Diagnosis and management of inflammatory bowel disease in children

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**Abstract**

Inflammatory bowel diseases (IBD), including Crohn’s disease and ulcerative colitis, are lifelong conditions that often begin in childhood. The implications of IBD are of particular importance in children because of the potential negative effects on growth, development, psychosocial function, and overall wellbeing. The key management strategy is to achieve sustained control of intestinal inflammation and monitor for potential complications of the disease and side effects of therapies. Overall, the evidence on the management of IBD in children is less extensive than in adults, but good quality multicenter studies and various guidelines and society consensus statements are available. This review summarizes the evidence on the pathophysiology, diagnosis, and approaches to management of children and adolescents with IBD.

**Introduction**

Crohn’s disease and ulcerative colitis are chronic relapsing conditions; Crohn’s disease involves the entire gastrointestinal tract from mouth to anus, whereas ulcerative colitis affects only the colon. The incidence and prevalence of inflammatory bowel diseases (IBD) is increasing, and 20-30% of cases present before the age of 20 years. IBD that starts in childhood is associated with more extensive disease, higher disease activity, and a more complicated course than adult onset IBD. The mean
delay from onset to diagnosis is 11 months in new onset pediatric IBD (PIBD).4 Before 2000 the mainstay of treatment was anti-inflammatory drugs and corticosteroids, but now the armamentarium has expanded to immunomodulators and biologics. As the genotypic-phenotypic understanding of IBD advances, customized treatment for individual patients will be developed. Shortening the time to diagnosis and adherence to diagnostic and therapeutic guidelines should lead to improved clinical outcomes.5 The focus of management should be on controlling gut inflammation and optimizing nutrition, growth, and quality of life (QOL), while preventing disease related or treatment related complications.6 This review summarizes the evidence on disease presentation, diagnostic approach, and treatment options in children aged up to 18 with IBD.

Sources and selection criteria
We searched PubMed through December 2016 using the following terms alone and in combination: “inflammatory bowel disease”, “Crohn’s disease”, “ulcerative colitis”, “pathophysiology”, “epidemiology”, “diagnosis”, “disease management”, “complications”, and “child/children”. We also searched bibliographies of articles identified from relevant studies. Evidence came from articles in English that included randomized studies, cohort studies, observational studies, meta-analyses, and systematic reviews. Owing to the paucity of pediatric data, we also included retrospective studies and case series/reports. Most studies pertinent to the review were included, irrespective of the number of participants. We included the most recent articles named as “guidelines” or “clinical practice”. We also included some studies in adults when no pediatric data were available.

Epidemiology
Rates of PIBD are increasing worldwide, but accurate estimates are lacking.7 Table 1 shows the incidence of PIBD worldwide. Ontario has one of the highest rates of childhood onset IBD, with an accelerated increase in incidence in younger children.23 Scotland has seen a 76% increase in diagnosis of PIBD since the mid-1990s, and the diagnosis was made at a younger age.24 People immigrating from low to high prevalence regions are at increased risk for developing IBD, particularly among first generation children.25 Australasian data indicate increasing incidence of PIBD, predominantly in children of European ancestry, with lower rates in indigenous populations.26 In a community based healthcare delivery system in northern California, the incidence of ulcerative colitis increased 2.7-fold over a period of 10 years. Hispanic and Asian children developed ulcerative colitis more often than Crohn’s disease.27 In British Columbia, South Asians had a threefold higher incidence of PIBD than non-South Asians.18 A population based study in Wisconsin found that the incidence of PIBD was similar in different ethnic groups, as well as in densely populated compared with sparsely populated counties.28 The relative risk for developing pediatric onset Crohn’s disease was higher in affluent areas, but this was not the case for ulcerative colitis.22 A higher prevalence with increasing latitudes has been noted for pediatric onset Crohn’s disease in Scotland and for ulcerative colitis in Finland,22 29 and an east-west gradient in IBD incidence was noted in Europe.30
Pathophysiology

IBD is an immune mediated disease. In recent years, the specifics of the interaction of innate and adaptive responses to the disease process are becoming clearer. Genome-wide association studies have identified more than 200 genetic loci associated with IBD.31 These genes code for proteins involved in innate and adaptive immunity, autophagy, and mucosal barrier integrity and play a key role in immune homeostasis. Thus, a dysregulated immune response to commensal intestinal bacteria due to an underlying genetic predisposition is thought to be the trigger for chronic inflammation.32 33 34 Environmental factors likely influence many steps of the pathophysiology, such as the effect of diet and antibiotic use on epithelial barrier function and microbial diversity.35

The microbiome in Crohn’s disease has an increased abundance of specific bacterial families and a decrease of others.35 In PIBD and adult IBD, an increased load of entero-invasive *Escherichia coli* strains has been observed.36 However, no specific organism has been shown to cause IBD. Recently, interest has shifted to the role of the microbiome and environmental factors in the risk of development of autoimmune and inflammatory conditions, including IBD. The hygiene hypothesis theorizes that people raised under sanitary conditions have a higher risk of developing immune mediated diseases, such as IBD.37 A systematic review found an inverse association of several factors related to environmental hygiene and the risk of IBD, which is in alignment with the hygiene hypothesis.38 Figure 1 summarizes the pathophysiology in IBD.
Genetics

PIBD is familial in 19-41% of cases, compared with 5-10% in adults. A highly significant association was reported between Crohn’s disease and interleukin 23R in non-Jewish people of European ancestry with ileal Crohn’s disease; however, a coding variant of interleukin 23R was also found to confer a strong protective effect in a cohort of pediatric Crohn’s disease. A positive family history is often present when Crohn’s disease is diagnosed before 11 years of age. Genetic factors have only a modest role, and epigenetic factors may play a role in disease development. Different patterns of DNA methylation have been observed in treatment-naive PIBD, which supports the hypothesis of epigenetic factors playing a role in the pathophysiology.

