

# Mistakes in paediatric inflammatory bowel disease and how to avoid them

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**A**round 1 in 10 cases of inflammatory bowel disease (IBD) will present before adulthood, with the median age at presentation being 11–12 years.<sup>1</sup> IBD in children and young people is associated with more extensive disease, increased disease activity and a higher rate of complications compared with adult-onset IBD.<sup>2</sup> Worldwide, estimates of paediatric IBD prevalence rates are lacking, but data suggest its incidence is increasing.<sup>3</sup>

Risk factors for paediatric IBD include immigration to high prevalence regions, particularly to countries that have Westernised diets, increasing geographical latitude, and European ancestry (versus belonging to an indigenous population).<sup>4</sup> The risk may also be higher in children of certain ethnicities (South Asian, Hispanic, and East Asian).<sup>5</sup>

While the pathophysiology and clinical presentation of paediatric IBD is well understood, the role of genetics and personalised treatment is currently the focus of a significant amount of international research. Better clinical outcomes—including optimal nutrition, improved growth, better quality of life and increased disease remission rates with decreased occurrence of complications—are increasingly being sought in children and young people with IBD.<sup>4</sup>



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infections, such as *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, and *Clostridium difficile* toxins are necessary in all children. Specialist investigations may include screening for primary immunodeficiencies, including chronic granulomatous disease, common variable immune deficiency, agammaglobulinaemia, Hyper-IgM, Hyper-IgE, and severe combined immunodeficiency. Diagnostically, atypical gastrointestinal presentations of primary immunodeficiencies can be challenging as therapy for ulcerative colitis and/or Crohn's disease may be inappropriate and sometimes harmful. Targeted and or unselected genetic analysis is then undertaken if available.<sup>8</sup>

Allergic disorders may mimic ulcerative colitis, particularly in children under 2 years of age. Endoscopically, eosinophilic gastroenteritis presents with skip lesions similar to that of Crohn's disease and may be associated with allergy.<sup>9</sup> Cow's milk protein allergic colitis and eosinophilic disorders are also IBD mimics.<sup>10</sup>

## Key points:

- All patients under 6 years of age who present with suspected IBD should have a full blood count (FBC) and immunoglobulins, neutrophil function, and lymphocyte subset measured at diagnosis. Any abnormalities identified should lead to more extensive and detailed investigation
- After infection is excluded, allergy and primary immunodeficiencies are part of the differential diagnosis in very young children. A genetic panel can be helpful in differentiating specific disease aetiologies in this age group

## Mistake 1 Failing to look for IBD 'mimics'

The differential diagnoses in a young child (<6 years of age) presenting with the signs and symptoms of IBD are extensive. The predominant presenting symptoms for Crohn's disease in children include abdominal pain,

diarrhoea, weight loss, anorexia and growth failure, whereas the predominant symptoms for ulcerative colitis in children are bloody diarrhoea and reduced activity. Extraintestinal manifestations are common in both Crohn's disease and ulcerative colitis, affecting up to 15% of patients at diagnosis.<sup>6</sup> They include arthritis, primary sclerosing cholangitis, autoimmune hepatitis, pyoderma gangrenosum and uveitis.

There is wide-ranging overlap between the potential infectious and noninfectious causes of these symptoms, and they are deemed 'mimics.' History taking and examination should include asking about a family history of primary immunodeficiency, consanguinity, therapy-refractory IBD symptoms and signs (including abscesses), recurrent infections in the absence of immunosuppressant drugs, and skin, hair and nail abnormalities/changes. A phenotypic aide-memoire when history taking for IBD mimics, "Young age MATTERS MOST", is shown in figure 1, and would be against a diagnosis of IBD.<sup>7,8</sup>

First-line investigations include upper and lower gastrointestinal endoscopy and histology, with imaging, to establish IBD-like pathology.<sup>8</sup> Exclusion of common

### Young age MATTERS MOST

- Young age onset
- Multiple family members and consanguinity
- Autoimmunity
- Thriving failure
- Treatment with conventional medication fails
- Endocrine concerns
- Recurrent infections or unexplained fever
- Severe perianal disease
- Macrophage activation syndrome and hemophagocytic lymphohistiocytosis (HLH)
- Obstruction and atresia of intestine
- Skin lesions, dental and hair abnormalities
- Tumours

Figure 1 | Phenotypic aide-memoire when history taking for IBD mimics.<sup>8</sup> The presence of one or more of the points listed in the aide-memoire are suggestive of a diagnosis other than IBD.

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Cite this article as: Chanchlani N. and Russell R.K. Mistakes in paediatric inflammatory bowel disease and how to avoid them. *UEG Education* 2018; 18: 1–6.

