

## Long-Term Follow-Up of Pediatric Patients with Crohn's Disease Involving Proximal Small Bowel

Facanali Jr MR\*, Facanali CBG, Sobrado Jr CW, Oba J and Safatle-Ribeiro AV

Department of Gastroenterology of the Hospital das Clinical Hospital, University of Sao Paulo Medical School, Brazil

### \*Corresponding author:

Marcio Roberto Facanali Junior,  
Department of Gastroenterology of the Hospital das  
Clinical Hospital, University of Sao Paulo Medical  
School, Brazil

Received: 18 Sep 2023

Accepted: 24 Oct 2023

Published: 30 Oct 2023

J Short Name: JJGH

### Copyright:

©2023 Facanali Jr MR, This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and build upon your work non-commercially.

### Citation:

Facanali Jr MR. Long-Term Follow-Up of Pediatric Patients with Crohn's Disease Involving Proximal Small Bowel. J Gastro Hepato. 2023; V10(4): 1-7

### Keywords:

Crohn's disease; Inflammatory bowel disease; Small intestine; Pediatrics; Double-balloon enteroscopy

## 1. Abstract

**1.1. Background:** Approximately 25% of inflammatory bowel diseases are diagnosed in childhood, which may have unfavorable repercussions over time, associated with the possibility of a worse prognosis when the proximal small bowel is involved. Thus, a better understanding of the course of this pathology in the pediatric population is necessary. The aim of this study is to describe the clinical and endoscopic activity of pediatric patients with Crohn's disease with involvement of the proximal small intestine in two periods, with an interval of 10 years between them.

**1.2. Methods:** A prospective cohort study was performed in pediatric patients with Crohn's disease and involvement of the proximal small bowel confirmed by double-balloon enteroscopy. These patients were evaluated clinically and endoscopically, both at the time of enteroscopy and after 10 years of follow-up.

**1.3. Results:** 20 pediatric patients diagnosed with Crohn's disease and proximal small bowel involvement were evaluated. The mean age was 11 years with the majority being male. There was a statistically significant improvement in the global indices of inflammatory and endoscopic activity after 10 years of follow-up, however, when analyzing patients with early or very early onset of the disease, clinical and especially endoscopic remission were not achieved in most of these patients, being that 4 progressed to surgery.

**1.4. Conclusion:** There was clinical and endoscopic improvement of patients over 10 years, nonetheless, in patients diagnosed before 10 years old, there was worse evolution and difficulty in achieving deep remission despite biological therapy, suggesting a distinct phenotype, with more aggressive disease.

## 2. Introduction

Crohn's disease, first described in 1932 [1] is a progressive chronic disease that can affect all segments of the gastrointestinal tract and, may also, progress to complications such as fistulas, abscesses, and strictures [2]. In children, there is also the possibility of impaired linear growth, malnutrition, decreased bone mineral density and delayed puberty [3-6].

Up to 30% of individuals with inflammatory bowel disease will have their first symptoms before age 18 years [7]. with studies showing an increasing incidence of Crohn's disease in this specific group of patients in several European countries [7-9].

Regarding the most affected segment, the ileocecal region accounts for 50% of cases, with the proximal small bowel accounting for only 5 to 15% of all cases [10,11]. However, there are few studies involving patients with Crohn's disease and involvement of the proximal small bowel, among them, Flamant et al., [12], in a retrospective series with 108 patients with Crohn's disease evaluated by capsule endoscopy, revealed that more than 50% of those with terminal ileum disease also had lesions in proximal small bowel. In another aspect, Kim et al., [13], in a Korean cohort with 1403 patients, hypothesized a higher prevalence of jejunal disease in specific populations, evidencing a higher prevalence in Orientals when compared to Western populations. Furthermore, Fong et al. reported a significant increase in surgeries and hospitalizations in these patients with proximal small bowel involvement, suggesting a worse long-term prognosis [14].