Evaluation and diagnosis

Clinical presentation

PIBD presents with wide variety of symptoms, both gastrointestinal and extra-intestinal. The initial presentation of ulcerative colitis is commonly abdominal pain and bloody diarrhea. This usually comes to medical attention sooner than the more varied and sometimes subtle presentation of Crohn’s disease. A child with Crohn’s disease may present with bloody diarrhea and abdominal pain when colitis is present or with vaguer symptoms such as non-bloody diarrhea, weight loss/growth failure, malaise, fatigue, anemia, or fever. Table 2 outlines characteristics of ulcerative colitis and Crohn’s disease in PIBD.

Extra-intestinal manifestations may be the initial presentation of IBD and are more common in Crohn’s disease than in ulcerative colitis. They include erythema nodosum, pyogenic granuloma, uveitis, episcleritis, arthritis, and primary sclerosing cholangitis.

Two retrospective cohort studies (n=160 and n=153) found no differences in clinical presentation or subsequent hospital admission between younger and older children with PIBD. In a PIBD consortium registry (n=998), 9.9% of children with Crohn’s disease were 0-5 years of age, and children in this age group were more likely to present with rectal bleeding and be initially diagnosed as having ulcerative colitis; they tended to have a more severe disease course and higher disease burden. Short stature, seen only in Crohn’s disease, occurred in about a fifth of the cases at presentation.
Very early onset IBD is defined as the onset of IBD in children 6 years and younger. Very early onset IBD is still considered “polygenic” in nature, but a subgroup of very young patients, including neonates, may have one of the monogenic forms of the disease (XIAP deficiency, interleukin 10 signaling defects, IPEX-like), which have more severe presentations and will likely not respond to traditional treatment.47, 48 The full spectrum of diagnostic testing and potential therapies for very early onset IBD will not be covered in this review.

Baseline tests

Baseline tests should include a complete blood count, liver enzymes, albumin, C reactive protein (CRP), and/or erythrocyte sedimentation rate (ESR).49 The sensitivity and specificity of anemia and increased ESR as predictors for IBD was 83% and 94% respectively (n=227, retrospective study).50 In children with intestinal or nutritional problems, anemia and thrombocytosis had a sensitivity of 90.8% and a specificity of 80% for ulcerative colitis and Crohn’s disease (n=103 IBD, 50 controls, screening test).51 Infectious causes should be excluded using stool nucleic acid amplification tests or culture.52 Fecal inflammatory markers such as calprotectin and lactoferrin can help in differentiating IBD from irritable bowel syndrome, but they can also be elevated in other inflammatory conditions. Calprotectin correlates significantly with mucosal inflammation in PIBD and can be used as a surrogate marker for inflammation; normalization indicates mucosal healing.53 A meta-analysis of 19 diagnostic studies in children with chronic gastrointestinal symptoms concluded that calprotectin, CRP, and albumin have potential clinical value to select children at low risk (negative calprotectin) or high risk (positive CRP or low albumin) for IBD (n=2806).54 Normal laboratory tests, however, may not always exclude IBD. In PIBD, normal platelets, ESR, albumin, or hemoglobin were found in 21% of mild Crohn’s disease cases, 54% of mild ulcerative colitis, and 4% of more severe Crohn’s disease or ulcerative colitis (n=392 CD, 134 UC; prospective multicenter study).55

Serology

Available serological markers are atypical perinuclear antineutrophil cytoplasmic antibody (pANCA), anti-saccharomyces cerevisiae antibody (ASCA), antibodies to Escherichia coli outer membrane porin, Pseudomonas fluorescens associated sequenceI2, and flagellin CBir1. In a retrospective study, the IBD Serology7 panel (Prometheus Laboratories, San Diego, CA), when compared with routine blood tests, had lower predictive value in screening for PIBD (n=394).56 A recent review concluded that the use of serum antibodies remains complementary in clinical practice.57 Serology may have a role in assessing prognosis. Children with Crohn’s disease who are ASCA IgA/IgG positive have a high prevalence of terminal ileal or ileocecal disease and are more likely to need surgery; in contrast, those with Crohn’s disease and positive pANCA are more likely to have pancolitis or left sided disease with sparing of the terminal ileum, and ileocecal resection is uncommon (n=139, retrospective cohort).58

Endoscopy

Colonoscopy including intubation of the terminal ileum and multiple biopsies for histology obtained
from all segments of the lower intestinal tract is essential to differentiate Crohn’s disease from ulcerative colitis and identify localization and extent of disease.\textsuperscript{49} Isolated ileal inflammation may occur in the presence of a normal colon in up to 9\% of children with Crohn’s disease, so ileal intubation should always be attempted.\textsuperscript{4} Unlike in adults, 10-34\% of children with new onset ulcerative colitis lack histological features of chronic colitis at presentation.\textsuperscript{59}

Esophagogastroduodenoscopy should be part of the first line investigation in all cases of suspected IBD. Absence of specific upper gastrointestinal symptoms does not preclude presence of upper gastrointestinal inflammation.\textsuperscript{60} In a retrospective study of 172 children with suspected IBD, the diagnosis was changed to Crohn’s disease on the basis of biopsies obtained at esophagogastroduodenoscopy.\textsuperscript{51} Data from a PIBD registry found that esophagogastroduodenoscopy helped to establish the final diagnosis in 10\% of the children with IBD.\textsuperscript{62}

