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Crohn's and colitis in children and adolescents

Andrew S Day, Oren Ledder, Steven T Leach, Daniel A Lemberg

Andrew S Day, Oren Ledder, Daniel A Lemberg, Department of Gastroenterology, Sydney Children's Hospital, Randwick, Sydney, NSW 2031, Australia
Andrew S Day, Steven T Leach, Daniel A Lemberg, School of Women's and Children's Health, University of New South Wales, Sydney, NSW 2031, Australia
Andrew S Day, Department of Paediatrics, University of Otago Christchurch, Christchurch 8140, New Zealand
Author contributions: Day AS and Lemberg DA generated the concept for this manuscript; Day AS provided the first draft, coordinated the preparation of the manuscript and prepared the final draft of the manuscript; Ledder O, Lemberg DA and Leach ST provided sections and contributions for the manuscript; all authors approved the final manuscript.
Correspondence to: Andrew S Day, Professor, Department of Paediatrics, University of Otago Christchurch, Riccarton Avenue, Christchurch 8140, New Zealand. andrew.day@otago.ac.nz
Telephone: +64-3-3640747 Fax: +64-3-3640919
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Abstract

Crohn's disease and ulcerative colitis can be grouped as the inflammatory bowel diseases (IBD). These conditions have become increasingly common in recent years, including in children and young people. Although much is known about aspects of the pathogenesis of these diseases, the precise aetiology is not yet understood, and there remains no cure. Recent data has illustrated the importance of a number of genes-several of these are important in the onset of IBD in early life, including in infancy. Pain, diarrhoea and weight loss are typical symptoms of paediatric Crohn's disease whereas bloody diarrhoea is more typical of colitis in children. However, atypical symptoms may occur in both conditions: these include isolated impairment of linear growth or presentation with extra-intestinal manifestations such as erythema nodosum. Growth and nutrition are commonly compromised at diagnosis in both Crohn's disease and colitis. Consideration of possible IBD and completion of appropriate investigations are essential to ensure prompt diagnosis, thereby avoiding the consequences of diagnostic delay. Patterns of disease including location and progression of IBD in childhood differ substantially from adult-onset disease. Various treatment options are available for children and adolescents with IBD. Exclusive enteral nutrition plays a central role in the induction of remission of active Crohn's disease. Medical and surgical therapies need to considered within the context of a growing and developing child. The overall management of these chronic conditions in children should include multi-disciplinary expertise, with focus upon maintaining control of gut inflammation, optimising nutrition, growth and quality of life, whilst preventing disease or treatment-related complications.

Key words: Children; Adolescents; Crohn's disease; Ulcerative colitis; Inflammatory bowel diseases

Peer reviewer: Pär E Myrelid, MD, PhD, Department of Surgery, Linköping University Hospital, 58185 Linköping, Sweden

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) comprise the inflammatory bowel diseases (IBD). These chronic conditions affecting the gastrointestinal tract are becoming increasingly common. At present there is an incomplete understanding of the causation of CD and UC. Although children and adolescents can be diagnosed with IBD at any age, the second decade of life is the most common period. From diagnosis these children face a lifetime of

illness, with many potential consequences and effects.

CROHN'S AND COLITIS

IBD is characterised by chronic inflammation of the intestinal tract with variable periods of remission and exacerbation. Traditionally IBD is thought of as the two major clinical subtypes (CD and UC). However, it can also be seen as a heterogeneous group of disorders of intestinal inflammation[1].

Classically, UC involves disease that extends proximally for a variable distance from the rectum, with involvement of the superficial layers of the colonic mucosa. Pediatric cohort studies show that pancolitis is the most frequent presentation of UC in childhood, with few children having isolated proctitis[2,3]. This finding contrasts greatly with the disease patterns seen in adults with UC[2]. Furthermore, those children without pancolitis at diagnosis commonly have extension of disease to involve the whole colon over the subsequent years.