Also considering the evidence described by Uhling et al, [15], that patients diagnosed under the age of 10 years are likely to develop more severe conditions and higher rates of complications, in addi-

tion to the fact that approximately 25% of all inflammatory bowel diseases diagnosed occur in pediatric age, associated with the lack of studies involving pediatric patients with Crohn's disease involving the proximal small bowel, the aim of this study was to describe the clinical and endoscopic activity in pediatric patients with Crohn's disease with involvement of the proximal small bowel, in two periods, with an interval of 10 years between them.

### 3. Methods

#### 3.1. Study Design

It was performed a single-center descriptive prospective cohort study in patients diagnosed with Crohn's disease with involvement of the proximal small bowel followed up at a specialized pediatric center.

#### 3.2. Population and Procedures

For 10 years, a group of pediatric patients with an established diagnosis of Crohn's disease and suspected involvement of the proximal

small bowel on contrast-enhanced intestinal transit radiography were consecutively selected.

Initially, they underwent double-balloon enteroscopy by a single endoscopist. Sedation was performed by the anesthesiology team, where general anesthesia was determined for patients under 12 years of age and deep sedation with propofol for patients aged 13 years and over. Enteroscopy findings were classified as "normal" when no endoscopic changes were found; as "mild" when enanthema and edema are found; and "intense" when lesions are found such as ulcers or erosions or inflammatory strictures, which can be passed to the enteroscopy or not, and as "remission" when scars are found and absence of enanthema and ulcerations.

The present project evaluated patients undergoing double-balloon enteroscopy 10 years ago and described the clinical and endoscopic findings at two times: when enteroscopy was performed and after 10 years (Figure 1).

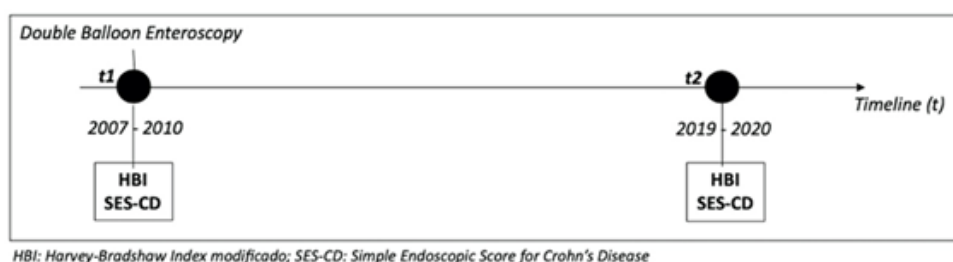


Figure 1: Study Design

#### 3.3. Clinical Assessment

Patients were clinically evaluated for disease activity using the modified Harvey-Bradshaw Index (HBI), which consists of the evaluation of five items: patient well-being, abdominal pain, number of liquid or soft stools per day, abdominal mass and presence of complications. Scores with indices lower than 5 are observed in patients who are in remission, between 5 and 7 in patients with mild clinical activity, between 8 and 16 in patients with moderate activity, and indices greater than 16 in patients with intense clinical activity [16].

#### 3.4. Endoscopic Assessment

Simple Endoscopic Score for Crohn's Disease (SES-CD) was performed for endoscopic evaluation, where the parameters evaluated are ulcer size, affected and ulcerated surfaces, and strictures, which receive a score of 0 to 3 in each segment evaluated. The following segments are scored and evaluated: ileum, right colon, transverse colon, left colon and rectum. For scores from 0 to 2, endoscopic remission is considered, between 3 and 6 mild endoscopic activity, between 7 and 15 moderate endoscopic activity, and indices greater than 15 are considered intense endoscopic activity [17].

#### 3.5. Statistical Analysis

Qualitative characteristics of patients were described using absolute and relative frequencies and quantitative characteristics using summary measures (mean, standard deviation, median, minimum and maximum). Treatment types, clinical and endoscopic scores were described at baseline and at 10 years and compared between time points

using the paired Wilcoxon test.

The associations of the characteristics of interest with clinical and endoscopic remission after 10 years were evaluated using Fisher's exact tests or likelihood ratio tests.

The analyzes were performed using the IBM-SPSS for Windows version 22.0 software and the bar graphs were constructed and the results were tabulated using the Microsoft-Excel 2010 software. The tests were performed with a significance level of 5%.

