childhood
	12800	15151	0.84	Adult
Herrinton et al ⁵² (per 100,000 period prevalence)	67	57	1.18	Childhood
	186	299	0.62	Adult
Sawczenko et al ⁵⁵	431	211	2.04	Childhood
Auvin et al ⁵⁶	367	122	3.01	Childhood
Newby et al ⁵⁴	116	74	1.57	Childhood
Heyman et al ⁵⁷	798	393	2.03	Childhood

Limbergen and colleagues¹ both demonstrated a progression of disease location with increasing ileocolonic disease at follow-up. Meanwhile, Van Limbergen and colleagues showed that more than one-third of adults had terminal ileal disease only. In multiple pediatric studies, up to 80% to 90% of children experience colonic disease (colon only or ileocolonic) whereas only approximately 50% of adults experience colonic CD. It is unclear why there is an increased ileocolonic/colonic disease in children and no accepted theory has been offered as to this observation. No treatment studies have suggested that children with ileocolonic disease require different treatment from terminal ileal disease alone. **Table 4** demonstrates the high rate of ileocolonic disease in children at both diagnosis and follow-up in 2 studies.

Pediatric UC location also differs from that of adult disease. Pediatric UC presents more often with pancolitis versus left-sided colitis/proctitis. In fact, most pediatric UC studies demonstrate up to 80% to 90% of children present with pancolitis, and a recent study by Van Limbergen and colleagues¹ suggested that pediatric UC progresses with increasing percentage of pancolitis at follow-up. The significance of the high percentage of pancolitis at presentation is unknown. **Table 5** demonstrates an increased pancolitis presentation in pediatric UC.

In summary, pediatric CD more often involves the ileocolonic/colonic regions whereas adult CD does not demonstrate a high proportion of colonic disease. Meanwhile, pediatric UC more often presents with pancolitis whereas adult UC more often presents with left-sided colitis. The mechanism behind these observations is not well understood and no data are available to support any concrete hypotheses.

Disease Phenotype

Disease phenotype in both CD and UC differs when comparing children with adults. Pediatric CD presents predominantly with inflammatory or nonstricturing, nonpenetrating disease. Stricturing and penetrating disease is relatively uncommon at presentation in pediatric CD. However, even with treatment, multiple studies have shown that

Table 4
Higher ileocolonic disease prevalence in pediatric CD compared to adult CD

	CD Location				
	Terminal Ileum (L1)	Colon Only (L2)	Ileocolonic (L3)	Upper Gastrointestinal Disease (L4)	
Vernier-Massouille et al ²	14%	17%	69%	34%	Childhood diagnosis
	9%	9%	82%	48%	Childhood follow-up (10 y)
Van Limbergen et al ¹	6%	36%	51%	51%	Childhood diagnosis
	5%	36%	54%	61%	Childhood follow-up (4 y)
	36%	38%	23%	12%	Adult
Kugathasan et al ⁵⁰	25%	32%	29%	14%	Childhood diagnosis
Sawczenko et al ⁵⁸	9%	7%	84%	50%	Childhood diagnosis
Auvin et al ⁵⁶	19%	10%	71%	—	Childhood diagnosis

	UC Location			
	Proctitis (E1)	Distal Disease (Left-sided) (E2)	Pancolitis (E3)	
Van Limbergen et al ¹	4%	21%	75%	Childhood diagnosis
	1%	16%	82%	Childhood follow-up
	17%	35%	48%	Adult follow-up
Hyams et al ⁵⁹	22%	39%	43%	Childhood diagnosis
Kugathasan et al ⁵⁰	—	10%	90%	Childhood diagnosis
Hyams et al ⁶⁰	—	—	80%	—
Sawczenko et al ⁵⁸	4%	—	81%	Childhood diagnosis
Auvin et al ⁵⁶	11%	57%	32%	Childhood diagnosis

CD progresses to stricturing and penetrating disease in many children. Adult disease presents more often with stricturing and penetrating disease. Two recent natural history articles reveal a significant progression of pediatric CD from inflammatory disease to stricturing disease, as illustrated in **Table 6**.