In contrast to UC, CD is characterised by transmural inflammation in a non-contiguous pattern (so-called skip lesions), anywhere from the mouth to the anus. Disease distribution of CD differs between children and adults[2]. In paediatric CD, the ileocolonic region is the most common location of disease. Disease limited to the colon is less frequently seen, and isolated terminal ileal disease is uncommon, occurring in less than 10% of children[2]. Involvement of the gut proximal to the terminal ileum occurs in more than half of children with CD, with common areas being the stomach and duodenum[2,4]. Aphthoid or serpiginous ulceration are particular endoscopic features of CD: other features such as friability, oedema, granularity and loss of vascular markings, may be seen in both UC and CD.

One particular histological feature of CD is non-caseating granuloma located in the inflamed mucosa. Perianal disease, including multiple large anal tags, perianal abscesses, non-healing deep fissures or fistulas, is a feature of CD, but not of UC. The inflammatory changes in CD may be complicated by stricturing or fistulising disease, with progression in many patients towards these phenotypes over time[5].

The term IBD-unclassified (IBDU) refers to those patients with chronic bowel inflammation whose pattern of disease is not clearly able to be classified as CD or UC. Over the course of the disease, IBDU is often reclassified as either CD or UC as the pattern and features of inflammation evolve. IBDU is more commonly reclassified as UC than CD[6]. The term indeterminate colitis, however, should be reserved for the situation where, following colectomy and histopathological examination of the colon, the distinction between UC and CD remains unclear[6].

EPIDEMIOLOGY

IBD can present at any age, with the peak age range of diagnosis in the second and third decades of life[7]. In childhood, rates of IBD increase from the first year of life, with highest rates in teenage years. Around 25% of all diagnoses of IBD are made in the first two decades of life[8,9]. A family history of IBD is more commonly elicited in children with IBD than in adults[7].

Generally UC is found to be more common than CD in the preschool age group, whilst CD is three times more frequent than UC in older children in many case series[10,11]. There is also a slight male preponderance (1.5:1) in prepubescent patients with CD as opposed to a slight female preponderance in adults[2].

Although the incidence and prevalence of IBD varies, there is overwhelming data showing increasing rates in many areas of the world[12,13]. In more recent years, an increasing incidence has been observed in countries that traditionally did not report IBD, such as Taiwan, China and other Eastern countries[14]. In addition, children of families migrating from the developing world to the developed world have increased rates of IBD[15]. There is also clear evidence that the incidence of IBD in the paediatric population is increasing, especially for CD. Benchimol *et al*[16] observed an increased incidence rate of paediatric CD in the Canadian province of Ontario from 9.5 to 11.4 per 100 000 per annum over an 11 year period to 2005; however the incidence of UC in this period remained unchanged (4.1 to 4.2 per 100 000). In Australia, recent Victorian studies clearly show increasing rates in children, with a greater than 10-fold increase in CD over the 30 year period to 2001[17]. In addition, an eleven-fold increase in paediatric UC was seen in the same area, with particular increases over the most recent two decades[18]. It is unclear why IBD has become more common over the last decades: suggested factors include changes in lifestyle, diet, urbanisation and other environmental changes.

PATHOGENESIS OF IBD

The most accepted hypothesis for the pathogenesis of IBD is that interactions between the gut luminal contents (especially the intestinal microflora) and the mucosa lead to dysregulated inflammation in a genetically-predisposed host. A wide range of microorganisms have been considered as potential causative agents for IBD. These include *Mycobacterium paratuberculosis*, *Listeria monocytogenes*, Novel Burkholderiales and *Escherichia coli* subtypes[19,20]. It is also speculated that viral agents may play roles in the development of IBD[21]. Recently, a small study conducted in Finland focused on faecal detection of viral agents in a group of 50 children being evaluated for possible IBD (33 were diagnosed with IBD whilst 17 were shown to not have IBD)[22]. Viral agents were not detected in the IBD group-but were present in 3 of the control group.

