Pediatric inflammatory bowel disease: Diagnostics, treatment and psychosocial consequences
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General introduction

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INTRODUCTION

Crohn’s disease (CD) and ulcerative colitis (UC), the two main subtypes of inflammatory bowel disease (IBD), are lifelong diseases characterized by chronic relapsing inflammation of the gastrointestinal tract. The distinction between CD and UC is based on clinical, radiological, endoscopic and pathological findings. In approximately 5-30% of children differentiation between CD and UC is not possible because of the presence of overlapping features between the two diseases, and a diagnosis of indeterminate colitis (IC) or IBD-unclassified (IBD-U) is made (1-6). Based on the Montreal World Congress of Gastroenterology Working Party 2005 and International Organization of Inflammatory Bowel Disease Working Party 2007 the following classification is currently used (7):

- The term IC or colitis of uncertain type etiology should be used only when colectomy has been performed and the pathologist is unable to make a definite diagnosis of either UC or CD after careful examination of the surgical specimen.
- The term IBD-U should be used when no colectomy is performed and a distinction between CD and UC cannot be made despite an extensive diagnostic work-up.

In contrast, the IBD Working Group for the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in the Porto criteria recommended the use of the term IC for children and adolescents with IBD, when a full endoscopic examination including biopsies of the upper gastrointestinal tract, colon and terminal ileum, in addition to a small bowel followthrough or enteroclysis, cannot establish a diagnosis of either CD or UC with certainty (8).

Pediatric-onset IBD represents a distinct disease entity with differences in disease phenotype: disease location and disease behavior and genetically attributable risk, compared with IBD in adults (9).

Epidemiology

IBD is most frequently diagnosed in adolescence and early adulthood, with a peak onset between 15 and 25 years of age (10,11). The incidence of CD and UC in children varies greatly around the globe, from 0.24 to 13.3 per 100,000 per year (12). Also in Europe the incidence of pediatric IBD varies, with higher incidence rates per 100,000 per year in Western European centers compared to Eastern European centers, respectively 6.9 and 4.7 (13). The variation in incidence rates may be due to heterogeneity of data collection techniques, differences in disease classification, differences in the age limit used, or referral bias, but also due to regional differences. Incidence rates of pediatric CD are usually higher than those for UC. The incidence of pediatric-onset CD seems to be increasing in several countries, while most studies have reported stable incidence of pediatric-onset UC (12).
Pathogenesis
IBD is thought to result from an inappropriate and continuing inflammatory response to commensal microbes in genetically susceptible individuals. There is sufficient evidence that IBD, in part, is the result of a genetic predisposition (14). Genome-wide association studies have identified multiple susceptibility genes, some common to both diseases (CD and UC) and some linked separately to one disease or the other. Most of these genes code for molecules that are crucial for epithelial barrier function, the innate immune regulation, autophagy and regulation of adaptive immunity (14). The first specific gene unequivocally associated with IBD was the NOD2/CARD15 gene for CD. NOD2 is an intracellular ‘alarm button’, a receptor recognizing invading bacteria that entered the mucosal wall. Also the pathway of autophagy has received a lot of attention following the discovery of ATG16L1 (15). The concordance rate in monozygotic twins of 16-18% in UC and 35-63% in CD points to strong environmental influences (16,17). Western lifestyle has been identified as a potential risk factor in the evolution of IBD; however the environmental triggers of IBD have not been well delineated (15).

The most consistent environmental triggers believed to be associated with IBD are smoking, diet, perinatal events (e.g. perinatal infections), domestic hygiene and childhood infections (18). The genes implicated in childhood-onset and adult-onset IBD overlap, suggesting similar contributory genetic predispositions and pathophysiological pathways (14). However, based on the relative short exposure time to environmental factors in children, genetic mutations are thought to play an increasing role in childhood-onset disease (9,19).

Clinical presentation
Children with IBD may present with a range of symptoms, depending on the location, severity and chronicity of inflammation. The most common presenting symptoms of CD are abdominal pain, weight loss and diarrhea; and for UC diarrhea, bleeding and abdominal pain. However, only one quarter of CD patients present with the ‘classical triad’ of CD symptoms, and nearly half do not report diarrhea. Other symptoms may be fever, lethargy, anorexia, arthritis/arthralgia, psychiatric symptoms, secondary amenorrhea, nausea and vomiting (20). Unique to pediatric-onset IBD is the potential for linear growth impairment as a complication of chronic intestinal inflammation. However, in UC linear growth impairment is seldom present at the time of diagnosis (20,21). Despite its name, IBD is not limited to the bowel. Extraintestinal manifestations may sometimes dominate the clinical picture especially in CD, causing diagnostic delay (8). Extraintestinal manifestations can be found in 17% of patients at the time of diagnosis, with arthritis/arthralgia, aphthous stomatitis and cutaneous changes (e.g., erythema nodosum) being most common (22). Perianal fistulas and/or abscesses can be found in 4-10% of children with CD at time of diagnosis.
(1,20,21,23). Suspicion of IBD is markedly increased in case of IBD in a first degree relative, 12% to 30% of the patients have a positive family history (21).