The possibility of avoiding ionizing radiation and deep sedation/general anesthesia with capsule endoscopy makes it an appealing tool for diagnosis and monitoring in PIBD. In a meta-analysis of children undergoing capsule endoscopy (n=723), 65.4\% had positive diagnosis, 69.4\% had a new diagnosis, 68.3\% had a change in treatment, and 2.6\% had capsule retention.\textsuperscript{63} In a prospective cohort study (n=18), capsule endoscopy helped in diagnosing Crohn’s disease in 83.3\%, affected medical decision making in 72.2\%, and led to a change in medical management in 77.8\% of the children.\textsuperscript{64} Capsule endoscopy was found to provide additional clinical information that affected management and improved outcomes in a tertiary PIBD center (n=66 established PIBD, 17 suspected; retrospective review).\textsuperscript{65} Nevertheless, because histology cannot be obtained with capsule endoscopy, it remains a complementary diagnostic tool.

**Guidelines**

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the working group of the North American Society for Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN)/Crohn’s and Colitis Foundation of America recommend total colonoscopy with ileal intubation, upper endoscopy (esophagogastroduodenoscopy), multiple biopsies, and complete small bowel exploration as diagnostic procedures.\textsuperscript{49, 66}

**Imaging**

Cross sectional imaging techniques can depict subtle features of active inflammation such as fibrofatty proliferation and mesenteric hypervasculartiy, as well as extraluminal complications such as enteric fistula, intra-abdominal abscess, and free intraperitoneal air. The non-invasive nature of imaging makes it an ideal tool for serial assessment of disease activity and treatment response in patients receiving immunomodulators. A meta-analysis found no significant difference in the diagnostic accuracy of the various imaging modalities, so the choice of imaging should be based on their specific advantages and disadvantages (table 3 \textsuperscript{69}).
Barium small bowel follow-through is no longer the primary imaging modality in PIBD. However, it is still favored by some people as it is easy to perform, is widely available, and does not require sedation.\textsuperscript{67, 68}

Computed tomography can be used to stage IBD at diagnosis and assesses complications. Computed tomography is valuable in determining the cause of symptoms such as abdominal pain, vomiting, and fever in children with PIBD presenting to the emergency department.\textsuperscript{70}

Ultrasonography is suitable for visualizing features of Crohn’s disease such as bowel thickness and dilatation, strictures, presence of fistulas, abscesses, or inflammatory changes in the mesentery.\textsuperscript{71}

Small intestine contrast ultrasonography (SICUS) can be performed using oral anechoic contrast solution to enhance the sensitivity. In a study of 51 consecutive children with suspected or diagnosed Crohn’s disease, the sensitivity and specificity of SICUS were 100% and 100% respectively in patients without a previous diagnosis and 96% and 100% respectively in proven Crohn’s disease.\textsuperscript{72}

Magnetic resonance enterography (MRE) has a higher specificity in children compared with a higher sensitivity in adults. A systematic review of 11 studies (n=496 children) concluded that MRE should supersede barium meal enteroclysis as the small bowel imaging technique in centers with appropriate expertise.\textsuperscript{73} Pelvic magnetic resonance imaging (MRI) is considered the gold standard for evaluating fistulas by identifying sinus tracts containing fluid with peripheral enhancement and abscesses, which appear as extraluminal focal fluid collections with a contrast enhanced rim.\textsuperscript{74} MRE is the imaging modality of choice in PIBD at diagnosis. It may detect small intestinal involvement and inflammatory changes in the intestinal wall and identify disease complications.\textsuperscript{74, 75}

Guidelines

The American College of Radiology (ACR) criteria for imaging of a child or young adult with suspected Crohn’s disease at initial presentation give equal weighting to computed tomography enterography and MRE. For imaging of children and young adults with known Crohn’s disease and an acute presentation (abdominal pain, fever, or leukocytosis), the ACR gives equal weighting to computed tomography of the abdomen and pelvis with contrast and MRE. The newer ACR recommendation for a child or young adult with known Crohn’s disease and stable non-acute mild symptoms on surveillance is to use MRE.\textsuperscript{71}

Management

Treatment of IBD has evolved in the past decades to multiple available therapies.\textsuperscript{76} To decide which treatment will be most successful for a given patient, disease severity, location, phenotype, effect of the disease on growth and development, and the psychosocial status of the patient should all be considered.\textsuperscript{76} The approach to treating IBD has been classically described as either “top down” or “step up.” The step-up approach uses drugs such as aminosalicylates, antibiotics, or enteral therapy and
escalates to immunomodulators, biologics, or surgical intervention if the disease worsens. In the top-down approach, treatment starts with drugs such as biologics on the basis of disease severity, with the hope that the therapy can be downgraded to “less aggressive” drugs.\textsuperscript{76} In reality, patients do not always go up or down the spectrum of available drugs used to treat IBD. Some phenotypes are predictive of a complicated course and therefore warrant early and ongoing aggressive treatment. De-escalating or trying the step-up approach could potentially prolong the course of active disease. In case of worsening disease, drugs may be added and not necessarily substituted, switching from monotherapy to combination therapy.\textsuperscript{77}

Once diagnosis is established, two important decisions will need to be made: which treatment should be used for induction of remission and which for maintenance therapy. This decision should be individualized to each patient and clinical scenario. In many cases, more than one acceptable treatment strategy exists. The STRIDE (Selecting Therapeutic Targets in IBD) initiative proposed the “treat to target approach,” providing 12 recommendations including goals such as mucosal healing and improvement of QOL.\textsuperscript{78} In pediatrics, restoration of appropriate growth and pubertal development are also important goals.\textsuperscript{79} Tables 4 and 5 outline the drugs used in PIBD, dosing, side effects, and screening tests.

