Early-Onset Paediatric Inflammatory Bowel Disease

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**Abstract**

The incidence of early-onset inflammatory bowel disease (IBD) (diagnosis aged <10 years) is increasing. Comprising Crohn’s disease, ulcerative colitis and IBD unclassified, it is a complex, multi-factorial and life-long condition with impacts on nutrition and psychological wellbeing. Over 200 genes have been implicated and a further 52 genes are known to cause monogenic disease, often presenting in infancy. The heritability of early-onset IBD is hypothesised to be between that of infantile and adult-onset disease, with genetic aetiology characterised by fewer genes with modest/large effect size.

Disease is typically more severe, although follow-up studies are not yet present assess long-term morbidity. Management is multifaceted and multi-disciplinary, with the requirement to safely induce remission and prevent relapse. The advent of monoclonal antibody therapy has significantly impacted on IBD but the outcomes in early-onset disease are less certain. Additional challenges include maintaining growth, navigating puberty and transition to adult services for long-term management.

**Search criteria**

We searched the Cochrane Library, MEDLINE, Embase and relevant specialty journals for articles published between Jan 1, 1980, to March 1 2017, with the terms:

(“Crohn’s disease”, “ulcerative colitis”, “inflammatory bowel disease unclassified”, “inflammatory bowel disease”, “IBD”, OR “IBDU”) AND (“pediatric”, “paediatric” “children”, OR “infant”) AND (“early-onset”, “early onset”, “< 10 years”, “<10 years”, “monogenic”, “single-gene”, “infantile” OR “under 10 years”)

We reviewed all publications from 2007 to 2017 and prioritising those published after 2012. Commonly referenced and highly regarded older publications were included. We searched only for articles published in English, or those translated into English. We also searched reference lists of articles identified by this strategy and selected those we judged relevant. Randomised controlled trials, observational studies, retrospective studies, meta-analyses, review articles, editorials, conference abstracts and case reports were included.

**Background**

Early-onset inflammatory bowel disease (IBD) disease is defined as those children diagnosed with Crohn’s disease, ulcerative colitis or inflammatory bowel disease unclassified below the age of 10 years (Paris classification A1a) and runs a chronic, relapsing course resulting in the potential for significant long-term morbidity (1). There is frequently a diagnostic delay, particularly in the younger child, where systemic autoimmune disease or immunodeficiency may present as IBD (2, 3). The median age of diagnosis in paediatric IBD is between 12-14 years, although a significant proportion of patients have symptoms before their 10th birthdays (2, 4, 5). Additionally young children presenting with features of inflammatory bowel disease must be considered for investigation of rare monogenic disorders, which are less likely in older patients (6, 7). Overall disease course is often more severe in those diagnosed under the age of 10 years with impact on growth, psychological wellbeing, nutrition and schooling (8-10).

The underlying disease process remains poorly understood; there is a genetic disposition leading to immune dysregulation in the presence of an abnormal intestinal microbiome (11-15). In single gene defects patients often have atypical or additional features (such as skin problems, frequent infections or dysmorphism).

In this review we will discuss the epidemiology, aetiology, investigation, diagnosis and management of early-onset PIBD.

**Epidemiology**

The overall incidence of paediatric IBD is increasing throughout the world, including lower/middle-income countries, the middle-east and Asia (4, 5, 16-19). Several studies have looked at the epidemiology of early-onset disease (2, 4, 5, 20); there is a male predominance at all ages of diagnosis and the incidence appears to be increasing with the most recent estimates from the UK (2014) showing incidence in 0-5 year olds (female 0.7, male 1.1 /100,000/year), 6-10 year olds (female 3.9, male 8.7 /100,000 per year) and an increase in incidence of 7.4% per year in Canada (0-10 year olds) (2, 5). Studies detailing incidence of early-onset disease over the last 25 years are summarised in figure 1. Ulcerative colitis is more common in very early-onset (< 6 years of age) but at all ages > 6 years Crohn’s disease is more common (4, 5, 20). These trends have been consistent for the last 20 years while there has been no discernible change in disease phenotype in any age group (3, 21-23). These data suggest an environmental influence leading to increased cases of PIBD, such as an increase in Westernised diets worldwide (24). The increase in incidence at a young age will result in result in an increasing IBD prevalence and an increase in patient numbers managed in the paediatric clinic.