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Conflicts of interest: N. Chanchlani declares no conflicts of interest. R.K. Russell has received consultation fees, research grants, or honorarium, from Nestlé, AbbVie, Takeda, Napp, Mead Johnson, Nutricia and Janssen.

Published online: January 25, 2018.

**Mistake 2 Incorrectly interpreting the full blood count and iron status**

Anaemia occurs in up to 70% of children with IBD, with iron deficiency anaemia (IDA) being the most frequent.<sup>11</sup> First-line investigations for diagnosis of IDA include taking a FBC (to obtain haemoglobin [Hb], haematocrit [Hct] and mean cell volume [MCV]), iron studies (to obtain levels of ferritin, iron and transferrin saturation [TfS]) and measuring inflammatory markers (including C-reactive protein [CRP] and the erythrocyte sedimentation rate [ESR]), though these are nonspecific indicators of gastrointestinal inflammation.<sup>6</sup>

In children with IDA, the levels of Hb, Hct, MCV, ferritin and TfS can be low, but the specific pattern is often mixed. Patients with active gastrointestinal inflammation will have elevated levels of CRP and an increased ESR. As ferritin is also an acute inflammatory protein, its levels may be elevated or normal in the presence of inflammation, which makes it unreliable when assessing IDA in those who have active IBD, as it can give a false-negative result. In patients without clinical, endoscopic or biochemical evidence of active disease, serum ferritin <30 µg/L is an appropriate criterion for diagnosing IDA, though reference ranges between laboratories may vary. In the presence of inflammation, a serum ferritin level up to 100 µg/L may still be consistent with iron deficiency.<sup>12</sup> In these circumstances, using a TfS of <16% as diagnostic of IDA is helpful, as TfS is not impacted by ongoing inflammation.

Vitamin levels, such as B12 and folate, may also be useful for differentiating or establishing the coexistence of different types of anaemia, particularly if no response to initial iron therapy is noted.<sup>13</sup> Patients on thiopurines are also likely to have deranged FBC results—the MCV is likely to be raised as a side effect of the medication—so interpretation of a patient's iron status should take this factor into account.

Testing for either IDA or anaemia of chronic disease (ACD) should take place at the time of IBD diagnosis and every 6–12 months for IBD in remission, but more frequently (at least every 3 months) for active IBD. Normal ranges vary by age group (table 1). Treatment with oral and/or intravenous iron therapy depends on the degree of severity of the anaemia and local protocols—European-wide guidance is available.<sup>12</sup> Blood transfusion for iron replacement is now indicated less often than it was previously.

**Key points:**

- TfS is diagnostic of IDA, independent of inflammation, and should be measured in patients with active disease
- Regular monitoring for anaemia with FBC and haematinics is part of good IBD care in children

**Mistake 3 Failure to recognise the 'normal' range of faecal calprotectin in children under 4 years of age**

Measuring faecal calprotectin levels is a key part of the initial investigations in children with suspected IBD. Elevated values suggest inflammation of the intestinal mucosa due to migration of neutrophils. Faecal calprotectin can be used for screening purposes to decide whether or not to perform a colonoscopy, as it has a sensitivity of 98% and modest specificity of 68% for the diagnosis of paediatric IBD.<sup>14</sup>

High levels of faecal calprotectin are not only seen in IBD, but also in other causes of diarrhoea, per rectal bleeding or abdominal pain, including infection and juvenile polyps. The commonly used cut-off level for diagnosis of IBD is around 200 mg/kg; however, this value is only appropriate in children older than 4 years of age. Children aged 1–4 years old have higher faecal calprotectin concentrations compared with children older than 4 years of age and adults.<sup>15</sup> In younger children, normal cut-off values are about 540 mg/kg under 6 months of age, 210 mg/kg from 6 months to 3 years of age, and about 75 mg/kg from 3–4 years of age.<sup>16</sup>

**Key points:**

- Faecal calprotectin levels are elevated in children with IBD, but normal ranges differ across age groups
- Juvenile polyps cause rectal bleeding and a significantly elevated faecal calprotectin level that can be confused as a potential IBD diagnosis

**Mistake 4 Only using exclusive enteral nutrition when there is small bowel Crohn's disease present**

A 6–8-week course of exclusive enteral nutrition (EEN) is given to patients with a new diagnosis or acute flare of Crohn's disease. EEN induces remission in approximately 80% of children, which is equivalent to the response achieved by corticosteroids, but EEN provides superior rates of mucosal healing.<sup>17,18</sup>

It has been hypothesised that better disease remission rates are achieved in patients given EEN if they have small bowel disease, or conversely, that children given EEN fare worse if they have isolated colonic disease than if they have disease at other gastrointestinal sites.

