REVIEW ARTICLE

Pediatric Inflammatory Bowel Disease

AKSHAY KAPOOR, VIDYUT BHATIA AND ANUPAM SIBAL

From Department of Pediatric Gastroenterology, Apollo Centre for Advanced Pediatrics, Indraprastha Apollo Hospital, Sarita Vihar, New Delhi, India.

Correspondence to: Dr Akshay Kapoor, Department of Pediatric Gastroenterology, Hepatology and Liver Transplantation, Indraprastha Apollo Hospital, Sarita Vihar, New Delhi, India. akshaydr80@yahoo.co.in

***Background*:** The incidence of inflammatory bowel disease is increasing in the pediatric population worldwide.

***Need and purpose of review*:** There is paucity of high quality scientific data regarding pediatric inflammatory bowel disease. Most of the guidelines are offshoots of work done in adults, which have been adapted over time to diagnose and treat pediatric patients. This is in part related to the small numbers in pediatric inflammatory bowel disease and less extensive collaboration for multicentric trials both nationally and internationally.

***Methods*:** A literature search was performed using electronic databases i.e. Pubmed and OVID, using keywords: pediatric, inflammatory bowel disease, Crohn's disease, Ulcerative colitis, epidemiology and guidelines. This article amalgamates the broad principles of diagnosing and managing a child with suspected inflammatory bowel disease.

***Main conclusions*:** 25% of the patients with inflammatory bowel disease are children and and young adolescents. The primary concern is its impact on growth velocity, puberty and quality of life, including psychosocial issues. Treatment guidelines are being re-defined as the drug armamentarium is increasing. The emphasis will be to achieve mucosal healing and normal growth velocity with minimal drug toxicity.

Keywords:*Crohn's diseases, Epidemiology, Management, Ulcerative colitis.*

Inflammatory Bowel disease (IBD) is a perplexing disease characterized by chronic mucosal inflammation. It results from a complex interplay of various factors including genetic and environmental, and adaptive immunity of the host. Crohn's disease (CD) and Ulcerative colitis (UC) are the two broad phenotypes of IBD. CD is characterized by its ability to involve any part of the gastrointestinal tract in a discontinuous fashion. The inflammation associated with CD is often transmural and granulomatous. UC on the other hand tends to involve the rectum and the adjoining colonic mucosa to a variable extent; albeit in a continuous fashion. The inflammation in UC is usually superficial when compared with CD. The term indeterminate colitis or IBD-U is used when the clinical and histopathological features are unable to distinguish between CD and UC [1]. Early onset IBD is important as researchers believe that it has a distinct phenotype when compared with adult onset IBD. Moreover, the genetically attributable risk is considered to be higher in early onset IBD, as exposure to environmental factors is proportionately less.

EPIDEMIOLOGY

Multiple studies have shown that 25% of all IBD cases have their onset in children less than 18 years of age [2]. However, the incidence of the disease seems to be increasing internationally. A systematic review of international trends in pediatric IBD revealed a statistically significant increase in the period 1950-2009. The SPIRIT registry from Spain collected data in 2100 pediatric patients with IBD (1996-2009). It showed a collective increase in incidence of IBD from 0.97 to 2.8/ 100,000 inhabitants <18 years/year in the study period. The median age at diagnosis was 12 years and the increase in CD cases was more than UC cases, with males being majorly affected [3]. A similar registry from Italy (1996-2003) showed a similar rise in the overall incidence of IBD cases from 0.89 to 1.39/10 in children <18 years of age. However, in this registry UC cases showed a greater increase than CD cases [4]. The incidence of IBD in a prospective study (<16 years) from UK was 5.2/100000 individuals/year. The proportion of CD was 60%, while the proportion of UC was 28%. The mean age at diagnosis was 12 years. Studies from other European countries have shown incidence rates of 0.6-6.8/100000 individuals/year for CD and 0.8-3.6 for UC. An evaluation of North American studies revealed an incidence of 3-4/100000 individuals/year. Although studies and data are lacking from South American, African and Asian nations, temporal trends are obvious from the studies in the western hemisphere [5]. There is a male preponderance in pediatric CD (1.5:1), while UC affects both sexes equally. CD is more common in children as compared to UC (2.8:1) when compared with

adult data (0.85:1). CD in children presents more commonly as ileocolonic or colonic disease. UC presents commonly (85-90%) as pancolitis [6]. Pediatric CD is predominantly an inflammatory disease; stricturing and penetrating variants are rarely seen at presentation. UC, as mentioned previously presents with a more severe phenotype which requires surgery more often as compared to the adult phenotype [7].

Data from India is limited. The first case series on CD was published from Southern India in 2005,detailing 10 children (5-15 years) with Crohn's disease [8]. There was female preponderance (9 out of 10), and interestingly, 50% of the children had received antitubercular therapy prior to diagnosis. Another tertiary referral center from Southern India reported 34 children with IBD (23 with CD and 11 with UC). These cases accounted for 7% of the total IBD load presenting to that centre. The proportion of IBD was 0.03% of all pediatric cases presenting to the outpatient department, and the median delay in diagnosis was 15 months [9]. A recent questionnaire-based survey from seven centers across India in 221 children and adolescents with IBD showed that children with IBD in India have features similar to adult-onset IBD. UC was present in 42% of these children while CD was found in 55%; the rest were classified as indeterminate colitis. These children shared similarities with adult-onset IBD in terms of distribution of the disease. However, as in other reports on IBD in children, growth failure and more severe forms of the disease were commonly observed. The UC cases had complications like toxic megacolon and bleeding in 12%, while 27% of CD cases had complications (fistulae, strictures, perforation). Biological agents were used in less than 1% of UC cases and in 12% of CD cases [10].

Genetics and environmental influence

Pediatric IBD has alerted researchers to the possibility of genetic susceptibility playing a role in disease pathogenesis. Epidemiological studies have highlighted a familial association in 25-30% cases of pediatric IBD. The *NOD2* gene for CD and the *MHC* region on 6p for UC were two of the first genes to be implicated in disease causation. With the availability of Genome wide association scanning (GWAS) using single nucleotide polymorphisms (SNP), more than 100 genes have been implicated in IBD [11].