#### 3.6. Ethical Approval

This study was approved by the ethics committee for analysis of research projects and registered on Plataforma Brasil under certificate number 35880720.3.0000.0068. All participants were informed about the research objectives and attested to their agreement by signing an informed consent form.

### 4. Results

In 2010, 20 pediatric patients diagnosed with Crohn's disease underwent Double-Balloon Enteroscopy and, after 10 years of follow-up, 3 patients changed their diagnosis as shown in Figure 2: patient 1 changed the diagnosis to monogenic disease, mutation of the Interleukin 10 / interleukin 10 receptor; patient 19 changed the diagnosis to juvenile idiopathic arthritis; patient 20 changed the diagnosis to ulcerative colitis. 7/17 had concomitant disease in the proximal small bowel with ileocolon involvement, 7/17 had colon involvement, 1/17 had terminal ileum involvement, and 2/17 had no ileocolon

disease.

The mean age of patients at baseline was 11 years (ranging from 3 to 20), with the majority being male (64.7%), with the inflammatory phenotype being the most prevalent (52.9%), followed by stenosing and fistulizing, each accounting for 23.5% of patients. At the beginning of the study, 35.3% of the patients had perianal involvement.

Of the 17 patients, 4 had ulcers in the proximal small intestine, 3 had enanthema and edema, and 10 patients had areas of scar retraction on BDE (Figures 3).

There was an improvement in Crohn's disease activity global index, with a statistically significant difference in clinical (Figure 4) and endoscopic (Figure 5) scores, when compared at baseline and after 10 years of follow-up (Tables 1 and 2).

Patients with active Crohn's disease in the proximal small bowel, visualized by double-balloon enteroscopy at baseline, had a lower frequency of clinical remission after 10 years, while the non-inflamma-

tory phenotype and perianal involvement had a lower frequency of endoscopic remission.

At baseline, 58% of patients were using immunosuppressants and, after 10 years, approximately 50% of patients are using biologics, either as monotherapy or in combination with immunosuppressants. Four patients (4/17) underwent intestinal resection, 2 with terminal ileostomy, one with ileotransverse anastomosis and one with ileorectal anastomosis.

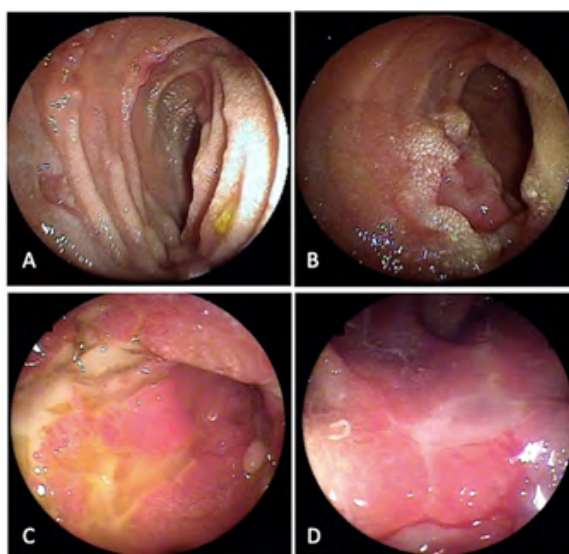
Of the 17 patients, one had primary sclerosing cholangitis (PSC) during follow-up and two others had intermittent and persistent joint pain. The same PSC patient had acute lymphoblastic leukemia that was treated with chemotherapy.

Sixteen patients underwent magnetic resonance enterography or computed tomography after 10 years of follow-up and only one patient showed signs of activity in the proximal small bowel.

