Review

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The emerging global epidemic of paediatric inflammatory bowel disease – causes and consequences

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Two decades ago, paediatric inflammatory bowel disease (IBD) drew only modest interest from the international paediatric community. Since then, dramatically globally increasing incidence rates have made childhood-onset IBD a priority for most paediatric gastroenterologists. The emerging pandemia of paediatric IBD has fuelled a quest to identify the recent changes in early life exposures that could explain the increasing risk for IBD amongst today's children. Treatment of children with IBD should aim for symptom control but should also target restoration of growth and prevention of pubertal delay. The paediatric IBD phenotype seems to be characterized by more extensive disease location, and some comparative studies have suggested that childhood-onset IBD also represents a more severe phenotype than the adult-onset IBD form.In this review, we analyse recent global incidence trends of paediatric IBD. We present an update on the known and suggested risk factors that could explain the emerging global epidemia of paediatric IBD. We also draw attention to differences in treatment between children and adults with IBD. Finally, we highlight latest follow-up studies that question the proposed dynamic and aggressive nature of childhood-onset IBD.

Keywords: Crohn's disease, epidemiology, growth, inflammatory bowel disease, ulcerative colitis.

Incidence

We have followed the incidence of paediatric inflammatory bowel disease (IBD) in northern Stockholm County since 1990. In a study covering 1990–2001, we observed a steep increase in paediatric IBD incidence and a shift in presentation from ulcerative colitis (UC) to Crohn's disease (CD) [1]. In a follow-up paper covering 2002–2007, we reported that the incidence of childhood-onset IBD had plateaued, although the incidence of paediatric CD was consistently higher in Stockholm than in other regions in the world [2].

These findings are in most aspects consistent with other epidemiological studies on paediatric IBD from the last decades. During this time frame, increasing incidence rates of both UC and CD have been reported in epidemiological studies from most continents [3]. The highest incidence rates of childhood-onset IBD have been observed in high-income countries located in the Northern Hemisphere [2, 4–6]. The increasing incidence of childhood-onset IBD seems in most countries to be due to a rising incidence of CD [1–3].

Increasing incidence of immune-mediated diseases (including allergic and autoimmune diseases and IBD) has been observed in Europe and North America during the last decades. Although the rise in some of these diseases might be attributed to increased awareness and improved diagnostic procedures, it is worth noting that the incidence of childhood-onset diabetes mellitus type 1 (DM1) has increased dramatically in Scandinavia during recent decades [7, 8]. DM1 has a rather precise definition and is fatal when untreated, so it is implausible that the increase in incidence could be explained by changes in diagnostic procedures or improved awareness of the disease. In northern Stockholm, the increase in paediatric IBD incidence at the end of the 1990s was paralleled by a steep increase in childhood-onset DM1 incidence [1, 9]. It should also be noted that the faecal calprotectin test as a screening tool for children with long-standing gastrointestinal problems was

not introduced in northern Stockholm until after the transition to high-incidence rates of paediatric IBD. All these facts strengthen the plausibility of the observed increase in childhood-onset IBD rates being real.

The higher incidence rate of CD than UC observed in our studies is consistent with most epidemiological studies on paediatric IBD from the last decade. However, a study performed in the Uppsala region, just north of Stockholm, on a contemporary cohort with childhood-onset IBD, reported an inverse distribution of the two diseases [4, 10]. Conflicting UC/CD ratios have also been reported in paediatric population-based studies from Canada [6, 11] and the Nordic countries [12–14]. These striking differences in distribution of differential diagnosis between paediatric population-based IBD cohorts from geographically, socio-economically and genetically comparable regions implies that the differences may lie in the disease classification rather than in the diseases themselves. Misclassification could be expected to be more common in childhood-onset IBD, as colitis is the most common disease presentation in children with CD and thus makes differentiation from UC more complicated. This observation underlines the need for more specific diagnostic criteria for childhood-onset IBD which would help to ensure the reliability of comparisons between populations [15].

All the characteristics of UC can also be caused by CD (although microscopic inflammation limited to the mucosa is very rarely seen in CD). Conversely, several endoscopic and microscopic CD manifestations exclude UC as a possible differential diagnosis. This explains why most follow-up studies report that a significant proportion of patients with UC (or inflammatory bowel disease unclassified (IBDU)) will ultimately be re-classified as having CD [16, 17]. It is probable that more frequent use of upper endoscopy, small bowel imaging and biopsy sampling in patients with adult-onset IBD would increase the proportion diagnosed with CD rather than UC. The reported differences in UC/CD ratio between childhood- and adult-onset IBD cohorts could thus be expected to be somewhat overestimated.

Risk factors

Twin studies have stressed the importance of both genetic and environmental factors in the development of both UC and CD [18, 19]. It could be assumed that the genetic influence on the pathogenesis is greater for patients that develop IBD during childhood, as they have been confronted with fewer exposures during their short life span. Studies on children that have developed IBD during infancy have demonstrated mutations in genes involved in the IL-10 signalling system, and this seems to be the cause of the intestinal inflammation in rare cases [20].

Several studies have shown that different ethnic groups living in the same region may have significantly different IBD incidence rates [21]. Whether this is explained by differences in genetic susceptibility or by differences in environmental exposures associated with ethnicity has been a source for debate. Second-generation immigrants to Great Britain, from Asian countries with low IBD incidence, seem to have a higher risk for IBD than both their parents and the indigenous European population [22]; this indicates that environmental factors, not genetics, are the major driving force in changes of disease risk, at least in high-incidence regions.