**Disease pathogenesis**

The exact aetiology of PIBD remains unclear. In early-onset disease there is a large genetic component and genome-wide association studies/monogenic IBD studies have implicated over 200 genes to date (7, 11, 25). Despite this only a maximum of 25% of the heritability is accounted for by these genes and it is presumed rare (individual) variation must also play an important role (11, 26). Genes associated with IBD are broadly related to: innate or adaptive immunity (cell recruitment, regulation and immune tolerance, bacterial recognition and response); epithelial barrier function (tight junctions); intracellular downstream signalling (*NFKB, JAK-STAT*); cellular death (apoptotic, autophagy; reactive oxygen species production) and antigen presentation (including dendritic cell activation)(11). A selection of the most important genes in IBD can be seen in table 1. To date mutations in the *NOD2* gene and *IL10* genes (including *IL10* receptors) are the best established risk variants for development of IBD. *NOD2* is closely associated with bacterial recognition and immune stimulation, mutations (including frameshift, non-synonymous and a range of allelic variants, such as Arg702Trp, Gly908Arg, and Leu1007C frame shift insertion) are well documented to be associated with Crohn’s disease occurring at any age, the *IL10* pathway is involved in regulation of the immune response and inflammation (27-31).

Non-coding DNA and epigenetic modifications (including methylation, histone modification and RNA interference) are other potential areas associated with disease (32, 33). The non-coding regulatory regions of known risk genes may harbour important genetic variation which have not yet been identified. Epigenetics provides a mechanisms whereby the environment can impact on long-term gene expression and cellular function. It is likely that some patients will have disease associated with epigenetic modification of candidate genes (32).

The complex, and multifactorial, nature of IBD makes the interpretation of potentially deleterious variants (including non-synonymous, splicing and stop-gain) in known genes difficult without functional immunological work alongside genomic interpretation. Additionally the role of synonymous variants and less common single-nucleotide polymorphisms (SNPs) is uncertain. There is an effort to improve the understanding of how subtle genetic changes influence disease, for example nucleotide changes that do not truncate proteins or impact amino acid sequences and nucleotide changes in intergenic regions that harbour potentially important regulatory switching.

In treatment-naïve patients there is disruption of the normal microbiota leading to an intestinal dysbiosis but it is not clear whether this is the cause of intestinal inflammation or the effect of chronic inflammation (13-15). Studies associating single bacterial genera with IBD have not found substantiated evidence of causation and it is the functional potential of whole bacterial communities that appears to be important in disease aetiology and subsequently in remission (34). The interaction of the host genetic-susceptibility with environmental factors (such as the intestinal microbiome and nutrition) through gene expression in gut tissue (the transcriptome) has identified specific gene-expression signatures in patients with PIBD, although the interpretation of whole-tissue gene expression is challenging (35-37). Studies detailing the transcriptome in treatment-naïve Crohn’s disease are single time point studies influenced by age-specific changes, do not follow patients through remission and are therefore subject to transient factors and are unable to account for temporal changes (14, 38). Nutrition, including the metabolome (all metabolites present in an organism, including nutrient breakdown products), is felt to play a role in disease pathogenesis; modulation of gut bacteria by diet, alongside the efficacy of exclusive enteral nutrition in induction of remission in paediatric CD indicates an expanding and understudied role for nutrition and diet in this process (39-43).

Overall it is thought that it is the interaction and interplay between the genes, the immune system and the microbial environment which is important in the development and ongoing inflammation seen in Crohn’s disease (see figure 2) (44). It is likely that there are many more subtypes of disease (than CD, UC and IBDU) and each individual (or family) may not have identical pathogenesis to another person. The potential to unpick these subtypes, understand the response to treatment and predict prognosis may usher in an age of personalised medicine in IBD.

