REVIEW ARTICLE

Pediatric Crohn's Disease

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Abstract

Inflammatory bowel disease (IBD) remains intriguing and challenging for a pediatrician and the causes remain elusive. Past decades have shown an increasing trend in the number of children diagnosed with IBD, and the treatment modalities and diagnostic aids have advanced significantly with increasing awareness and growing scientific evidence. Treatment has evolved from steroids to biologicals, and a majority of children have been managed aggressively with medical treatment solely. The Indian subcontinent has seen an increasing number of children with IBD, as reported by data from various centers, which is very challenging for clinicians and has led to better sensitization of this conundrum in pediatric practice. This review article aims to offer better clarity and to enrich the knowledge of clinicians who either want to know about the multifaceted presentations of pediatric Crohn's disease (CD) or the complexity involving the management of pediatric Crohn's disease has intestinal and extra-intestinal manifestations and literally can involve anywhere from mouth to anus. This review aims to cover extensively from the incidence to the complications of Crohn's disease and the newer evolutions in the treatment.

Keywords: Crohn's disease, Inflammatory bowel disease, Pediatric, Review.

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Introduction

Crohn's disease (CD) in children was relatively unknown and underreported in the Indian subcontinent in the past decades, but recent years have shown an upsurge owing to the sensitization of clinicians and the availability of diagnostic aids for this particular IBD.

Crohn's disease (CD) comprises a major portion of the pediatric IBD conundrum globally, followed by ulcerative colitis (UC), indeterminate colitis, and the newly termed very early onset IBD (VEO-IBD).

Epidemiology

Crohn's disease (CD) was always thought of and recognized as a western disease, its relevance to the Indian context was only considered after tuberculosis (TB) and human immunodeficiency virus in pediatric gastroenterology. The incidence of CD was patchy as Indian data were scarce, with only a few available reports[1,2]

A preliminary study[3] showed that IBD comprises 0.03% of the outpatient case workload in South India and subsequent studies which followed suit showed that the incidence of IBD and its variability of the caseload in various parts of the country.[4–6]

Global data show a wide distribution of 3–4/100,000 individuals every year, with variation in North America, Europe, and the rest of the world.[7] There seems to be male preponderance (1.5:1).

The disease incidence is variable in Indian children with CD, and it is hard to predict in the Indian subcontinent. There is also a genetic predominance.

The concordance rate for CD in monozygotic twins is between 35 and 63%, while for UC, it is 16–18%.

Clinical Presentation

To understand the clinical presentation of CD, one has to understand the clinical picture of UC too. The tabular column is adapted from the Pediatric IBD Collaborative Research Group registry.[1,5]

Tables 1 and 2 clearly show the most common presentation of pediatric CD and the global presentation of CD. The key to the diagnosis is to "first think of IBD as a possibility" and subsequently identify its clinical presentations. IBD may present from any age ranging from above 1 month, giving rise to the novel term VEO-IBD. CD may present at any age in Indian children and it is extremely important to differentiate it from its Indian cousin, TB.

The following are the clinical presentations of CD in the pediatric age group with both intestinal and extraintestinal manifestations:

- The classic triad of CD is composed of abdominal pain, chronic diarrhea, and weight loss [(25% of the cases) Porto criteria].
- Intestinal manifestations (impairment of growth parameters can precede the intestinal mucosal lesion by months to years).
  - Abdominal pain (recurrent, nocturnal).
  - Chronic diarrhea.
  - Rectal bleeding.
  - Weight loss.
  - Perianal skin tags.
  - Sentinel piles.
  - Perianal fistulae.
  - Recurrent oral ulcers.
  - Clubbing.
  - Poor growth or failure to thrive.
  - Delayed puberty.
  - Urgency to go to the toilet.
  - Nocturnal defecation.
  - Lack of energy.