Studies in twins have not shown a very strong concordance. The concordance rate for CD in monozygotic twins is between 35-63%, while for UC, it is 16-18%. Concordance rate in dizygotic twins is around 4%. This suggests a greater role of the environment in IBD causation. The cold chain hypothesis and the hygiene hypothesis were formulated to explain the increased incidence of IBD as a by-product of alteration of the gut microbiota due to refrigeration and increased cleanliness [12]. Refrigeration altered the bacteria in the diet and supported the growth of disease causing organisms; while increased cleanliness, smaller families and less exposure to animals made children in developed countries more susceptible to IBD. This altered/impaired immunological tolerance in response to low bacterial load forms the basis of hygiene hypothesis, wherein alteration between the balance of Th1 and Th2 helper cells was proposed as a mechanism of increasing IBD [13].

To summarize, IBD manifests in a genetically susceptible individual when he/she is exposed to certain environmental triggers (infections, diet, domestic hygiene, smoking, etc.) which evoke an aberrant adaptive immune response.

CLINICAL PRESENTATION

A diagnosis of IBD should always be entertained in children with persistent (>1 month) or recurrent (>2 in 6 months) gastrointestinal symptoms. Abdominal pains, chronic diarrhea, rectal bleeding and weight loss are some of the common symptoms seen in IBD patients. In children with UC, rectal bleeding, chronic diarrhea and abdominal pain are more common; while weight loss is a prominent feature of CD (58% *vs* 35%). The classic triad of pediatric CD; abdominal pain, chronic diarrhea and weight loss is seen in only one-fourth of the cases; 25% of the children may present with only nonspecific symptoms – vague abdominal discomfort, lethargy and anorexia [2]. Perianal lesions in the form of skin tags, sentinel piles and fistulae are more common in CD. Impaired growth velocity and growth failure are more commonly seen in CD patients. Impairment of growth parameters can precede the intestinal mucosal lesion by months to years. Extra-intestinal manifestations of IBD may be the presenting feature in 6-17% of the patients. Arthropathy, skin manifestations and aphthous stomatitis are commonly seen. Primary sclerosing cholangitis (PSC) is more commonly associated with UC [14].

DIAGNOSIS

The diagnosis of IBD is not straightforward. It rests on an accurate history and thorough clinical examination, supplemented by a supportive biochemistry, serology, accurate and complete endoscopy and characteristic histopathology. Radiological examination in the form of a barium meal, CT/MRI enteroclysis or PET scan may further aid in the diagnosis.

History and Examination

A complete history should be obtained with regard to the

frequency and type of stools, the presence of blood/pus per-rectum, and associated abdominal pain, nausea, vomiting, lethargy and weight loss. Always ask for presence of nocturnal emergency and tenesmus. In infants with suspected UC, ask about the type of feeds being given to the child, as allergic colitis is a close differential. Record family history of IBD and history of antibiotic usage. Look for extra-intestinal manifestations like joint swelling, oral ulcers, skin lesions or visual problems. Chart height and weight centiles, including BMI. Carry out tanner staging for sexual maturity in all pre-pubertal and pubertal children. Perform abdominal examination for any tenderness, masses, lumps, or distension. Examine the perianal area for any skin tags, abscess, sentinel piles or fistulae [15,16].

Investigations

A complete blood count with ESR, liver function tests (including albumin), iron status and CRP should be done in all cases of suspected IBD. Stool culture is necessary to rule out infectious diarrhea. *Clostridium difficile* toxin should be investigated in a fresh stool sample, especially if the child has received multiple antibiotics. However, it is pertinent to note that a documented enteric infection does not rule out the possibility of IBD [15].

Anemia, thrombocytosis, hypoalbuminemia with increased ESR and CRP values are expected in patients with IBD. However, the values may be falsely normal in mild UC (54%) or mild CD (21%).

Serological markers and stool tests

Antibodies to anti-Saccharomyces cerevisiae (ASCA) are associated with 60% cases of CD; while perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) are associated with 60% of cases with UC. As, there is considerable overlap among the antibodies with each other and for other diseases like tuberculosis, they cannot be used in isolation to diagnose IBD. Additional markers like anti-E.coli outer membrane porin C antibody (anti-OmpC), antibodies to bacterial flagellin (anti-CBir1) and anti-glycan antibodies are being studied [17,18].

Non-invasive stool markers like fecal calprotectin and lactoferrin are increasingly been recognized as useful markers of small and large bowel inflammation in IBD patients [19, 20]. Serial values may be of more benefit than single values as mucosal inflammation needs time to subside. Values of more than 100-150 µg/g of stool may differentiate IBD from functional causes. Stool markers need to be interpreted with caution in settings where invasive enteric infections are prevalent.

Endoscopy and histopathology

Ileocolonoscopy and upper gastrointestinal endoscopy (UGI) are absolutely essential for diagnosis of IBD. The EECO and ESPGHAN guidelines recommend UGI endoscopy even in suspected UC cases to rule out CD. UGI involvement in CD cases is estimated to vary between 30-80%. Esophageal involvement was seen in 27% cases while gastro-duodenal involvement in 56% of the cases from the Pediatric IBD Collaborative research group registry [21-23]. The characteristic clinical, macroscopic and microscopic findings for CD and UC are given in ***Table* I**.

The recently adapted Paris classification for Pediatric IBD, which was derived from the adult Montreal classification, has elucidated both the macroscopic and microscopic features of UC and CD in children. As the disease location and disease severity are determinants of the treatment strategy and the ultimate outcome, a uniform classification ameliorates any ambiguity in disease differentiation, phenotype and severity. The Paris classification for CD and UC are given in ***Tables* II** and **III,** respectively [21,24].

Imaging studies

Fluoroscopy, CT, MRI and nuclear medicine scans are available to image the bowel in pediatric IBD. The Porto criteria formulated in 2005 advocated small bowel imaging (Barium meal follow through) in IBD patients, especially those with CD, to rule out structuring and fistulae [21]. CT enterography and MR enterography are emerging as modalities with better resolution and delineation of the lumen and folds, with MR having less radiation exposure [25]. The use of PET scan to find areas of increased functional uptake and identify metabolically active tissue is still experimental. Video capsule endoscopy (VCE) is helpful in children, where ileal intubation is unsuccessful or not possible. It is also useful in classifying patients of IC. The drawbacks include inability to make a tissue diagnosis and the possibility of a retained capsule in stricturing CD [26-29].