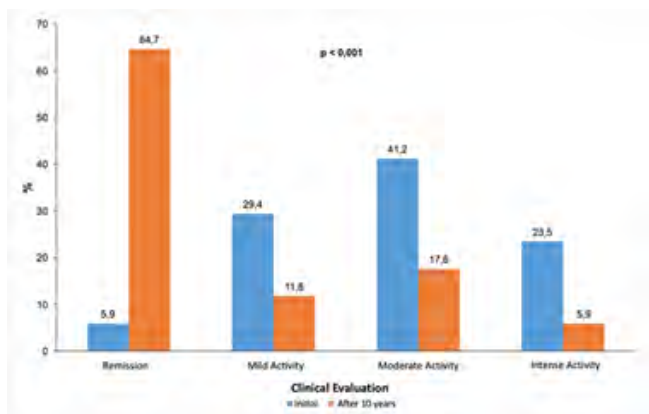
PATIENT	CLASSIFICATION ACCORDING TO AGE	PROXIMAL SMALL BOWEL ENTEROSCOPY (2010)	ILEOCOLON DISEASE ASSOCIATED
1 *	Infantile-Onset (< 2 yo)	MILD ACTIVITY	COLON
2	Infantile-Onset (< 2 yo)	REMISSION	COLON
3	Very-Early-Onset (< 6 yo)	MILD ACTIVITY	COLON
4	Very-Early-Onset (< 6 yo)	REMISSION	COLON
5	Very-Early-Onset (< 6 yo)	INTENSE ACTIVITY	COLON
6	Very-Early-Onset (< 6 yo)	REMISSION	TERMINAL ILEUM AND COLON
7	Very-Early-Onset (< 6 yo)	REMISSION	TERMINAL ILEUM AND COLON
8	Early-Onset (< 10 yo)	MILD ACTIVITY	COLON
9	Early-Onset (< 10 yo)	INTENSE ACTIVITY	TERMINAL ILEUM AND COLON
10	Early-Onset (< 10 yo)	REMISSION	TERMINAL ILEUM AND COLON
11	Pediatric-Onset (< 17 yo)	INTENSE ACTIVITY	NO
12	Pediatric-Onset (< 17 yo)	INTENSE ACTIVITY	NO
13	Pediatric-Onset (< 17 yo)	REMISSION	TERMINAL ILEUM
14	Pediatric-Onset (< 17 yo)	REMISSION	TERMINAL ILEUM AND COLON
15	Pediatric-Onset (< 17 yo)	REMISSION	COLON
16	Pediatric-Onset (< 17 yo)	REMISSION	COLON
17	Pediatric-Onset (< 17 yo)	REMISSION	TERMINAL ILEUM AND COLON
18	Pediatric-Onset (< 17 yo)	MILD ACTIVITY	TERMINAL ILEUM AND COLON
19 *	Pediatric-Onset (< 17 yo)	REMISSION	TERMINAL ILEUM
20 *	Pediatric-Onset (< 17 yo)	NORMAL	COLON

\* Changed the diagnosis

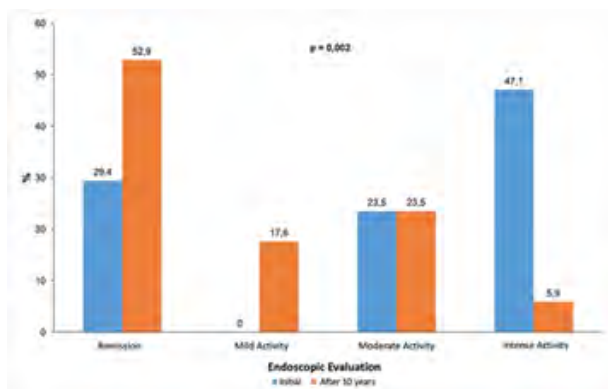
**Figure 2:** Classification according to age, enteroscopy findings and ileocolon involvement.



**Figure 3:** Double balloon enteroscopy showing ulcers in the jejunum (Patient 11). A. Shallow, oval, bare ulcers throughout the proximal jejunum. B. Deep jejunal ulcer with raised, whitish margins. C and D showing deep, serpiginous, confluent ulcers covered by thick fibrin (Patient 12).



**Figure 4:** Description of the clinical score classifications (modified Harvey Bradshaw Index) at the moments of evaluation and results of the comparative test.



**Figure 5:** Description of the endoscopic score classifications (SES-CD) at the moments of evaluation and results of the comparative test.