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Table 1: Crohn's disease vs UC

Feature	*CD*	*UC*
Fever and weight loss	More common and growth delay.	Less common.
Disease extent	Anywhere in the gastrointestinal tract from mouth to anus; rectum is rarely involved.	Limited to colorectal mucosa, usually beginning at the rectum and spreading upwards to the caecum.
Inflammation	Transmural; can lead to fistula Patchy areas of inflammation (skin lesions).	Mucosal and no fistula, continuous area of inflammation.
Perianal involvement	Fistulas, anal fissures, and skin tags common.	Not so common.
Stenosis	Common	Rare
Typical features on endoscopy	Discontinuous inflammation with intervening normalcy Ulceration, structuring, fistulae, and cobblestoning.	Continuous inflammation with variable proximal extension from rectum Erythema, friability, and ulceration Loss of vascular pattern and pseudopolyp formation.
Typical features on histology	Submucosal/ transmural inflammation, chronic ileitis/colitis, nonpericrypt granuloma, focal biopsy changes, patchy distribution, crypt distortion, and abscess.	Mucosal inflammation, chronic colitis with crypt distortion and crypt abscess, goblet cell depletion, lymphoplasmacytosis, and plasma cell metaplasia.

Table 2: The Paris classification of CD

Age at diagnosis	A1a	<10 years
	A1b	10 to <17 years
	A2	17–40 years
	A3	>40 years
Location	L1	Distal one-third ileum ± limited cecal disease
	L2	Colonic disease
	L3	Ileocolonic disease
	L4	Isolated upper gastrointestinal disease
	L4a	Esophageal disease
	L4b	Gastroduodenal disease
Behavior	B1	Nonstricturing and nonpenetrating
	B2	Stricturing
	B3	Penetrating
	B2B3	Stricturing and penetrating
	P	Perianal disease modifier
Growth	G0	No evidence of growth delay
	G1	Growth delay

Source: Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis. 2011; 17(6):1314–1321. https://doi.org/10.1002/ibd.21493

- Extraintestinal manifestations.
  - Uveitis.
  - Erythema nodosum.
  - Joint pain (arthralgia).

Diagnosis

History and Physical Examination

The diagnosis of CD includes the following four checks (Fig. 1):

- Good clinical history and examination.
- Endoscopy (esophagogastroduodenoscopy and ileocolonoscopy).
- Radiology [computed tomography (CT) enterography of the abdomen, magnetic resonance imaging enterography].
- Histology (to confirm the diagnosis).

There is no single test to confirm the diagnosis of CD, and all of the above tests need to be done and repeated in all follow-up cases, as these form the basis of management and follow-up as well.

Good clinical history and examination start from the scalp and extends to the perianal area, as these are very important places that may be missed and can provide a valuable lead for the diagnosis.

Close observation of the symptoms and elicitation of the clinical signs are of paramount importance in the clinical diagnosis.

Pediatric clinical history taking is never complete without the plotting of anthropometry on the World Health Organization, or Indian Academy of Pediatrics growth charts. This not only helps in the diagnosis but also in the long-term follow-up and management of these children, and it will help in timely intervention when growth falters owing to the disease itself.

Diagnostic Tools

Blood Investigations

The following tests aid in the diagnosis or support the diagnosis and are very useful in the follow-up of children with CD:

- Complete blood count.
- C-reactive protein.
- Liver function tests.
- Erythrocyte sedimentation rate.
- Anti-*Saccharomyces cerevisiae* antibodies; this association is known to be positive in only about 60% of cases.

Fecal Calprotectin

Multiple studies have shown the sensitivity and specificity of this test in both the diagnoses and the follow-up of children with CD. The significance of this test in Indian children has been shown to be of use in the diagnosis of IBD in a very small cohort, and this is also the only available study to this date.[8] This is a newer and noninvasive test that has found a significant role in CD in the past decades.

Endoscopy

Esophagogastroduodenoscopy or upper gastrointestinal endoscopy and ileocolonoscopy remain the primary diagnostic tools in the hands of a pediatric gastroenterologist. It helps in establishing the macroscopic findings and in localizing the disease area.[9] The biopsies obtained during the procedure help in confirming the diagnosis.