Pediatric UC more often presents with pancolitis, and has been suggested to be a more severe phenotype in children than in adults. Recent epidemiologic data demonstrate that indeed, time from diagnosis to first surgery in UC is significantly shorter in children than in adults. By 10 years after diagnosis more than 40% of children had undergone colectomy, whereas only 20% of adult-onset UC patients had undergone colectomy.¹

In summary, pediatric CD frequently displays an inflammatory phenotype at diagnosis that progresses to fistulizing/stricturing disease in some patients, whereas adult CD more often presents with fistulizing/stricturing disease. Although some investigators have suggested disease duration and a delay in diagnosis may be the reason for this difference in CD, no data have been published to support this hypothesis. Pediatric UC frequently displays an aggressive phenotype, with pancolitis and early time to first surgery compared with adult UC, which is more often limited to the left colon.

Genetics

When studying early-onset presentations of disease, there is an assumption that these represent a more severe, more genetically influenced group of patients. It is appealing

	CD Phenotype			
	B1: Inflammatory (NS, NP)	B2: Stricturing	B3: Penetrating	
Van Limbergen et al ¹	91%	4%	5%	Childhood diagnosis
	76%	13%	11%	Childhood 4 y follow-up
	66%	14%	20%	Adult follow-up
Vernier-Massouille et al ²	71%	25%	4%	Childhood diagnosis
	41%	44%	15%	Childhood 10 y follow-up

to geneticists to study these patients because of the increased chance of finding novel risk variants. One of the most compelling hypotheses is that pediatric-onset IBD is more likely to be influenced by genetics compared with late- or adult-onset IBD, as there is less time for environmental modifiers to have influenced the disease.

IBD is highly heritable. This concept is strongly supported by family, twin, and phenotype concordance studies, and now is confirmed by the discoveries of many susceptibility genes.⁴ Initial family-based linkage studies of IBD implicated the NOD2 gene in CD and the MHC region on chromosome 6p in UC for increased susceptibility.⁵ Genome-wide association scanning (GWAS), which employs high-density single nucleotide polymorphism (SNP) array technology, has recently increased the possible genetic factors linked to IBD pathogenesis. This method of broad, unbiased screening for the contribution of common genetic variation for disease susceptibility has provided strong evidence for many CD and UC susceptibility loci.⁶ GWAS has identified loci in both UC and CD that are already known to be involved in adaptive immunity genes such as IL23R, IL12B, STAT3, loci on 3p21 (MST1), and 10q24 (NKX2-3). Variants in innate immunity genes, particularly those mediating autophagy and bacterial sensing (ATG16L1, IRGM, and NOD2) have also been discovered through these methods in CD. To date, the majority of this genetic analysis in IBD has been done in adult cohorts with adult-onset disease as the primary phenotype, therefore even less is known about early-onset variants.

Several CD susceptibility alleles have been confirmed in both pediatric and adult populations. However, most of the genetic variation seen in adults has not been studied in children in a large cohort with adequate power. Two pediatric studies attempting to replicate the effect of adult-onset IBD loci in children have been performed recently. These studies have demonstrated that autophagy genes play a role in pediatric CD but also that known genetic risk factors found in adults may not distinguish early- and late-onset IBD.^{7,8}

The first pediatric GWAS IBD scan was performed recently, revealing 2 risk variants not previously reported in adults, in addition to confirming the most significant adult risk variants. Two novel loci, the TNFRSF6B and PSMG1 genes, were discovered using more than 1000 cases of pediatric IBD.⁹ The gene TNFRSF6B, which encodes a decoy receptor for the FasL pathway (DCR3), was found to increase the risk for pediatric-onset CD and UC. On comparison with adult GWAS scans these same loci were identified, but were below the expected threshold when correcting for multiple tests. However, until a GWAS is performed in an exclusively pediatric-onset IBD cohort, it is very difficult to deny that additional pediatric-onset IBD susceptibility genes do not exist. As such, GWAS studies involving larger pediatric-onset CD cohorts and early-onset UC are presently underway.

Adult and pediatric GWAS studies have yet to discover risk variants that are specific to pediatric or adult IBD. Instead, all risk variants that have been discovered are present in both adult and pediatric scans, although not necessarily in the statistically significant range. This observation, if confirmed in additional larger GWAS studies, may further suggest that pediatric and adult IBD have similar genetics and thus are the same disease with different age of presentation.