<table>
<thead>
<tr>
<th>Table 4 Dosing for commonly used drugs in pediatric inflammatory bowel disease\textsuperscript{34, 76}</th>
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<table>
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<tr>
<th>Table 5 Recommended tests before starting treatment with immunomodulators or biologics and for monitoring of treatment\textsuperscript{80, 81, 82, 83}</th>
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<tbody>
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</table>

**Guidelines**

European Crohn’s and Colitis Organisation (ECCO)/ESPGHAN provide evidence based guidance on management of pediatric Crohn’s disease. Nutrition therapy is recommended as first line to induce remission in active Crohn’s disease.\textsuperscript{34} Nevertheless, this is not common practice in the US, mainly owing to acceptance by patients/families. The ESPGHAN consensus on management of acute severe ulcerative colitis in children provides a stepwise approach to escalating therapy based on Pediatric Ulcerative Colitis Activity Index (PUCAI) progression (fig 2).\textsuperscript{85} Clinical reports and consensus statements are also available from NASPGHAN for long term health supervision, management of pediatric Crohn’s disease with perianal manifestations and penetrating phenotype, and approach to infectious diseases in children receiving anti-tumor necrosis factor- (TNF-) drugs.\textsuperscript{86, 87, 88}
Induction therapy

Exclusive enteral nutrition

Exclusive enteral nutrition (EEN) can be used for six to eight weeks to induce remission in patients with a new diagnosis or an acute flare of the disease. Evidence shows that elemental formulas are not superior to polymeric formulas, supporting the use of such formulas, which are less expensive and more palatable. Limited data from meta-analyses in 2000 and 2007 suggest that enteral nutrition has similar efficacy to corticosteroids in induction of remission in children with Crohn’s disease. EEN was shown to be superior to corticosteroids alone in treatment of active disease when the primary outcome was mucosal healing (n=37 children with Crohn’s disease; 19 polymeric diet, 18 steroids; randomized control, open label trial). Many theoretical explanations exist for how EEN works, but the mechanism is likely related to a diet induced modulation of intestinal microbiome. Partial enteral nutrition (PEN), when only a percentage of the total calorie intake is composed of a formula, has been shown to be ineffective in inducing remission in children with active Crohn’s disease (pediatric Crohn’s Disease Activity Index >20; see fig 3 for scoring). However, PEN can be used to improve nutritional status and maintenance of remission along with maintenance drugs.
### Table 1: Pediatric Crohn's Disease Activity Index (PCDAI)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Response Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>None, Mild, Severe, Diarrhea</td>
<td>0, 1</td>
</tr>
<tr>
<td>Stools</td>
<td>None, Liquid, Blood</td>
<td>0, 1</td>
</tr>
<tr>
<td>Patient functioning, general wellbeing</td>
<td>No limitations of activity, well</td>
<td>0, 1</td>
</tr>
<tr>
<td>Hematocrit 8-10 years</td>
<td>Moderate, severe, bleeding, diarrhea</td>
<td>0, 1</td>
</tr>
<tr>
<td>Hematocrit 4-6 years</td>
<td>Severe, bleeding, diarrhea</td>
<td>0, 1</td>
</tr>
<tr>
<td>Hematocrit 4-6 weeks</td>
<td>Severe, bleeding, diarrhea</td>
<td>0, 1</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td>30, 50, 70</td>
<td>0, 1, 2</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>Normal, low, albuminuria</td>
<td>0, 1</td>
</tr>
<tr>
<td>Weight</td>
<td>Stable, increased, decreased</td>
<td>0, 1</td>
</tr>
<tr>
<td>Height at diagnosis</td>
<td>Normal, decreased, increased</td>
<td>0, 1</td>
</tr>
<tr>
<td>Height velocity</td>
<td>Normal, decreased, increased</td>
<td>0, 1</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Tenderness, no tenderness</td>
<td>0, 1</td>
</tr>
<tr>
<td>Perianal disease</td>
<td>Active, no evidence, no mass</td>
<td>0, 1</td>
</tr>
<tr>
<td>Extra-intestinal symptoms</td>
<td>None, unstable, inflammatory</td>
<td>0, 1</td>
</tr>
</tbody>
</table>

Maximum score: 100
Interpretation of score: moderate to severe disease >90

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**Corticosteroids**

Systemic corticosteroids should be used only for induction of remission. When patients need steroids for a longer period than expected to achieve remission (>6-8 weeks) or, in other words, when there is steroid dependence, consideration should be given to step-up therapy or evaluation of the need for surgical intervention. Prednisone, or its equivalent, is recommended, and tapering should be gradual owing to the risk of adrenal insufficiency. Different available formulations of budesonide are modulated to be released in the ileum or throughout the colon and can be beneficial for induction of remission with lower systemic bioavailability and side effects.

**Antibiotics**

Antibiotics such as metronidazole and ciprofloxacin can be used for inducing remission in perianal fistulizing disease. They are particularly beneficial when initiation of immunosuppressants has to be postponed owing to concomitant infection and need for surgical intervention. With the advantage of being minimally absorbed, rifaximin has also been shown to be of benefit in inducing remission of Crohn’s disease, particularly with colonic disease (n=402; phase II multicenter double blind placebo controlled trial).