Data from published studies suggest disease location is unlikely to be a significant confounder in treatment outcome.<sup>19,20</sup> A Cochrane review concluded there was insufficient evidence to support the impact of disease location on disease remission.<sup>19</sup> Although one UK prospective cohort study demonstrated an 11% difference in remission rates between ileal (92%) and ileo-colonic (83%) disease rates, this study suffered from a 50% response rate.<sup>21</sup> Data from Scotland suggest that children with colonic, ileo-colonic, and upper gastrointestinal disease have similar rates of remission on EEN.<sup>22</sup> Those with disease isolated to the terminal ileum had a lower rate of remission, though this was suggested to be a false-positive result related to the small number of patients in the category.

**Key points:**

- Studies have consistently shown no significant difference between disease location with respect to response to EEN
- Regardless of the specific disease phenotype, EEN should be offered as induction therapy to all paediatric individuals who have active luminal Crohn's disease

**Mistake 5 Routinely using elemental feeds as exclusive enteral nutrition in Crohn's disease**

Nutritional disturbances are common in patients with IBD, ranging from 25% of outpatients to 85% of inpatients.

There are no significant differences in treatment outcomes based on whether elemental (amino acid), semi-elemental

Age group	Hb (lower limit [g/L])	HCT (lower limit [%])	MCV (fl)	Ferritin (µg/L)	TfS
18 months–3 years	105	33	70–86	4–74	>16%
3–7 years	115	35	75–87		
7–13 years	115	35	77–94	11–93	
14–18 years (female)	120	36	78–102	4–122	
14–18 years (male)	130	37	78–98	10–98	

Table 1 | Reference ranges used when testing for anaemia in paediatric IBD patients at Great Ormond Street Hospital, London, UK.<sup>12</sup> Local laboratories should also be consulted for guidance. Hb, haemoglobin; HCT, haematocrit; TfS, transferrin saturation.

(peptide), or polymeric (whole protein) formula is used as EEN. In addition, data suggest that elemental formulas are not superior to polymeric formulas when compared directly.<sup>23,24</sup> One trial demonstrated better weight gain for children on a polymeric diet compared with those on an elemental diet (+2.9 kg; 95% CI 1.4–4.5;  $p = 0.001$ ), but no difference in disease remission rates.<sup>25</sup> In one UK cohort, nasogastric tube administration of formula was more frequent if the formula was elemental compared with polymeric formula (55%, 95% CI 42–68 versus 31%, 95% CI 17–45;  $p = 0.02$ ).<sup>26</sup>

Children prefer polymeric formulas because they taste better, and some data suggest better weight gain with these formulas compared with an elemental diet.<sup>26</sup> Polymeric formulas are also usually less expensive compared with semi-elemental and elemental formulas. Elemental formulas should, therefore, be reserved for the minority of patients who have a coexistent cow's milk protein allergy or another clear contra-indication for using a polymeric formula.

#### Key points:

- Lower nasogastric usage rates and better weight gain have been documented in children given polymeric formulas compared with elemental formulas
- Children should be routinely offered polymeric formulas as EEN, as they are more palatable and cost effective than elemental formulas

#### Mistake 6 Not considering enteral nutrition as an option for maintenance of remission in Crohn's disease

Evidence is emerging in favour of partial enteral nutrition (PEN) as an alternative maintenance therapy, with both elemental and polymeric feeds conferring beneficial effects on disease remission rates and relapse rates.<sup>27</sup> PEN has already been shown to maintain disease remission without concomitant medication and to improve nutritional status and disease activity scores.<sup>28,29</sup>

The results of a 1-year retrospective cohort study demonstrated that remission rates were 45% lower in children who received no treatment post-EEN completion than in those who underwent maintenance enteral nutrition (MEN) (60% in the MEN group compared with 15% in the no treatment group,  $p = 0.001$ ).<sup>30</sup>

In a detailed Japanese prospective adult cohort study, patients with a Crohn's disease activity index (CDAI)  $\leq 150$  were randomly assigned to receive either 6-mercaptopurine (0.5–1.5 mg/kg/day,  $n = 30$ ), an elemental diet ( $\geq 900$  kcal/day,  $n = 32$ ) or nothing (control,  $n = 33$ ), whilst continuing 5-aminosalicylic

therapy.<sup>31</sup> At 24 months, 60%, 46.9%, and 27.2% of patients maintained remission in their respective groups ( $p < 0.05$  for both active groups compared with the control group). No significant differences were demonstrated between the active groups, and more adverse effects were seen with the 6-mercaptopurine group ( $n = 3$ ) compared with the elemental diet.