Monogenic causes of disease

In early-onset disease there must be special consideration for monogenic causes of IBD. Two recent reviews by Uhlig et al have covered this topic extensively (6, 7). It is important to identify at risk patients who may have particular features, need specific surveillance (for malignancy, infection etc.) and require specific treatments (such as bone marrow transplant) (6, 7). Monogenic conditions should be considered in those presenting with atypical features, patients refractory to conventional treatment and those diagnosed < 6 years of age and these patients should be considered for further investigation including genetic testing with next-generation sequencing panels (45). Although monogenic causes of IBD typically present in < 6 year olds, mutations in genes such as *XIAP* (x-linked lymphoproliferative disorder) and *CYBA/CYBB* (chronic granulomatous disease) may present in later childhood or even adulthood (46, 47). Potentially clinically relevant heterozygous mutations in genes known to cause IBD through recessive inheritance have recently been identified through whole-exome sequencing in older children, these variants may account for some of the missing heritability in early-onset disease and there is likely to be significant overlap between monogenic and polygenic disease in some patients (48).

**Presenting phenotype- when to consider a diagnosis of IBD?**

The symptoms of PIBD are well established, the most common features being abdominal pain, diarrhoea and blood in stool; atypical presentations are common, particularly in the younger child (21). Early-onset patients are also more likely to present with isolated rectal bleeding (49, 50). Growth failure is common (up to 20% in Crohn’s disease) and failure to thrive is reported in up to 44% of children < 6 years subsequently diagnosed with PIBD (50, 51).

Early-onset disease is characterised by pancolitis in both Crohn’s disease and ulcerative colitis with up to 89% of patients having colonic involvement at diagnosis. This is reflected through the Paris classification A1a (diagnosis aged less than 10 years) providing a general (but not always precise) age distinction characterised by early-onset patients presenting with more colonic disease (1). Isolated ileal disease is rare (50, 52, 53). Stricturing disease is less common, although that may partially reflect diagnosis being made earlier in the disease course (22). Initial misclassification of disease (incorrectly assigning Crohn’s disease/ulcerative colitis) in < 6 year olds is common (up to 40%) and reflects many factors including the difficulty in full assessment and characterisation of disease (50). Extra-intestinal features are present in up to 28% including arthralgia/arthropathy, skin and eye involvement (50). Family history is common; 44% in children diagnosed < 6 years of age (6).

In most children with Inflammatory Bowel Disease, particularly Crohn’s disease, inflammatory markers will be raised. The following investigations should be considered.

* Inflammatory markers (C-reactive protein, erythrocyte sedimentation rate)
* Full blood count
* Renal function, Liver function (including albumin, transaminases)
* Faecal calprotectin
* Stool microscopy and culture

A referral pathway, including relevant investigations is shown in figure 3.

The role of faecal calprotectin as a screening test for IBD is increasingly recognised, with a high sensitivity, although it’s utility in early-onset disease remains poorly defined. Several studies have looked at the diagnostic accuracy of a raised faecal calprotectin in those with early-onset disease (54, 55). In one study looking at over 350 children referred to paediatric gastroenterology aged less than 6 years, only 5.5% of those tested had a diagnosis of early-onset IBD, however 58.8% had a faecal calprotectin above 50mg/kg indicating that the test is not specific in this age group and the cut-off for a normal value may vary with age (54). In contrast the diagnostic accuracy of faecal calprotectin in older children, as assessed by systematic review and meta-analysis, is both more specific (0.682) and more sensitive (0.978)(56). It is important to be aware that a normal faecal calprotectin does not exclude a diagnosis of early-onset IBD and some patients will present with normal values, although this is uncommon (54, 56). Faecal calprotectin can also be used (in conjunction with clinical and serological markers) to monitor disease activity (57). Other conditions associated with a raised faecal calprotectin in the infant and young child included gastroenteritis, systemic immune conditions, eosinophilic enterocolitis, autoimmune enteropathy and post-transplant conditions (graft versus host disease, colitis related to immunosuppressive agents) (57).

**Diagnostic testing**

The Porto criteria for diagnosis of paediatric IBD recommends all patients with suspected IBD (based on history, physical examination and laboratory tests) should undergo upper and lower gastrointestinal endoscopy with histological examination of all sites (oesophagus, stomach, duodenum, terminal ileum, colonic series and rectum), alongside with small bowel imaging (58). Further biopsy of oral lesions should be considered in some cases. In most countries this will be under the guidance of a specialist paediatric gastroenterologist.