**Diagnostics**

It is essential to diagnose IBD early in the course of disease and to distinguish CD from UC, since the course and prognosis of the disease and the choice of treatment depend on type, localization and extent of the disease at first presentation. There is no single diagnostic test, as “gold standard”, which can reliably distinguish between CD and UC. A definite diagnosis of the type of IBD is based upon a combination of clinical presentation, endoscopic findings, histological abnormalities and small bowel imaging studies (8,24).

**Laboratory investigations**

Initial laboratory investigations should include a full blood count, liver enzymes, serum albumin, serum levels of urea and creatinine, erythrocyte sedimentation rate (ESR) and C-reactive protein (8,24). A reduced level of hemoglobin, raised markers of inflammation (erythrocyte sedimentation rate, C-reactive protein), elevated platelet count and reduced serum albumin are suggestive of IBD (25). However, laboratory tests may be normal in children with active colitis, especially in mild disease (26-28). Serum inflammatory markers are higher in CD compared with UC (27,29). Presence of serological markers anti-neutrophil cytoplasmic antibody (ANCA) and anti-saccharomyces cerevisae antibody raises the suspicion for a diagnosis of CD or UC, respectively. The diagnostic sensitivity of these serological markers ranges between 60 and 80% (30-33). Calprotectin, a fecal inflammatory parameter, is a useful screening tool to differentiate colitis from non-inflammatory diarrhea (34). This fecal inflammatory marker is superior to markers of inflammation in the blood (35). Furthermore, stool culture is mandatory to exclude infectious diarrhea, and testing for Clostridium difficile toxin is recommended on at least 3 independent stool samples. In children younger than 2 years additional immunological investigations and allergy testing may be necessary to exclude colitis related to primary immunodeficiency or allergic conditions. Testing for the interleukin (IL)-10 axis should be considered for those younger than 1 year (36).

**Rectosigmoidoscopy versus (ileo)-colonoscopy**

Unlike adult-onset UC, childhood-onset UC is more likely to be extensive, meaning that inflammation extends beyond the splenic flexure or involves the whole colon (table 1). Therefore differentiation between CD and UC can be difficult in children. Data from 8 pediatric studies showed extensive UC in 43% of the children (24). However, more recent studies found extensive UC in up to 90% of children (1,20,22,39).
The higher rates of extensive colitis in the recent studies may reflect a change in diagnostic assessment of children with suspected IBD, using full colonoscopy instead of flexible sigmoidoscopy.

In CD, ileoscopy is of great importance, as isolated small bowel inflammation may occur in the presence of a normal colon in up to 38% of children (table 2).

In children, as in adults, the most commonly affected sites are the terminal ileum and right colon. In contrast, when CD is diagnosed in very young children a higher proportion have colonic disease (38,41). Ileoscopy also gives information regarding the extent of inflammation in CD.
Ileocolonoscopy: differentiating Ulcerative Colitis from Crohn’s disease

Many endoscopic lesions in IBD are not specific. Endoscopic features supporting CD are segmental distribution with “skip” areas of normal mucosa, edematous areas (cobblestone), ulcers (aphthous, linear or serpiginous), terminal ileitis, strictures and fistulas (42). Endoscopic features supporting the diagnosis UC includes diffuse and continuous inflammation, beginning in the rectum and extending proximally to a variable extent, erythema, edema and loss of vascular pattern, granularity (wet sand-paper appearance), friability (bleeding with gentle rubbing) and shallow ulcerations or erosions on a background of generalized inflammation (42). During ileocolonoscopy multiple biopsies for histology should be obtained from all segments of the lower intestinal tract (ileum, cecum, ascending colon, transverse colon, descending colon, sigmoid and rectum), from areas of inflammation as well as from healthy looking mucosa. Chong et al. introduced a spectrum of histological criteria which proved to be useful for the clinical assessment of IBD in children (table 3) (43). In children with UC unusual features have been reported like peri-appendiceal inflammation, rectal sparing and rectal patchiness (39,44-48). The prevalence of complete rectal sparing, defined as normal appearance during endoscopy and normal histology, ranges between 3-7% in children (20,45,47). Inflammation of the distal ileum, called backwash ileitis, may develop due to incompetence of the ileocecal valve, which might cause retrograde flow of colonic contents into the terminal ileum. Backwash ileitis is present in 10% of children with UC and pancolitis (39).