More detailed functional exploration of genes associated with susceptibility loci reported in GWAS will be instrumental in shedding light on their role in IBD pathogenesis. Taken together, recent pediatric GWAS results substantially advance the current understanding of pediatric-onset IBD by highlighting key pathogenetic mechanisms, and allowing for the first time a comparison between genetic susceptibility in an exclusively pediatric cohort and the previously described populations with predominantly adult-onset disease.

Clinical Presentation

Clinical presentation is similar in adult and pediatric IBD, and for the most part correlates with disease location. Pediatric CD presents with more ileal and colonic disease than adult CD, and therefore more often presents with hematochezia. Small bowel disease presents with diarrhea regardless of childhood or adult onset. Pediatric and adult IBD share many of the same gastrointestinal symptoms which, as one would expect, are associated more with mucosal disease than with age.

Extraintestinal manifestations similarly are present in both children and adults in similar numbers. Extraintestinal manifestations are present in 6% of children prior to diagnosis in one recent study, and cumulative incidence approaches 25%, similar to adult data.¹⁰

Growth is the most significant difference in presentation between adult and pediatric IBD. Poor growth prior to diagnosis has been documented in multiple studies examining growth in pediatric IBD.^{11–14} Furthermore, puberty has been shown to be delayed¹² and some patients have decreased final adult height.^{14,15} In addition, a recent study has demonstrated that despite new treatments, catch-up growth does not occur in patients diagnosed with IBD, although it remains to be seen whether these patients have delayed puberty and ultimately achieve their expected adult height.¹⁶ Persistent poor growth may also be one of the only signs of increased disease activity, thus it is important not only in presentation but also in disease activity during treatment.

TREATMENT

Pediatric IBD treatment employs many of the same treatment paradigms as adult IBD. Most medication clinical trials have largely been performed only on adults, and therefore much of the evidence given here is based on adult data. Only a few well-designed clinical trials have been performed in children, and most of those show similar efficacy to adult trials.

The authors have chosen to separate the Treatment section into Induction and Maintenance of remission. What follows is not meant to be an exhaustive review of current literature; rather a review some of the current data and a report on any additional data specific to children.

Corticosteroids

Crohn disease

Induction of remission Two recent Cochrane review articles examined budesonide and conventional corticosteroids (prednisone) as therapy for the induction of remission in CD. A majority of these were adult studies, although in some studies children older than 16 years were included. The reviews clearly show efficacy for induction of remission with both budesonide and conventional steroids, and show slightly less efficacy of budesonide compared with conventional steroids, at least in severe disease.^{17,18}

Maintenance of remission Corticosteroids, including both conventional steroids and budesonide, are not recommended for maintenance of remission. Any benefits in maintenance of remission are offset by treatment-related adverse events and thus these medications should be avoided for maintenance of remission, especially in children in whom corticosteroids can significantly affect growth.¹⁹

Ulcerative colitis

Induction of remission The use of corticosteroids for induction of remission in UC was first described in 1974,²⁰ and has been the mainstay for induction of remission in

moderate to severe UC. More recently, approximately 84% of adults with UC demonstrated a complete or partial improvement of disease activity with corticosteroids, and approximately 49% had prolonged response at 1 year.²¹ Budesonide, which has significant first-pass metabolism, is delivered to the distal ileum and proximal colon and thus likely has little efficacy in UC, although a randomized controlled trial has never been published.

Maintenance of remission As with CD, corticosteroids are not recommended for the maintenance of remission in UC as any benefits are more than offset by side effects, especially in growing children.

Summary

In practice, corticosteroids are often used in induction of remission in CD and UC but are often avoided if possible after induction, due to growth side effects and other morbidity associated with persistent corticosteroid usage. Studies have clearly shown that morbidity in CD is associated with corticosteroid use. Therefore, children with new diagnosis CD and UC are often started on corticosteroids with a taper over 2 months. Corticosteroids are avoided, if possible at all other times other than induction of remission.

Nutritional Therapy

Crohn disease

Induction of remission A recent Cochrane review compared nutritional therapy (liquid formula by mouth or via tube) to corticosteroid therapy for induction of remission. Although sole nutritional therapy has been shown to be effective in induction of remission in CD, it remains inferior to corticosteroids in induction of remission. In addition, the same review concluded that protein composition (ie, elemental or nonelemental protein) has no effect on efficacy of nutritional therapy.²² The only study that favors enteral nutrition over corticosteroids was a pediatric study.²³

However, practically speaking, the induction of remission with sole nutritional therapy remains difficult due to adherence in children. Most parents are reluctant to commit total enteral nutrition for their children for 6 to 8 weeks as required. In addition, few children are able to consume adequate formula volume by mouth, and thus would require insertion of nasogastric tubes or possibly a gastrostomy tube.