Small bowel imaging (MRI, CT, contrast study or ultrasound) is recommended in all suspected cases but may be deferred in ulcerative colitis depending on the clinical presentation and response to treatment.

Histological confirmation of disease must focus on clear identification of features of inflammatory bowel disease by an experienced histopathologist, in discussion with the clinical team (58). These include, but are not necessarily limited to presence of inflammatory changes in the mucosa (acute or chronic gastritis/duodenitis/oesophagitis, cryptitis, crypt abscesses, and granulomas), architectural abnormalities (crypt distortion, crypt branching, and crypt atrophy), and epithelial abnormalities such as mucin depletion and metaplasia, alongside surface irregularities (epithelial active/regenerative changes)(59). The distinction between Crohn’s Disease and Ulcerative colitis is not always straightforward and in many cases the biopsy changes are indeterminate particularly in children with only colitis. The presence of extensive disease, patchy change and granulomas is makes Crohn’s disease more likely.

The Paris classification allows for grouping of disease by location of bowel inflammation. It is a validated and useful tool to assist with management and diagnosis based on endoscopic and radiological disease extent (1). Increasingly there is evidence of a discrepancy between endoscopic and histological disease extent, leading to a call for additional classification including histology in order to help guide treatment decisions (59, 60).

Additional serology should be considered but may not be helpful in determining disease subtype (61). Anti-Saccharomyces cerevisiae antibodies (ASCA) are common in Crohn’s disease (50-70%) and may predict a severe course (62). Perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) are more common in ulcerative colitis (60-70%) but may exist in up to 50% of Crohn’s disease patients (63).

Specialist genetic investigations to consider in early-onset disease have been proposed by several groups (6, 45). These are focused on 52 genes implicated in monogenic forms of PIBD, the most contemporary methodology for identifying disease causing variants is next-generation sequencing (targeted gene panel or whole exome sequencing). Increasingly multi-centre studies such as the international early-onset paediatric IBD cohort study (NEOPICS, multi-national) and the 100,000 genome project (UK) are targeting very early onset IBD patients in an attempt to identify novel genes and mutations leading to disease (6, 64).

**Important differential diagnoses**

The difficulty in diagnosis of IBD in children is exacerbated in early-onset disease. Many common conditions present with features of IBD such as abdominal pain, diarrhoea, blood in stools and poor growth. These include some common conditions seen in paediatric clinic such as functional gastrointestinal disorders, food allergy, coeliac disease and constipation.

There are much less frequent illnesses, specific to early-onset disease that may masquerade as IBD including eosinophilic enterocolitis and immune deficits such as chronic granulomatous disease systemic immune conditions, autoimmune enteropathies and post-transplant conditions (graft versus host disease, CMV colitis, drug-related colitis etc.).

It is extremely important to exclude infection as a cause for acute or chronic symptoms as this is often easily treatable. A low threshold for basic investigations is important in those children who have chronic gut symptoms. It is important that the differential diagnosis of IBD is not ignored due to young age or slightly atypical symptoms.

**Treatment strategies**

*General principles of management*

Treatment of early-onset PIBD focuses on the safe induction of remission, nutritional stabilisation and prevention of relapse (maintaining remission). Careful attention to issues such as compliance with treatment, psychological complications and patient education are vital parts of treatment Growth, puberty, patient understanding and educational needs are specific difficulties encountered in early-onset disease.

*Multi-disciplinary care*

Involvement of dietetic, specialist nursing, education and psychological services in the early stages of disease can have important impacts in the long-term. Maintaining good relationships, compliance with medication, family engagement and nutritional optimisation are key factors in achieving effective medical treatment (65).

*Nutrition and Growth*

Alongside symptom management it is important to ensure patients are not nutritionally compromised. Height, weight and BMI should be assessed and plotted on a centile chart. A recent guideline published by ESPEN gives a detailed and thorough overview of nutritional management of IBD (66). As a minimum, measurement of iron indices, calcium, vitamin D, phosphate and magnesium should be considered in all patients, with replacement where indicated.