Upper gastrointestinal tract endoscopy

The value of upper gastrointestinal tract endoscopy is a topic of debate. The ESPGHAN-IBD Working Group recommends upper gastrointestinal tract endoscopy (UGT) at initial presentation in every child suspected of IBD (8). In contrast, a report from the working group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the Crohn’s and Colitis Foundation of America (CCFA) refrained from recommending routine diagnostic use of UGT endoscopy in the diagnostic assessment of children with suspected IBD (49). In general we state that the inflammatory process in UC is limited to the large bowel, whereas CD may occur throughout the entire gastrointestinal tract including the UGT. However, several reports have shown that pathological changes in the UGT can also be found in patients with UC (50-54). Microscopic mucosal lesions in the UGT have been identified in 64%-90% of children with CD and 38%-70% of children with UC (50,51,54,55). Most of these microscopic findings are non-specific and not discriminating between CD and UC. Non-caseating-epitheloid granulomas, the histological hallmark of CD, can be identified by UGT endoscopy in up to 40% of all pediatric CD patients (40,54,56). The fraction of pediatric CD patients whose diagnosis relies on the detection of granulomas in UGT ranges between 3% and 20% (40,51,55,57).
### Table 3. Histological criteria by Chong et al

<table>
<thead>
<tr>
<th>Definite ulcerative colitis</th>
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<tr>
<td>- Acute, diffuse, mucosal inflammation</td>
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<tr>
<td>- Severe crypt distortion</td>
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<tr>
<td>- Diffuse goblet cell depletion (mucus depletion)</td>
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<td>- Increased vascularity</td>
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<th>Probable ulcerative colitis</th>
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<tbody>
<tr>
<td>- Diffuse, mucosal inflammation</td>
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<tr>
<td>- Mild or moderate crypt distortion</td>
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<tr>
<td>- Mucosal atrophy or mucus depletion</td>
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<tr>
<td>or</td>
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<tr>
<td>- Diffuse acute and chronic inflammation</td>
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<tr>
<td>- Increased vascularity</td>
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<tr>
<td>- Little mucus depletion (suggesting resolving phase)</td>
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<th>Probable Crohn’s disease</th>
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<tr>
<td>- Focal inflammation</td>
</tr>
<tr>
<td>- Submucosal or transmural inflammation</td>
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<tr>
<td>- Lymphocytic aggregates (without germinal cells)</td>
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<tr>
<td>- Mucus retention in the presence of more than minimal acute inflammation</td>
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<th>Definite Crohn’s disease</th>
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<tr>
<td>- Any or all of the above together with non-caseating epitheloid granulomas</td>
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**Small bowel imaging**

Small bowel investigation, small bowel follow through (SBFT) or MRI enteroclysis, is indicated in all patients at diagnosis (except in definite cases of UC) to guide therapeutic management and to detect possible complications of small bowel involvement in CD including stenosis, structuring or internal fistulae (8). Batres et al. showed that SBFT is limited by its low sensitivity (46%) in detecting terminal ileum involvement, with the terminal ileum biopsy as the “gold standard”. Approximately 31% of patients had a normal SBFT study and abnormal terminal ileum histology (58). Contrast enhanced magnetic resonance imaging (CE-MRI) is a newer, more sensitive and specific test for the detection of distal ileitis compared to SBFT (59,60), but more validation studies are needed. With CE-MRI superficial mucosal lesions can be missed due to inadequate spatial resolution of the CE-MRI (61). Capsule endoscopy is another promising imaging technique that allows endoluminal examination of the small bowel using a wireless capsule-shaped tool which is usually swallowed and then propelled through the gastrointestinal tract by gut motility (62,63).
Imaging studies of the small bowel play an important role in the complete diagnostic assessment of childhood IBD, although up till now these imaging techniques cannot replace ileocolonoscopy.

**Treatment**

The management principles of treatment of IBD are to induce (control inflammation) and to maintain remission, and specifically in children to restore growth. Although remission can be considered at clinical and biochemical levels, histological remission (normalization of histological abnormalities or mucosal healing) is seen as ideal goal of treatment. In clinical practice, a ‘step-up’ approach of adding therapies if first-line or less-toxic approaches are unsuccessful within an appropriate period, is commonly used.

Figure 1. and 2. show a treatment flow chart for CD and UC in children, based on the national guideline on diagnosis and treatment of pediatric IBD (24).