Maintenance of remission Only 2 randomized studies have been published regarding maintenance of remission in CD with nutrition in adults, and no studies have examined this in children. Takagi and colleagues²⁴ conducted a randomized controlled trial of 51 adults in remission, assigning one group a half-elemental diet and another group a regular diet with no instructions or limitations, with all patients taking mesalamine. The study demonstrated a significantly lower relapse rate in the half-elemental diet group (34.6% vs 64.0%). A recent Cochrane review suggested that there may be some efficacy in enteral nutrition for maintenance therapy, although larger studies are needed to confirm this possibility.²⁵

Ulcerative colitis

No studies have been reported for the induction or maintenance of remission with enteral therapy for UC.

Summary

Although both the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Japanese Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommend nutritional therapy as sole primary therapy for CD, it is often

a difficult treatment to initiate in the United States. The most significant deterrent continues to be the resistance by many parents and children to commit to 8 weeks of specialized formula alone (either by mouth or through a feeding tube such as a nasogastric tube) without taking any other food by mouth. Furthermore, it is unclear whether a child can be maintained on nutritional therapy alone and therefore, other maintenance medications need to be initiated. In addition, the short-term side effects with corticosteroid induction are debatably minimal.

5-Aminosalicylate

Crohn disease

Induction of remission No randomized controlled studies have been performed examining the induction of remission by aminosaliculates in pediatric CD. Hanauer and colleagues²⁶ published a meta-analysis examining aminosaliculates in active CD and showed a modest effect (if any) on improvement of Crohn Disease Activity Index (CDAI).

Although some pediatric gastroenterologists continue to use aminosaliculates for the induction of remission in CD, there are no good data to support the use for induction of remission, although there may be modest beneficial effects.

Maintenance of remission No randomized studies have been published for maintenance of remission in pediatric CD. A recent Cochrane review examined aminosaliculates in the maintenance of remission in CD. The results do not show any benefit of aminosaliculates compared with placebo.²⁷

Ulcerative colitis

Induction of remission A recent Cochrane review that includes only adult studies demonstrated a benefit from high-dose aminosaliculates (>3 g) in the induction of remission in UC, although remission rates remain significantly lower than in those using corticosteroids.²⁸

Most importantly in pediatric UC, a majority of patients present with moderate to severe disease, as demonstrated by the high percentage of pancolitis. Whereas aminosaliculates can be used for induction of remission, due to severity of disease in pediatric UC they are rarely used as sole induction, but rather in conjunction with corticosteroids for induction of remission.

Maintenance of remission As with many of the medications mentioned here, no randomized trials have been conducted in children examining the use of aminosaliculates in maintenance of remission in children. A Cochrane review has demonstrated efficacy of aminosaliculates in maintaining remission in UC compared with placebo.²⁹

Summary

There are no randomized controlled trials for the induction or maintenance of remission of aminosaliculates in pediatric IBD. Aminosaliculates are still often used in pediatric IBD. These agents are well tolerated in children, have few side effects, and thus have continued to be used by pediatric gastroenterologists despite the lack of evidence in CD and efficacy only in mild to moderate UC. Even though aminosaliculates are well tolerated, the most significant "side effect" is decreased quality of life due to the number of pills or capsules ingested each day, which often is considered in treatment of children with IBD.

However, it should be noted that aminosaliculates likely have most efficacy in colonic disease regardless of whether the diagnosis is CD or UC. Given the data demonstrating more colonic disease in children (up to 80%), the use of

aminosalicylates in colonic CD may be of some benefit, although there are no data examining this question. Whether aminosalicylates could be used as sole therapy in colonic CD has never been examined.

Based on the current data, the authors cannot support the usage of aminosalicylates in ileal CD, as there seem to be no compelling data to support their use. However, there are data to support the use of high-dose aminosalicylates in the management of UC, and there may be some efficacy in colonic CD, although there are no data for this possibility.