**5-aminosalicylates**
In mild to moderate ulcerative colitis, oral 5-aminosalicylates (5-ASAs) can be used for induction of remission but have little effect on severe disease.\textsuperscript{85} 5-ASAs have also been used for induction of remission in very mild pediatric Crohn’s disease. However, a retrospective study of 43 children with Crohn’s disease (25 mild, 18 moderate-severe) treated with 5-ASA monotherapy compared with various combination therapies (steroids, enteral therapy, antibiotics, or immunomodulators) reported more exacerbations, shorter duration of first remission, and longer eventual duration of steroid use.\textsuperscript{96}

**Biologics**

Anti-TNF treatment is recommended as induction therapy in severe PIBD.\textsuperscript{34} It is the preferred first choice for patients with perianal fistulizing disease, growth failure, or extra-intestinal manifestations.\textsuperscript{34,76} Two biologic drugs are approved for the treatment of PIBD: infliximab (25% murine/75% human monoclonal antibody) and adalimumab (100% human recombinant monoclonal antibody).

**Maintenance therapy**

**5-aminosalicylates**

Different oral preparations of 5-ASA differ in their location of action (table 6). Rectal preparations can be used to treat distal disease and proctitis.\textsuperscript{76} The ESPGHAN consensus recommends that 5-ASA (oral or topical) should be stopped in the setting of an acute flare, owing to the potential for worsening diarrhea.\textsuperscript{85} A prospective observational study in 213 children with newly diagnosed ulcerative colitis and taking maintenance 5-ASAs found that 43% remained in steroid-free remission at one year.\textsuperscript{98} A placebo controlled randomized trial in 122 children with Crohn’s disease found that mesalamine was not an effective maintenance therapy (one year relapse 57% and 63% in treatment and placebo groups respectively).\textsuperscript{99} Prolonged use of 5-ASAs requires monitoring with yearly urinalysis for interstitial nephritis, a rare but severe side effect.\textsuperscript{97,100}

**Table 6 Mesalamine formulations and their site of action\textsuperscript{97}**

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**Immunomodulators**

Immunomodulators, such as thiopurines and methotrexate, are used as maintenance therapy and/or as combination therapy along with a biologic to decrease antibody formation against the anti-TNF in patients of all ages, thereby optimizing therapy.\textsuperscript{76,101} These drugs are slow acting and their effect may take two to three months to be optimal, assuming an appropriate dose.\textsuperscript{34,76}

*Thiopurines (6-mercaptopurine and azathioprine)*—Thiopurines are effective drugs in maintenance therapy for PIBD. A multicenter placebo controlled randomized controlled trial (RCT) in 55 children
newly diagnosed as having moderate to severe Crohn’s disease found a relapse rate of 9% in the group receiving steroids and 6-mercaptopurine compared with 47% in those receiving steroids and placebo (P<0.007). \textsuperscript{102} Important considerations are risk of myelosuppression and hepatotoxicity, warranting periodic monitoring (complete blood count and liver profile at least every three months on stable dosing and more frequently while the dose is being increased).\textsuperscript{34} Thiopurine S-methyltransferase is involved in azathioprine/6-mercaptopurine metabolism, and decreased/absent activity can lead to severe bone marrow suppression. Its activity should be measured before starting treatment; if it is undetectable, alternative treatment is needed. Patients with low to intermediate activity should be placed on a lower dose.\textsuperscript{34 103 104}

\textit{Methotrexate} can be used as maintenance therapy in patients with Crohn’s disease at risk for poor outcomes or failure of azathioprine/6-mercaptopurine, with remission rates of 23-53% at one year (based on a review of mainly retrospective studies in children from 1966 to August 2015).\textsuperscript{105} Methotrexate is contraindicated during pregnancy; if it is necessary in a female patient with potential for pregnancy, birth control methods should be provided. Methotrexate, although well tolerated, has potential for hepatotoxicity. A retrospective cohort study of 60 children with Crohn’s disease who were taking methotrexate reported transient elevation of liver enzymes in 27% and persistent elevation in 15%.\textsuperscript{106} Liver enzymes should be monitored.\textsuperscript{34 76}

\textbf{Biologics}

Biologic (anti-TNF) therapy is indicated as induction and maintenance therapy in situations in which the patient has not responded to previous therapies or when the step-up approach is not likely to be successful.\textsuperscript{34 76} Recommendations for dosing and frequency of infliximab and adalimumab are available, but the doses and intervals should be adjusted on the basis of proactive monitoring of drug concentrations and antibody formation.\textsuperscript{34 76}

The REACH study (randomized, multicenter, open label study) has shown the benefit of an every eight week regimen compared with every 12 weeks in children with moderate to severe Crohn’s disease (n=112). At 10 weeks, 88.4% (95% confidence interval 82.5% to 94.3%) of the children responded to infliximab.\textsuperscript{107} Children on the every eight weeks regimen did better than those on the every 12 weeks regimen, with rates of clinical remission of 55.8% and 23.5% respectively (P<0.001).\textsuperscript{107} Similar findings on efficacy and safety have been reported in an RCT of 60 children with moderate to severe ulcerative colitis taking infliximab and also in children with moderate to severe Crohn’s disease taking adalimumab (n=192; double blind maintenance dosing regimens following open label induction).\textsuperscript{108 109}

Treatment failure with infliximab can be related to low trough drug concentrations resulting from inadequate dosing and/or formation of antibodies against the drug, which accelerates drug clearance.\textsuperscript{110} The recommended approach is proactive drug concentration monitoring to allow recognition of low drug concentrations and presence of antibody before the symptoms arise.\textsuperscript{111} Infliximab concentrations between 3 and 7 g/mL were found to be associated with better clinical response.\textsuperscript{112} In pediatric Crohn’s disease, higher concentrations of infliximab during the induction
phase predict a sustained response to the drug.\textsuperscript{113}

