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Inflammatory bowel disease: recent developments

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ABSTRACT

Paediatric-onset inflammatory bowel disease (IBD) is a complex and heterogenous condition. Incidence of disease in those aged <18 years has doubled over the last 25 years, with concurrent increased prevalence and no decrease in disease severity. The tools available at diagnosis for investigation have developed over the last 10 years, including better utilisation of faecal calprotectin, improved small bowel imaging and video capsule endoscopy. Alongside this, management options have increased and include biological and small molecule therapies targeting alternative pathways (such as interleukin 12/23, integrins and Janus kinase/signal transducers and activators of transcription, JAK-STAT pathways) and better understanding of therapeutic drug monitoring for more established agents, such as infliximab. Dietary manipulation remains an interesting but contentious topic.

This review summarises some of the recent developments in the diagnosis, investigation and management of IBD in children and young people. IBD is increasingly recognised as a continuum of disease, with a proportion of patients presenting with classical Crohn's disease or ulcerative colitis phenotypes. Future implementation of personalisation and stratification strategies, including clinical and molecular biomarkers, implementation of predictors of response and outcome and use of additional therapies, will continue to require working within clinical networks and multiprofessional teams.

BACKGROUND

There has been a significant increase in the incidence and prevalence of paediatric-onset inflammatory bowel disease (IBD) over the last 25 years, alongside significant progress in the tools for investigation and management. Paediatric-onset IBD constitutes most chronic patients under the care of paediatric gastroenterologists. In the UK, many patients requiring close monitoring and shared care with colleagues in district hospitals. IBD, traditionally separated into Crohn's disease and ulcerative colitis, is increasingly recognised and a complex 'continuum' disorder with a similarly complex aetiology including genetic, environmental and microbial factors. Despite this, the treatment remains largely empirical.[1] The complexity of disease, coupled with an evolving range of investigations, more therapeutic options and improving disease prediction tools, requires contemporary input to ensure the best long-term outcomes for patients. In this review, we highlight recent clinical developments in paediatric IBD, relevant to all paediatricians, and focus on current investigative and therapeutic advances in practice.

KEY PRACTICE POINTS

⇒ The rapid and sustained increase in paediatric-onset inflammatory bowel disease (IBD) incidence has significant impact for service provision and planning.
⇒ Correct use of faecal calprotectin (FCp) as a screening tool has the potential to prevent diagnostic delay in IBD. Red flags in the presence of relatively normal FCp should not delay referral.
⇒ Prediction and personalisation of management in IBD is coming, with current elements such as therapeutic drug monitoring and genomic testing for monogenic forms of disease likely to be joined by clinical and molecular biomarkers of response and outcome.
⇒ The availability of newer treatments, including biological and small molecular therapies, will allow diversification of management.
⇒ Combining contemporary medicines, with prediction of response, will improve clinical outcomes.

EPIDEMIOLOGY OF PAEDIATRIC IBD: THE GROWING EPIDEMIC

Paediatric IBD incidence and prevalence has dramatically increased across Europe and North America over the last 25 years, with contemporaneous data from Asia and South America pointing to a similar trend, although with lower overall patient numbers.[2] In the UK, we have observed a doubling of incident IBD cases over the last 20 years with estimates from the Wessex region in 2021 of 12/100 000 population <18 years per year, increased from 6/100 000 per year in 2002.[3 4] This significant increase in incidence has resulted in a significant increase in prevalence with up to 60 cases per 100 000 population (aged <18 years) in the region.[3] However, this is somewhat dwarfed by the patient numbers in adult services, where estimates from Scotland in 2018 were 784 cases per 100 000 population.[3 5]

Internationally, the highest incidence figures come from Northern Europe (Scandinavia, up to 23.1/100 000/year), Western Europe (Scotland, up to 17.4/100 000/year) and Canada (up to 15.4/100 000/year).[2] Typically, Crohn's disease continues to predominate in these populations, with incidence around double that of ulcerative colitis. Similarly, male patients are more common compared with female patients, and the main driver of increased incidence appears to be the male patients with Crohn's disease aged 11–17 years.[3] Conflicting evidence exists on incidence trends in very-early-onset IBD (<6 years at diagnosis), with studies from

Canada describing an increase, but most studies from Europe reporting static incidence of around 1–2/100 000/year over the last 15 years.

The cause of increased incidence of disease is uncertain, although change in genetic risk does not account for more patient numbers, as the increase is too quick to be related to any underlying change in genetic landscape. Theories related to reduced exposure to microbes in early childhood, increased westernisation of diet and the hygiene hypothesis appear possible, and it must be acknowledged that increased disease awareness and improved diagnostic tools may play a role in improved diagnostic rates.

CROHN'S DISEASE VERSUS ULCERATIVE COLITIS, OR JUST IBD?