Immunomodulators (6-Mercaptopurine, Azathioprine, Methotrexate)

Crohn disease

Induction of remission Because of its delay in efficacy, 6-mercaptopurine (6-MP) and azathioprine (AZA) are not used for induction of remission; however, they are often used in conjunction with corticosteroids or other therapy used to induce remission with the knowledge that by the time corticosteroids are weaned, 6-MP and AZA will be effective in maintaining remission (**Table 7**).

A Cochrane review concluded efficacy for methotrexate in induction of remission in CD based on one study.³⁰ Methotrexate has demonstrated efficacy in inducing remission after failure of induction therapy with steroids in one large double-blind, placebo-controlled multicenter study (n = 141) when compared with placebo.³¹ Other smaller studies did not show a significant difference. In children, only retrospective studies have been conducted. One retrospective, multicenter study (n = 61) demonstrated improvement in disease or complete remission in 80% of children who were not responding to AZA.³² A second retrospective study (n = 60) demonstrated remission at 6 and 12 months in 42% of children placed on methotrexate after 6-MP/AZA failure.³³

Maintenance of remission 6-MP and AZA have demonstrated efficacy in maintaining remission in CD in multiple studies, and a recent Cochrane review confirms significant efficacy compared with placebo.³⁴

In children, one prospective multicenter, double-blind, placebo-controlled trial demonstrated induction of remission with prednisone and 6-MP, and maintenance of remission with 6-MP. Seventy-five children were randomized to prednisone and 6-MP or prednisone alone, with similar induction of remission rates (89%). At 548 days after remission, 91% of the 6-MP group continued to be in remission whereas

Table 7
Immunomodulators in pediatric IBD

			Induction of Remission	Maintenance of Remission
Markowitz et al ³⁵ n = 75	Prospective	Steroids Steroids + 6-MP	89% 89%	53% at 548 d 91% at 548 d
Uhlen et al ³² n = 61	Retrospective	MTX after failed 6-MP/AZA	39% at 3 mo	45% at 12 mo
Weiss et al ³⁶ n = 25	Retrospective	MTX after failed 6-MP/AZA	64%	60% at 12 mo
Turner et al ³³ n = 60	Retrospective	MTX after failed 6-MP/AZA	42% at 6 mo	42% at 6 mo

only 53% of the steroid only group remained in remission. Initiation of 6-MP at diagnosis also has a significant steroid-sparing effect.³⁵

Ulcerative colitis

Induction of remission Similar to CD, due to the slow onset of action of 6-MP and AZA these medications are rarely used as primary therapy for induction. No studies evaluating methotrexate in adults or children are available for the induction of remission. A recent Cochrane review concluded that there are no published reports to demonstrate efficacy of methotrexate in the induction of remission in UC.³⁷

Maintenance of remission No large studies have examined the use of 6-MP and AZA for the maintenance of remission in UC. A Cochrane review identified 4 studies that showed efficacy of 6-MP/AZA compared with placebo. Another Cochrane review concluded no efficacy in methotrexate in maintaining remission in UC.³⁸

In children, one retrospective study of 20 corticosteroid dependent or refractory patients revealed efficacy, with discontinuation of corticosteroids in 75% and 67% continuing to be steroid free at follow-up.³⁹

Summary

6-MP and AZA clearly show efficacy in maintaining remission in pediatric CD in a well-designed pediatric study. In addition, these medications have a significant steroid-sparing affect. Because of these data they are often initiated at diagnosis for the management of moderate to severe CD. 6-MP and AZA also have a role in the maintenance of remission in moderate to severe pediatric UC.

Methotrexate induced and maintained remission in one pediatric trial. Methotrexate is often used due to its quick action, unlike 6-MP and AZA that have slow onset of action. The most significant issue with methotrexate is its bioavailability, as oral medication may not be as efficacious as subcutaneous injections. Despite this, methotrexate is an excellent option when immediate action is necessary and when one wants to avoid biologics.