The increasing incidence of paediatric IBD indicates that early environmental exposures are involved in the aetiology of the diseases. Known risk factors for adult-onset CD such as smoking [23] and use of oral hormonal contraceptives [24] would be expected to have little or no influence on the incidence of childhood-onset IBD. Perinatal [25] and childhood infections [26] have been associated with the risk of IBD later in life, but the global inverse relation between infant mortality (which is most often caused by infections) and IBD incidence argues against early infections as an important cause for the present epidemic of paediatric IBD. The protective effect of breast feeding has been demonstrated in several studies [27] but sheds no light on the enigma of rising childhood-onset IBD incidence, as breast feeding has increased in high-incidence regions like Scandinavia during the last decades [28].

The pathogenesis of IBD involves an inappropriate immunological response to bowel microbiota. This has been demonstrated in studies showing that colonic inflammation in patients with CD heals when a diverting ileostoma is constructed but recurs after re-anastomosis and re-establishment of the faecal stream [29]. Genetic studies have widened our understanding of this inappropriate

response by showing that failure of the innate immune system to identify and handle luminal bacteria is associated with an increased risk for IBD [30, 31]. It is believed that impaired control of the microbiota by the innate immune system may result in a compensatory but poorly balanced response from the adaptive immune system [32]. In this model, certain environmental exposures might trigger dysfunctional immune reactions to the commensal microbiota and thus cause chronic intestinal inflammation.

Mammalian young are normally confronted with appreciable numbers of microbiota for the very first time when passing through the birth canal during delivery. In humans, and other mammalian species that harbour large numbers of bacteria in the lower gastrointestinal tract, the normal colonization of the bowel thus starts with faecal microbes from the mother. The commensal microbiota improve the host's extraction of energy from food and also protects the host from pathogenic strains by competing for substrate and space [33]. The gastrointestinal tract is the primary site of interaction between the host immune system and microorganisms. Invading microorganisms are detected by the mucosal innate immune system, which responds with activation of inflammatory responses [34]. If the host is to develop tolerance to the microbiota, the primitive nonselective inflammatory response of the innate immune system has to be balanced by down-regulation of the adaptive immune system.

After birth, microbial colonization of the bowel in the healthy child is dependent on hygiene and feeding practices [33] and the maturation of bowel flora diversity is influenced by the intestinal immune response of the host [35, 36]. Significant differences in the composition of bowel flora have been demonstrated between Swedish infants born at the end of the 20th century and in preceding decades [37]. Comparisons between children raised in an industrialized lifestyle in Europe and children living in rural Burkina Faso in West Africa have demonstrated profoundly greater gut microbial diversity and lower quantities of potentially pathogenic strains in the latter group [33].

Whilst the immune system shapes the microbiota, it is also true that certain bacterial strains appear to be able to modulate the mucosal and systemic immune function of the host [38]. However, there seems to be a rather narrow time window for establishing persistent bacterial colonization of the bowel, as demonstrated in studies showing that organisms introduced during infancy may establish chronic persistence, whereas the same organisms are promptly cleared if first encountered later during childhood [39, 40]. Consistent with this, it has been demonstrated that mode of delivery and early antibiotic treatment have an impact on the composition of the intestinal microbiota many years after the exposure [41, 42]. Atypical or disturbed early colonization of the bowel might thus hinder the establishment of appropriate microorganisms, required for normal development of homoeostasis between microbiota and immune system, and may allow pathogens to persist. Abnormal microbial colonization of the gut in early life might thus have implications for the risk of developing immune-mediated diseases in general and IBD specifically later in life [35].

In two case–control studies, we have made use of Swedish national population registers to test the hypothesis that atypical initial or disturbed early microbial colonization might increase the risk for CD later in life [43, 44].

In the first study, we used inpatient treatment as a proxy marker of significant antibiotic treatment. We found that inpatient treatment for pneumonia between birth and age 5 years was associated with a significantly increased risk of both childhood-onset CD and adult-onset CD [43]. Recently published studies from Denmark and Finland, which have used nationwide databases of antibiotic purchases, have confirmed the association of antibiotic prescription during early childhood with an increased risk for CD later in childhood [45, 46]. It could be speculated that the increase in prescription of antibiotics to children in Sweden, which lasted until the mid-1990s [47], could have contributed to the increasing incidence rates of childhood-onset CD during the past two decades [1, 2, 4, 10, 48, 49]. If this is true, one would expect to see a decline in paediatric CD incidence rate in the next decade, as the prescription of antibiotics to children 0–4 years of age fell by 37% between 1995 and 2004 in Sweden [47]. However, results from a comparative European study covering 1994–1997 argue against the early use of antibiotics being of major importance for the epidemic of childhood-onset CD in Scandinavia, as prescription of antibiotics in a country such as Spain, with low incidence of paediatric CD [50], was estimated to be almost twice as high as in Sweden [51].

In the second study, we analysed if birth mode was associated with CD risk during childhood. We demonstrated that birth by caesarean section was associated with a significantly increased risk for CD amongst males. Our findings is supported by a recent national cohort study from Denmark that found that individuals born by caesarean section were at a modest but significantly increased risk of developing IBD (including both CD and UC) during childhood [52]. Although the association of birth mode with paediatric CD seems to be consistent, the association is modest and does not suggest that advice on delivery procedures should be altered. In conclusion, the increasing incidence of paediatric IBD in Sweden does not seem to be explained by increasing use of antibiotics or more frequent deliveries by caesarean section. However, the association of these exposures with CD risk suggests that an atypical (from an evolutionary perspective) pattern of bowel colonization early in life seems to alter the susceptibility to disease later in life in some individuals.

