pISSN: 2234-8646 eISSN: 2234-8840
https://doi.org/10.5223/pghn.2019.22.1.50
Pediatr Gastroenterol Hepatol Nutr 2019 January 22(1):50-56

Review Article

PGHN

Clinical Aspects and Treatments for Pediatric Inflammatory Bowel Diseases

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The incidence of pediatric inflammatory bowel disease (IBD) is increasing worldwide, especially in the developing countries. It differs from adult disease in clinical manifestations, especially with regard to genetic predisposition in monogenic IBD. Pediatric disease also have a tendency to show more aggressive inflammation and greater extent of lesion. Newer drugs such as anti-tumor necrosis factor α have been known to make a difference in treating pediatric IBD. Recent studies suggested that the patients with high risk factors might have some benefits from earlier use of biologics. To achieve treatment goals such as relieving symptoms, optimizing growth, and improving quality of life while minimizing drug toxicity, more research is needed to develop tools for risk stratification in the use of biologics for pediatric IBD.

Key Words: Pediatrics, Inflammatory bowel diseases, Crohn disease, Ulcerative colitis, Anti-tumor necrosis factor-α blockers

INTRODUCTION

Pediatric inflammatory bowel disease (IBD) is a growing concern in pediatric health care. Nearly a quarter of all patients with IBD develop the disease during childhood [1]. In recent decades, the incidence and prevalence of pediatric IBD have increased and the highest incidence has been reported from Canada, Norway, Sweden, Finland, the United Kingdom, and Ireland [2]. The incidence and prevalence of pediatric IBD in Singapore showed a 10-fold rise from 0.23 to 2.28 per 100,000 in the past 20 years, even though previously published data on the incidence of IBD in Asia showed differences among countries [3,4]. In Korea, recently published local data showed a rapidly rising trend in the incidence between 2011 and 2016; the incidence for all pediatric IBD increased from 0.86 to 3.33 per 100,000, with an increase from 0.67 to 2.78 for Crohn disease (CD) and from 0.19 to 0.56 for ulcerative colitis (UC) [5].

Received : November 24, 2018, Revised : November 27, 2018, Accepted : November 28, 2018

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This article has been published simultaneously in *Pediatric Gastroenterology, Hepatology & Nutrition* and *Intestinal Research* by the permission of editor-in-chief of two journals.

After the introduction of anti-tumor necrosis factor α blockers for use in IBD, pediatric IBD showed dramatically improved outcomes, similar to those in adults. However, it is still difficult for physicians to understand the current strategy for treatment of pediatric IBD, because of the lack of information and experience. In this article, clinical aspects and treatment of pediatric IBD will be discussed in the context of biologics.

CHARACTERISTICS OF PEDIATRIC IBD

More aggressive disease course than in adults

Childhood-onset IBD seems to be a more aggressive and rapidly progressive disease compared to adult-onset IBD [6,7]. CD is more prevalent than UC in children. The ratio of boys to girls is as high as 1.8:1. The most common type of disease distribution is pan-enteric or pan-colic. These cases were more often treated with systemic steroids and azathioprine and had a higher frequency of steroid dependence. The patients showed a more severe disease course compared to that in adults with IBD. These patients were more likely to have upper gastrointestinal involvement, extraintestinal manifestations, and stricturing and penetrating disease. Among pediatric IBD patients, 44% required surgery at some point, with a 34% risk within the first 5 years after diagnosis [7-10]. In CD, no differences were found when comparing corticosteroid responsiveness between pediatric and adult patients; however, the inflammatory phenotype is more common than the stricturing or penetrating phenotype in childhood [11,12].