Dietetic input is essential to ensure nutritional intake is adequate for the patient. Whilst there will often be poor nutritional status through disease course this is not ubiquitous, and careful management of diet and macro/micronutrient supplementation is vital to ensure some patients do not become overweight and some patients are not left nutritionally impaired. Nutritional care should be considered in the acute phase, during recovery and subsequently in ‘catch-up growth phase’, when well. The challenge is to safely navigate the patient through childhood, puberty and achieve satisfactory growth and development.

*Life-long condition*

There has been an increase in the thought and attention paid to transition of paediatric patients to adult services. Early-onset patients should be well established and comfortable in paediatric services for at least 8 years. It is important to prepare them, and their families, for transition and this should be discussed early. The use of joint paediatric and adult transition clinics, alongside thorough communication between teams can help to make this process run as smoothly as possible.

Specific treatments

There are multiple difference national and international guidelines on treatments in paediatric IBD, mostly extrapolated from adult studies with supporting paediatric data which are relevant to and cover children of all age ranges (see table 2). All drug treatments have potential toxic effects and require a risk benefit discussion prior to use. There is increasing debate about early use of anti-TNF monoclonal therapy (as first line treatment) in preference to thiopurine use, balancing the risk/benefit of these medication in refractory and chronic disease is important and uncertain. This issue will be best answered by multicentre prospective trials, with a need to stratify patients by age.

*Induction of remission*

Choice of induction agent of remission at diagnosis (or relapse) is dependent on disease type, location, extent, severity and patient/clinician choice. Joint ECCO/ESPGHAN guidelines on treatment of Crohn’s disease and ulcerative colitis have been published within the last 5 years and provide an excellent framework for treating early-onset disease (67, 68). There are very few specific data and most treatment strategies are extrapolated from studies focused on paediatric populations as a whole (including patients diagnosed <10 years) and from adult studies.

*Exclusive enteral nutrition (EEN)*

EEN (polymeric feeds such as Modulen, *Nestle* or elemental feeds such as E028, *Nutricia*) is recommended as first line treatment in paediatric Crohn’s disease. Elemental feeds are preferred in severe cows-milk allergy/intolerance or when the polymeric feed is not tolerated. There is no role for partial enteral nutrition as a sole therapy for induction of remission (67). There is no role for EEN in ulcerative colitis (68). Treatment should be for 6-8 weeks and if there is no response within 2 weeks an alternative therapy must be considered (67). There is good evidence for the efficacy of EEN in paediatric Crohn’s disease, although there is no specific RCT/meta-analysis data on early-onset disease, however children diagnosed <10 years have been included in all previous analyses (42, 69).

EEN has the additional benefit of providing substantial nutritional benefits to patient (66).The use of continued nutritional supplementation is controversial although but there may be a role in prolonging remission in selected cases (66).

*Corticosteroids*

Oral steroids are recommended for moderate/severe Crohn’s disease as a second line agent. Most evidence is extrapolated from adult studies but 30 day paediatric remission rates range from 57-79% (67). In ulcerative colitis oral steroids are recommended in moderate/severe disease, they have up to a 90% response rate (68, 70). Steroids may be combined with a 5-amino salicylic acid preparation to induce remission.

The dose of prednisolone should be 1mg/kg, up to 40mg, once daily for 2-4 weeks with the dose weaned over the next 10-12 weeks. Intravenous steroids are indicated for acute severe colitis (67, 68). There is no role for steroids as maintenance therapy.

*Others*

5-amino salicylic acid (5-ASA) preparations (mesalazine, sulphasalazine) are recommended as first line induction therapy for mild/moderate ulcerative colitis, most children will require an oral preparation, in few will a topical agent suffice (68).

Antibiotics are recommended in the treatment of perianal fistulating disease as an additional therapy (67).