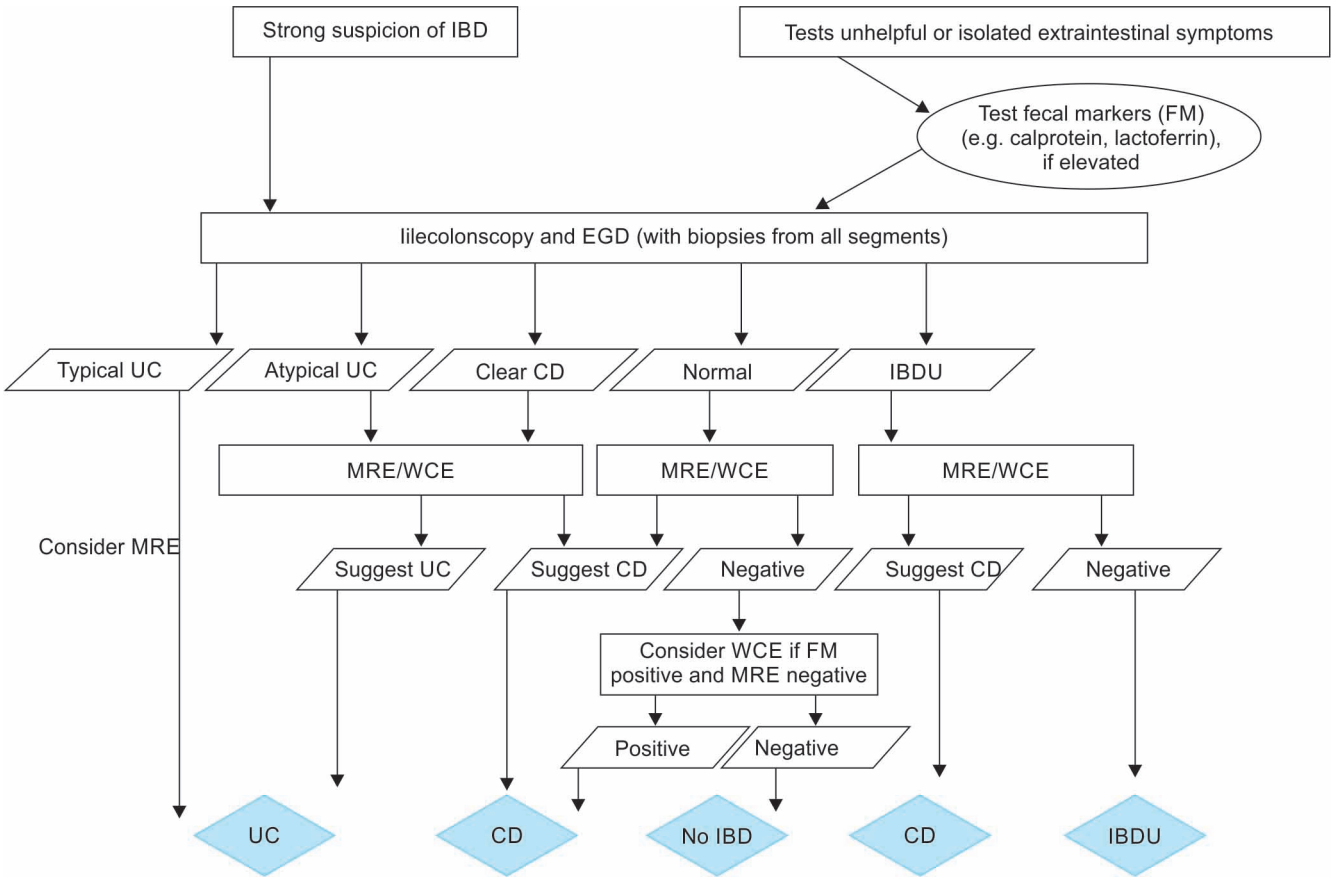

Fig. 1: Evaluation of child/adolescent with intestinal or extraintestinal symptoms suggestive of IBD.
Source: Levine A, Koletzko S, Turner D, et al. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. J Pediatr Gastroenterol Nutr. 2014; 58(6):795–806.

Pertaining to the Indian context, interpretation of the biopsies by an experienced histopathologist is very important as granulomas can be seen in both TB and CD. The granulomas of TB are numerous, large, and well-defined granulomas, which often feature caseation and confluence, whereas the granulomas of CD are characterized by fewer, smaller, and poorly organized granulomas without confluence or caseation.

Radiological Imaging

- Barium meal follow through. Although this test is practically getting outdated because of the amount of radiation involved and the quantity of the contrast that needs to be consumed, it is still being performed, though definitely losing vogue.
- Magnetic resonance enterography (MRE): This investigation of choice in pediatric CD[10] carries the advantage of identifying small bowel involvement, mucosal changes, and identification of abscesses and fistulae with no radiation and is now being considered in all centers worldwide.