**Management of CD:**

*Corticosteroids*

Historically, corticosteroids have been the most commonly used class of medication for induction of remission in CD. Corticosteroids are effective for induction of remission, but not recommended for maintenance therapy in pediatric CD (64). Although most pediatric patients with CD respond to corticosteroids, initial steroid resistance occurs in 12-20% of pediatric patients with CD (65). In adults with CD, conventional corticosteroids have been found to be more effective for induction of remission than budesonide, although budesonide may be equivalent to systemic corticosteroids for ileal, cecal and ascending colon inflammation (66). In children with disease confined to the ileum or ascending colon conventional corticosteroids seem to be superior to budesonide (67). Budesonide is not recommended for maintenance of remission in pediatric CD (68).
Exclusive enteral nutrition

Whilst corticosteroids have traditionally been utilized to induce remission in active IBD, there is increasing support and rationale for exclusive enteral nutrition (EEN) in CD. EEN involves the sole administration of a nutritional formula (elemental, semi-elemental or polymeric formula), with exclusion of normal diet, for a period of up to 10 weeks (69). EEN has remission rates equivalent to those of corticosteroids, but has numerous advantages such as avoiding steroid related side effects and more importantly leads to superior rates of mucosal healing and promotes growth (69-71).
Aminosalicylates
The role of 5-aminosalicylate (5-ASA) compounds as maintenance treatment in children with CD is unclear, because no studies are available in children. Extrapolation from the adult literature suggests that 5-ASA therapy has no advantage over placebo (72).

Immunomodulators: thiopurines and methotrexate
There are two types of thiopurines approved for the treatment of pediatric IBD; azathioprine and 6-mercaptopurine. Both are effective for the maintenance of remission in pediatric CD. Early introduction of thiopurines at the time of remission induction in moderate-severe CD leads to more prolonged remission and less steroid requirement (73-75). Methotrexate, another immunomodulator, is an alternative if these drugs are not tolerated or are ineffective, and has shown steroid-sparing effects in retrospective cohort studies (76-79).

Biologics
Currently, two anti-tumor necrosis factor (TNF) agents are approved for the treatment of pediatric CD, infliximab and adalimumab. Infliximab is a monoclonal chimeric anti-TNF antibody (75% human, 25% murine), whereas adalimumab is a fully humanized monoclonal anti-TNF antibody. Both anti-TNF agents are effective for induction of remission and as a maintenance therapy in pediatric CD patients with moderate-severe disease who are refractory to or intolerant of conventional therapy (80-84). Maintenance infliximab and adalimumab have a steroid-sparing effect (81,83), as well as a benefit on growth (81,83,85,86). Data on the use of alternative anti-TNF agents, such as certolizumab and natalizumab, are only available for adults, results from pediatric trials are awaited.

Probiotics
Probiotics have not been proven to be beneficial in treating children and adults with CD (87).

Surgery
Surgical treatment may be indicated in the treatment of complications such as strictures, perianal fistulas and abscesses and sometimes in children with disease resistant to medical therapies. Early intervention should be considered in the presence of growth failure in pre-pubertal or early pubertal children with localized ileo-cecal disease, because the ‘window of opportunity’ might have lapsed once puberty has started (72).

Management of UC
Aminosalicylates
For mild to moderately active UC, mesalazine and sulfasalazine, both oral 5-ASA compounds, are recommended as first-line induction therapy and for maintenance of remission (88). Sulfasalazine is associated with more adverse effects compared to mesalazine. 5-ASA
therapy is effective for inducing remission in mild to moderate UC in children (89-91) and for maintaining remission (92). Monotherapy with topical 5-ASA may be effective in selected children with mild to moderate proctitis, however this is a rare pediatric phenotype (93).

*Corticosteroids*
Patients who fail to respond to 5-ASA or who have severe disease can be initially treated with oral steroids. Oral steroids are effective for inducing remission in pediatric UC, but not recommended for maintaining remission (88,95,96). Initial steroid resistance occurs in 4-21% of pediatric patients with UC (65). At present, there is no evidence to recommend the clinical use of oral budesonide for the induction of remission in active UC (94). In IBD patients receiving steroids growth is a special concern (97).

*Imunomodulators: thiopurines and methotrexate*
In children with 5-ASA intolerance, frequently relapsing or steroid-dependent disease, thiopurines are recommended for maintaining remission. Thiopurines are effective for the maintenance of remission in children with UC and has shown steroid-sparing effects, but is ineffective for induction of remission (75,98,99). The presently available evidence is insufficient to recommend the use of methotrexate in pediatric UC (100).