While small bowel imaging using fluroscopy may show superficial mucosal disease better than any other modality, extra-luminal disease is poorly visualized. CT scan has greater resolution and can show extramural disease and its attendant complications; its use in pediatrics is limited due to the risk associated with ionizing radiation. MRI is costly and time consuming when compared to the other modalities, but can be used when soft tissue characterization is required (perianal CD). Pediatric CT protocols are now available to limit the total radiation dose being given to children [30].

TABLE I CLINICAL DIFFERENCES BETWEEN ULCERATIVE COLITIS AND CROHN'S DISEASE

Feature	*Crohn's disease*	*Ulcerative colitis*
Fever and weight loss	More common	Less common
Disease extent	Anywhere in the GI tract from mouth to anus; rectum is rarely involved.	Limited to colorectal mucosa, usually beginning at the rectum and spreading upwards to the cecum
Inflammation	Transmural; can lead to fistula. Patchy areas of inflammation (Skin lesions)	Mucosali, no fistula. Continous area of inflammation.
Perianal involvement	fistulas, anal fissures and skin tags common	Not as common
Stenosis	common	rare
Feature	Crohn's disease	Ulcerative Colitis
Typical features on endoscopy	Discontinuous inflammation with intervening normalcy**.** Ulceration, structuring and fistulae, Cobblestoning.	Continuous inflammation with variable proximal extension from rectum. Erythema, friability and ulceration**. Loss of** vascular pattern, pseudopolyp formation
Typical features on histology	Submucosal/ Transmural inflammation; Chronic ileitis/ colitis; Non pericrypt granuloma; Focal biopsy changes; Patchy distribution; Crypt distortion and abscess	Mucosal inflammationChronic colitis with crypt distortion and crypt abscess**;** Goblet cell depletion; Lymphoplasmacytosis; Plasma cell metaplasia

TABLE II PARIS CLASSIFICATION OF CROHN'S DISEASE

Age at diagnosis	*A1a*	*< 10 years*
	A1b	10-<17 years
	A2	17-40 years
	A3	> 40 years
Location	L1	Distal 1/3 ileum +/- limited cecal disease
	L2	Colonic disease
	L3	Ileocolonic disease
	L4	Isolated Upper GI disease
	L4a	Esophageal disease
	L4b	Gastroduodenal disease
Behaviour	B1	Non stricturing, nonpenetrating
	B2	Stricturing
	B3	Penetrating
	B2B3	Stricturing and penetrating
	P	Perianal disease modifier
Growth	G0	No evidence of growth delay

Source: Crohn's & Colitis Foundation of America.

TABLE III PARIS CLASSIFICATION OF ULCERATIVE COLITIS

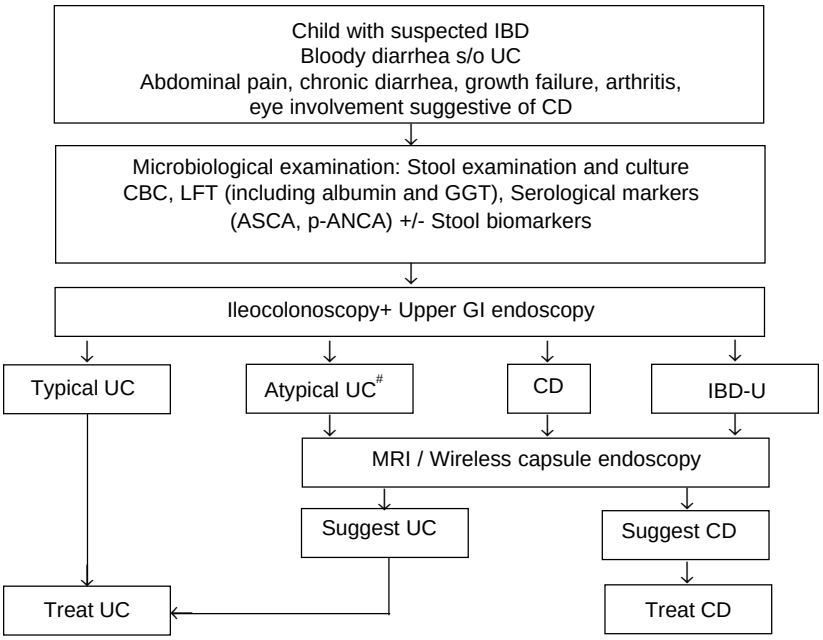
Extent	E1	Ulcerative proctitis
	E2	Left sided colitis distal to splenic flexure
	E3	Extensive colitis distal to hepatic flexure
	E4	Pancolitis, proximal to hepatic flexure
Severity	S0	Never severe
	S1	Ever severe

Source: Crohn's & Colitis Foundation of America.

In countries and settings where tuberculosis (TB) is endemic, all efforts should be made by the treating clinician to distinguish it from CD, which is its closest differential. The fact that treatment approaches of the two diseases are diametrically opposite (antibacterials in TB *vs* immunomodulators in CD), it is all the more important to differentiate between the two. Colonoscopic features which suggest CD include perianal lesions, longitudinal ulcers, aphthous ulcers and cobblestoning. Features suggestive of TB include transverse ulcers, involvement of fewer colonic segments, a patulous ileocecal valve and pseudopolyp formation. Radiological features of CD include symmetric concentric bowel wall thickening with transmural enhancement. Segmental intestinal stenoses and fistulae formation is nearly always associated with CD. Extramural features like mesenteric vascular stranding and fibrofatty proliferation are pathognomonic of CD. Intestinal TB is characterized by asymmetric bowel wall thickening with predominant involvement of the ileocecal area and large necrotic lymphnodes in the mesentry. Tissue diagnosis is mandatory for confirming either disease. Caseating granulomas are specific for TB while non-caseating epitheloid cell granulomas are more often found (though not specific) in CD [31,32]. ***Fig.*1** shows schematic diagram to evaluate a child with IBD isregretted.