There is not yet clear data to support a role for any one of these organisms as the primary factor in the aetiology of IBD. Our recent work has focused upon several mucous-associated organisms, including members of the

Helicobacter and *Campylobacter* families[23,24]. Although these studies show that such organisms are commonly present at the time of diagnosis of IBD, it is unclear if they have a causative role.

Some of the most exciting recent developments in our understanding of the pathogenesis of IBD have been in the field of genetics. A decade ago, *NOD2/CARD15* was identified as the first susceptibility gene for CD[25]. NOD2 is a member of a family of intracellular proteins that respond to bacterial proteins and contribute to host defence[26,27]. In one large study 50% of patients with CD were found to have at least one *NOD2* gene mutation, with 17% having a double mutation[28]. Those patients with 2 mutations were characterised as having a younger age of onset, more frequent stricturing disease, and less frequent colonic involvement, suggesting a link with earlier onset of disease. NOD2 mutations are present at the same rates in patients with UC as in controls and are also not seen in non-European populations, such as in Japan, India and South Korea[29-31]. Furthermore, NOD2 mutations are not associated with early onset of disease in children of Ashkenazi background[32]. Tumour-necrosis factor (TNF)-α promoter gene mutations were, however, associated with early onset in this group of children.

In more recent years, a number of other genes have been shown to be important for IBD-most in CD but some in UC. A recent transatlantic collaboration scanned a cohort of 3426 childhood-onset IBD patients and identified 5 new loci associated with paediatric IBD[33]. In 2010, a multi-national collaboration identified many further loci implicated in CD, bringing the total of loci identified to 71[34]. Mutations in the interleukin (IL)-10 receptor were recently shown in a group of infants with very early onset of severe and treatment resistant disease. Mutations in the coding for one of chains of the IL-10 receptor were identified: this change renders the patients' cells unresponsive to the anti-inflammatory effect of IL-10[35]. A recent review article highlighted the findings of two paediatric gene wide association studies[36]. Although emphasising key genetic pathways common to adult-onset disease, these studies also identified novel regions associated with early-onset disease, including genes encoding IL-27. The relevance of these potential links was recently outlined in a hypothesis article[37]. In addition, a current prospective study (www.neopics.org) focusing on genetic influences on children aged less than 6 years of age should further define key aspects in this group.

PATTERNS OF PRESENTATION OF IBD IN CHILDREN

Children with IBD may present with a range of symptoms, depending on the location, severity and chronicity of inflammation. Classically, CD most commonly presents with pain, diarrhoea and weight loss, whilst UC most commonly starts with bloody diarrhoea[38]. Children with distinct disease locations may present with other defined gastrointestinal symptoms. For instance, oesophageal involvement may lead to odynophagia and dysphagia whilst perianal presentation may include pain, discharge or a mass. Recent studies suggest that fewer children have the so-called classical symptoms, and that children may have a range of presenting features (including atypical symptoms) including abdominal pain, diarrhoea, short stature or weight loss[2,38]. Some children presenting with atypical or non-gastrointestinal symptoms may have delayed recognition and diagnosis. Although many of the gastrointestinal symptoms seen in paediatric IBD are similar to those reported in adults, particular features in children include linear growth failure and pubertal delay.

Despite its name, IBD is not limited to the bowel. Up to 30% of patients will develop an extra-intestinal manifestation (EIM) at some point during their lifetime[39]. The most common EIM in children are arthritis (axial or peripheral), cutaneous changes (e.g., erythema nodosum and pyoderma gangrenosum), eye diseases (such as episcleritis and uveitis that occur in approximately 1% of patients with IBD) and liver disease[40]. Hepatobiliary complications can take the form of primary sclerosing cholangitis, autoimmune hepatitis or overlap syndrome[40].