*Refractory Disease*

In Crohn’s disease patients resistant to initial therapy (refractory disease), anti-TNF monoclonal therapy (infliximab, adalimumab) are an effective 2nd line induction agents (up 88% response rate was observed in the REACH trial- infliximab in paediatric Crohn’s disease), they are also effective in induction in ulcerative colitis (infliximab produced a 73% response rate in refractory UC) (71, 72). These therapies are typically reserved for treatment-resistant disease, however there is an emerging ‘top-down’ therapy approach in adult IBD which, although not yet used commonly is a potential approach in early-onset disease. The long term impact of the ‘top-down’ approach is not known. The risk/benefit of the different treatments, particularly in the young necessitate caution and careful evaluation of outcome (73).

*Maintenance therapy*

Therapy focuses on preventing the reoccurrence of disease and with the intent to achieve, then maintain, mucosal healing (74). Nutritional supplements should be considered in children who are underweight for height in order to optimise the response to treatment, wellbeing and growth. Discontinuation of therapy when patients have prolonged remission is challenging but must be discussed and trailed where appropriate. The risk of recurrence is generally felt to be high although there is little data in early-onset patients (67).

*5-ASA*

Maintenance therapy with 5-ASA is effective in mild/moderate paediatric ulcerative colitis and should be continued long term for the cancer protective effect (75). In Crohn’s disease there is very little evidence to suggest that they are useful and should be reserved for very mild colonic involvement, rarely seen in early-onset disease (67). 5-ASA preparations have no role in the long term treatment of Crohn’s disease.

*Thiopurines*

Azathioprine and 6-mercaptopurine (pro-drug) are recommended as a first-line agent for maintaining remission in both Crohn’s disease and ulcerative colitis. Prior to starting a thiopurine it is important to assess the TPMT enzyme activity in order to correctly dose and to avoid toxicity (76). In paediatric Crohn’s disease the remission rates at 1 year vary from 60-90% (77, 78). In ulcerative colitis thiopurines are recommended for those failing to be controlled on 5-ASA and for maintenance (following induction). In those with acute severe colitis multi-agent therapy should be considered (68). Most data on efficacy of thiopurines in IBD is from adult studies but the limited paediatric data that is present indicates 1 year remission rates of around 50% (79).The typical dose is 2-2.5mg/kg azathioprine and 1-1.5mg/kg of 6-mercaptopurine.

Thiopurines are not without side effects and regular monitoring of full blood count and liver function is necessary (67). Drug level (metabolite level) is important to guide dosing/assess compliance and avoid toxicity (80). The efficacy of thiopurines may take 8-14 weeks to occur and patients should be counselled thus. There has been longstanding concerns raised regarding the development of malignancy (specifically hemophagocytic lymphohistiocytosis) following use of thiopurines in paediatric IBD (81). There is little contemporary data but methotrexate may present a potentially useful alternative maintenance therapy.

*Anti-TNF monoclonal therapy*

The advent of biological therapy in paediatric IBD has enabled steroid-sparing, effective therapy resulting in prolonged remission, good growth and mucosal healing (71, 72, 74). In Crohn’s disease anti-TNF therapy is recommended in chronic luminal disease refractory to prior immunomodulatory therapy (67). Remission rates range from 50-60% at 1 year but response may be lost over time (72, 82). A small study of 33 patients aged <8 years showed a poorer response to infliximab with only 28% of patients achieving remission at 1 year; many patients did not respond or were intolerant to the medication and there was a low steroid sparing effect (83). In ulcerative colitis anti-TNF therapy is recommended for disease refractory to immunomodulation or in steroid-dependent disease. Remission rates are variable with reports ranging from 38-64% remission at 1 year and long-term use is associated with antibody formation and loss of efficacy (71, 84).

Testing for tuberculosis prior to commencement of therapy is indicated to avoid reactivation and disseminated disease. The typical dose of infliximab (intravenous infusion) is 5mg/kg at 0, 2 and 6 weeks, followed by a maintenance dose every 8 weeks. Dosage can increase to 10mg/kg and dosing interval reduced to 4 weeks if required. Adalimumab (subcutaneous injection) induction therapy is 2.4 mg/kg (maximum 160 mg) at week 0, 1.2 mg/kg (maximum 80 mg) at week 2, followed by 0.6 mg/kg (maximum of 40 mg) every 2 weeks. Dosing can be increased to weekly if required (67, 68). A recent study appears to indicate that infliximab use may not be associated with an increased risk of malignancy in children; the incidence of malignancy in those exposed to infliximab was 0.46/1000 patient-years compared to 1.12/1000 patient-years in those not exposed to infliximab, however these data must interpreted cautiously as the overall incidence of malignancy was very low (81).