TREATMENT AND MONITORING STRATEGIES

The treatment protocols in IBD are aimed at mucosal healing, with consequent reduction in complications and



CD: Crohn's disease; IBD: Inflammatory bowel disease; UC: ulcerative colitis.

FIG. 1 *Diagnostic algorithm in a child with suspected IBD (adapted from ESPGHAN Revised Porto Criteria for the Diagnosis of Inflammatory Bowel Disease in Children and Adolescents 2014). #Atypical UC includes the following phenotypes: Rectal sparing, Cecal Patch, UGI involvement, Short duration, acute severe colitis.*

increased quality of life. The goals of therapy are to maximize efficacy, minimize toxicity, prevention of complications, and maintaining/re-establishing growth velocity and pubertal growth.

The treatment paradigm in pediatric IBD as in the adult world is the 'Step- up' approach, wherein medications with milder toxicity are used as first line therapy, before moving onto more aggressive therapies with higher toxicity. The Pediatric Ulcerative Colitis Activity Index (PUCAI) is a validated score to assess disease activity in UC. It has the advantage of being non-invasive and can be calculated easily in clinical practice (***Web Table* I**). Studies have documented its high correlation with colonoscopy findings [33,34].

PUCAI score <10 indicates remission; 10-34: mild disease activity; 35-64: moderate disease activity; >65: severe disease activity. A clinically significant response to therapy is a fall of more than 20 points. A similar score known as the Pediatric Crohn's Disease Activity index (PCDAI) is available for disease monitoring in CD (***Web Table* II**). The PCDAI score can range from 0-100, with higher scores signifying more active disease. A score of <10 is consistent with inactive disease, 11-30 indicates mild disease, and >30 is moderate- severe disease. A decrease of 12.5 points is taken as evidence of improvement.

Ulcerative Colitis

The treatment can be divided into induction of remission and maintenance. The therapies available to induce remission include 5-aminosalicylic acid (5-ASA), corticosteroids, anti-tumor necrosis factor (TNF) therapy and calcineurin inhibitors. The drugs that can be used to maintain remission include 5-ASA, thiopurines, anti-TNF therapy and a few selected probiotics.

Most guidelines recommend oral 5-ASA regimes as first line therapy during induction in mild-to-moderate UC. These are also to be used as maintenance therapy regardless of other treatments. Combination of oral and rectal 5-ASA compounds has been shown to be more effective than an oral drug alone. Topical 5-ASA (enemas) can be used as monotherapy in children with proctitis alone. Mesalazine and Sulfasalazine are the 5-ASA agents of choice. A wide variety of ASA preparations are available in the market including azo-compounds (sulfasalazine, olsalazine), controlled release (Pentasa), pH-dependent (Salofalk, Asacol); however, there is no difference in the mucosal healing rate of the different compounds [35].

Oral steroids (in a single daily dose) are effective agents in inducing remission in UC; however, they are not to be used in maintenance phase. These are recommended

in moderate UC with systemic symptoms or severe UC without symptoms, and they can also be used in children who fail to achieve remission with optimal dose of 5-ASA agents. The dose of prednisolone is 1-2 mg/kg/day (max: 40mg/day) for 2-4 weeks till remission is achieved. It can then be tapered gradually over the next 4-8 weeks. Children with severe colitis require hospitalization with vitals monitoring, complete blood counts and abdominal *X*-ray. Intravenous steroids, hydrocortisone (2 mg/kg four times a day) or methyl prednisolone (2 mg/kg/day), should be given in such cases. Failure to respond requires rescue therapy with either intravenous cyclosporine or infliximab [34].

Antibiotics have no role in either induction of remission or maintenance in UC. Intravenous antibiotics like third generation cephalosporins and metronidazole can be considered if infection is suspected, especially in cases of toxic megacolon. Probiotics (VSL#3 and *E.coli Nissle*) can be considered as adjuvant therapy in patients with mild UC and residual activity not responding to standard therapy.

Immunomodulators (Azathioprine (AZA) and Mercatopurine (MP)) are indicated only for maintenance of remission. The scenarios for their potential use include: 5-ASA intolerance, frequently relapsing disease or steroid dependant disease. They can also be given after inducing remission with steroids in acute severe colitis. If calcineurin inhibitors like cyclosporin/ tacrolimus were used in acute severe colitis, the patients would ultimately need AZA/MP. The therapeutic effect of the thiopurines is delayed and may take 2-3 months to reach full effect. Western literature recommends assay of thiopurine methyltransferase (TPMT) genotype or phenotype to identify child at risk of myelosuppression [36,37]. However, the facility to measure TPMT is not available at many centers in low-and middle-income countries. Thus, regular monitoring of complete blood counts and liver function tests needs to be done as proxy markers for TPMT activity (2 weekly for the first 4 weeks, monthly thereafter) till metabolite levels become available. Pancreatitis is the commonest hypersensitivity reaction which can occur in 3-4% of all cases. Thiopurines, in conjunction with biologicals, have also been shown to increase the risk of Non-Hodgkin lymphoma and Hepatosplenic T-cell lymphoma [35].

Infliximab (IFX) in a dose of 5 mg/kg at 0, 2 and 6 weeks followed by 5 mg/kg 8 weekly for maintenance is the agent of choice in patients with persistently active or steroid-dependant UC, not controlled by 5-ASA or steroids. It can also be considered in steroid-refractory disease. The usage of Adalimumab (ADA) in pediatric UC is anecdotal and limited to case reports; however, it can be considered in Infliximab failure or intolerance, prior to colectomy [38].

Surgery should only be considered in cases of treatment failure with all first line and second line agents. Surgery can also be considered in symptomatic children who are on multiple immunosuppressants and are steroid-dependant. The dose of immunosuppressants and biologicals need to be optimized before referring an ambulatory case for surgery. Sometimes changing IFX to ADA can also prove useful. It can also be considered in cases of toxic megacolon. A two step procedure (colectomy and pouch formation with ileostomy as the first step followed by ileostomy closure) is the most commonly performed surgery. Sometimes a single step procedure (restorative proctocolectomy/ ileo-anal pouch without ileostomy) can be performed in children who are not on high dose steroids. As with major surgeries, pre-operative clinical status (malnutrition, hypoalbuminemia, steroids) influence post-operative disease outcomes [2,39].