Reported incidence rates of paediatric IBD from the Scandinavian countries are amongst the highest in the world. However, the rates seem to differ significantly between the neighbouring countries [2, 5, 13, 53]. This finding should prompt further comparative studies in the continuing quest for environmental factors that have changed recently and could explain the ongoing global, but by country borders varying, epidemic of paediatric IBD [3].

Diagnosis

There are as yet no internationally accepted criteria for the diagnosis of CD or UC. The current expert view is that the diagnoses should be established on the basis of nonstrictly defined combinations of clinical presentation, macroscopic appearance (endoscopy and radiology) and microscopic findings [9–15].

The Porto criteria from 2005 were the first consensus recommendations from the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) on how children with IBD should be examined [54]. According to the Porto standard, all children with suspected IBD should be examined with both gastro-duodenoscopy and ileocolonoscopy and all children with suspected CD or IBDU should also be examined with imaging of the small bowel. The revised Porto criteria from 2013 state that all invasive procedures in children with IBD should be performed under anaesthesia or deep sedation [55].

Classification

Inflammatory bowel diseases are disorders of multifactorial cause that can present in many different ways, and the disease burden throughout life can vary considerably from one patient to another.

The observed associations of certain early disease characteristics with a more severe disease course have influenced the creation and development of IBD classification systems. The subdivision of IBD patients in these phenotypes allows for more specific risk assessment that can be used to guide the choice and timing of medical and surgical treatment for the individual patient. The creation of international IBD classification systems has also enabled more valid comparisons of disease characteristics over time and between regions and populations.

The most important classification when trying to predict the disease course in an IBD patient is still the categorization into CD or UC. Although there is a huge span in disease burden within both entities, there are distinct group differences in prognosis between patients with CD and UC. Most UC patients can expect a quiescent disease course with little impact on life prospects [56, 57]. However, with the diagnosis comes a risk of an acute bout of severe colitis that might demand a life-saving colectomy and an increased hazard of developing colorectal cancer [58]. Thanks to modern treatment and follow-up strategies, patients diagnosed with UC in developed countries now seem to have an expected life span equal to that of the general population [59]. Patients diagnosed with CD can also expect to spend more time in clinical remission during the first decade after diagnosis [60, 61]. Nonetheless, the potential of the intestinal inflammation in CD to produce fibrosis and fistulas explains why the majority of patients with this diagnosis eventually seem to require surgical treatment [62]. Moreover, children diagnosed with CD (in contrast to children with UC) also face a risk of permanent growth retardation and delayed puberty [63]. It is thus not surprising that comparative studies have shown that CD patients in general have lower self-reported quality of life than UC patients [64]. Most contemporary studies still report a shorter life expectancy amongst CD patients, which primarily seems to

be explained by progressive intestinal complications in a subgroup of patients [65, 66]. Some recent studies have not been able to demonstrate any significant difference in mortality rate between patients with CD and the general population [67, 68].

The first paper to demonstrate that certain initial disease characteristics of CD have bearing on the future disease course was published in 1975 by Farmer *et al.* [69] and provided evidence of the influence of anatomical disease location on prognosis. This landmark study was the foundation for the first international CD classification system, which was developed in Rome in 1988 [70] and later revised and simplified in Vienna in 1998 [71] and Montreal in 2005 [72]. The Montreal consensus document was the first that applied a classification of UC based on the extent of colonic inflammation and the severity at presentation or relapse [57, 58].

The Paris classification (Table 1) from 2010 is a paediatric modification of the Montreal classification [73]. As an adaption to paediatric practice, the presence or absence of growth failure during childhood was added as a discriminatory phenotype characteristic. It was also proposed that childhood-onset IBD be subdivided according to whether the disease was diagnosed before or after the patient was 10 years old [74]. The Paris classification also introduced subdivision of upper gastrointestinal disease into jejunal versus oesophago-gastro-duodenal disease.

Although already mentioned in the Vienna classification, the Paris classification stresses that the demarcation of the disease territory should be guided by observed inflammation at endoscopy or imaging and not by microscopic involvement.

Table 1 *The Paris classification is the first inflammatory bowel disease (IBD) classification system that has been developed for childhood-onset IBD. The Paris classification is a modification of the Montreal IBD classification scheme for patients with adult-onset IBD*

Paris phenotype classification of childhood-onset IBD	
Age	
A1a	<10 years
A1b	10–<17 years
A2	17–<40 years
Growth retardation	
G0	No growth retardation
G1	Growth retardation
Ulcerative colitis	
Extension	
E1	Ulcerative proctitis
E2	Left sided Ulcerative colitis (UC) (distal to splenic flexure)
E3	Extensive UC (distal to hepatic flexure)
E4	Pancolitis (proximal to hepatic flexure)
Crohn's disease	
Location	
L1	Distal ileum ± limited caecal disease
L2	Colonic disease
L3	Ileocolonic disease
L4a[a]	Upper GI disease, proximal to ligament of Treitz
L4b[a]	Upper GI disease, distal to ligament of Treitz and proximal to distal ileum
Behaviour	
B1	Nonstricturing, nonpenetrating disease
B2	Stricturing disease
B3	Penetrating disease
B2B3	Both stricturing and penetrating disease
P[b]	Perianal disease

[a]L4a and L4b are modifiers that can be added to L1–L3 when concomitant upper gastrointestinal disease is present.
[b]P is added to B1–B3 when concomitant perianal disease is present.

Symptoms and signs

Children with IBD do often present with the same symptoms as adult-onset IBD patients. In both UC and CD, loose stools often with blood, abdominal pain and weight loss are common features. Perianal (fissures, fistulae and abscesses) or oral disease manifestations (ulcers and swelling) might be the major problem for some children with CD [75].