Secondary loss of response to anti-TNF therapy is associated with production of anti-infliximab/adalimumab antibodies, the formation of these antibodies is reduced by co-immunosuppression with other agents (85).

*Other treatment options*

In refractory disease several other agents such as methotrexate (increasingly used and an important therapy), tacrolimus and thalidomide may be considered however this should only following failure of fully optimised therapy discussed above and these therapies have little efficacy or safety data in (especially early onset) paediatric IBD. For further information see joint ECCO/ESPGHAN guidelines (67, 68, 86, 87).

It is important for prospective clinical trials to include early-onset patients, including studies looking at the optimal and safe point for step-down of treatment, specifically thiopurines and anti-TNF monoclonal therapy, which are associated with significant toxicity.

*Surgery*

There is a role for surgical intervention in early-onset IBD, for acute complications, fistula, strictures and disease refractory to medical therapy whether acute (severe) or long-term (88, 89). Whilst there is little data available the studies reporting surgical intervention in early-onset Crohn’s disease report surgery occurring in 60% of patients, with multiple surgeries being common (40 procedures in 18 patients). Despite this there were positive outcomes following intestinal resection in >90% of cases (90). However there remains a significant 30-77% risk of immediate or long-term complication in as reported by paediatric studies including patients aged <10 years of age (89, 91).

In ulcerative colitis a colectomy may provide complete resolution of symptoms but risks of immediate and longer-term complications (obstruction etc.) are high (40-47%) and subsequent operations are often needed (intestinal obstruction). There are no studies focused on early-onset disease only (88, 92, 93).

**Prognosis**

Outcome data for those diagnosed <10 years is sparse. Benchimol et al reported lower attendances at hospital (outpatient and hospitalisations) in those aged <6 years than >10 years. Additionally hazard ratios for surgery were 0.35-0.88 for children diagnosed <6 years compared to all children with IBD, there was no difference if comparing all children <10 with those aged >10 at diagnosis (2). However anecdotal evidence would appear to indicate that early-onset disease is more severe. A retrospective analysis by Gasparetto et al of 80 children aged 5-10 years of age at diagnosis found higher levels of disease activity and greater disease extent in both Crohn’s disease and ulcerative colitis (94). Additionally they were more likely to have early escalation of immunosuppression and require more repeat endoscopies than children diagnosed >10 years of age (94). Ledder et al described the outcomes of 30 consecutive children diagnosed with IBD <6 years of age, they found a more aggressive disease requiring greater immunosuppression and increased risk of surgery (9). Significant problems with linear growth have been reported in both early-onset ulcerative colitis and Crohn’s disease although this is not ubiquitous (95).

The longer-term health, educational and economic outcomes of children with early-onset IBD are not yet apparent, but present different issues to older patients. The relatively recent increase in incidence results in a lack of data from prospective or retrospective studies on how these children fare in the long term. It will be vital to collect these data to ensure these children are receiving the healthcare, nutrition and educational support they require throughout childhood, adolescence and into adulthood. This should be by prospective registration of cases.

*Problems and future strategies/therapies*

The result of an increase in incidence is an increase in disease prevalence. This confers a need for services to care for an increasing number of patients and as younger patients are diagnosed more frequently the prevalence of PIBD will increase further. This increase in disease burden requires an increase in investment, planning and specialist services for the future care of (early-onset) PIBD.

There has been a parallel increase in research in PIBD, driven in a large part by the availability and reduction in cost of next-generation sequencing. This allows the genetic, transcriptomic and microbiome aspects of disease to be investigated in patient number and depth not previously available. The potential impact of these data types and increased understanding of disease aetiology to improve treatment seems closer than ever before. Perhaps the most intriguing future strategy for successful treatment of early-onset disease centres on personalised therapy in IBD. The use of machine learning (computational analysis allowing inclusion of multiple data types such as blood markers, immune function markers, drug response, genetic variation, microbiome, transcriptome etc.) to assist with classification and to guide treatment is not yet routine but may yield the most clinically useful progress in early-onset IBD and prognostic work has been recently published based on the large RISK cohort of paediatric Crohn’s disease (96-98).