**Table 1:** Harvey Bradshaw Index initial and after 10 years by age at diagnosis.

	Patients n = 17			
	HBI initial		HBI after 10 years	
	Remission	Activity	Remission	Activity
<b>Infantile</b>	1	0	1	0
<b>Very Early</b>	0	5	4	1
<b>Early</b>	0	3	0	3
<b>Pediatric</b>	0	8	6	2
<b>TOTAL</b>	1	16	11	6

**Table 2:** Endoscopic activity by SES-CD, initial and after 10 years by age at diagnosis.

	Patients n = 17			
	SES-CD initial		SES-CD after 10 years	
	Remission	Activity	Remission	Activity
<b>Infantile</b>	0	1	1	0
<b>Very Early</b>	1	4	1	4
<b>Early</b>	0	3	0	3
<b>Pediatric</b>	4	4	7	1
<b>TOTAL</b>	5	12	9	8

## 5. Discussion

This is the first long-term prospective cohort study in pediatric-onset Crohn's Disease (CD) involving the proximal small bowel. The most common phenotype of CD is ileocecal, affecting about 50% of cases, as previously described [10]. Nevertheless, in this series, it was observed when CD was present in the proximal small bowel, 80% of them had ileocolonic or colonic involvement and only 20% of these patients had isolated concomitant disease of the terminal ileum or absence of ileocolonic disease, showing a divergence from the findings of Flamant et al., [12], who reported in their sample weak association between colon CD concomitant with proximal small bowel CD. A possible hypothesis for such divergence could be that the population base of Flamant et al. was adult individuals and early-onset CD may present with distinct phenotypes at onset ages above 10 years. If, in this study, the concomitance of disease involving the ileum and colon is evaluated by age group according to the phenotype proposed by the Paris classification [18], in the pediatric group, A1b (individuals between 10 and 17 years), more than 50% have ileal disease associated with proximal small bowel CD, and only 25% with concomitant colon involvement, numbers closer to the Flamant et al. findings.

In this study, 3/20 changed the diagnosis during follow-up, representing 15% of the sample. In spite of that, it has already been reported in other studies, such as the one by Aloï et al., [19], which showed a change in diagnosis of around 2% over the course of 40 months of follow-up in their sample, but when specific ages were analyzed, it was observed that an even higher rate, 40% of diagnostic change throughout the study.

In one of the patients diagnosed with CD before 2 years of age, there was a change in the diagnosis to monogenic disease, in agreement with what Uhling et al., [15], where individuals diagnosed with CD at ages younger than 6 years of age and, mainly, younger than 2 years of age, called infantile-onset inflammatory bowel disease (IBD), have a high chance of monogenic disease, including mutations in the interleukin 10 gene or receptor gene, as in the case of this study, or other mutations such as severe combined immunodeficiency, common immunodeficiency variable, chronic granulomatous disease, Wiskott-Aldrich syndrome, X-linked polyendocrinopathy and enteropathy (IPEX), and X-linked lymphoproliferative syndrome (XLP).

IBD can be associated with a variety of immune-mediated diseases [20], and, although rare, there are reports of an association between IBD and juvenile idiopathic arthritis (JIA) [21]. In the case of this study, the patient presented International League of Associations for Rheumatology (ILAR) criteria for JIA [22], an inflammatory disease characterized by high levels of interleukin 1 and 6 [23] and in addition with a prominent eosinophilic infiltrate in colon biopsies, it was decided to associate these findings with JIA with manifestation extra-articular, as described by some authors [24,25].



The authors of this study also believe that double balloon enteroscopy played an important role in changing the diagnosis to ulcerative colitis in the patient initially diagnosed as CD.

Eleven patients (64.7%) were male, in agreement with Sauer et al., [26] even so, when analyzing the group of individuals younger than 6 years of age, described as very-early onset by Uhling and collaborators [15], 5/6 were male, which may be a trend in this specific population of children or even have some unknown protective factor in females.