Growth failure and retarded puberty are well-known features in children with IBD [63, 76–79]. Both features are found more often in CD than in UC. Growth failure may be the first sign of CD, occurring years before other symptoms [63] (Fig. 1). Growth failure are more often observed in children with CD involving the small bowel [80]. The aetiology of growth failure is multifactorial.

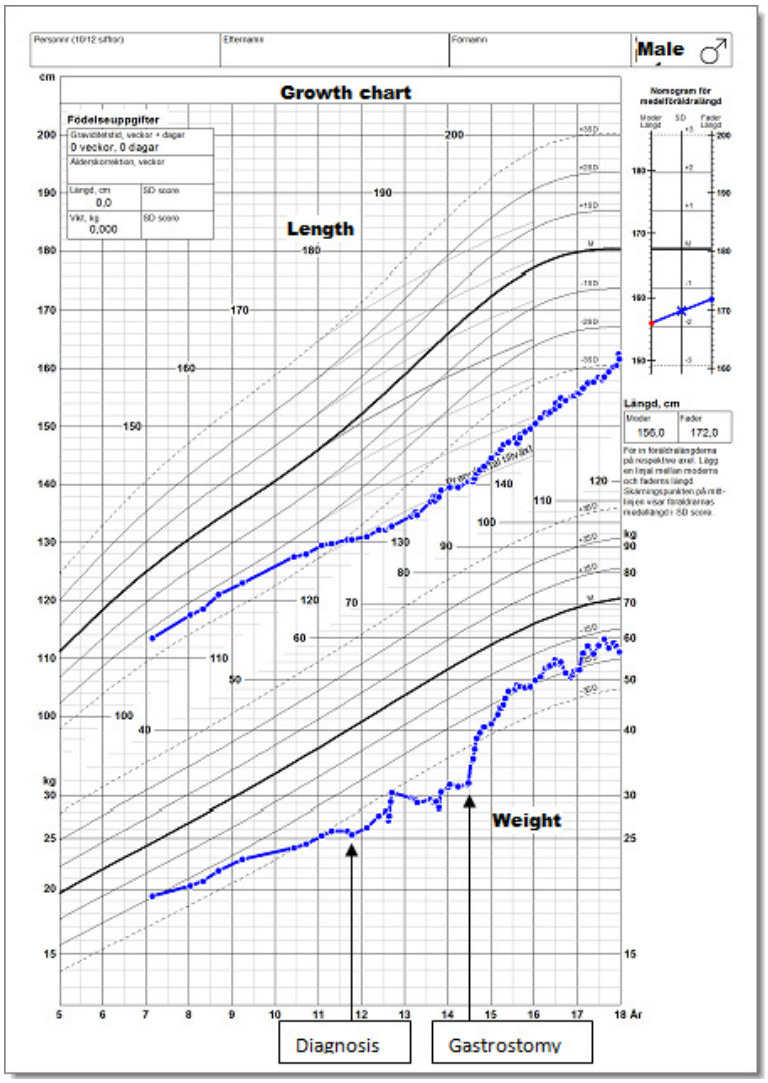

Fig. 1 *Growth chart of a boy diagnosed with Crohn's disease at the age of 11 years. The upper blue line shows height in centimetres; the lower line shows weight in kilograms. A retardation of growth velocity could already be seen some years before diagnosis and long before any significant gastrointestinal symptoms developed. Following insertion of a gastrostomy at the age of 14 and intensified nutritional support, his growth rate increased and he entered puberty. Despite intensive nutritional therapy and later addition of combined (anti-TNF and azathioprine) immunomodulatory treatment, he never experienced normal growth spurt velocity. However, he went on growing until the age of 21 (not seen in the growth chart) and ultimately attained a height close to what could be expected from his parents' heights.*

Undernourishment, corticosteroid therapy and direct effects of pro-inflammatory cytokines each seem to be important factors [81]. Available evidence suggests that chronic undernourishment is the main factor in the growth failure seen in children with IBD [82]. Children with active CD tend to eat less than healthy children of the same age [83]. Nutritional supplementation improves the linear growth of most children with CD [84]. As IBD in childhood most often starts just before or during puberty, it is important to establish the diagnosis early and to initiate therapy as soon as possible to minimize negative impact on the growth spurt. Children with UC usually reach puberty at the normal time and attain normal height, whereas children with CD often have delayed puberty and do not grow to their full potential height [63, 78]. Any therapy that decreases inflammation and improves nutrition has a positive impact on growth. Increased caloric intake [82], enteral nutrition [85, 86], drug therapy – especially biological [87] – and surgery [88] have all been shown to improve growth in children with CD.

Phenotype

A few studies have compared childhood-onset phenotype characteristics at presentation with contemporary adult-onset IBD cohorts from the same region [89–92]. Data from these studies

suggest that childhood-onset IBD is characterized by more extensive intestinal involvement at diagnosis. We could confirm this finding in our studies [1, 2] when comparing our childhood-onset IBD cohort with contemporary adult-onset IBD cohorts from Stockholm and Uppsala [4, 93]. However, the predominance of isolated colonic disease observed in our CD cohort conflicts with reports from most other contemporary paediatric IBD cohorts [14, 89, 94]. These suggest a paediatric CD phenotype characterized by even more widespread intestinal inflammation, often involving the large and small bowel as well as the upper gastrointestinal tract (pan-enteric disease). The significantly different disease distribution observed in our cohort might reflect real differences. However, the distinct difference in dominating phenotype – a difference seen even between the Scandinavian countries [14] – rather suggests differences in classification. The conflicting findings even between childhood-onset IBD cohorts from neighbouring countries emphasizes the importance of the recently created Paris IBD classification [73] as a common platform for upcoming paediatric studies.