New therapeutic targets in IBD will continue to filter into paediatric practice. Monoclonal therapies such as vedolizumab (an α4β7 integrin antibody, blocking lymphocyte movement in the intestine) have shown efficacy in adult practice (99, 100). Studies of vedolizumab in paediatric Crohn’s disease and ulcerative colitis have shown 40-100% remission rates at 6 months but with no data on early-onset disease (101, 102).

Small-molecule drugs with targets such as JAK (Tofacitinib), S1P (Ozanimod) and anti-inflammatory properties (Mongersen, Laquinimod) are currently under investigation as oral therapeutic options in adult IBD. These novel classes of drug may improve care by enabling oral administration, simpler (cheaper) manufacturing, reduced antigenicity (less likely to lose response) and increasing potential treatment targets (103). As with most new therapies it will be a significant time before these medications transition to adult clinical practice, with use in paediatric and early-onset disease likely to lag behind further.

Children diagnosed with PIBD before the age of 10 will be spending a minimum of 8 years in paediatric services prior to transition to adult gastroenterology. It is vital for a positive outcome that both the child and the family engage fully with services offered. At the paediatric gastroenterology centre care is improved by the presence of a multi-disciplinary team including an IBD nurse specialist, IBD dietetic services and paediatric surgeons with expertise in IBD surgery (65).

It is extremely important to have a shared care pathway between the specialist paediatric gastroenterology service and the local hospitals with a named consultant with an interest in paediatric gastroenterology who can act as a direct liaison for the specialist centre (65). Prompt referral for specialist review, repeat investigation and early escalation of treatment is important to ensure patients remain well and in remission. All patients should have access to specialist support services including nurses, dieticians and mental health support.

Additional support is offered to families through specialist charities such as Crohn’s in childhood research association (CICRA), Crohn’s and colitis United Kingdom (CCUK), the Crohn’s and colitis foundation of America (CCFA) and these are supported by a network of local charities. Charity events, patient, parental and professional literature and support of research is vital to improve PIBD care.

**Conclusions**

The incidence of early-onset IBD is increasing and disease severity appears to be increased in comparison to IBD presenting in those aged >10 years. Whilst we are beginning to understand the disease pathophysiology there is significant work to do in order to fully establish the mechanisms underlying gut inflammation to better classify disease, personalise therapy and create new treatments. Early referral, based on correct interpretation of symptoms and investigations, to specialist paediatric gastroenterology services, resulting in structured and effect treatment is likely to lead to a positive outcome for this group of vulnerable patients.

**Tables and Figures**

*Table 1*

Selection of genes associated with inflammatory bowel disease revealing the most common physiological functions and pathways associated with disease.

*Table 2*

Summary of the most frequently used induction and maintenance treatments used in early-onset paediatric inflammatory bowel disease

*Figure 1*

Incidence of early-onset paediatric inflammatory bowel disease over the last 25 years (2, 4, 5). Incidence is reported per 100,000 per year and separated into disease presenting 0-5 and 6-10 years of age. Data from Henderson et al is additionally reported as male and female incidence.

*Figure 2*

Host genetic, immune and microbiome interaction in inflammatory bowel disease. Disruption of epithelial barrier function and invasion of bacteria into the mucosa, abnormal immune receptors (such as *IL10R*), an increased inflammatory response (mediated through pro-inflammatory cytokines), disrupted downstream immune signalling and abnormal handling of bacteria may all contribute to disease pathogenesis. Environmental factors (such as diet and medication) influence intestinal microbiota composition, in active Crohn’s disease there is an abnormal ratio of beneficial and harmful bacterial species (dysbiosis). The complex interaction between these factors underlies disease process; in healthy patients there is a normal synergy between diverse, immune tolerated bacteria and the host immune system.

*Figure 3*

Flow chart for referral and investigation of patients with suspected early-onset inflammatory bowel disease (aged <10 years).

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