Biologics

Crohn disease

Induction and maintenance of remission A Cochrane review clearly shows efficacy for the use of infliximab in the induction and maintenance of remission in CD.^{40,41} In addition, there are multiple pediatric studies that demonstrate efficacy in induction of remission in children with CD. The first pediatric trial of infliximab in moderate to severe CD demonstrated clinical remission at 30 weeks in 60% of patients, and prolonged remission in 56% of patients at 54 weeks when continued on an every 8 week course.⁴² Although these results are significantly higher than the adult studies, it should be mentioned that 90% of patients in this study were on concomitant immunomodulators. Therefore, the results may be higher than seen in clinical practice. A recent study evaluated maintenance of remission in children receiving infliximab for more than 1 year, and demonstrated withdrawal of corticosteroids and clinically inactive disease in 30% to 40% of children who were maintained on infliximab.⁴³ A recent French study confirms the necessity of scheduled and not random infliximab doses in children.⁴⁴

Ulcerative colitis

Induction and maintenance of remission As with many of the other therapeutic agents for IBD, there are no randomized controlled trials of biologics in children with IBD. There are several retrospective studies that demonstrate efficacy in inducing and maintaining remission in children with moderate to severe UC. Data are available in adults with

moderate to severe UC, demonstrating efficacy of infliximab in inducing remission, promoting mucosal healing, and reducing the need for colectomy.⁴⁵

Summary

Biologics clearly demonstrate efficacy in inducing and maintaining remissions in pediatric IBD. Perhaps the more pressing debate is the proper use of biologics and the results of more long-term follow-up. Although it is clear that some children fail other treatments for IBD and require biologics, it is difficult to recommend biologics as first-line therapy given the paucity of long-term follow-up data. With no current “exit strategy,” biologic initiation requires treatment for an indefinite period of time.

Special Considerations in the Treatment of Inflammatory Bowel Disease in Children

Children with IBD require special consideration in their treatment, specifically regarding growth, hepatosplenic T-cell lymphoma, and goals of therapy.

Growth

In children, growth remains one of the most significant outcomes, as poor growth often can be the only “symptom” of disease. As discussed in the Presentation section, growth is poor prior to diagnosis, children with CD have delayed puberty and decreased final adult height, and many do not exhibit catch-up growth after diagnosis. Growth parameters are included in the Pediatric CDAI, as poor growth remains a clinical sign. Close attention to both height velocity and weight are necessary during the treatment of pediatric CD, as this may be the only clinical sign of persistent disease activity.

No specific treatment paradigms have been shown to be superior in improving growth. Biologics and surgical resection have been shown to improve growth; however, these may not be superior to immunomodulators.⁴⁶ No other treatments such as growth hormone have shown superiority. Regarding growth, treatment should thus focus on controlling disease activity and providing sufficient calories, which may require supplementation with high-calorie formula.

Hepatosplenic T-cell lymphoma

Although overall increased risk of lymphoma has been reported in patients with IBD who have been exposed to biologic or immunomodulator therapy, a rare fatal form of lymphoma, hepatosplenic T-cell lymphoma (HSTCL), is now linked only in children and young adults with IBD. Cases of HSTCL have been reported with both combination therapy with 6-MP/AZA and monotherapy with 6-MP/AZA, but not with infliximab monotherapy alone. There are now approximately 18 cases of HSTCL with individuals on both 6-MP/AZA and infliximab. These cases reveal preponderance for young male patients, although the mechanism of this observation is unknown. Due to this potential risk of this fatal disease, the treatment of pediatric IBD does not currently include combination therapy with biologics and immunomodulators. However, with recent data from the SONIC trial showing superior efficacy of combination immunomodulator and biologic therapy compared with either therapy alone, there is considerable debate regarding combination therapy, at least in young females.

Goals of therapy

Growth and clinical remission remain the most important goals of therapy. Clinical remission may be best defined by the appropriate activity index. A Pediatric Crohn Disease Activity Index (PCDAI)⁴⁷ and a Pediatric Ulcerative Colitis Activity Index (PUCAI)⁴⁸ have been developed and validated, and are currently in use both clinically

and for research purposes. These indices are similar to adult indices, with some specific differences. In children, the PCDAI includes growth measures in addition to symptoms, physical examination, and laboratory measures. The PUCAI was more recently developed and is completely symptom based, as growth abnormalities are less likely to be observed in pediatric UC. Endoscopic healing remains a debated topic, although repeated endoscopy is not recommended in children.