Crohn's Disease

For management of CD, it is helpful to categorize children into mild, moderate and severe phenotypes based on disease location, extent and severity. In addition, issues like decreased bone mass and impaired growth velocity have to be factored into the treatment regimen.

Induction of remission

Exclusive enteral nutrition (EEN) has been recommended by ESPGHAN as the modality of choice in inducing remission in children with luminal CD. While steroids have been conventionally used, EEN has the obvious advantage of lacking the toxicity of parenteral steroids. Few studies have shown higher remission rates with EEN as compared to steroids. EEN is to be given for 6-8 weeks [40,41]. Towards the end of the exclusive feeding period, reintroduction of regular diet should be started gradually over a period of several weeks. Factors influencing the use of EEN include the childs' and parents' choice, palatability, compliance and cost. Both polymeric and elemental feeds are available in the Western market. Various guidelines have advocated the use of nasogastric tubes and even gastrostomy to meet the volume required for providing adequate caloric intake (120% of total caloric requirement/day). If EEN does not induce a clinical response in two weeks, alternative therapeutic strategies should be employed. EEN is of questionable significance in children with severe pancolitis, oral and perianal CD [22].

Oral corticosteroids (prednisolone 1-2 mg/kg/d) can be used for inducing remission in children with moderate to severe luminal CD, especially if EEN is not available or not tolerated. Steroids are helpful in achieving quick clinical remission though only a small percentage of cases demonstrate mucosal healing on endoscopy [42]. Budesonide has been used in mild to moderate ileo-cecal CD to induce remission. The drug is known for its high topical activity and low systemic absorption, by virtue of its affinity to the intestinal glucocorticoid receptor [43,44]. The steroids are to be given at full dose for 2-4 weeks followed by gradual tapering over the next 8 weeks. There is no role of steroids in the maintenance therapy of pediatric CD [45].

Metronidazole (10-20 mg/kg/day) and ciprofloxacin (20 mg/kg/day) are the two antibiotics utilized for perianal CD, especially of the fistulizing type. A meta-analysis showed that antibiotics are superior to placebo in active CD [46]. Metronidazole is thought to be more efficacious in children with colitis while Ciprofloxacin is preferred in those with ileitis. Azithromycin and rifaximin are the other antibiotics that have shown benefit during induction of remission in mild luminal CD.

Anti-TNF therapy with agents like infliximab (IFX) is recommended to induce remission in children with steroid refractory CD and children with active peri-anal fistulizing CD. It can also be considered in children with high risk of poor outcome (deep ulcerations on endoscopy, pan-enteric disease, advanced osteoporosis, marked growth failure, and poor response to adequate initial therapy). The induction dose is same as for patients with UC [47].

Maintenance of remission

Thiopurines (AZA/ 6MP) are the recommended agents for maintaining steroid-free remission in children with CD. Patients who received 6-MP after induction of remission are more likely to remain in remission, when compared with placebo [48]. These immunomodulators should be prescribed in full doses from the beginning as they require 8-14 weeks to achieve full efficacy.

Methotrexate can also be used as monotherapy for maintenance of remission in CD [49]. It can also be used as a second line drug in children with thiopurine failure [50]. MTX is prescribed in a dose of 15 mg/m^2 (max 25 mg) weekly as a subcutaneous injection. It can also be given intramuscularly and orally. The bioavailability of oral MTX is variable. Oral folic acid (5 mg) 24 hours after MTX administration is necessary. Nausea and vomiting are a frequent side effects, and can be tackled by giving pre-injection Ondansetron. Other side effects include hepatotoxicity, myelosuppression and pulmonary toxicity [51]. Thiopurines are the agent of choice in maintaining remission in patients post-surgery.

Biologicals (anti-TNF agents) are recommended for maintaining remission in children with chronic active luminal CD, especially those in whom remission was induced with IFX. Other categories include children with perianal CD, in combination with appropriate surgical intervention for fistulizing disease. Severe extra-intestinal manifestations like arthropathy and pyoderma gangrenosum also respond well to anti-TNF therapy. The maintenance dose is 5 mg/kg every 8 weeks. Higher doses of 10 mg/kg, or shorter intervals of dosing *i.e.*, 4-weekly intervals may be required in cases where drug response or drug levels are low [47]. The REACH study evaluated the safety and efficacy of IFX in children with CD who had moderate to severe disease activity. They concluded that those children who had IFX in their induction regimen were more likely to be in remission at week 54 when given maintenance IFX at 8 weekly intervals [52]. ADA is another biological, which can be used in a dose of 0.6 mg/kg (maximum 40 mg) every alternate week. Switch from one biological agent to another can be made in case of non-response to one agent. Patients with sustained response to biological agents can be considered for step-down therapy to immunomodulators, especially if they are treatment-naïve [53]. Combinations of thiopurines and biologicals have also been tried in children with CD. The benefit of lower antibody development against IFX and greater response has to be weighed against the possibility of lymphoma [54]. The development of antibodies to anti-TNF drugs is responsible for causing loss of drug efficacy, drug infusion reactions and delayed hypersensitivity reactions. Anti TNF therapy can be associated with severe life threatening infections like meningitis, sepsis, herpes and fungal infections. Immunization schedules should be completed prior to initiation of IFX therapy [54].

Amino-salicylates can be used in very mild colonic disease in doses similar to UC [55]. There use in pediatric population is limited to information from only two clinical trials [56,57]. However, there is no evidence to suggest that they induce mucosal healing or be used as stand-alone therapy. Partial enteral nutrition cannot be used to induce remission. However, it can be used as maintenance therapy in patients with very mild disease or low risk of relapse. Omega-3 fatty acids and probiotics are not recommended for maintenance of remission.

The indications for surgery in CD include failure of medical therapy, growth failure despite maximal therapy, extraintestinal involvement (eyes and joints), and disease complications like obstruction, fistulae and perforation. The surgical paradigm in CD is to resect areas with

macroscopic disease, that mainly is the ileocolonic area, with a right hemicolectomy. The use of strictureplasty and balloon dilatation of strictures is limited to adult literature [39]. Perianal CD behaves like a distinct disease subtype and requires optimal use of biologicals, early and correct use of antibiotics and abscess drainage along with seton placement, if required.