The inflammatory phenotype was the predominant, responsible for 52.9% of the patients, followed by the stenosing and fistulizing phenotypes, both representing 23.5% of this series, differing in part from the systematic review performed by Benchimol et al., [27] which, despite reporting the inflammatory phenotype being the most common, concluded that stenosing and fistulizing forms are rare. Another study published by Fumery et al., [28] who followed 535 patients with pediatric CD for 11 years, showed that, at baseline, 73% of patients had an inflammatory phenotype, and at the end of follow-up, this rate decreased to 42% of patients, number closest to the sample of the present study. In this sample, the change in behavior was not evaluated, since the Paris classification of the behavior of the disease was given at the worst moment of the patients described in this study, and it is not possible to describe whether there was a worsening in the behavior during the follow-up.

Some studies [29,30] reported that perianal disease affects older children, over 10 years of age, differing from the findings described in this study, where it was observed that 6 of the 17 patients had perianal involvement (35%), with 4 of these patients under 10 years of age. Perhaps this difference can be explained by the presence of CD in the proximal small bowel, conferring a distinct phenotype for this complication.

In the general, there was a significant improvement in clinical and endoscopic scores when compared at the beginning and at the end of the 10-year follow-up, with the pediatric group (between 10 and 17 years of age) achieving remission in 7/8 patients. Although, when analyzing the group of children diagnosed with CD before 10 years of age, it was observed that 7/9 are still undergoing endoscopic activity, and it is possible to note a divergence of clinical and endoscopic activity in the age group between 2 and 5 years as well, which can be explained by the few symptoms of CD in these patients. Several studies [19,27,28] have already mentioned that patients with early onset of CD have some phenotypic characteristics that distinguish them from CD diagnosed in adolescence and, in this study, a worse response can be observed in patients diagnosed at an early-onset or very-early-onset age, in agreement with the literature.

During the follow-up, 4/17 patients progressed to surgery, approximately 23% of the population studied in this study. When evaluated by age group, it is observed that 50% of patients between 2 and 10

years of age underwent intestinal resection and they are still in endoscopic and clinical activity after 10 years follow-up, another factor that suggests a more aggressive phenotype and difficulty of management in this age group, even in the presence of biological therapy. In a systematic review published by Mao et al., [31] which aimed to assess the efficacy of biological and immunomodulatory therapy in adult patients with IBD, five randomized clinical trials for CD were evaluated and concluded that anti-tumor necrosis factor (TNF) significantly reduced the progression to surgery. In pediatric patients, referral centers reported [32,33] a 43% probability of surgery in 10 years, data that are similar to the present study. There was an important reduction in the use of immunosuppressants in this study, possibly explained by the worse evolution of the disease with the need for treatment progression and, moreover, with the arrival of new biological therapies in the study period from 2010 to 2020, which in theory does not decrease the possibility of surgical evolution in patients with early-onset or very early-onset CD. Anyhow, the authors of this study admit that more studies need to be carried out to better elucidate the role of biological therapy in the surgical evolution of CD diagnosed before 10 years of age.

Of the 17 patients, three evolved with extraintestinal manifestations during the follow-up, being one PSC and the other two with joint manifestations, less than 15% of the patients in this sample. This data is similar to that reported by Fumery et al., [28] who showed extraintestinal manifestations in 23.5% of the 535 patients followed up with CD, with 11% of the 535 patients with joint manifestations, 0.2% with hepatobiliary manifestations, and the others with cutaneous manifestations.

In this study, there was no mortality, but there was one report of acute lymphoid lymphoma. Other studies [33-36] also reported some cancers such as leukemia and cholangiocarcinoma, but with an incidence of less than 1%.

As limitations of this study, the small sample size and the inability to statistically identify changes in treatment levels during follow-up are highlighted. As a strong point, it is noteworthy that this is the first study with patients diagnosed with CD of the proximal small bowel with long-term follow-up.

## 6. Conclusion

In view of the study carried out with pediatric patients, it can be concluded that patients diagnosed with Crohn's disease and involvement of the proximal small bowel showed statistically significant clinical and endoscopic improvement after 10 years of follow-up. Nonetheless, patients diagnosed before 10 years of age presented worse evolution and difficulty in achieving deep remission. Approximately half of patients diagnosed with Crohn's disease before age 10 years progressed to surgery despite biological therapy, suggesting a distinct phenotype of more aggressive disease.