The different presentation and differential diagnoses of IBD in small children are acknowledged in the Paris classification scheme [73]. Children that contract IBD before 10 years of age almost always present with extensive colitis that cannot be classified as either UC or CD until several years later [95].

Therapy

Most treatment provided to children with IBD is the same as that recommended for adults, but there are some important differences.

Most of the drugs that are used in paediatric IBD have only been tested on children in small uncontrolled trials. There are only a couple of paediatric IBD studies that have used a randomized placebo-controlled trial setting to test the efficacy of a drug [96, 97]. Drug effect data come primarily from pharmacological studies on adults from whom the results have been extrapolated to a paediatric IBD setting. Few of the drugs used in paediatric IBD have been approved for use in children, which means that a substantial proportion of the drugs are prescribed off-label. However, there is growing awareness amongst paediatricians, authorities and the drug industry that the effect of modern immunomodulatory drugs should also be studied in children and adolescents with IBD.

5-aminosalicylic acid

5-Aminosalicylic acid (5-ASA) compounds were the first drugs that could be demonstrated to have an effect on the symptoms caused by IBD [98, 99]. In consistent with guidelines for adult IBD patients, 5-ASA is recommended for paediatric UC patients with mild to moderate disease activity [100]. In contrast to adult IBD guidelines, the updated paediatric guidelines still recommend that 5-ASA also should be considered as maintenance treatment in mild to moderate CD [101]. This recommendation acknowledges the lack of evidence to support treatment in CD patients but takes into consideration the long experience of using 5-ASA on children, the predominance of colitis in patients with childhood-onset CD and the fear of severe side effects of immunomodulatory drugs.

Corticosteroids

Corticosteroids are frequently used in children with IBD. However, as prolonged use of corticosteroids is associated with growth retardation, these drugs must be used with great care in paediatric IBD patients. When treating adolescents with corticosteroids, one must also take into consideration that from a medical perspective, less severe side effects as acne and moon face appearance might be considered unbearable from a teenager's viewpoint. The main indication for corticosteroids is to induce remission in severe cases of IBD, and the drugs are used in both UC and CD [100–102]. As in adult gastroenterology, maintenance therapy with corticosteroids should be avoided if possible.

Nutrition

In growing IBD patients, it is crucial to estimate the patient's daily food intake to ensure that they get enough energy and nutrients for normal growth [82–84]. A substantial proportion of children with CD need daily supplementation with energy dense formulas to normalize growth [82]. Some children with CD and severe growth retardation who are unable to increase their energy intake will benefit from nutritional support via a gastrostomy [103].

The potential of exclusive enteral nutrition (EEN) therapy to induce remission in patients with CD was first described in adult patients [104] and later confirmed in paediatric patients [105]. Owing to the high costs of nutrition formulas and the observation that EEN is somewhat less likely than

corticosteroids to induce clinical remission in adults [106], nutritional therapy is seldom used in adult CD patients. Conversely, EEN has gained general acceptance in paediatrics; in the recently published transatlantic paediatric CD guidelines, this strategy is recommended as the first choice of therapy to induce remission in children with CD [101]. A meta-analyses restricted to paediatric studies have concluded that EEN has the same potential as corticosteroids to induce remission, whilst promoting rather than restricting growth [86]. Protein composition (elemental or polymeric) does not seem to influence the effectiveness of EEN in the treatment of active CD [85]. The anti-inflammatory mechanism of action of EEN is still unclear. It is suggested that the proven modification of the gut microbiota caused by the diet might explain the down-regulation of the pathogenic immune response [107]. Studies have demonstrated that biochemical markers of inflammation are reduced within days after the start of EEN and that this change precedes clinical improvement and weight gain [108]. Mucosal healing seems to occur more often in patients treated with EEN than amongst those prescribed corticosteroids [109, 110]. Despite the treatment's psychosocial side effects (no normal food is allowed during the treatment period of 6–8 weeks), most children seem to tolerate the treatment well and experience improved life quality [111]. There is some evidence that supplementary enteral nutrition without restriction of normal diet is associated with the prolongation of EEN-induced remission in children and adolescents [112].

No studies have been able to demonstrate a substantial anti-inflammatory effect of EEN in patients with UC.

Surgery

Because childhood-onset IBD was a rare condition until recently, data on paediatric IBD surgery are sparse. As in adult patients, surgery should be considered in children with CD whose symptoms do not respond to medical therapy or who have intestinal complications (strictures or fistulas) [101]. Indications for surgery in children with UC include fulminant colitis, failure of medical therapy and presence of colonic dysplasia [100, 102]. The timing of IBD surgery is important in growing children. If growth retardation is present, surgery is recommended prior to or early in puberty. Improved growth following surgery has been reported in children with CD [113] and with UC [114].

Immunomodulatory drugs

The introduction of corticosteroids during the 1950s provided potent anti-inflammatory drugs that radically reduced mortality owing to acute colitis in patients with UC [115]. The experience that most patients who were saved from colectomy by corticosteroids during an attack of severe colitis nevertheless eventually required surgery [116] and that most patients with CD, despite pharmacological treatment, developed intestinal complications [62] led to the somewhat defeatist conclusion that medical treatment was unable to alter the natural disease course. The introduction of immunomodulators (azathioprine, mercaptopurine and methotrexate) during the 1990s and inhibitors of tumour necrosis factor (anti-TNF) (infliximab and adalimumab) during the first decade of the new millennium have evoked hopes that modern treatments might have the potential to prevent attacks of severe acute colitis in patients with UC [117] and development of complications in those with CD [118].