Several trials in adults have demonstrated the effectiveness of a 'half elemental diet' as maintenance therapy for Crohn's disease. These trials have been conducted in mostly Japanese populations, but may be replicated in other IBD populations in the future.<sup>32</sup>

#### Key points:

- PEN may be offered as maintenance therapy in paediatric patients who have Crohn's disease, with PEN conferring reasonable disease outcomes at the 1-year and 2-year follow-up. It is especially useful in patients who are receiving no other maintenance therapy
- PEN is usually given as between 25–50% of a patient's total daily requirements and often needs to be 'rotated' to reduce taste fatigue

#### Mistake 7 Inadequate dosing and delivery of thiopurines

Thiopurines are the most frequently used medication for maintenance therapy in children with IBD.<sup>33</sup> They are used in 'high risk' Crohn's disease cases at diagnosis, Crohn's disease that relapses soon after the initial diagnosis, or in ulcerative colitis patients who experience two or more relapses per year following initial successful therapy.

Azathioprine is more frequently used than mercaptopurine; however, if patients are intolerant to azathioprine, many will subsequently tolerate mercaptopurine.<sup>23</sup>

The current recommended dose of azathioprine is 2.5 mg/kg/day in a single dose and for mercaptopurine is 1.25 mg/kg/day.<sup>23</sup> For example, in a 25 kg child, 62.5 mg of azathioprine is the optimal dose—as they should be swallowed whole, tablets should be given as 50mg one day followed by 75mg the following day in order to achieve the desired dose. Proprietary liquid preparations of thiopurine agents are helpful for very young children who are unable to take tablets, usually those under 5 years of age. In this regard, mercaptopurine is preferable to azathioprine due to more favourable stability and costing. Children should be reviewed at their follow-up to see when they can convert to tablets or capsules.<sup>34</sup>

The most recent recommendation is to start on the maximum dose of thiopurine<sup>23</sup> with no need to 'build up' the dose as was practiced historically.<sup>35</sup> The therapeutic effect of

thiopurines may not be seen until 10–14 weeks after commencement of treatment with the full dose. High-dose azathioprine (3 mg/kg/day) has also been well tolerated by children with either Crohn's disease or ulcerative colitis. In one retrospective cohort study, only 2 of 107 patients had to stop treatment due to persistent adverse effects, such as headache, rash, gastrointestinal disturbance and, more rarely, influenza-like rash and pancreatitis.<sup>36</sup>

Dose adjustment may be required in relation to the thiopurine methyltransferase (TPMT) genotype or phenotype, as risk of early severe myelosuppression attributable to homozygote mutant/very low TPMT activity status may be present.<sup>6</sup> Consensus expert recommendations suggest halving the recommended dose of azathioprine in those patients who are heterozygous or who have low (but not extremely low) enzyme activity.<sup>35</sup>

#### Key points:

- Maximum-dose thiopurine should be commenced from initial prescribing with no need to 'build up' the dose
- Liquid mercaptopurine or alternate day dosing can be used for younger patients to achieve appropriate weight-based optimal dosing
- Measure TPMT levels prior to commencing azathioprine; 50% dose reduction is recommended in patients who are heterozygous and dose avoidance is recommended in patients who are homozygous

#### Mistake 8 Not using the correct 5-ASA formulation for the age of the ulcerative colitis patient

5-aminosalicylates (5-ASA) are effective for either induction or maintenance of disease remission in mild-to-moderate ulcerative colitis.<sup>37</sup> Once daily dosing is frequently used during maintenance in teenage patients or if compliance is poor, although specific studies of this strategy in this age group are awaited. In one induction trial in paediatric ulcerative colitis patients, once daily dosing of 5-ASA was as effective as twice daily dosing for reducing disease activity, in terms of treatment response, inducing remission and adverse events.<sup>38</sup> Maintenance studies in children are currently taking place. One open-label arm of a randomised controlled trial demonstrated that clinical remission can be markedly increased in children who have ulcerative colitis refractory to oral mesalazine by adding mesalazine enemas for 3 weeks, before commencing steroids.<sup>39</sup>

5-ASA preparations are preferred to sulfasalazine due to their superior safety profile and similar efficacy.<sup>6</sup> However, the choice of 5-ASA formulation differs by disease site and also by age (table 2). For example, in

Drug	Formulation	Optimal drug-release pH	Site of drug release	Licensing status
Asacol	Enteric coated with Eudragit S	pH-dependent delayed release (>7)	Terminal ileum and colon	Not licensed for use in children <18 years of age
Pentasa	Ethyl-cellulose-coated microgranules	Diffusion through semipermeable membrane (enteral pH)	Duodenum to colon	Tablets and suppositories: not licensed for use in children <15 years of age Granules: not licensed for use in children <6 years of age
Salofalk	Tablets: enteric coated with Eudragit L Granules: Eudragit L plus matrix granule structure	pH-dependent delayed release (>6) Granules have extra delayed release	Terminal ileum and colon	Enema: not licensed for use in children <18 years of age Suppositories: not licensed for use in children <15 years of age Granules: not licensed for use in children <6 years of age
Ipocol	Enteric coated with Eudragit S	>7	Terminal ileum and colon	
Octasa	Enteric coated with Eudragit S	pH-dependent delayed release (>7)	Terminal ileum and colon	

