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. 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. Worldwide, estimates of paediatric IBD prevalence rates are lacking, but data suggest their incidence is increasing. 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). The risk may also be higher in children of certain ethnicities (South Asian, Hispanic, and East Asian).

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.

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. They include arthritis, primary sclerosing cholangitis, autoimmune hepatitis, pyoderma gangrenosum and uveitis.

There is a 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.

First-line investigations include upper and lower gastrointestinal endoscopy and histology, with imaging, to establish IBD-like pathology. Exclusion of common infections, such as Salmonella, Shigella, Yersinia, Campylobacter, and Clostridium difficile toxins is 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.

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. Cow’s milk protein allergic colitis and eosinophilic disorders are also IBD mimics.

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 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. First-line investigations for diagnosis of IBD 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.

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. In these circumstance, 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. 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.

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. 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. 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.

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.

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.

A Cochrane review concluded there was insufficient evidence to support the impact of disease location on disease remission. 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. Data from Scotland suggest that children with colonic, ileo-colonic, and upper gastrointestinal disease have similar rates of remission on EEN. 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.

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...
(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.\textsuperscript{22,24} 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.\textsuperscript{25} 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 17–65; p = 0.02).\textsuperscript{26}

Children prefer polymeric formulas because they taste better, and some data suggest better weight gain with these formulas compared with an elemental diet.\textsuperscript{24} 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 contraindication 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.\textsuperscript{27} PEN has already been shown to maintain disease remission without concomitant medication and to improve nutritional status and disease activity scores.\textsuperscript{28,29}

The results of a 1-year retrospective cohort study demonstrated that remission rates were 65% 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).\textsuperscript{20}

In a detailed Japanese prospective adult cohort study, patients with a Crohn's disease activity index (CDAI) ≤150 were randomly assigned to receive either 6-mercaptopurine (0.5–1.5 mg/kg/day, n = 30), an elemental diet (≥900 kcal/day, n = 32) or nothing (control, n = 33), whilst continuing 5-aminosalicylic acid therapy.\textsuperscript{21} 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.\textsuperscript{22}

Key points:
- PEN may be offered as maintenance therapy in paediatric patients who have Crohn's disease, with PEN conferring favourable 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.\textsuperscript{23} 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.\textsuperscript{24}

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.\textsuperscript{25} 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.\textsuperscript{26}

The most recent recommendation is to start on the maximum dose of thiopurine\textsuperscript{27} with no need to 'build up' the dose as was practiced historically.\textsuperscript{28} 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.\textsuperscript{30}

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.\textsuperscript{31} 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.\textsuperscript{32}

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.\textsuperscript{33} 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.\textsuperscript{34} 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.\textsuperscript{35} 5-ASA preparations are preferred to sulfasalazine due to their superior safety profile and similar efficacy.\textsuperscript{4} However, the choice of 5-ASA formulation differs by disease site and also by age (table 2). For example, in
Mistakes in...

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Optimal drug-release pH</th>
<th>Site of drug release</th>
<th>Licensing status</th>
</tr>
</thead>
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<td>Asacol</td>
<td>Enteric coated with Eudragit S</td>
<td>pH-dependent delayed release (&gt;7)</td>
<td>Terminal ileum and colon</td>
<td>Not licensed for use in children &lt;18 years of age</td>
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<tr>
<td>Pentasa</td>
<td>Ethyl-cellulose-coated microgranules</td>
<td>Diffusion through semipermeable membrane (enteral pH)</td>
<td>Duodenum to colon</td>
<td>Tablets and suppositories: not licensed for use in children &lt;15 years of age Granules: not licensed for use in children &lt;6 years of age</td>
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<tr>
<td>Ipocol</td>
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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).

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.  

**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 transfusion 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.  

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. 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%) and delayed infusion reactions are rare (0.7–3%). Figures on secondary loss of response to infliximab also vary, from 16% in one retrospective cohort study to 50% in one observational, multicentre study.

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. 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. 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. In one retrospective cohort study, administration of corticosteroids and antihistamines for 3 months had a protective role against the development of antibodies.

**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. 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%). 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.

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. However, this short-term growth improvement is not always sustained long term. 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.

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. Useful therapies include optimised nutrition and optimised
control of inflammation, including biologics, and for selected patients, the use of growth hormones or resection surgery.

**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**
Online courses

Algorithms

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].
- ‘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
- 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].