Wireless Capsule Endoscopy (WCE)

In centers where MRE is not available or has not yielded any results, or if the child is too young to undergo the procedure (under 2 years of age), WCE must be considered. It is comparatively expensive and more time-consuming than other modalities. A prospective blinded four-way comparison trial of WCE, CT, ileocolonoscopy, and small bowel follow-through in adults revealed a diagnostic sensitivity of 83, 82, 74, and 65%, respectively, whereas the specificity of WCE (53%) was significantly lower than that of all other tests (100%).[10,11]

Single and Double Balloon Enteroscopy

These tests are not available in all global centers but have found a place in evaluating children with suspected CD. They are not generally used in the initial evaluation leading to diagnosis.

Differential Diagnosis

- Intestinal TB.
- Primary immunodeficiency.
- Allergic enterocolitis.
- Gastrointestinal lymphomas.
- Yersinia infection.
- Campylobacter infection.

Management

Approach to Treatment

The two main objectives of the treatment are to achieve remission and prevent relapses in children with CD. The management of CD may be divided into mild, moderate, and severe for convenience and easier understanding.

Drug Therapy

Induction of Remission

The two arms of the treatment for mild CD are the use of exclusive enteral nutrition (EEN) and steroids. The use of EEN has shown very good clinical outcomes in terms of improvement in anthropometry and achieving clinical remission without any adverse effects. This is shown in the global data[12] and reflected in the prototype Indian study as well as in children.[13] Polymeric formulas, semi-elemental formulas, or elemental formulas have all elicited a good clinical response in achieving remission in CD.[13] EEN used is given at a 120% calorie requirement and gradually increased from day 1 to prevent the refeeding syndrome, improve tolerance, and ensure compliance. The total duration of EEN therapy is 6–8 weeks. If children do not tolerate EEN or if the desired clinical response is not achieved in the first 2 weeks of EEN therapy, oral steroids are recommended. EEN has no significant role in pancolitis, active arthritis, and perianal disease.

Oral prednisolone at a dose of 1–2 µg/kg/day to achieve clinical remission and gradual tapering with time is recommended.[14]

The real time progress and spot clinical assessment of the child can be made using the Cincinnati pediatric CD activity index online calculator.[15,16]

When clinical remission is being achieved, the child will need to be started on immunomodulators, preferably azathioprine or mercaptopurine as maintenance therapy because it takes about 8–14 weeks to achieve optimal effect.[17]

In cases of fistulizing CD, ciprofloxacin (20 µg/kg/day) and metronidazole (10–20 µg/kg/day) are recommended. Metronidazole is efficacious in children with colitis and ciprofloxacin in ileitis. Other antibiotics that have shown benefits during induction are azithromycin and rifaximin. Antibiotics are superior to placebo in active CD.[18]

Biological antitumor necrosis factor (anti-TNF) therapy, such as infliximab (IFX), is used to induce remission in children who are steroid refractory and have an active perianal fistulizing disease.[19]

The following markers suggest a high risk of poor outcomes:

- Deep ulcerations on endoscopy.
- Pan-enteric disease.
- Advanced osteoporosis.
- Marked growth failure.
- Poor response to adequate initial therapy.
- The dose will be the same as for children with UC.

Maintenance of Remission

Azathioprine and 6-mercaptopurine (6-MP) are the recommended drugs for achieving steroid-free remission in CD. Children who are on 6-MP are more likely to remain in remission when compared to those on a placebo.[20] To achieve full efficacy of these drugs, the optimal dosage should be given, as it takes 8–14 weeks to achieve therapeutic levels.

- Indications for immunomodulators.
- Maintenance of remission.

Methotrexate (MTX)

- It may be used as the sole therapy for achieving remission.
- It is the second-line treatment in children with thiopurine failure.
- Methotrexate (MTX) is prescribed at a dose of 15 µg/m^2 (maximum 25 µg) weekly as a subcutaneous injection.
- It has the convenience of an intramuscular or oral route.
- As it is a folate antagonist, a dose of folic acid (5 µg) is given 24 hours after a dose of MTX.
- Nausea and vomiting, hepatotoxicity, myelosuppression, and pulmonary toxicity are the known adverse effects of MTX.