Stopping/stepping-down therapy

There are no definite guidelines on when to stop therapy. Immunomodulators and anti-TNF therapy, if effective, should be continued for a prolonged period, and should not be stopped during critical growth phases, especially during or before adolescence. Drug de-escalation can be considered in children, who have been in prolonged steroid-free remission, especially those with complete mucosal healing. Surrogate markers like CRP, hemoglobin level, fecal calprotectin can also be used as adjuncts to de-escalate therapy. Complete stoppage of therapy is generally not advisable and often not possible, except in few patients with very mild/ limited disease. Stepping down from combination therapy (anti-TNF + thiopurines) to IFX monotherapy should be done after mucosal healing is achieved [35].

Step-up therapy has been conventionally used in CD. It involves giving steroids, 5-ASA agents, nutrition and antibiotics to ameliorate symptoms of the disease. The non-responders are then given immunomodulators and subsequently biologicals. This approach is gentler, with lesser side effects and avoids over-treatment of a low risk patient. On the other hand, failure to optimize conventional therapy can lead to serious side effects including surgery and the need for potentially toxic drugs at higher doses for a prolonged period of time. Top-down therapy involves the early use of immunosuppressants and biologicals in certain disease phenotypes with a known poor outcome (perianal CD) to induce remission [58]. Several recent studies have shown lesser relapses, lesser complications, less need for surgery and less use of steroids with this approach [59-61]. Top-down therapy offers the potential for altering the natural history of CD, and might help in changing treatment paradigms. This approach; however, is fraught with complications like increased risk of life-threatening infections, tuberculosis and herpes zoster re-activation. In addition, it imposes an economic burden on the family.

CONCLUSION

Pediatric IBD is a complex disease, which continues to evolve. Diagnostic and treatment strategies are based mainly on multicentric adult studies and pediatric series. Treatment paradigms are gradually shifting from the step-up approach to the step-down approach, with increasing experience of the severity of certain disease sub-types. With more-and-more work being done in the field of genetics, the genotype-phenotype combination may ultimately guide disease treatment.

REFERENCES

1. Carvalho RS, Abadom V, Dilworth HP, Thompson R, Oliva-Hemker M, Cuffari C. Indeterminate colitis: a significant subgroup of pediatric IBD. Inflamm Bowel Dis. 2006;12:258-62.
2. Abraham BP, Mehta S, El-Serag HB. Natural history of pediatric-onset inflammatory bowel disease: a systematic review. J Clin Gastroenterol. 2012;46:581-9.
3. Martin-de-Carpi J, Rodriguez A, Ramos E, Jimenez S, Martinez-Gomez MJ, Medina E, *et al*. Increasing incidence of pediatric inflammatory bowel disease in Spain (1996-2009): the SPIRIT Registry. Inflamm Bowel Dis. 2013; 19:73-80.
4. 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; 14:1246-52.
5. 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;146:35-40.
6. Sauer CG, Kugathasan S. Pediatric inflammatory bowel disease: highlighting pediatric differences in IBD. Med Clin North Am. 2010;94:35-52.
7. Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. Inflamm Bowel Dis. 2011;17:423-39.
8. Sathiyasekaran M, Raju BB, Shivbalan S, Rajarajan K. Pediatric Crohn's disease in South India. Indian Pediatr. 2005;42:459-63.
9. Avinash B, Dutta AK, Chacko A. Pediatric inflammatory bowel disease in South India. Indian Pediatr. 2009;46:639-40.
10. Sathiyasekaran M, Bavanandam S, Sankaranarayanan S, Mohan N, Geetha M, Wadhwa N, *et al*. A questionnaire survey of pediatric inflammatory bowel disease in India. Indian J Gastroenterol. 2014;33:543-9.
11. Biank V, Broeckel U, Kugathasan S. Pediatric inflammatory bowel disease: clinical and molecular genetics. Inflamm Bowel Dis. 2007;13:1430-8.
12. Aujnarain A, Mack DR, Benchimol EI. The role of the environment in the development of pediatric inflammatory bowel disease. Curr Gastroenterol Rep. 2013;15:326.
13. Timm S, Svanes C, Janson C, Sigsgaard T, Johannessen A, Gislason T, *et al*. Place of upbringing in early childhood as related to inflammatory bowel diseases in adulthood: a population-based cohort study in Northern Europe. Eur J Epidemiol. 2014;29:429-37.
14. Aloi M, Cucchiara S. Extradigestive manifestations of IBD in pediatrics. Eur Rev Med Pharmacol Sci. 2009;13:23-32.