IMPACT OF IBD UPON GROWTH AND NUTRITION IN CHILDREN

Weight loss, or lack of weight gain, is a presenting feature in 85% of children with CD and at least 65% of children with UC[7]. This impairment of weight is predominantly a result of decreased oral intake due to anorexia, early satiety, nausea or pain. In addition to compromised weight, linear growth may also be impaired at diagnosis or subsequently[41]. These consequences are primarily related to the systemic circulation of pro-inflammatory cytokines, such as TNF-α and IL-6. IL-6 influences the activity of key proteins, including insulin-like growth factor (IGF)-1, and interferes with the effects of growth hormone and other key pathways[42].

An additional consequence of nutritional impairment and elevated levels of cytokines is delayed pubertal development. Given that many children present in the pre-pubertal or peri-pubertal period, pubertal delay can be of significant concern and importance. Failure to adequately induce disease remission at this crucial stage can have significant consequences such as missed or delayed pubertal growth spurt and reduced final height, abnormal bone mineralisation, and maintenance of prepubertal sex hormone levels[38].

Children with IBD can also have micronutrient deficiencies. The most common of these are iron, vitamin D, vitamin B12, calcium and zinc. In a cohort of children with IBD from Sydney, Australia, only 40% had normal Vitamin D status[43]. Lack of Vitamin D along with inadequate calcium intake (and also vitamin K deficiency) contributes adversely to bone health. Since 90% of peak bone mass is attained during childhood and adolescence, failure to attain maximal potential may increase future

fracture risk[44]. Underlying systemic inflammation is an independent detrimental influence on bone health[44]. Sylvester *et al*[45] have shown low mean bone mineral density (BMD) scores in children with IBD and also demonstrated that BMD scores are associated with body mass index and IL-6 levels.

APPROACH TO POSSIBLE IBD IN CHILDREN

Diagnostic pathways begin with the consideration of possible IBD as an important first step. A suggestive history of gut symptoms may be present, but children may present with atypical symptoms. Examination findings of weight loss, chronic disease (e.g., clubbing) or extra-intestinal features of IBD (e.g., erythema nodosum) may be detected. Weight and height should be accurately measured and plotted on an appropriate growth chart. Previous growth data should be obtained from the child's health records and parental heights should be recorded to calculate mid-parental height.

Exclusion of other potential pathologies, especially enteric infections, is important. Several stool cultures should be requested to exclude an enteric infectious cause in children presenting with diarrhoea and/or abdominal pain, with inclusion of less common organisms such as Yersinia and Aeromonas. Stool can also be sent for faecal markers of inflammation-these include the presence of faecal white cells, stool α-1-antitrypsin, lactoferrin and calprotectin (where available). S100A12, another non-invasive marker of gut inflammation shows high sensitivity and specificity in differentiating between children with IBD and non-IBD conditions[46]. Non-invasive tests such as calprotectin and S100A12 may also have roles in disease monitoring after diagnosis[47].

Blood tests should be requested for full blood count (especially Hb, platelets, and white count), erythrocyte sedimentation rate (ESR), C-reactive protein, albumin and liver chemistry. Further baseline assessment should include iron studies, B12/folate levels and vitamin D. Serum based markers of systemic inflammation may be helpful in children with IBD, but exclusion of the diagnosis can not be made with normal tests. A recent North American study suggests that normal bloods (platelets, ESR, albumin or Haemoglobin) may be seen in 21% of mild CD, 54% of mild UC and 4% of more severe CD or UC[48]. The addition of specific serological tests (ASCA, ANCA and pANCA) to a standard diagnostic approach is shown to improve and enhance diagnostic yield[49].

If IBD is suspected on the basis of history, examination findings and/or the results of preliminary tests, then further investigations should be arranged. Definitive diagnosis relies on endoscopic and histologic findings, often supported by radiologic findings. Upper gastrointestinal endoscopy and ileo-colonoscopy should both be undertaken in any child or adolescent with suspected IBD, along with multiple mucosal biopsies[50]. As an upper gut location of IBD is present in at least two thirds of children with CD, findings in this region may be sufficient firstly to make a diagnosis of IBD or secondly assist in differentiating between CD and UC[4].