**Combination therapy: immunomodulators and anti-TNF**

Immunomodulators such as azathioprine/6-mercaptopurine and methotrexate have recently been used in an attempt to restore response to an anti-TNF agent once the patient has developed antibodies against the drug (n=5, young adults).\textsuperscript{114} In a retrospective review of the PIBD Collaborative Research Group Registry, infliximab plus an immunomodulator was found to increase the chance that the patient would benefit from infliximab for five years (n=502).\textsuperscript{101}

**Surgery**

Restorative proctocolectomy is a curative procedure in confirmed ulcerative colitis, although there is a risk for ongoing morbidity due to chronic pouchitis. In pediatric ulcerative colitis, surgery is reserved for patients with severe disease refractory to aggressive medical treatment.\textsuperscript{85} Between 8% and 26% of children with ulcerative colitis will need a colectomy in the first five years from diagnosis.\textsuperscript{115, 116, 117} Postoperative complications tend to be more common in children who have emergent colectomy compared with elective colectomy (n=30, retrospective review).\textsuperscript{118} The post-colectomy general health status and overall QOL in pediatric onset ulcerative colitis was found to be comparable to the that of normal population (n=52, controls=117; questionnaire survey).\textsuperscript{119}

In Crohn’s disease, resection surgery can be an option to induce remission of localized disease, although it is not curative; this should be seen as a “surgically induced remission” and followed by initiation or optimization of maintenance therapy.\textsuperscript{34} In a Danish cohort (n=115 children with Crohn’s disease), the clinical recurrence rate after surgery was 50% at one year and 77% at 10 years.\textsuperscript{120} In a retrospective review (n=81 children), recurrence of Crohn’s disease was related to younger age at resection, and the likelihood of a second surgery was related to disease site and occurrence of operative complications at the initial surgery.\textsuperscript{121} Postoperative azathioprine did not decrease the rate of recurrence after surgery.\textsuperscript{120} In an open label randomized trial including patients with Crohn’s disease from 12 to 65 years of age (n=31), early intervention with infliximab monotherapy (compared with no infliximab) prevented clinical, serological, and endoscopic Crohn’s disease recurrence following ileocolic resection.\textsuperscript{122}

Decision making regarding colectomy in children should take into consideration the toxicity of prolonged use of drugs, QOL, and self image, as well as functional outcomes and, in female patients, fertility after pouch procedures.\textsuperscript{123}

**Nutritional therapy**

As previously discussed, EEN can be used for induction of remission. PEN can be used as adjuvant maintenance therapy along with drugs in selected patients.\textsuperscript{34}

Many other dietary approaches have been discussed as potential adjuvant maintenance therapy for IBD,
such as specific carbohydrate diet, anti-inflammatory diet, low FODMAP diet, and Paleolithic diet. No strong evidence exists to support any of these approaches, but it is encouraging to see research about potential mechanisms of action. Research efforts have been directed to studying how the microbiome composition affects the development and severity of IBD. The known dietary effect on microbiome composition makes it likely that dietary modifications can affect IBD. What dietary modifications should be made remains to be answered.

Complications

Nutritional complications

Children with IBD are at risk for macronutrient and micronutrient deficiencies. Weight loss occurs in up to 70% of children with Crohn’s disease and in 34% with ulcerative colitis.

Nutritional support in IBD is essential to long term survival and QOL. From ensuring appropriate calorie intake to monitoring bone health and micronutrients that can affect risks for thromboembolisms and malignancies, nutrition management should be taken as seriously as drug management of PIBD.

Protein-energy malnutrition is more likely to be seen in severe, active disease, but a watchful approach to micronutrient deficiencies should be taken in the long term for all patients with IBD. Location of disease as well as history of surgical resection should guide the clinician to a proactive approach in terms of screening for specific micronutrient concentrations: vitamin B₁₂ deficiency in the setting of terminal ileum resection or zinc loss in the setting of profuse diarrhea or high output fistula.

Growth failure

Delayed skeletal maturation (which eventually leads to growth failure) is more common in Crohn’s disease than in ulcerative colitis and often leads to suboptimal linear growth and sometimes delayed puberty. Patients with Crohn’s disease are at risk for growth failure for many reasons including the inflammatory nature of the disease, the malabsorption of nutrients, and the chronic use of steroids. A retrospective review of 223 patients reported severe growth retardation in 6.4% of adolescents with Crohn’s disease. Treatment strategies known to be effective in promoting significant catch-up growth in Crohn’s disease include infliximab and surgical resection. The REACH study noted improved z scores in children with moderate to severe Crohn’s disease treated with infliximab (n=52). Thirty eight children with Crohn’s disease at Tanner stage 1-3 increased from a mean height centile of 11.1 at time of resection to a height centile of 29.5 (P<0.001). Efforts to minimize steroid exposure are essential.