15. Bousvaros A, Sylvester F, Kugathasan S, Szigethy E, Fiocchi C, Colletti R, *et al*. Challenges in pediatric inflammatory bowel disease. Inflamm Bowel Dis. 2006;12:885-913.
16. Kwon YH, Kim YJ. Pre-diagnostic clinical presentations and medical history prior to the diagnosis of inflammatory bowel disease in children. Pediatr Gastroenterol Hepatol Nutr. 2013;16:178-84.
17. Davis MK, Andres JM, Jolley CD, Novak DA, Haafiz AB, Gonzalez-Peralta RP. Antibodies to Escherichia coli outer membrane porin C in the absence of anti-Saccharomyces cerevisiae antibodies and anti-neutrophil cytoplasmic antibodies are an unreliable marker of Crohn disease and ulcerative colitis. J Pediatr Gastroenterol Nutr. 2007; 45:409-13.
18. Davis MK, Valentine JF, Weinstein DA, Polyak S. Antibodies to CBir1 are associated with glycogen storage disease type Ib. J Pediatr Gastroenterol Nutr. 2010;51:14-8.
19. Aomatsu T, Yoden A, Matsumoto K, Kimura E, Inoue K, Andoh A, *et al.* Fecal calprotectin is a useful marker for disease activity in pediatric patients with inflammatory bowel disease. Dig Dis Sci. 2011;56:2372-7.
20. Chang MH, Chou JW, Chen SM, Tsai MC, Sun YS, Lin CC, *et al*. Faecal calprotectin as a novel biomarker for differentiating between inflammatory bowel disease and irritable bowel syndrome. Mol Med Rep. 2014;10:522-6.
21. Levine A, Koletzko S, Turner D, Escher JC, Cucchiara S, de Ridder L, *et al*. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. J Pediatr Gastroenterol Nutr. 2014;58:795-806.
22. Ruemmele FM, Veres G, Kolho KL, Griffiths A, Levine A, Escher JC, *et al*. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J Crohns Colitis. 2014;8:1179-207.
23. Turner D, Griffiths AM. Esophageal, gastric, and duodenal manifestations of IBD and the role of upper endoscopy in IBD diagnosis. Curr Gastroenterol Rep. 2009;11:234-7.
24. Eszter Muller K, Laszlo Lakatos P, Papp M, Veres G. Incidence and paris classification of pediatric inflammatory bowel disease. Gastroenterol Res Pract. 2014; 2014: 904307.
25. Alliet P, Desimpelaere J, Hauser B, Janssens E, Khamis J, Lewin M, *et al*. MR enterography in children with Crohn disease: results from the Belgian pediatric Crohn registry (Belcro). Acta Gastroenterol Belg. 2013;76:45-8.
26. Gralnek IM, Cohen SA, Ephrath H, Napier A, Gobin T, Sherrod O, *et al*. Small bowel capsule endoscopy impacts diagnosis and management of pediatric inflammatory bowel disease: a prospective study. Dig Dis Sci. 2012;57:465-71.
27. Hudesman D, Mazurek J, Swaminath A. Capsule endoscopy in Crohn's disease: are we seeing any better? World J Gastroenterol. 2014;20:13044-51.
28. Min SB, Le-Carlson M, Singh N, Nylund CM, Gebbia J, Haas K, *et al*. Video capsule endoscopy impacts decision making in pediatric IBD: a single tertiary care center experience. Inflamm Bowel Dis. 2013;19:2139-45.
29. North American Society for Pediatric Gastroenterology Hepatology and Nutrition, Crohn's and Colitis Foundation of America, Bousvaros A, Antonioli DA, Colletti RB, *et al*. Differentiating ulcerative colitis from Crohn disease in children and young adults: report of a working group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Crohn's and Colitis Foundation of America. J Pediatr Gastroenterol Nutr. 2007;44:653-74.
30. Frush DP, Goske MJ. Image Gently: toward optimizing the practice of pediatric CT through resources and dialogue. Pediatr Radiol. 2015;45:471-5.
31. Weng MT, Wei SC, Lin CC, Tsang YM, Shun CT, Wang JY, *et al*. Seminar Report From the 2014 Taiwan Society of Inflammatory Bowel Disease (TSIBD) Spring Forum (May 24th, 2014): Crohn's disease versus intestinal tuberculosis infection. Intest Res. 2015;13:6-10.
32. Makharia GK, Srivastava S, Das P, Goswami P, Singh U, Tripathi M, *et al*. Clinical, endoscopic, and histological differentiations between Crohn's disease and intestinal tuberculosis. Am J Gastroenterol. 2010;105:642-51.
33. Turner D, Hyams J, Markowitz J, Lerer T, Mack DR, Evans J, *et al*. Appraisal of the pediatric ulcerative colitis activity index (PUCAI). Inflamm Bowel Dis. 2009;15:1218-23.
34. Turner D, Travis SP, Griffiths AM, Ruemmele FM, Levine A, Benchimol EI, *et al*. Consensus for managing acute severe ulcerative colitis in children: a systematic review and joint statement from ECCO, ESPGHAN, and the Porto IBD Working Group of ESPGHAN. Am J Gastroenterol. 2011;106:574-88.
35. Aloi M, Nuti F, Stronati L, Cucchiara S. Advances in the medical management of paediatric IBD. Nat Rev Gastroenterol Hepatol. 2014;11:99-108.
36. Weinshilboum RM, Sladek SL. Mercaptopurine pharmacogenetics: monogenic inheritance of erythrocyte thiopurine methyltransferase activity. Am J Hum Genet. 1980;32:651-62.
37. Dubinsky MC, Lamothe S, Yang HY, Targan SR, Sinnett D, Theoret Y, *et al*. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. Gastroenterology. 2000; 118:705-13.
38. Yang LS, Alex G, Catto-Smith AG. The use of biologic agents in pediatric inflammatory bowel disease. Curr Opin Pediatr. 2012;24:609-14.
39. Baillie CT, Smith JA. Surgical strategies in paediatric inflammatory bowel disease. World J Gastroenterol. 2015;21:6101-16.
40. Berni Canani R, Terrin G, Borrelli O, Romano MT, Manguso F, Coruzzo A, *et al*. Short- and long-term therapeutic efficacy of nutritional therapy and corticosteroids in paediatric Crohn's disease. Dig Liver Dis. 2006;38:381-7.
41. Whitten KE, Rogers P, Ooi CY, Day AS. International survey of enteral nutrition protocols used in children with Crohn's disease. J Dig Dis. 2012;13:107-12.
42. Bousvaros A. Mucosal healing in children with Crohn's disease: appropriate therapeutic goal or medical overkill? Inflamm Bowel Dis. 2004;10:481-3.
43. Escher JC, European Collaborative Research Group on Budesonide in Paediatric IBD. Budesonide versus prednisolone for the treatment of active Crohn's disease in children: a randomized, double-blind, controlled, multi-