Strong genetic influences

Among patients with IBD onset at a young age, 29% have one or more family members with IBD. The subgroup of children younger than 3 years of age with UC had the highest prevalence of first-degree relatives with IBD (44%) [13]. Several genetic defects that disturb intestinal epithelial barrier function or affect innate and adaptive immune function have incomplete penetrance of the IBD-like phenotype [14]. Monogenic defects, especially those affecting the interleukin-10 (IL-10) signaling pathway, result in severe or intractable disease [15]. Patients with IL-10 pathway defects often show initial presentation before 1 year of age. Intractable per-

Table 1. Montreal and Paris Classification of Crohn Disease

Characteristics	Montreal	Paris
Age at diagnosis (y)	A1: <17	A1a: 0 to <10
	A2: 17-40	A1b: 10 to <17
	A3: >40	A2: 17-40
		A3: >40
Location	L1: Terminal ileal±limited cecal disease	L1: Distal 1/3 ileal±limited cecal disease
	L2: Colonic	L2: Colonic
	L3: Ileocolonic	L3: Ileocolonic
	L4: Isolated upper disease	L4a: Upper disease proximal to Ligament of Treitz
		L4b: Upper disease distal to Ligament of Treitz and proximal to distal 1/3 ileum
Behavior	B1: Non-stricturing non-penetrating	B1: Non-stricturing non-penetrating
	B2: Stricturing	B2: Stricturing
	B3: Penetrating	B3: Penetrating
	p: Perianal disease modifier	B2B3: Both penetrating and stricturing disease either at the same or different times
		p: Perianal disease modifier
Growth	Not available	G0: No evidence of growth delay
		G1: Growth delay

Modified from Levin A et al. Inflamm Bowel Dis 2011;17:1314-1321 [21].

ianal fistula is a cardinal manifestation and diarrhea with bloody stools is also common with this defect [16,17]. There is no specific treatment for IL-10 pathway defects, except for hematopoietic stem cell transplantation [18,19].

Paris classification for very-early-onset and monogenic IBD

Very-early-onset IBD (VEOIBD) is usually defined when IBD occurs in children less than 6 years of age. A child less than 2 years of age can be classified as having infantile IBD [20]. However, in the Paris classification, which is a modified pediatric version of the Montreal classification and is frequently cited in textbooks, pediatric onset IBD is only classified as A1a and A1b, which occur at less than 10 years of age or between age 10 and 17 years, respectively (Table 1) [21]. Recent advances in translational research and next generation sequencing or whole exome sequencing have made it possible to change the diag-

Table 2. Pediatric Crohn's Disease Activity Index

Category	Parameter	Detailed description	Point
History (recall, 1 wk)	Abdominal pain	None	0
		Mild (brief, does not interfere with activities)	5
		Mod/severe (daily, longer lasting, affects activities, nocturnal)	10
	Stools (per day)	0-1 liquid stools, no blood	0
		Up to 2 semi-formed with small blood, or 2-5 liquid	5
		Gross bleeding, or ≥6 liquid, or nocturnal diarrhea	10
Patient functioning, general well-being (recall, 1 wk)	No limitation of activities		0
	Occasional difficulty in maintaining age appropriate activities		5
	Frequent limitation of activity, very poor		10
Laboratory	Hematocrit (%) (use age-specific reference)	Normal	0
		Mild decrease	2.5
		Mod/severe decrease	5
	Erythrocyte sedimentation rate (mm/h)	<20	0
		20-50	2.5
		>50	5
	Albumin (g/dL)	≥3.5	0
		3.1-3.4	5
		≤3.0	10
Examination	Weight	Weight gain or voluntary weight stable/loss	0
		Involuntary weight stable, weight loss 1%-9%	5
		Weight loss ≥10%	10
	Height at diagnosis	<1 channel decrease	0
		≥1, <2 channel decrease	5
		≥2 channel decrease	10
	Height follow-up	Height velocity ≥−1 SD	0
		Height velocity <−1 SD, >−2 SD	5
		Height velocity ≤−2 SD	10
	Abdomen	No tenderness, no mass	0
		Tenderness, or mass without tenderness	5
		Tenderness, involuntary guarding, definite mass	10
	Perirectal disease	None, asymptomatic tags	0
		1-2 Indolent fistula, scant drainage, no tenderness	5
		Active fistula, drainage, tenderness, or abscess	10
	Extraintestinal manifestations (n)	0	0
		1	5
		≥2	10