Anemia

In IBD, anemia is likely owing to a combination of chronic iron deficiency (microcytic) and anemia of chronic disease (normocytic). The mean corpuscular volume of red blood cells is an unreliable method of determining the cause of anemia in the setting of IBD because of the many factors that can affect it. For example, thiopurines cause megaloblastosis, so a normal mean corpuscular volume does not
truly reflect a normal iron status. The effect of inflammation on iron metabolism means that intravenous infusion of iron is preferred in the setting of active disease. Vitamin B₁₂ or folate deficiency should be considered as a cause of anemia in patients with extensive small bowel resection.¹³³

**Vitamin D**

Low 25-hydroxy vitamin D concentrations are more prevalent in IBD patients than in age matched controls.¹³⁴ Accordingly, the importance of vitamin D status in IBD patients has received attention. Its benefits go beyond bone health, with evidence of an effect on morbidity, disease severity, and hospital admissions, likely related to the immunologic effects of vitamin D.¹³⁵ Appropriate screening and monitoring for vitamin D deficiency should be routine. The treatment of choice for hypovitaminosis D should be 50 000 IU/week to ensure a concentration above 32 ng/mL of 25-hydroxy vitamin D.¹³⁶ ¹³⁷ ¹³⁸

**Psychosocial dysfunction**

IBD, like other chronic diseases, can have a substantial effect on mental health and QOL. Unique features of IBD have the potential to affect social function and self esteem. A meta-analysis that included 1167 IBD patients concluded that depressive disorders were more prevalent in young people with IBD than in those with other chronic conditions (odds ratio 5.80, 95% confidence interval 1.60 to 21.03; P=0.007). The analysis also stated that the unpredictability of symptoms of the disease, along with the embarrassment related to frequent visits to the bathroom, can affect psychosocial adjustment. In addition, the possibility of short stature and delayed puberty, depending on disease phenotype, has the potential to affect self acceptance.¹³⁹ A multicenter observational study of 99 adolescents with Crohn’s disease concluded that disease severity increased parental stress and affected the patient’s QOL.¹⁴⁰

A multidisciplinary approach, coordinated to occur during the same visit, is the optimal approach for patients with PIBD. Awareness of the potential for mental health problems is key, and routine inclusion of a psychosocial evaluation is important.¹⁴¹ Symptoms such as fatigue, decreased energy level, and disturbed appetite should not be automatically attributed to disease, without consideration of a mood disorder.

**Malignancy**

**Lymphoma**

Cases of lymphoma (Hodgkin’s and non-Hodgkin’s) have been reported in patients with IBD, but a systematic review found that the increase in risk compared with the general pediatric population was not significant.¹⁴² Epstein-Barr virus associated lymphoma has also been reported in IBD.¹⁴³ A rare but feared complication of IBD treatment, hepatosplenic T cell lymphoma (HSTCL), has been associated with the use of anti-TNF drugs and thiopurines or long term thiopurines alone.¹⁴⁴ Most of the reported cases have occurred in male patients less than 35 years of age. The rarity of the condition means that
strong recommendations in favor or against the use of specific therapies in specific populations cannot be made. On the basis of a systematic review (n=36 patients with IBD who developed HSTCL; median age 22.5 years), the current recommendation is to consider not using combination therapy of anti-TNF and thiopurines in young male patients, unless this is judged to be the best option for that specific patient. It is important to counsel hesitant families that the risk of not treating or inadequately treating IBD is much higher than the risk of the development of HSTCL.

Colon cancer

Data on the incidence of colorectal cancer related to IBD in the pediatric population are scarce, as the increased cancer incidence is related to longer duration of disease. In a pediatric population based cohort of 698 patients with IBD (160 with ulcerative colitis) diagnosed at a median age of 14 and with a median follow-up of 15 years, two patients developed colon cancer.

Pediatric gastroenterologists should discuss this complication with families, especially in cases of early onset IBD and during discussion for transition of care to an adult provider. The absolute risk for developing colorectal cancer over a 35 year period was higher if IBD was diagnosed before 15 years of age. Colon cancer has been reported as early as 15 years of age in a child with ulcerative colitis for 10 years. A patient diagnosed as having ulcerative colitis at 18 months of age was reported to develop adenocarcinoma resulting in death in the third decade of life. Another young adult was found to have colon cancer 13 years after the diagnosis of IBD. Colon cancer surveillance recommendations in adults with IBD by the American Society for Gastrointestinal Endoscopy, ECCO, and the American College of Gastroenterology are extrapolated to children and surveillance endoscopies are done every one to two years from seven to 10 years after diagnosis. Concomitant primary sclerosing cholangitis increases the risk of colorectal cancer, necessitating more frequent colonoscopies.

Toxic megacolon

Toxic megacolon is a known and feared complication of IBD, especially ulcerative colitis. Characterized by a combination of systemic toxicity (fever, tachycardia, leukocytosis, altered mental status) and segmental or total colonic dilatation, it carries a high morbidity, sometimes requiring bowel resection, and mortality. Infections can also be a causal factor for the development of toxic megacolon. Many gastrointestinal infections, particularly Clostridium difficile, are not unusual in IBD patients, so an increased index of suspicion for toxic megacolon should exist in the setting of active colonic inflammation with or without concomitant infection. Colectomy may be needed in children with toxic megacolon who are refractory to medical treatment.

Infections

The following is a brief review of the infections most pertinent to PIBD. For a more comprehensive review, refer to the consensus report by Rahier et al that discusses additional opportunistic infections in IBD.
**Clostridium difficile**

*Clostridium difficile* infections are common in patients with IBD, who are more likely than other patients to develop severe disease.[156][157] However, they are also more likely to be asymptomatic carriers. To avoid unnecessary treatment, screening should be done in the case of colonic flares and should include cytotoxin A and B.[157]

**Cytomegalovirus**

Exclusion of cytomegalovirus infection is strongly recommended in acute steroid resistant colitis, preferably by doing a flexible sigmoidoscopy to obtain tissue for polymerase chain reaction testing. If this is positive, appropriate treatment is warranted.[155]

**Hepatitis B virus**

The standard recommendation by ECCO is to test all patients for hepatitis B virus at diagnosis of IBD and to provide immunization in patients found to be non-immune by serology.[155] The discussion about treatment of hepatitis B virus in the setting of IBD is beyond the scope of this review, but, if encountered, the situation should be assessed with evaluation of risks and benefits of treatment.