centre trial. Eur J Gastroenterol Hepatol. 2004;16:47-54.
44. Levine A, Weizman Z, Broide E, Shamir R, Shaoul R, Pacht A, *et al*. A comparison of budesonide and prednisone for the treatment of active pediatric Crohn disease. J Pediatr Gastroenterol Nutr. 2003;36:248-52.
45. Dimakou K, Pachoula I, Panayotou I, Stefanaki K, Orfanou I, Lagona E, *et al*. Pediatric inflammatory bowel disease in Greece: 30-years experience of a single center. Ann Gastroenterol. 2015;28:81-6.
46. Khan KJ, Ullman TA, Ford AC, Abreu MT, Abadir A, Marshall JK, *et al*. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol. 2011;106:661-73.
47. Olbjorn C, Nakstad B, Smastuen MC, Thiis-Evensen E, Vatn MH, Perminow G. Early anti-TNF treatment in pediatric Crohn's disease. Predictors of clinical outcome in a population-based cohort of newly diagnosed patients. Scand J Gastroenterol. 2014;49:1425-31.
48. Markowitz J, Grancher K, Kohn N, Lesser M, Daum F. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. Gastroenterology. 2000;119:895-902.
49. Uhlen S, Belbouab R, Narebski K, Goulet O, Schmitz J, Cezard JP, *et al*. Efficacy of methotrexate in pediatric Crohn's disease: a French multicenter study. Inflamm Bowel Dis. 2006;12:1053-7.
50. Turner D, Grossman AB, Rosh J, Kugathasan S, Gilman AR, Baldassano R, *et al*. Methotrexate following unsuccessful thiopurine therapy in pediatric Crohn's disease. Am J Gastroenterol. 2007;102:2804-12.
51. Sunseri W, Hyams JS, Lerer T, Mack DR, Griffiths AM, Otley AR, *et al*. Retrospective cohort study of methotrexate use in the treatment of pediatric Crohn's disease. Inflamm Bowel Dis. 2014;20:1341-5.
52. Hyams J, Crandall W, Kugathasan S, Griffiths A, Olson A, Johanns J, *et al*. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology. 2007;132:863-73;.
53. Nobile S, Gionchetti P, Rizzello F, Calabrese C, Campieri M. Mucosal healing in pediatric Crohn's disease after anti-TNF therapy: a long-term experience at a single center. Eur J Gastroenterol Hepatol. 2014;26:458-65.
54. Assa A, Hartman C, Weiss B, Broide E, Rosenbach Y, Zevit N, *et al*. Long-term outcome of tumor necrosis factor alpha antagonist's treatment in pediatric Crohn's disease. J Crohns Colitis. 2013;7:369-76.
55. Ford AC, Kane SV, Khan KJ, Achkar JP, Talley NJ, Marshall JK, *et al*. Efficacy of 5-aminosalicylates in Crohn's disease: systematic review and meta-analysis. Am J Gastroenterol. 2011;106:617-29.
56. Griffiths A, Koletzko S, Sylvester F, Marcon M, Sherman P. Slow-release 5-aminosalicylic acid therapy in children with small intestinal Crohn's disease. J Pediatr Gastroenterol Nutr. 1993;17:186-92.
57. Cezard JP, Munck A, Mouterde O, Morali A, Lenaerts C, Lachaux A, *et al*. Prevention of relapse by mesalazine (Pentasa) in pediatric Crohn's disease: a multicenter, double-blind, randomized, placebo-controlled trial. Gastroenterol Clin Biol. 2009;33:31-40.
58. Lin MV, Blonski W, Lichtenstein GR. What is the optimal therapy for Crohn's disease: step-up or top-down? Expert Rev Gastroenterol Hepatol. 2010;4:167-80.
59. Kim MJ, Lee JS, Lee JH, Kim JY, Choe YH. Infliximab therapy in children with Crohn's disease: a one-year evaluation of efficacy comparing 'top-down' and 'step-up' strategies. Acta Paediatr. 2011;100:451-5.
60. Krupoves A, Mack DR, Seidman EG, Deslandres C, Bucionis V, Amre DK. Immediate and long-term outcomes of corticosteroid therapy in pediatric Crohn's disease patients. Inflamm Bowel Dis. 2011;17:954-62.
61. Mayberry JF, Lobo A, Ford AC, Thomas A. NICE clinical guideline (CG152): the management of Crohn's disease in adults, children and young people. Aliment Pharmacol Ther. 2013;37:195-203.

WEB TABLE I THE PEDIATRIC ULCERATIVE COLITIS ACTIVITY INDEX

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

Source: Turner D, Otley AR, Mack D, et al. Development and evaluation of a Pediatric Ulcerative Colitis Activity Index (PUCAI): A prospective multicenter study. Gastroenterology. 2007;133:423-32.

WEB TABLE II THE PEDIATRIC CROHN'S DISEASE ACTIVITY INDEX

Items	*Points*
Abdominal pain	
None	0
Mild (brief episodes, not interfering with activities)	5
Moderate/severe (frequent or persistent, affecting with activities)	10
Stools	
0-1 liquid stools, no blood	0
2-5 liquid or up to 2 semi-formed with small blood	5
Gross bleeding, >6 liquid stools or nocturnal diarrhoea	10
Patient functioning, general well-being (Recall, 1 week)	
No limitation of activities, well	0
Occasional difficulties in maintaining age appropriate activities, below par	5
Frequent limitation of activities, very poor	10
Weight	
Weight gain or voluntary weight loss	0
Involuntary weight loss 1-9%	5
Weight loss >10%	10
Height	
<1 channel decrease (or height velocity >-SD)	0
>1 <2 channel decrease (or height velocity <-1SD> -2SD)	5
>2 channel decrease (or height velocity <-2SD)	10
Abdomen	
No tenderness, no mass	0
Tenderness, or mass without tenderness	5
Tenderness, involuntary guarding, definite mass	10
Peri-rectal disease	
None, asymptomatic tags	0
1-2 indolent fistula, scant drainage, tenderness of abscess	5
Active fistula, drainage, tenderness or abscess	10
Extra-intestinal manifestations	
Fever >38.5 × 3 days in week, arthritis, uveitis, erythema nodosum, or pyoderma gangrenosum	
None	0
One	5
Two	10
Hematocrit	
<10yrs 11-14 (male) 11-19 (female) 15-19 (male)	
>33 >35 >34 >37	0
28-33 30-34 29-33 32-36	2.5
<28 <30 <29 <32	5
ESR (mm/hr)	
< 20	0
20-50	2.5
> 50	5
Albumin (g/L)	
>35	0
31-34	5
<30	10

Source: Hyems JS, Ferry GD, Mardel FS, et al. Development and Validation of a Pediatric Grohn's Disease Activity Index. J Pediatr Gastroenterol Nurt. 1991;12:439-47.