nosis and treatment in VEOIBD. A gene panel or gene chip showed promising results in the diagnosis of VEOIBD [14]. The Clinical course of monogenic IBD, which is a subgroup of VEOIBD, is more severe than adolescent onset disease. The initial Pediatric Crohn's Disease Activity Index (PCDAI) and Pediatric Ulcerative Colitis Activity Index (PUCAI) scores, the annual incidence of surgery, and the number of hospitalization per year were higher in the monogenic IBD group than that in other IBD groups [22]. There is no specific treatment for VEOIBD; however, a few reports showed that hematopoietic stem cell transplantation showed effectiveness in IL-10 receptor deficiency and *XIAP* mutations. VEOIBD could be useful in identifying the pathophysiology of IBD, because pediatric cases have a relatively stronger genetic background and less exposure to environmental and behavioral influences than adults [23,24]. As recent advances in VEOIBD make this category important in pediatric IBD, the Paris classification alone is unable to categorize all patient groups.

Treat to target

The traditional treatment strategy based on clinical symptom improvement does not improve long-term outcomes in CD and patients cannot avoid bowel damage. Therefore, the "treat to target" concept was introduced to incorporate use of biological markers and mucosal healing into IBD treatment [25]. This new method was adopted from the experience with rheumatic diseases, and can be tentatively regarded as an active approach to the severe disease group [26]. However, there are insufficient data with regard to optimal indications, biomarkers, and treatment strategies, especially in children. Early introduction of biologics in patients with poor prognostic factors, such as deep colonic ulcerations, extensive disease, marked growth retardation, severe osteoporosis, B2 and/or B3 behavior, and severe perianal disease, can be recommended to reduce bowel damage [27].

Scoring system

Endoscopic evaluation is the gold standard for diagnosis of CD in children. However, esophagogastroduodenoscopy and colonoscopy are more difficult and dangerous in children. To overcome the gap between the need to frequently evaluate disease severity and the difficulty of performing endoscopy in children, the PCDAI and PUCAI have been developed [28,29]. The PCDAI includes growth in children as an important parameter. These scoring systems are often used to determine treatment parameters in many clinical settings and investigational trials, as well as for insurance reimbursement (Tables 2 and 3).

TREATMENT STRATEGY

The aims of therapy in pediatric IBD traditionally have been to relieve symptoms, optimize growth, and improve quality of life while minimizing drug toxicity [27]. To ensure growth in pediatric patients with CD, aggressive control of inflammation is

Table 3. Pediatric Ulcerative Colitis Activity Index

Item	Point
1. Abdominal pain	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
2. Rectal bleeding	
None	0
Small amount only, in <50% of stools	10
Small amount with most stools	20
Large amount (>50% of stools)	30
3. Consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
4. Number of stools per 24 hours	
0-2	0
3-5	5
6-8	10
>8	15
5. Nocturnal stools (any episode causing awakening)	
No	0
Yes	10
6. Activity level	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10

Sum of Pediatric Ulcerative Colitis Activity Index (0-85).