*Biologics*
Currently, one anti-tumor necrosis factor (TNF) agent is approved for the treatment of pediatric UC, infliximab. Infliximab should be considered for treatment of children with persistently active, or steroid-dependent UC, uncontrolled by 5-ASA and thiopurines. Infliximab is effective for induction of remission and as a maintenance therapy in pediatric UC patients (101-103) and has been effective in avoiding or at least delaying the need for surgery (103). Data on the use of alternative anti-TNF agents, such as adalimumab, certolizumab and natalizumab, are not available.

*Cyclosporin*
Cyclosporin is successful in children with severe acute colitis but its use should be restricted to 3-4 months while bridging to thiopurine treatment, because of its relatively high toxicity profile. In those already on thiopurine, infliximab should be preferred. The short-term success rate of infliximab is similar to cyclosporine. However, infliximab seems to be superior on the long term (104).
**Figure 2.** Treatment flowchart for UC in children

1. **Ulcerative colitis**
   - **5-aminosalicylate**
     - **Remission**
       - Yes → **5-aminosalicylate maintenance treatment**
       - No → **5-aminosalicylate and corticosteroids (po/iv)**
         - **Remission**
           - Yes → **5-aminosalicylate maintenance treatment**
           - No → **5-aminosalicylate and 6-MP/AZA maintenance treatment and corticosteroids (po/iv)**
             - **Remission**
               - Yes → **5-aminosalicylate and 6-MP/AZA maintenance treatment**
               - No → **Infliximab and 5-aminosalicylate and 6-MP/AZA maintenance treatment**
                 - **Relapse**
                   - ↓ **Colectomy**
Probiotics
Three small pediatric trials have suggested efficacy of probiotics in pediatric UC, VSL#3 (in addition to standard treatment) and Escherichia coli Nissle 1917 (105-107). Another pediatric study showed that in children with active distal ulcerative colitis, rectal infusion of Lactobacillus reuteri is superior to placebo in improving mucosal inflammation (108). However, there is insufficient evidence to recommend routine probiotic therapy to pediatric patients with UC for induction or maintenance of remission (88).

Surgery
As a last resort elective colectomy may be indicated in children with active or steroid-dependent UC despite maximal treatment. The colectomy rate in pediatric-onset UC is 20-29% at 5 years (109-111), although one pediatric study reported a colectomy rate of 5% at 5 years (112).

One important factor in achieving optimal outcomes for children with IBD is medication adherence. The documented rates of medication adherence in adolescents have been reviewed and are presented in chapter 6.

Psychosocial consequences
Pediatric IBD can affect many areas of psychosocial functioning. Adolescents with IBD seem to be more depressed than adolescents with other chronic diseases and healthy adolescents (113-115), with rates as high as 25% (116). In addition, depressed adolescents with IBD have been shown to be at higher risk for anxiety (117,118). Data suggest that adolescents with IBD have lower health related quality of life (HRQoL) compared to healthy peers based on both adolescents and parent-report, specifically in total, psychosocial and physical health domains (116,119). Several domains of risk factors for impaired HRQoL have been cross-sectionally investigated, including disease-related, psychosocial, and relationship factors. Higher disease activity (120-124), the use of less adaptive coping strategies (121), and family problems related to problem-solving, communication, and general functioning (123) have all been associated with poorer HRQoL. Furthermore, symptoms of IBD, in addition to changes in physical appearance due to treatment, can cause withdrawal from social activities and problematic social functioning. Adolescents with IBD report significantly worse social functioning compared to healthy children (116). Onset of IBD during adolescence is associated with worse social functioning (125). Pediatric IBD can also affect parents and siblings and can be a source of increased stress among family members. This can disrupt overall family function and adversely affect the physical and psychosocial health of adolescents (126). However, research findings on family function in pediatric IBD are inconsistent. Some have documented significantly more dysfunction among families of patients with IBD compared to healthy controls (127),
whereas others report no differences (125). In pediatric IBD, parents are found to exhibit heightened levels of emotional stress (128) and increased rates of depression (129). Poorer psychosocial functioning among mothers of adolescents with IBD has been linked to greater adolescent depressive symptoms, more negative IBD outcomes (130) and greater IBD-related functional disability in daily activities (131). Moreover, higher levels of parental stress are associated with poorer adolescent HRQoL (123).

Health care physicians working with children and adolescents with IBD should be attentive to the increased risk for internalizing disorders (e.g. depression, anxiety), poor HRQoL and social problems. Patients at risk for an unfavorable psychosocial development should be identified and psychosocial support should be offered. Psychoeducational group interventions can have a positive effect on the HRQoL and feelings of competence of adolescents with IBD (132).
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