Baseline investigations should also include an assessment of the small bowel[50]. The vast length of the small bowel is not accessible to standard endoscopy. An increasingly preferred method to view the small bowel is a small bowel series magnetic resonance imaging, which can provide detail of the extent of inflammatory changes through the mucous without radiation exposure[51]. This has largely supplanted the small bowel meal and follow-through as a tool to assess the small bowel. Capsule endoscopy also has an increasing role, with this modality able to identify superficial and smaller mucosal lesions[52]. Other potential modalities include white-blood cell scans, positron emission tomography scans and ultrasound scanning[53-55]. CT scanning, however, is rarely required in children and adolescents (and is generally discouraged due to potential cumulative radiation exposure).

MANAGEMENT OF IBD IN CHILDREN

Although the key concept in the management of IBD is inducing and maintaining remission, the pervasive effects of IBD in children mean that holistic care is essential, with consideration of multiple aspects of the condition and its complications. Provision of these management aspects in a child (and family) focused multi-disciplinary team setting is optimal to ensure superior outcomes.

In terms of control of gut inflammation, the management principles are to induce remission (control inflammation) and to then maintain remission. Although remission can be considered at clinical (relief of symptoms) and biochemical levels (normalisation of systemic markers of inflammation), histological remission (normalisation of histologic changes or mucosal healing) is seen as the ideal goal of therapy. Therapies to induce remission (e.g., corticosteroids or exclusive enteral nutrition) can be considered separately to those utilised to maintain remission [e.g., amino-salicylates (ASA) or immunomodulators such as thiopurines].

Whilst corticosteroids have traditionally been utilised to induce remission in active IBD, there is increasing support and rationale for exclusive enteral nutrition (EEN) in paediatric CD. EEN involves the sole administration of a nutritional formula, with exclusion of normal diet, for a period of up to 8 wk[56,57]. EEN has remission rates equivalent to those of CS, but has numerous advantages such as avoiding steroid-related side-effects and in addition leads to superior rates of mucosal healing[58]. Antibiotics (especially metronidazole and/or ciprofloxacin) may have roles in mild luminal or perianal CD. Aminosalicylates may have particular roles in inducing remission in mild to moderate active UC. Tacrolimus[59] or cyclosporin may have a role in the management of severe colitis, whilst biologic drugs (such as infliximab) have roles in the induction of remission of severe disease.

ASA drugs have roles in the maintenance of remission

of UC, and although often also used for maintenance in CD, they are not as well supported for this by available evidence. Steroids and antibiotics do not have roles in the maintenance of remission of IBD in children. The immunosuppressive drugs have defined roles in the maintenance of remission of IBD in children. Thiopurines (azathioprine or 6-mercaptopurine) are typically used first: methotrexate tending to be used in the setting of thiopurine failure or intolerance[60]. Early commencement of thiopurines in moderate-severe disease leads to less steroid requirement, more prolonged remission and better growth[61]. Other drugs (such as thalidomide, tacrolimus or mycophenolate) may play a role in maintenance of remission. Supplementary nutrition can also have a role in maintaining remission in CD, but the subgroup most likely to benefit from this approach has not yet clearly been defined[57].

Biological therapies have clear roles in the induction of remission in severe disease and in the subsequent maintenance of disease with ongoing dosing. The efficacy and safety of both infliximab[62] and adalimumab[63] has been considered in children and adolescents.

In addition to the current standard therapies, numerous other therapies are being developed or considered for roles in IBD. Many of these are biologic therapies that are able to be considered consequent to improved understanding of the complex inflammatory events in IBD. Other therapies that may play adjunctive roles include fish oils[64] and probiotics[65]. Additional novel therapies reported recently include low dose naltrexone[66] and pig whip-worm therapy[67]. The definitive roles for these therapies in children have not yet been proven.