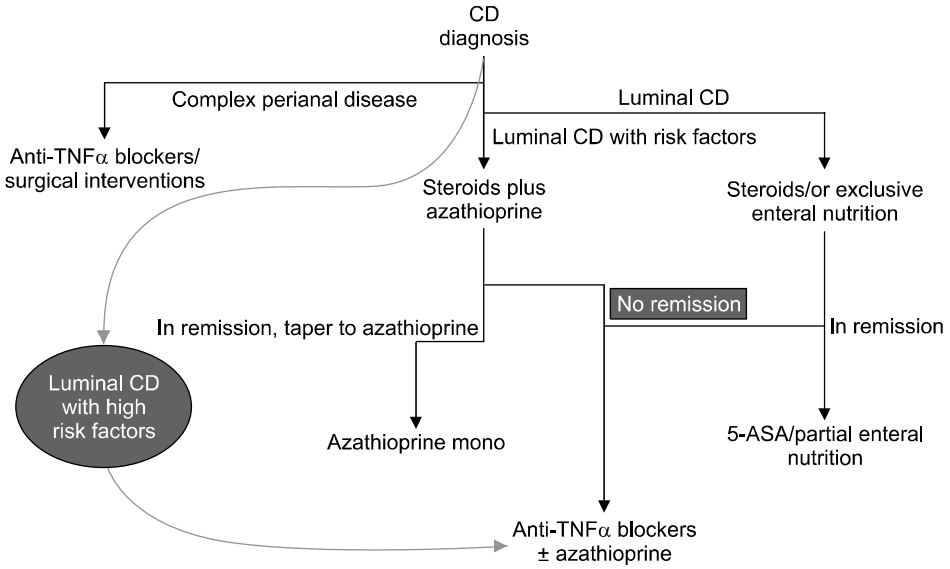

Fig. 1. Simplified treatment algorithm for pediatric CD according to risk factors. Dashed line indicates early use of biologics, that is, the "top down" strategy. High-risk factors in children for luminal CD are deep colonic ulcerations, extensive disease, marked growth retardation, severe osteoporosis, B2 and/or B3 behavior, and severe perianal disease [27]. Generally accepted risk factors are a history of more than 2 steroid courses, steroid dependence, hospitalization, chronic (>12 months) symptoms, need for immunosuppressants or need for surgery, terminal ileal location, stricturing and penetrating behavior, smoking, positive serologic markers such as Anti-*Saccharomyces cerevisiae* antibody/perinuclear antineutrophil cytoplasmic antibodies, positive genetic markers such as *NOD2/IBD5*, and elevated C-reactive protein [30]. CD: crohn disease, TNF: tumor necrosis factor, ASA: aminosalicylic acid.

essential. A recent consensus about the achievement of mucosal healing, especially in patients with poor prognostic factors, could not be fully supported because of the lack of evidence. It is difficult to identify patients with definite risk in order to initiate early aggressive immunotherapy and to define the necessary degree of mucosal healing and depth of transmural healing [27]. Current recommended strategy in pediatric CD is based on escalating medical therapy, beginning with nutritional intervention and/or steroids to achieve targets [30]. Overall, no differences in drug response were found when comparing pediatric and adult CD patients; therefore, current treatment options based on steroid responsiveness can be the same in adults and children. However, it is very important to avoid steroids in children as much as possible (Fig. 1) [27,30].

Nutritional intervention in pediatric patients is essential to control the disease, especially in CD. Exclusive Enteral Nutrition is recommended as first-line therapy to induce remission in children with active luminal CD. However, there is no evidence for the use of nutritional intervention in fistulizing CD or pediatric UC. The possibility of the development of colon cancer in pediatric IBD should be kept in mind. Even though pediatric colon cancer is very rare, children with VEOIBD can develop colon cancer at an earlier age than expected. In our institution, we reported a patient with VEOIBD and sigmoid colon cancer a few years ago [31].

TRANSITION TO ADULT CLINICAL CARE

The transition from pediatric to adult clinical care in IBD has been problematic. Transition requires careful coordination and collaboration among key persons in a multidisciplinary team, including the patient as well as the parents/caregivers and providers. Adult gastroenterologists who participate in the care of young adults should develop competence in key areas of adolescent and young adult care and should make an effort to collaborate with the pediatrician.

Providing adequate care for transitioning patients includes education for the development of self-management skills and developmental processes relevant to young adults with IBD [32]. Recent models suggested by European groups should be reviewed by Korean academic societies, and further prospective research is needed [33,34].

CONCLUSION

The incidence of pediatric IBD is increasing worldwide, especially in the developing countries. It differs from adult disease in clinical manifestations, especially with regard to genetic predisposition in monogenic IBD. To achieve treatment goals of relieving symptoms, optimizing growth, and improving quality of life while minimizing drug toxicity, more research is needed to develop tools for risk stratification in pediatric IBD.

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