Table 2 | Mesalazine preparations frequently used for the management of ulcerative colitis and their licensing status. Adapted from Fell J.M., et al. (CC BY 4.0).<sup>6</sup>

preschool children, there is no liquid preparation for 5-ASA and sulfasalazine will therefore often be used in this age group. For those children who are not able to swallow tablets, such as those of primary school age, 5-ASA preparations are available as granules.<sup>6</sup>

#### Key points:

- The choice of 5-ASA formulation is dependent on disease site, age and patient tolerance
- Sulfasalazine is often used in under 5s as it is available in liquid preparation
- Mesalazine enemas are a good treatment choice in children failing oral mesalazine therapy

### Mistake 9 Not taking steps to reduce infliximab immunogenicity

The development of antibodies to biological agents is a well-documented side effect of infliximab infusions and can cause acute and delayed infusion reactions, shortened response, and loss of response to biologic therapy (often due to reduced trough levels of active drug). Risk factors for the development of antibodies include single and episodic infusions, female sex, a long gap between the first and second infusion, and a previous infusion reaction.<sup>40</sup>

The risk of developing immunogenicity, with loss of response to anti-TNF treatment, is particularly worrisome in children, because of the potential need for long-term treatment and the lack of licensed alternatives available if anti-TNF medications fail.<sup>41</sup> Data on the incidence and type of infusion reaction vary depending on how the data are collected, but acute transfusion reactions are most common (8–11%)<sup>42</sup> and delayed infusion reactions are rare (0.7–3%).<sup>43</sup> Figures on secondary loss of response to infliximab also vary, from 16% in one retrospective cohort study<sup>44</sup> to 50% in one observational, multicentre study.<sup>45</sup>

Concomitant immunosuppressive therapy with thiopurines or methotrexate in patients treated with infliximab reduces immunogenicity. In addition, starting immunomodulators may reverse the immunogenicity state in patients on infliximab monotherapy who have secondary loss of response due to antibodies.<sup>23</sup> In one cohort study, immunosuppressive therapy given for about 10 months before commencing infliximab therapy reduced the magnitude of the immunogenic response at the 2-month follow-up.<sup>46</sup>

Strategies to prevent antibodies to infliximab being formed are based on low-quality evidence, primarily from adult cohorts,

but are supported by a systematic review that concluded administration of corticosteroids and antihistamines can prevent acute transfusion reactions.<sup>47</sup> In one retrospective cohort study, administration of corticosteroids and antihistamines for 3 months had a protective role against the development of antibodies.<sup>48</sup>

#### Key points:

- Prevent acute transfusion reactions to infliximab with corticosteroids and antihistamines
- Concomitant immunosuppressive therapy with thiopurine and methotrexate in patients receiving infliximab may delay or reverse the development of antibodies to infliximab

### Mistake 10 Failing to involve a multidisciplinary team and use multimodal therapy to minimise the impact of growth impairment in Crohn's disease

Signs of IBD onset vary, but statural growth deficiencies, noted as a decreased height velocity, often precede intestinal manifestations by several years.<sup>49</sup> Growth impairment in patients with paediatric IBD is multifactorial, with disease aetiology and treatment medications often contributing. Growth deficiency can occur in up to 85% of patients, and is more often identified in patients with Crohn's disease (10–56%) than in those with ulcerative colitis (0–10%).<sup>50</sup> Up to 22% of children with paediatric IBD may not reach their target adult height, which may in part be due to pubertal growth disturbance and/or mineral, trace element and vitamin deficiency reflecting the disease process, in addition to the presence of common comorbidities.<sup>51,52</sup>

Some reports conclude that children with Crohn's disease have an improved short-term gain in height when enteral feeds are used to induce remission, with the addition of pharmacological management as required.<sup>53</sup> However, this short-term growth improvement is not always sustained long term.<sup>54</sup> Immunomodulators given to maintain remission have a minimal positive effect on growth, whereas anti-TNF treatments can potentially improve growth velocity via induction and maintenance of disease remission, though the impact of anti-TNFs on final height is still infrequently studied.<sup>55–57</sup>