## References

- Crohn BB, Ginzburg L, Oppenheimer GD. Regional Ileitis. *JAMA*. 1932; 99(16): 1323–9.
- Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. *Lancet*. 2017; 389(10080): 1741–55.
- Ferguson A, Sedgwick DM. Juvenile onset inflammatory bowel disease: height and body mass index in adult life. *BMJ*. 1994; 308(6939): 1259–63.
- Walters TD, Gilman AR, Griffiths AM. Linear Growth Improves during Infliximab Therapy in Children with Chronically Active Severe Crohn's Disease. *Inflamm Bowel Dis*. 2007; 13(4): 424–30.
- Walters TD, Kim M-O, Denson LA, Griffiths AM, Dubinsky M, Markowitz J, et al. Increased Effectiveness of Early Therapy with Anti-Tumor Necrosis Factor- $\alpha$  vs an Immunomodulator in Children With Crohn's Disease. *Gastroenterology*. 2014; 146(2): 383–91.
- Wong K, Isaac DM, Wine E. Growth Delay in Inflammatory Bowel Diseases: Significance, Causes, and Management. *Dig Dis Sci*. 2021; 66(4): 954–64.
- Heyman MB, Kirschner BS, Gold BD, Ferry G, Baldassano R, Cohen SA, et al. Children with early-onset inflammatory bowel disease (IBD): Analysis of a pediatric IBD consortium registry. *J Pediatr*. 2005; 146(1): 35–40.
- Martín-de-Carpi J, Rodríguez A, Ramos E, Jiménez S, Martínez-Gómez MJ, Medina E, et al. Increasing Incidence of Pediatric Inflammatory Bowel Disease in Spain (1996–2009). *Inflamm Bowel Dis*. 2013; 19(1): 73–80.
- Castro M, Papadatou B, Baldassare M, Balli F, Barabino A, Barbera C, et al. Inflammatory bowel disease in children and adolescents in Italy: Data from the pediatric national IBD register (1996–2003). *Inflamm Bowel Dis*. 2008; 14(9): 1246–52.
- Feuerstein JD, Cheifetz AS. Crohn Disease: Epidemiology, Diagnosis, and Management. 92: Mayo Clinic Proceedings. Mayo Foundation for Medical Education and Research. 2017; 1088–103.
- Gajendran M, Loganathan P, Catinella AP, Hashash JG. A comprehensive review and update on Crohn's disease. *Disease-a-Month*. 2018; 64(2): 20–57.
- Flamant M, Trang C, Maillard O, Sacher-Huvelin S, Rhun M Le, Galliche JP, et al. The prevalence and outcome of jejunal lesions visualized by small bowel capsule endoscopy in Crohn's disease. *Inflamm Bowel Dis*. 2013; 19(7): 1390–6.
- Kim OZ, Han DS, Park CH, Eun CS, Kim YS, Kim YH, et al. The clinical characteristics and prognosis of Crohn's disease in Korean patients showing proximal small bowel involvement: Results from the CONNECT Study. *Gut Liver*. 2018; 12(1): 67–72.
- Fong SCM, Irving PM. Distinct management issues with Crohn's disease of the small intestine. *Curr Opin Gastroenterol*. 2015; 31(2): 92–7.
- Uhlig HH, Schwerdt T, Koletzko S, Shah N, Kammermeier J, Elkadri A, et al. The Diagnostic Approach to Monogenic Very Early Onset Inflammatory Bowel Disease. *Gastroenterology*. 2014; 147(5): 990–1007.
- Harvey RF, Bradshaw JM. A Simple Index of Crohn's-Disease Activity. *Lancet*. 1980; 315(8167): 514.
- Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: The SES-CD. *Gastrointest Endosc*. 2004; 60(4): 505–12.
- Levine A, Griffiths A, Markowitz J, Wilson DC, Turner D, Russell RK, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease. *Inflamm Bowel Dis*. 2011; 17(6): 1314–21.
- Aloi M, Lionetti P, Barabino A, Guariso G, Costa S, Fontana M, et al. Phenotype and Disease Course of Early-onset Pediatric Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2014; 20(4): 597–605.
- Kappelman MD, Galanko JA, Porter CQ, Sandler RS. Association of paediatric inflammatory bowel disease with other immune-mediated diseases. *Arch Dis Child*. 2011; 96(11): 1042–6.
- Hügler B, Speth F, Haas J-P. Inflammatory bowel disease following anti-interleukin-1-treatment in systemic juvenile idiopathic arthritis. *Pediatr Rheumatol*. 2017; 15(1): 16.
- Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 2004; 31(2): 390–2.
- Mellins ED, Macaubas C, Grom AA. Pathogenesis of systemic juvenile idiopathic arthritis: some answers, more questions. *Nat Rev Rheumatol*. 2011; 7(7): 416–26.
- Kokkonen J, Arvonen M, Vähäsalo P, Karttunen TJ. Intestinal immune activation in juvenile idiopathic arthritis and connective tissue disease. *Scand J Rheumatol*. 2007; 36(5): 386–9.
- Pichler J, Ong C, Shah N, Sebire N, Kiparrissi F, Borrelli O, et al. Histopathological features of gastrointestinal mucosal biopsies in children with juvenile idiopathic arthritis. *Pediatr Res*. 2016; 79(6): 895–901.
- Sauer CG, Kugathasan S. Pediatric Inflammatory Bowel Disease: Highlighting Pediatric Differences in IBD. *Med Clin North Am*. 2010; 94(1): 35–52.
- Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, et al. Epidemiology of pediatric inflammatory bowel disease: A systematic review of international trends. *Inflamm Bowel Dis*. 2011; 17(1): 423–39.
- Fumery M, Pariente B, Sarter H, Savoye G, Spyckerelle C, Djeddi D, et al. Long-term outcome of pediatric-onset Crohn's disease: A population-based cohort study. *Dig Liver Dis*. 2019; 51(4): 496–502.
- Rinawi F, Assa A, Hartman C, Mozer Glassberg Y, Nachmias Friedler V, Rosenbach Y, et al. Evolution of disease phenotype in pediatric-onset Crohn's disease after more than 10 years follow up—Cohort study. *Dig Liver Dis*. 2016; 48(12): 1444–50.
- Adler J, Dong S, Eder SJ, Dombkowski KJ. Perianal Crohn Disease in a Large Multicenter Pediatric Collaborative. *J Pediatr Gastroenterol Nutr*. 2017; 64(5): e117–24.
- Mao EJ, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthakrishnan AN. Systematic review with meta-analysis: comparative efficacy of immunosuppressants and biologics for reducing hospitalisation and