Biologicals

These "new generation" drugs deserve an entire chapter for themselves. Our discussion will be limited to the use of biologicals (anti-TNF) in CD.

Antitumour necrosis factor (anti-TNF) has to be considered in the following conditions:

- Perianal fistulating disease.
- Chronic luminal active CD.
- Steroid refractory CD.
- Arthropathy.
- Pyoderma gangrenosum.

Commonly used biologicals that are licensed and used in the pediatric population are as follows:

Infliximab's (IFX) maintenance dose is 5 µg/kg every 8 weeks and a higher dose of 10 µg/kg every 4 weeks may be used in severe cases, that is, in children with low drug levels or poor drug response. A randomized, multicenter, open-label study to evaluate the safety and efficacy of anti-TNF-α chimeric monoclonal antibody in pediatric subjects with moderate-to-severe Crohn's disease (REACH) study has shown that children who were commenced on IFX during induction therapy were more likely to be in remission by week 54.[19,21]

Adalimumab's dose of 0.6 µg/kg (maximum 40 µg) every alternate week has also been advocated. Combination therapy of thiopurines and biologicals has been used in children.[22] In children where a sustained response to biologicals has been achieved, the treatment may be stepped down to immunomodulators.

The risks of biologicals or anti-TNF therapy are as follows:[21]

- Antibodies developing to anti-TNF therapy.
- Possibility of lymphoma.
- Loss of drug efficacy.
- Drug infusion reactions.
- Delayed hypersensitivity reactions.
- Life-threatening infections (meningitis, sepsis, herpes, and fungal infections).

Hence, it is mandatory that vaccination schedules are completed prior to commencing therapy.

Use of 5-aminosalicylates (ASAs) in CD

The 5-ASAs is used in mild colonic diseases, though poor evidence exists about its achieving mucosal healing. Its role is very useful in mild diseases and it has a low risk of relapse.[23]

There is no role for probiotics or omega-3 supplements in the management of pediatric CD.

Step down/up therapy and the future of CD

The primary aim of CD management in children involves achieving optimal growth, optimal quality of life, reducing complications owing to the disease and drug therapy, and to achieve prolonged periods of remission with minimal therapy.

No guidelines exist for step up or step down therapy in children with CD, and the disease requires constant monitoring with surrogate markers, such as blood investigations, fecal calprotectin, and endoscopy to assess mucosal healing.

Step up or step down therapy is generally based on the clinical experience of the treating clinician and anecdotal evidence with multidisciplinary management.

The drug range for CD management has expanded in the past 2–3 decades with less or minimal drug management and newer therapies, such as anti-TNF therapy. Varying and widespread interest in pediatric IBD has evolved into genetic tests, such as whole exome sequencing and gut microbiota (fecal) transplant.

Clinical outcomes in children have improved, with a majority of them leading a near-normal life with fewer hospital visits. Sensitizing clinicians about pediatric CD and early diagnosis of the disease have been the hallmarks in the management of CD.

Treatment Procedures

Surgery

The following is a short summary of the indications of surgery:[22,24]

- Failure of medical therapy.
- Growth failure despite maximal therapy.
- Extraintestinal involvement (eyes and joints).
- Disease complications, such as obstruction, fistulae, and perforation.

The commonly performed surgeries in the CD are strictureplasty, resection of disease segment, and right hemicolectomy. Surgery is delayed or avoided if the disease can be brought to clinical remission with medical therapy and if optimal growth is achieved.

Perianal disease in children is the most challenging to treat, and biologicals, steroids, optimal nutrition, and seton placement may all be needed to manage this condition.

Evidence Summary

Guideline Links

The relevant guidelines are as follows:

Ruemmele FM, G Veres, KL Kolho, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J Crohns Colitis. 2014; 8(10):1179–1207. https://doi.org/10.1016/j.crohns.2014.04.005.

Levine APA, Arie, Koletzko S, et al. ESPGHAN revised Porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. J Pediatr Gastroenterol Nutr. 2014; 58(6):795–806. https://pubmed.ncbi.nlm.nih.gov/24231644/.

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