Thiopurines

In one of the few randomized placebo-controlled trials performed in children with IBD, Markowitz *et al.* [97] demonstrated that the addition of mercaptopurine significantly increased the steroid-free remission rate at 1 year after diagnosis in children with CD. Since the publication of this study in 2000, thiopurines have been widely used as maintenance treatment in children with moderate-to-severe IBD. By tradition, azathioprine is the thiopurine most often used in Europe including Scandinavia.

Methotrexate

The effect of methotrexate has been evaluated in several, albeit small, studies in children with CD [119, 120]. Most children in these studies had previously failed to respond to or been intolerant to thiopurines. There are very few paediatric studies on the effect of methotrexate in children with UC, and these lend no support to the drug being more effective in children than in adults patients [121]. The widespread use of methotrexate in paediatric CD is hampered by the parenteral drug administration route advocated in most guidelines [101, 122].

The absence of an association of immunomodulatory treatment with lymphoma amongst patients with juvenile rheumatoid arthritis [123] has increased the interest for methotrexate as an alternative to thiopurines for children with IBD. Despite the rarity of effect studies, the recently published transatlantic paediatric guidelines states that methotrexate should be regarded as an option instead of thiopurines as the first-line immunomodulatory treatment in paediatric CD patients [101].

Anti-TNF

The first IBD patient who was treated with anti-TNF was a 12-year-old girl with disabling CD who was given infliximab in 1992 [124]. Infliximab was approved for the treatment of paediatric CD in 2007 and for paediatric UC in 2012. The first fully human anti-TNF, adalimumab, was approved for the treatment of paediatric CD in 2012. The two anti-TNFs were frequently used in the treatment of children with severe IBD long before the paediatric drug indications were approved by the authorities. As for adult patients with IBD, anti-TNFs are effective for the induction and maintenance of remission in children with moderate-to-severe active CD and UC.

Since the introduction of anti-TNF, the maintenance therapy in children with IBD has been guided by a step-up model, in which 5-ASA represents step one, IM step two and anti-TNF step three (Fig. 2). This easy-to-grasp model is now challenged by some paediatric IBD experts as the pattern of associations of immunomodulatory treatment with lymphomas seems to be more complicated than formerly believed.

Immunomodulatory drugs and lymphoma

A paper published in 2007, based on data from the US Federal Drug Administration's Adverse Event Reporting System, reported eight cases of hepatosplenic T-cell lymphoma in young male patients with CD who had been exposed to combination therapy with infliximab and thiopurine. This type of lymphoma is a severe and very rare cancer, comprising only a few per thousand cases of lymphoma. This report has since had a major impact on the recommendations in national [122] and international paediatric guidelines [100, 101] that advocate for restrictive use of combined thiopurine and anti-TNF treatment in children with IBD (especially boys).

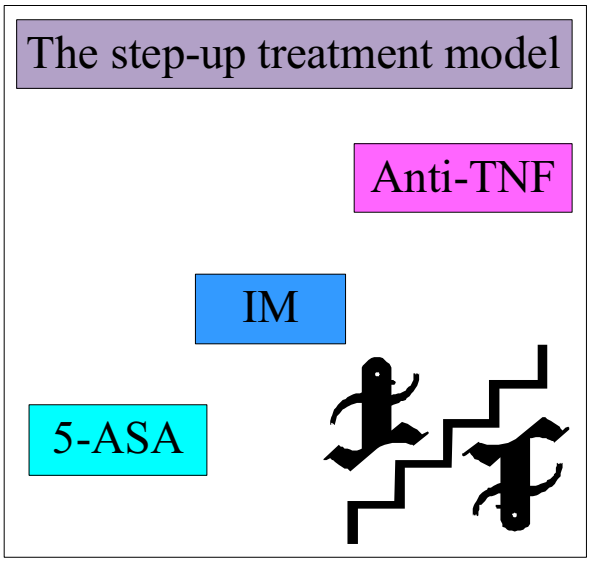

Fig. 2 *Maintenance therapy categorized according to the step-up model in which 5-ASA represents step one, IM (azathioprin, mercaptopurin and methotrexate) step two and anti-TNF (infliximab and adalimumab) step three.*

During recent years, the association of lymphoma with immunomodulatory therapy in patients with IBD has been analysed in several studies. A meta-analysis has demonstrated that ongoing (but not previous exposure to) treatment with thiopurine is associated with a four- to fivefold increased risk of developing non-Hodgkin lymphoma in adult IBD patients [125]. As the absolute risk for lymphoma seems to increase steeply with age, one could presume that the risk of thiopurine-induced lymphoma is probably much lower amongst children than amongst adults with IBD [126].

The fact that the vast majority of IBD patients who have been treated with anti-TNF have also been exposed to combination therapy with azathioprine makes it hard to clarify which of the two drugs should be blamed for the increased lymphoma risk. Available safety data from drug manufacturing companies and authorities have yet not been able to show that mono-treatment with anti-TNF increases the risk of lymphoma in IBD patients [127, 128].

Prognosis

Clinical experience suggests that there are several differences between childhood- and adult-onset

IBD patients [129]. Patients that have acquired UC during childhood seem to have a higher risk of developing colorectal cancer later in life [58]. During the last decade, several studies have been published that describe the early disease course of patients with childhood-onset IBD. Some of these studies present a childhood-onset phenotype characterized by increasing intestinal involvement over time and rapid progression to complicated disease behaviour [89, 94, 130]. The reported substantial risks for corticosteroid dependency [94, 130–132] and surgery [94, 130, 131] and a more frequent requirement for immunomodulatory therapy [133] in some of these studies have lent further support to the hypothesis that childhood-onset IBD represents a more severe phenotype.