- surgery in Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther.* 2017; 45(1): 3–13.
32. Van Limbergen J, Russell RK, Drummond HE, Aldhous MC, Round NK, Nimmo ER, et al. Definition of Phenotypic Characteristics of Childhood-Onset Inflammatory Bowel Disease. *Gastroenterology.* 2008; 135(4): 1114–22.
  33. Duricova D, Fumery M, Annese V, Lakatos PL, Peyrin-Biroulet L, Gower-Rousseau C. The natural history of Crohn's disease in children. *Eur J Gastroenterol Hepatol.* 2017; 29(2): 125–34.
  34. Adamiak T, Walkiewicz-Jedrzejczak D, Fish D, Brown C, Tung J, Khan K, et al. Incidence, Clinical Characteristics, and Natural History of Pediatric IBD in Wisconsin. *Inflamm Bowel Dis.* 2013; 19(6): 1218–23.
  35. Cosnes J, Cattan S, Blain A, Beaugerie L, Carbonnel F, Parc R, et al. Long-Term Evolution of Disease Behavior of Crohn's Disease. *Inflamm Bowel Dis.* 2002; 8(4): 244–50.
  36. Urlep D, Trop TK, Blagus R, Orel R. Incidence and Phenotypic Characteristics of Pediatric IBD in Northeastern Slovenia, 2002–2010. *J Pediatr Gastroenterol Nutr.* 2014; 58(3): 325–32.