**Varicella zoster virus**

Patients with IBD should be screened for immunity to varicella zoster virus. However, seronegative patients face a challenge as the vaccine for varicella zoster virus is a live vaccine and contraindicated in the setting of immunosuppressant drug use. These patients should be advised about the potential need for post-exposure prophylaxis.[155][158]

**Epstein-Barr virus**

Attention has been more recently directed to primary Epstein-Barr virus infection in the setting of immunomodulator and biologic therapy for IBD, owing to the potential for development of Epstein-Barr virus associated lymphoproliferative disease and immune dysregulation. For this reason, serological screening for immunity to Epstein-Barr virus should be considered at diagnosis of IBD to guide the decision making process for treatment and to increase watchfulness in case of a future primary infection.[155]

**Mycobacterium tuberculosis infection**

Because of the risk of reactivation of latent tuberculosis in the setting of immunosuppressant use, screening should be done in all IBD patients before anti-TNF treatment is started. Skin tests may be unreliable owing to anergy in patients with IBD, so a careful clinical history, a physical examination, and a high level of suspicion are necessary.[158] Appropriate treatment should be started if screening is positive.[155]
Fistulizing or penetrating disease

Small pediatric studies have shown long term response rates to infliximab from 56% to 100% in fistulizing Crohn’s disease.\textsuperscript{87 159 160 161 162} Patients with strictureing or penetrating Crohn’s disease have a high risk of needing at least one surgical procedure related to their disease in their lifetime. Possibilities include bowel resection, ostomy creation, stricturoplasty, fistulotomy, and abscess drainage (either intra-abdominal or perirectal).\textsuperscript{163}

Complications after ileal pouch-anal anastomosis

Complications can occur in patients with ulcerative colitis having total colectomy with ileal pouch-anal anastomosis (IPAA). They can be mechanical, inflammatory, functional, neoplastic, and metabolic. Pouchitis is the most common complication, but a retrospective study of 14 children with IPAA found that it was infrequent.\textsuperscript{164} Children with a higher PUCAI at the time of surgery have a higher risk of developing pouchitis.\textsuperscript{165} Most patients respond to a course of metronidazole or ciprofloxacin.\textsuperscript{165 166}

Mortality

Data on mortality in PIBD are scarce. In a retrospective population based cohort study of pediatric onset IBD with a median follow-up of 11.4 years (n=698), three patients died of IBD related causes (two Crohn’s disease, one ulcerative colitis) and IBD related mortality was not increased compared with the reference population. The difference in mortality risk between Crohn’s disease and ulcerative colitis could not be determined owing to the small number of deaths.\textsuperscript{146}

Emerging therapies

Certolizumab, vedolizumab, and ustekinumab have been used off-label or in clinical trials in PIBD.\textsuperscript{76} Certolizumab, a monoclonal antibody to TNF-\(\alpha\), is used in adults with moderate to severe Crohn’s disease as first line treatment or after failure of other anti-TNF agents.\textsuperscript{167} Vedolizumab, a humanized 4-7 integrin, is another option to induce and maintain remission in adults with IBD and has a role in severe IBD that is non-responsive to anti-TNF drugs.\textsuperscript{168 169} In an observational prospective cohort study (n=21) and a retrospective review (n=52) in refractory PIBD, vedolizumab was found to be safe and efficacious.\textsuperscript{170 171} A multicenter prospective cohort study to predict vedolizumab response in PIBD is ongoing (NCT02862132). Ustekinumab, a human monoclonal antibody against interleukins 12 and 23, is efficacious in adults with Crohn’s disease.\textsuperscript{172} The data in pediatrics are limited to a few case reports with conflicting results.\textsuperscript{173 174}

Conclusions

The worldwide prevalence of IBD is increasing. Increasing numbers of novel therapies mean that the management of IBD is improving, with treatment customized to individual patients. However, more studies in children are needed to assess whether therapeutic options available in adults can be used in children. Research into the pathogenesis of IBD, especially linked to the role of the microbiome and genetic predisposition, has the potential to guide future treatment. A more comprehensive
understanding of interactions between the microbiome and disease phenotype and activity could identify new treatment targets including the use of innovative dietary approaches as modulators of the intestinal microbiome. Multicenter collaborations are essential in overcoming the challenges of studying IBD, which is somewhat heterogeneous in its presentation. Improved understanding of the immunologic aspects of IBD pathogenesis has helped to develop new targets for treatment. Early diagnosis, prompt management, and tailored treatment will improve prognosis and outcomes for children with IBD.

Research questions

1. Do children with inflammatory bowel disease (IBD) diagnosed at a younger age have more severe disease and need more aggressive treatment?

2. What is the role of the microbiome in the pathogenesis and severity of IBD and utility of probiotics?

3. What is the role of fecal microbial transplantation in pediatric IBD?

4. Will customizing treatment to phenotype and genotype of IBD lead to better outcomes?

Glossary of abbreviations

- 5-ASA—5-aminosalicylate
- ACR—American College of Radiology
- ASCA—anti-\textit{Saccharomyces cerevisiae} antibody
- CRP—C reactive protein
- ECCO—European Crohn’s and Colitis Organisation
- EEN—exclusive enteral nutrition
- ESPGHAN—European Society for Paediatric Gastroenterology, Hepatology and Nutrition
- ESR—erythrocyte sedimentation rate
- HSTCL—hepatosplenic T cell lymphoma
- IBD—inflammatory bowel diseases
- IPAA—ileal pouch-anal anastomosis
Footnotes

Series explanation: State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason they are written predominantly by US authors.

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