One systematic review concluded that the optimal management of paediatric IBD and growth requires a multidisciplinary multimodal approach, including dietetic support, a nurse specialist, paediatric endocrinology and closely linked medical and surgical care.<sup>51</sup> Useful therapies include optimised nutrition and optimised

control of inflammation, including biologics, and for selected patients, the use of growth hormones or resectional surgery.<sup>58</sup>

**Key points:**

- About 1 in 5 children with IBD will not reach their target final height, despite optimal disease control
- Early involvement of a multidisciplinary team and multimodal therapy is necessary to achieve better growth outcomes for individual patients

**References**

- Ghione S, et al. Dramatic Increase in Incidence of Ulcerative Colitis and Crohn's Disease (1988-2011): A Population-Based Study of French Adolescents. *Am J Gastroenterol*. Epub ahead of print 15 August 2017. doi: 10.1038/ajg.2017.228.
- Pigneur B, et al. Natural history of Crohn's disease: comparison between childhood- and adult-onset disease. *Inflamm Bowel Dis* 2010; 16: 953-961.
- Benchimol EI, et al. Epidemiology of pediatric inflammatory bowel disease: A systematic review of international trends. *Inflamm Bowel Dis* 2011; 17: 423-439.
- Oliveira SB and Monteiro IM. Diagnosis and management of inflammatory bowel disease in children. *BMJ* 2017; 357: j2083.
- Abramson O, et al. Incidence, prevalence, and time trends of pediatric inflammatory bowel disease in Northern California, 1996 to 2006. *J Pediatr* 2010; 157: 233-239.e1.
- Fell JM, et al. Management of ulcerative colitis. *Arch Dis Child* 2016; 101: 469-474.
- Levine A, 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.
- Uhlig HH, et al. The diagnostic approach to monogenic very early onset inflammatory bowel disease. *Gastroenterology* 2014; 147: 990-1007.e3.
- Rothenberg ME. Eosinophilic gastrointestinal disorders (EGID). *J Allergy Clin Immunol* 2004; 113: 11-28.
- Boyce JA, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. *J Am Diet Assoc* 2011; 111: 17-27.
- Gerasimidis K, et al. The epidemiology of anemia in pediatric inflammatory bowel disease: prevalence and associated factors at diagnosis and follow-up and the impact of exclusive enteral nutrition. *Inflamm Bowel Dis* 2013; 19: 2411-2422.
- Dignass AU, et al. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. *J Crohns Colitis* 2015; 9: 211-222.
- Thayu M and Mamula P. Treatment of iron deficiency anemia in pediatric inflammatory bowel disease. *Curr Treat Options Gastro* 2005; 8: 411-417.
- Henderson P, et al. The diagnostic accuracy of fecal calprotectin during the investigation of suspected pediatric inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol* 2014; 109: 637-645.
- Zhu Q, et al. Fecal calprotectin in healthy children aged 1-4 years. *PLoS One* 2016; 11: e0150725.
- Oord T and Hornung N. Fecal calprotectin in healthy children. *Scand J Clin Lab Invest* 2014; 74: 254-258.
- Heuschkel RB, et al. Enteral nutrition and corticosteroids in the treatment of acute Crohn's disease in children. *J Pediatr Gastroenterol Nutr* 2000; 31: 8-15.
- Swaminath A, et al. Systematic review with meta-analysis: enteral nutrition therapy for the induction of remission in paediatric Crohn's disease. *Aliment Pharmacol Ther* 2017; 46: 645-656.
- Zachos M, et al. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2007; 1: CD000542.
- Day AS, et al. Systematic review: nutritional therapy in paediatric Crohn's disease. *Aliment Pharmacol Ther* 2008; 27: 293-307.
- Afzal NA, et al. Colonic Crohn's disease in children does not respond well to treatment with enteral nutrition if the ileum is not involved. *Dig Dis Sci* 2005; 50: 1471-1475.
- Buchanan E, et al. The use of exclusive enteral nutrition for induction of remission in children with Crohn's disease demonstrates that disease phenotype does not influence clinical remission. *Aliment Pharmacol Ther* 2009; 30: 501-507.
- Ruemmele FM, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *J Crohns Colitis* 2014; 8: 1179-1207.
- Critch J, et al. Use of enteral nutrition for the control of intestinal inflammation in pediatric Crohn disease. *J Pediatr Gastroenterol Nutr* 2012; 54: 298-305.
- Ludvigsson JF, et al. Elemental versus polymeric enteral nutrition in paediatric Crohn's disease: a multicentre randomized controlled trial. *Acta Paediatr* 2004; 93: 327-335.
- Rodrigues AF, et al. Does polymeric formula improve adherence to liquid diet therapy in children with active Crohn's disease? *Arch Dis Child* 2007; 92: 767-770.
- Yamamoto T, et al. Enteral nutrition for the maintenance of remission in Crohn's disease: a systematic review. *Eur J Gastroenterol Hepatol* 2010; 22: 1-8.
- Schulman JM, et al. Maintenance of remission with partial enteral nutrition therapy in pediatric crohn's disease: a retrospective study. *Can J Gastroenterol Hepatol* 2017; 2017: 5873158.