Population-based follow-up studies have shown that most patients with adult-onset UC have a mild disease course with relatively little impact on everyday life [57]. However, within the first decade after diagnosis, almost all patients with UC seem to be confronted with a relapse of symptomatic disease and roughly one-fourth of the patients will need a colectomy [57, 134]. The surgery rate for UC patients seems not to have changed after the widespread introduction of immunosuppressive drugs [134].

Prognostic studies of patients with adult-onset CD have concluded that most patients at any given time during the first decade after diagnosis are fully capable of working [61]. Nevertheless, data from referral centres (i.e. data that tend to overestimate risks) indicate that most patients with CD will in time develop intestinal complications (strictures or fistulas) that demand surgical treatment [62]. There are conflicting results about whether the surgery rates have decreased amongst CD patients during the era of immunosuppressive therapy [134, 135].

We have studied the prognosis of all children diagnosed with IBD in northern Stockholm County 1990–2007 [136]. The majority of the 280 patients in this population-based childhood-onset IBD cohort could be followed until the end of the study period in 2010. Follow-up over a median of almost 10 years did not support the hypothesis that childhood-onset IBD represents a particularly dynamic and aggressive IBD phenotype. The rates of intestinal complication and intra-abdominal surgery were significantly lower in our cohort than those observed in earlier population-based studies of childhood-onset IBD cohorts [91, 94, 130, 137]. The patients in our cohort had, compared with contemporary adult-onset IBD cohorts, similar stability of disease location over time and comparable or somewhat lower rates of intestinal complications and surgery [56, 60, 138]. Prospective studies that compare progression of IBD between cohorts of children and adults with a common standardized follow-up protocol would be of great interest to further explore the differences in phenotype by age.

The observed relatively mild and decreasing disease burden in our cohort over time implies that the natural disease course in childhood-onset IBD might be less aggressive than previously believed [136]. This finding is of major importance as the focus of IBD treatment is now shifting from symptom control to prevention of irreparable intestinal damage [139]. This treatment strategy has attracted great interest amongst paediatric gastroenterologists, as childhood-onset IBD has long been considered a more aggressive phenotype and as paediatric patients have to face a lifetime accompanied by disease. The ongoing era of biologics has raised hopes that modern immunosuppressive treatments should have the capacity to change the natural disease course of IBD [118].

Most biologics have initially been tested in rheumatological diseases and then later moved on to trials for other inflammatory diseases such as IBD. The frontline experience gained in treating rheumatoid arthritis has thus served as an inspiration for gastroenterologists when trying to develop care for patients with IBD [139]. The concept of treating even subclinical inflammation in rheumatoid arthritis is now well established, as treatment guided by biochemical inflammatory markers has been associated with reduced joint destruction and lower levels of functional disability [140–142]. Analogous with this concept, earlier and more intense pharmacological treatment to prevent structural damage to the intestine is now also advocated by some experts in IBD [139]. Most attention has been directed to CD, where there is a weaker association between symptoms and intestinal inflammation [143], and complications (strictures and fistulas) necessitating intra-abdominal surgery seem to develop in almost all patients over time [62]. To alter the natural disease course of CD, it is suggested that treatment choices should be guided not only by symptoms but also by more objective markers of intestinal inflammation [144].

Intestinal mucosal healing has repeatedly (as demonstrated in our cohort [136] (Fig. 3)) been associated with a low risk of developing intestinal complications in prognostic studies [145, 146]. Some experts thus recommend that treatment of CD should aim to achieve and maintain both clinical remission and mucosal healing (a combination for which the term 'deep mucosal healing' is proposed) [147]. Ongoing and forthcoming trials will provide evidence on whether thiopurines and anti-TNF have the capacity to prevent structural damage to the intestine and thus their potential to modify the natural disease course in IBD.

The concept of treating beyond symptom control might be less controversial in paediatric CD, where impaired growth is already used as a marker of significant inflammatory activity that prompts more active treatment, even in the absence of overt gastrointestinal symptoms. However, if one looks to the rheumatology experience for guidance, it should be kept in mind that treatment concepts designed for joint inflammation probably have to be adapted to suit the gastrointestinal tract. Intestinal damage may not necessarily cause a functional disability in the way a destroyed joint will [148]. In our study, several of the patients with CD who had significant fibrotic tissue transformation (strictures) also had relatively mild symptoms during the following years and did not require intra-abdominal surgery [136]. Future studies of ways of modifying the course of IBD should thus ideally also include the newly developed functional disability index for IBD patients as end-point [149].

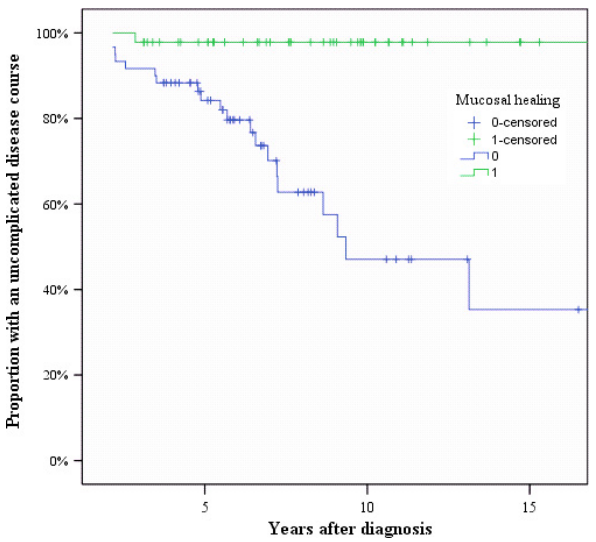

Fig. 3 *Kaplan–Meier curve of the rate of progression to a complicated disease course 2 years after diagnosis by mucosal healing at 1-year re-endoscopy for patients (n = 106) presenting with an uncomplicated childhood-onset Crohn's disease in northern Stockholm 1990–2007 [173]. Individuals who showed mucosal healing at 1-year re-endoscopy are shown in green; individuals who did not are shown in blue.*

When comparing with current treatment concepts in rheumatology, one should also note that disease-modifying treatment of rheumatic conditions does not seem to be associated with an increased risk for the development of lymphoma [123]. Conversely, immunomodulatory treatment of IBD entails a modest but nonetheless increased risk for the development of lymphoma [150]. Given the risks associated with immunomodulatory treatment in IBD, early intensive therapy could only be justified in those patients who face a high risk of a complicated disease course [151, 152].