One important factor in achieving optimal outcomes for children of any age with medical therapies is adherence. Recent work highlights an important relationship between adherence and disease severity[68].

As well as medical therapies, many children with IBD require surgical intervention. Common indications in children with CD include the management of perianal disease, resection of disease unresponsive to medical therapy, or resection of a fibrotic stricture. In children with UC the indications for colectomy include fulminant UC unresponsive to medical therapy, severe colitis complicated by toxic megacolon and/or perforation, chronic colitis unresponsive to medical agents and following the development of pre-cancerous changes.

The cumulative risk of surgery in a series of 404 children with CD was 20% at 3 years and 34% at 5 years[3]. A lower rate of resective surgery was seen in a Scottish series, with 20.2% having undergone surgery by 5 years[2]. In this series, the authors demonstrated that the median time to first surgery was longer in their group of children with CD than a comparative adult group (13.7 years from diagnosis compared to 7.8 years; $P < 0.01$). In contrast, the reverse was seen in the individuals with UC (11.1 years from diagnosis in children contrasting to > 50 years in adults; $P = 0.38$)[2].

The various therapeutic options need to be considered within the context of the individual patient and their disease pattern/location. Clearly the potential side-effects of an individual therapy need to be outlined in candid discussions with the patient and parents: these aspects need to be considered in the context of the potential benefits and the relative risk of the adverse effects.

In addition to the use of specific nutritional therapies to induce or maintain remission, the overall management of paediatric IBD requires close attention to growth and nutrition. Weight and height should be monitored regularly, with calculation of height velocity and assessment of pubertal development. Successful growth can be considered as an indicator of the success of therapy for IBD. Provision of a full well-balanced diet, with inclusion of adequate macronutrients (protein, fat, carbohydrates) and micronutrients (e.g., calcium and iron), should be reviewed by a paediatric dietitian regularly, with at least annual review. Monitoring of micro-nutrients is also important. Levels of iron, B12, folate and vitamin D should be reviewed on an annual basis.

The psychosocial aspects and consequences of IBD also require attention. IBD can impact greatly upon the quality of life of young patients[69]. Disruption to schooling and social activities is common, especially in those with unstable or severe disease. Attention to coping and provision of supports, may require psychological intervention. Peer-support activities and supports also play important roles in the overall management of children with IBD.

PROGNOSIS AND OUTCOMES OF IBD IN CHILDREN

Given diagnosis in the first decades of life, infants and children have many decades of disease in front of them. Several recent cohorts have illustrated key aspects of the natural history and outcomes of IBD in children, with emphasis of key differences from adult-onset cohorts[2,3,70].

Immune reactivity based upon a series of specific serological responses, has been shown to associate with disease outcome in children[71]. In this group of 796 children with CD, an increased number of serological responses were linked with more aggressive disease pattern and earlier progression of disease. Subsequently, Siegel *et al*[72] have developed a tool to outline predicted disease course in children with CD, incorporating serologic responses, along with patient and disease factors. The need for surgery has also been linked with NOD2 mutations in children with CD[73]. Risk scores have also been considered in paediatric UC: Moore *et al*[74] showed that white blood count and haematocrit values at diagnosis were associated with colectomy at 3 years in a cohort of 135 children with UC.

CONCLUSION

Crohn's and colitis has become an increasingly common diagnosis in children of all ages. These conditions have particular features and patterns in children, compared to adults. Early consideration of the diagnosis is important to avoid additional adverse impact upon growth, nutrition and normal functioning. Nutritional aspects are critical in the overall management of IBD. Whilst EEN is the therapy of choice to induce remission in CD, overall monitoring of growth and nutrition are key elements of ongoing management. Further work on the utility of drugs, such as antibiotics, will likely proceed in conjunction recognition of the importance of the intestinal microflora in the pathogenesis of IBD. The care of children and adolescents with IBD needs to be considered within a multi-disciplinary focus, with many different health professionals playing important roles.

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