- Akobeng AK and Thomas AG. Enteral nutrition for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2007; 3: CD005984.
- Duncan H, et al. A retrospective study showing maintenance treatment options for paediatric CD in the first year following diagnosis after induction of remission with EEN: supplemental enteral nutrition is better than nothing! *BMC Gastroenterol* 2014; 14: 50.
- Hanai H, et al. Nutritional therapy versus 6-mercaptopurine as maintenance therapy in patients with Crohn's disease. *Dig Liver Dis* 2012; 44: 649-654.
- Takagi S, et al. Effectiveness of an 'half elemental diet' as maintenance therapy for Crohn's disease: A randomized-controlled trial. *Aliment Pharmacol Ther* 2006; 24: 1333-1340.
- Guariso G and Gasparetto M. Treating children with inflammatory bowel disease: Current and new perspectives. *World J Gastroenterol* 2014; 23: 5469-5485.
- Nuffield Orthopaedic Centre NHS Trust and Oxfordshire Primary Care Trust Shared Care Protocol and Infocation for GPs. Azathioprine (paediatric), [http://www.ouh.nhs.uk/oxpar/professionals/documents/Azathioprine\\_PAEDIATRIC\\_Rheumatologyshare\\_careprotocolJuly11.pdf](http://www.ouh.nhs.uk/oxpar/professionals/documents/Azathioprine_PAEDIATRIC_Rheumatologyshare_careprotocolJuly11.pdf) (2011, accessed 15 January 2018).
- Turner D, et al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. *J Pediatr Gastroenterol Nutr* 2012; 55: 340-361.
- Fuentes D, et al. High-dose azathioprine in children with inflammatory bowel disease. *Aliment Pharmacol Ther* 2003; 17: 913-921.
- Feagan BG and Macdonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2012; 10: CD000543.
- Turner D, et al. Once- versus twice daily mesalazine to induce remission in paediatric ulcerative colitis: a randomised controlled trial. *J Crohns Colitis* 2017; 11: 527-533.
- Levine A, et al. Mesalamine enemas for induction of remission in oral mesalamine-refractory pediatric ulcerative colitis: a prospective cohort study. *J Crohns Colitis* 2017; 11: 970-974.
- Parashette KR, et al. Infliximab therapy in pediatric Crohn's disease: a review. *Clin Exp Gastroenterol* 2010; 3: 57-63.
- de Ridder L, et al. Use of biosimilars in paediatric inflammatory bowel disease: a position statement of the ESPGHAN Paediatric IBD Porto Group. *J Pediatr Gastroenterol Nutr* 2015; 61: 503-508.
- Hyams J, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology* 2007; 132: 863-873.
- Friesen CA, et al. Safety of infliximab treatment in pediatric patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2004; 39: 265-259.
- Dupont-Lucas C, et al. Identifying patients at high risk of loss of response to infliximab maintenance therapy in paediatric Crohn's Disease. *J Crohns Colitis* 2016; 10: 795-804.
- De Bie CI, et al. The duration of effect of infliximab maintenance treatment in paediatric Crohn's disease is limited. *Aliment Pharmacol Ther* 2011; 33: 243-250.
- Baert F, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003; 348: 601-608.
- Lichtenstein L, et al. Infliximab-related infusion reactions: systematic review. *J Crohns Colitis* 2015; 9: 806-815.
- Miele E, et al. Human antichimeric antibody in children and young adults with inflammatory bowel disease receiving infliximab. *J Pediatr Gastroenterol Nutr* 2004; 38: 502-508.
- Kirschner BS and Rich BH. Puberty and pediatric-onset inflammatory bowel disease. In: Mamula P, Markowitz JE and Baldassano RN (eds) *Pediatric Inflammatory Bowel Diseases*. New York: Springer; 2008. pp 133-139.
- Abraham BP, et al. Natural history of pediatric-onset inflammatory bowel disease: a systematic review. *J Clin Gastroenterol* 2012; 46: 581-589.
- Heuschkel R, et al. Guidelines for the management of growth failure in childhood inflammatory bowel disease. *Inflamm Bowel Dis* 2008; 14: 839-849.
- Sawczenko A, et al. Adult height in patients with early onset of Crohn's disease. *Gut* 2003; 52: 454-455.
- Grover Z and Lewindon P. Two-year outcomes after exclusive early enteral nutrition inductions are superior to corticosteroids in pediatric Crohn's disease treated early with thiopurines. *Dig Dis Sci* 2015; 60: 3069-3074.
- Day AS and Lopez RN. Exclusive enteral nutrition in children with Crohn's disease. *World J Gastroenterol* 2015; 21: 6809-6816.
- Church PC, et al. Infliximab maintains durable response and facilitates catch-up growth in luminal pediatric Crohn's disease. *Inflamm Bowel Dis* 2014; 20: 1177-1186.
- Malik S, et al. Growth in children receiving contemporary disease specific therapy for Crohn's disease. *Arch Dis Child* 2012; 97: 698-703.
- Malik S, et al. The effects of anti-TNF- $\alpha$  treatment with adalimumab on growth in children with Crohn's disease (CD). *J Crohns Colitis* 2012; 6: 337-344.
- Hosjak I, et al. Long-term outcomes after elective ileocecal resection in children with active localized Crohn's disease—a multicenter European study. *J Pediatr Surg* 2015; 50: 1630-1635