The relatively mild disease course of the patients in our cohorts suggests that a substantial proportion of childhood-onset CD patients might not need disease-modifying treatment and that aiming for symptomatic alleviation in these patients might be sufficient. For the time being, the initiation of treatment aiming beyond symptomatic control might only be justified in paediatric CD patients that present with early significant intestinal (or perianal) damage (deep ulcerations or stricturing or fissuring disease behaviour [60, 94, 137, 153]). However, the stronger association of mucosal non-healing than persistent symptoms with the development of a complicated disease course in our study suggests that maintenance treatment intensity in childhood-onset CD should also be guided by assessing disease activity endoscopically.

Challenges

The global epidemic of childhood-onset IBD seems to be explained by changes in early environmental exposures (to a large extent yet unknown but proposed to act by altering the intestinal microbiota) associated with the modern lifestyle that is now enjoyed by most people in high- and middle-income countries.

The recent mapping of the full human microbiome has gained much attention and fuelled interest in the intricate symbiosis or commensalism between

host and microbiota and its implications for human health [154]. Future research ought to explore further the role of the bowel microbiota in the pathogenesis of IBD; to characterize the pattern of bowel flora before disease onset in those who later in life develop IBD [155]; to examine whether modification of the bowel flora with pre- or probiotics might have an impact on disease activity in already afflicted patients [156]; to study whether transplantation of faecal matter from a healthy donor is a way of correcting the imbalance between the immune system and the bowel microbiota in patients with IBD [157]; to learn if there is an association between IBD and modern agriculture's increasing use of biocides (that are potentially harmful also to human bowel flora) [158]; and to discover if the expanding use of food additives might disrupt the fine-tuned balance between immune system and microbiota in IBD susceptible individuals [159]. If the recently changed early environmental exposures that explain the ongoing global epidemic of childhood-onset IBD could be identified, we would have a possibility of preventing children from contracting a life-long disease.

Most children with IBD will have to adapt to long life with a chronic disease. It is hoped that the future will provide us with better treatment options that can enable even children with severe forms of IBD to develop according to their psychosocial and physical potential. The concept of treating of paediatric IBD with immunosuppression has been questioned as onset of IBD in early childhood seems to be associated with defective anti-inflammatory responses in some patients [55]. Nevertheless, this concept could be expected to be the ruling paradigm for some years to come as several studies have proven that immunosuppressive drugs effectively relieve symptoms and promote growth in paediatric IBD patients [97, 160, 161]. New biologics with somewhat different modes of action than anti-TNF are also now on the verge of being added to the pharmacological repertoire for the treatment of paediatric IBD [162–164]. Autologous haematopoietic stem cell transplantation have been tried in several CD patients (also some children) with severe and drug therapy-resistant disease with some success [165, 166]. The repopulation of the bone marrow by uncommitted stem cells have in a minority of these patients led to long-term remission of drugs and time will show if the treatment in these patients could be regarded as curative. Nevertheless, the pretransplantatory chemical bone marrow ablation might cause severe side effects and treatment-associated deaths have been reported in patients treated for other immune-mediated diseases [167]. It is possible that progress in stem cell research in the near future will provide other concepts of stem cell therapy in CD that is associated with less immunosuppression and also may involve direct stimulation of intestinal regeneration [168, 169].

Coming studies ought to further study the association of clinical, endoscopical, histological, radiological, biochemical, genetic, serological and microbial characteristics with severe disease course in order to build predictive models that can identify high-risk groups as early as possible at diagnosis, groups for whom the advantages of immunosuppressive therapy could perhaps outweigh the risks [170]. Future studies should also address whether noninvasive measures of disease activity such as faecal calprotectin or imaging techniques could be used to guide the intensity of treatment of children with IBD [143, 171, 172].

Summary

The incidence of IBD in childhood has increased considerably during the last decades worldwide. The highest incidence rates have been reported from Scandinavia and Canada. It has been suggested that recent changes in the early microbial colonization of the bowel might explain the global epidemic of childhood-onset IBD. The paediatric IBD phenotype seems to be characterized by extensive disease. Treatment of children with IBD should aim beyond symptom control and also include restoration of growth and prevention of pubertal delay. Exclusive enteral nutrition rather than steroids is recommended as the first-line therapy to induce remission in children with Crohn's disease (CD). The association of combined anti-TNF and azathioprine therapy with hepatosplenic T-cell lymphoma in young males with CD has led to more restrictive recommendations in paediatric IBD treatment guidelines on when to use immunomodulatory therapy. Most children with IBD could expect a normal life span but will have to adapt to living with a chronic disease. In a recently published follow-up study, we have demonstrated that patients with onset of IBD during childhood seem to have a markedly better long-term prognosis than reported in former population-based studies of childhood-onset IBD. The treatment of patients with IBD has improved dramatically during the last decades, but better treatment options

that can enable even children with severe forms of IBD to attain their full psychosocial and physical potential are badly needed.

Conflict of interest statement

No conflicts of interest to declare.

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