Treatment Conclusions

Crohn disease

The treatment paradigm for CD remains similar to adult treatment of IBD. Prednisone remains the most effective medication for induction of remission and is often used as a short course for induction only purposes, then avoided due to growth side effects. Although nutritional therapy has proven to be effective in inducing remission, no well-performed studies have shown efficacy in maintaining remission, and sole nutritional therapy remains an option for induction of remission for those willing to commit to this treatment. Research demonstrates a minimal (if any) benefit for aminosalicylates in the induction of remission in CD, and no benefit in the maintenance of remission. However, more children with CD have colonic disease and therefore aminosalicylates may be of some benefit, given their proven efficacy in UC. Due to the high frequency of moderate to severe CD disease in children, immunomodulators are frequently used at or shortly after diagnosis. Markowitz and colleagues demonstrated a steroid-sparing effect and maintenance of remission in children treated with immunomodulators, and a short course of prednisone at diagnosis. Biologics remain an option although given the high efficacy of immunomodulators, biologics are most often reserved for children who fail immunomodulator therapy. At this time, biologics cannot be recommended as first-line therapy. However, continued research may predict those children with more severe disease, and at that point biologics may be suggested as first-line therapy for those with severe disease.

Ulcerative colitis

Ulcerative colitis treatment continues to be similar for children and adults, although research has demonstrated more pancolitis and shorter time to surgery in pediatric UC, perhaps supporting more aggressive treatment for children with UC. Prednisone remains the most effective induction of remission therapy, but is only recommended at diagnosis with a short course due to growth effects. Aminosalicylates show efficacy in induction and maintenance of remission, but are reserved as sole treatment only in the mildest cases of pediatric UC. Immunomodulators are often necessary in pediatric UC due to its moderate to severe presentation in children, and are effective in maintaining remission. Biologics are effective in inducing and maintaining remission in pediatric UC but are reserved at this time primarily for immunomodulator failures.

The Future of IBD Treatment in Children

Perhaps the most pressing issue in the treatment of IBD in children is the identification of a more severe phenotype that would respond best to biologics at diagnosis and thus prevent the need for surgical therapy. Over the next decade, determining which patients are at most risk for surgery and other complications may reveal a tool to predict disease severity and potentially prove that these individuals fare better with top-down therapy. However, at this time it is difficult to argue the top-down approach, given the unknown effects of biologic therapy used for decades in children diagnosed at an early age.

SUMMARY

While this question about differing age of onset among the chronic complex inflammatory disorders such as IBD encourages debate, a fundamental issue in IBD remains unanswered. Does pediatric IBD represent the same disease process occurring in adults but merely at an earlier age (ie, age of onset is a random event), or does pediatric IBD display different pathogenesis (hence different natural history) but simply with the same clinical presentation as adults? An argument can be made suggesting a different spectrum of the same disease or different pathogenesis that leads to similar disease phenotypes.

Although no hard scientific evidence exists regarding differing etiology, pediatric-onset IBD does “differ” from adult IBD in many aspects.⁴⁹ As highlighted in this article, there is growing evidence from clinical observations as well as epidemiologic and natural history studies that pediatric-onset IBD represents a distinct disease with differences in disease type, disease location, disease behavior, gender preponderance, and genetically attributable risk compared with its adult counterpart.⁵⁰ These differences need to be further explored, as they may someday hold the key to understanding the pathogenesis of IBD.

More specifically, children are more likely to be diagnosed with CD versus UC, and there is a predilection for males in pediatric CD but not pediatric UC. In addition, pediatric CD more often presents with ileocolonic disease and inflammatory phenotype, which progresses in some to structuring and fistulizing phenotype, although predicting this progression is difficult. Pediatric UC presents with more pancolitis and may be more severe, as suggested by an earlier time to first surgery.

Very early onset IBD (age <5–8 years) also exhibits a male preponderance and presents with colonic disease more often than when diagnosed in later childhood or adulthood. It remains unclear whether very early onset IBD has different genetic variations or other differences in pathogenesis.

Treatment paradigms are similar in adult and pediatric IBD, with only a few prospective trials available in pediatrics, but all with similar results to adult trials. Outcome remains the most significant driver of treatment options, and in children disease activity, and specifically growth, are important outcome measures. There are some important risks that seem to affect children more than adults including HSTCL, which has a predilection for younger males. These factors affect treatment paradigms, and further study is necessary to determine the precise risk (if any) for and to better understand the pathology of this serious lymphoma.

Overall, pediatric IBD may hold the key to understanding the pathogenesis of IBD, with the hopes of leading to prevention. As expected, highlighting the differences and similarities between pediatric and adult IBD has generated more questions than answers. It is important that these specific differences are further explored through high-quality research in the search for the cause and cure of IBD.

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