## Your paediatric IBD briefing

**Online courses**

- ECCO e-Course on 'Exclusive enteral nutrition in CD' [<https://e-learning.ecco-ibd.eu/enroll/index.php?id=55>].

**Algorithms**

- ECCO e-Guide: Crohn's disease in children and adolescents [<http://www.e-guide.ecco-ibd.eu/algorithm/crohns-disease-children-adolescents>].

**UEG Summer School**

- 'Session 2: IBD/Small bowel' session at UEG Summer School 2017 [<https://www.ueg.eu/education/session-files/?session=1703&conference=147>].

**UEG Week**

- 'Drug development for digestive diseases: From clinical needs to regulatory perspectives' session at UEG Week 2016 [<https://www.ueg.eu/education/session-files/?session=1623&conference=144>].
- 'Characteristics of children with Crohn's disease failing sustained remission despite anti-tnf exposure' presentation at UEG Week 2016 [<https://www.ueg.eu/education/document/characteristics-of-children-with-crohn-s-disease-failing-sustained-remission-despite-anti-tnf-exposure/129078/>].
- 'Thiopurines in early CD: Paediatric population/ Thiopurines in early CD: Adult population' presentation at UEG Week 2014

[<https://www.ueg.eu/education/document/thiopurines-in-early-cd-paediatric-population-thiopurines-in-early-cd-adult-population/109283/>].

- 'Susceptibility genes for IBD differences between adults and children' presentation at UEG Week 2013 [<https://www.ueg.eu/education/document/susceptibility-genes-for-ibd-differences-between-adults-and-children/104020/>].
- 'Paediatric IBD' session at UEG Week 2013 [<https://www.ueg.eu/education/session-files/?session=790&conference=48>].

**Society conferences**

- 4th P-ECCO Education Course at the 12th Congress of ECCO [<https://www.ecco-ibd.eu/ecco17.html>].

**Standards and Guidelines**

- de Ridder L, et al. Use of biosimilars in paediatric inflammatory bowel disease: a position statement of the ESPGHAN Paediatric IBD Porto Group. *J Pediatr Gastroenterol Nutr* 2015; 61: 503–508 [<https://www.ueg.eu/education/document/use-of-biosimilars-in-paediatric-inflammatory-bowel-disease-a-position-statement-of-the-espghan-paediatric-ibd-porto-group/128281/>].
- Ruemmele F, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of

paediatric Crohn's disease. *J Crohns Colitis* 2014; 18: 1179–1207 [<https://www.ueg.eu/education/document/consensus-guidelines-of-ecco-espghan-on-the-medical-management-of-paediatric-crohn-s-disease/125374/>].

- Veereman-Wauters G, et al. Risk of infection and prevention in pediatric patients with IBD: ESPGHAN IBD Porto Group commentary. *J Pediatr Gastroenterol Nutr* 2012; 54: 830–837 [<https://www.ueg.eu/education/document/risk-of-infection-and-prevention-in-pediatric-patients-with-ibd-espghan-ibd-porto-group-commentary/125976/>].
- Turner D, et al. Management of pediatric ulcerative colitis: Joint ECCO and ESPGHAN evidence-based consensus guidelines. *J Pediatr Gastroenterol Nutr* 2012; 55: 340–361 [<https://www.ueg.eu/education/document/management-of-pediatric-ulcerative-colitis-joint-ecco-and-espghan-evidence-based-consensus-guidelines/125488/>].
- Further relevant articles can be found by navigating to the 'IBD' category in the UEG 'Standards & Guidelines' repository [<https://www.ueg.eu/guidelines/>] and on the Guidelines section of the ECCO website [<https://www.ecco-ibd.eu/publications/ecco-guidelines-science.html>].