The continuum of IBD has traditionally been separated into Crohn's disease and ulcerative colitis, with patients lying between being referred to as IBD unclassified. Features typifying Crohn's disease or ulcerative colitis are largely related to disease location, and to a lesser extent histological appearances. Increasingly, the divide is arbitrary, with significant overlap in everything from therapies to genetic risk loci to disease location. Whether this is a paediatric phenomenon or not, the descriptive term IBD, better captures all disease phenotypes. This has the potential to drive management towards a risk stratification approach considering disease severity, disease location, disease behaviour, response to initial treatment and additional phenotypic factors such as concurrent illnesses. In the future, a personalised molecular diagnosis will help inform a more precise diagnosis for individuals, with the ability to produce a personalised prognosis and treatment.[6]

DIAGNOSTIC AND REFERRAL STRATEGIES

Making a prompt diagnosis is key to good management of IBD, preventing malnutrition at diagnosis and allowing early therapeutic intervention. Unfortunately, there is frequently a delay of months or years in referral to specialist care, preventing the diagnostic process of endoscopy and histological confirmation.[7] Drivers of this are varied including varied presentations, alongside inflammatory markers not always being raised and fluctuating symptoms.[8] Family history is common and should lower the threshold for investigation.

Faecal calprotectin

One of the biggest advances in screening of patients for potential IBD has been the rapid expansion of faecal calprotectin (FCp) testing. This dimer, formed of two protein subunits (S100A8 and S100A9), is released by immune cells, particularly neutrophils, into the intestinal lumen and can be measured in stool. While it is a relatively stable biomarker, it will begin to degrade after days, and measurements may be falsely low if stool is not stored at low temperatures. Normal levels are described at <50 mcg/g, although there is a spectrum of normal, impacted by age, diet and time of day. Particular care must be taken in interpreting results from younger children (aged <6), who have inherently higher FCp values (up to 500 mcg/g in some cases) due to immune maturation of the intestine.[9] Typically, children with IBD will have values in the high 100s, or 1000s, but rarely some patients will have low, or even normal FCp measurements, likely to be reflective of isolated upper gastrointestinal inflammation, limited small bowel disease or sampling error.[10]

As availability of FCp has increased, so has the false positive referral rate to gastroenterology. Many illnesses or medications can cause a raised FCp, particularly acute gastrointestinal infection which can result in significantly elevated levels. FCp should not be measured during acute or short-term diarrhoea or blood stool (<14 days) and should always be accompanied by a stool bacterial and viral screen. Medications, such as non-steroidal anti-inflammatory drugs, other inflammatory gastrointestinal conditions including coeliac disease or graft versus host disease, and benign paediatric polyps, can also lead to typically more modest increases in FCp.[9] Repeating an FCp if the initial result was mildly increased can help stratify the urgency of referral to specialist care, although if red flag symptoms are present a referral should not be delayed.

FCp is also routinely used as a measure of response to therapy and to monitor flares in patients with known IBD. Increasingly remote measures, including point-of-care and postal FCp, are providing reliable, flexible and patient-friendly monitoring that can guide treatment and ensure symptoms correlate with inflammation being present.[9]

Recent developments in endoscopy and imaging

All patients with IBD require a histological diagnosis consistent with the modified Porto criteria.[11] Standard practice involves an upper and lower gastrointestinal endoscopy with multiple biopsies. Endoscopy is also used to monitor disease, response to therapy (particularly biological), 10-year colorectal carcinoma screening and prior to transition to adult therapy.

Small bowel imaging is a ubiquitous part of investigation, at diagnosis and during follow-up. Typically, magnetic resonance enterography is used to characterise the small bowel. An exciting area of development is point-of-care small bowel ultrasound, where quick measures of bowel wall thickness, hyperaemia and evidence of fat wrapping can aid with both diagnosis and monitoring of patients.[12]

Video capsule endoscopy (wireless capsule endoscopy) is established in paediatric practice for patients with IBD. Diagnostic uncertainty following biopsy, strong suspicion of small bowel disease and a drive towards better characterisation of disease extent have all increased the use of this technique.[13] It is possible to perform this examination in children as young as 2 years of age. A dummy, or patency, capsule can be administered prior to the video capsule to ensure this will not be retained by a stricture. Additional considerations are the interpretation of images, bowel preparation or specific diet prior to administration and deployment of capsule (swallowing vs endoscopic). It may be, in time and if services develop, that this will become part of the initial diagnostic workup particularly for patients with small bowel disease.

GENETIC TESTING

A new area of investigation in paediatric IBD is the concept of genetic testing. In a minority of cases (less than 0.5%) of patients with paediatric-onset IBD, the disease is due to a single-gene disorder masquerading as IBD.[14] Typically, these disorders are primary immunodeficiencies, autoinflammatory conditions or dysfunction of the epithelial barrier, with the number of implicated genes now being over 100.[15] Now, a commissioned National Health Service test (Genomic Medicine Service R15 panel), screening of around 70 monogenic IBD genes for causative variants, is available for all patients diagnosed below 2 years of age and for selected others who are older than this (table 1).[16]

The potential impact for the small number of patients receiving a monogenic IBD diagnosis is great. Depending on the specific genetic defect identified there may be additional

Table 1 Genomic testing eligibility criteria for patients with IBD

When to consider genomic testing	Additional criteria when considering eligibility
A. All children with IBD onset under 2 years of age. B. Children with IBD onset under 6 years of age, in particular when one or more of the additional criteria (1–6) are present. C. In patients >6 years of age only if there is a strong suspicion for a monogenic IBD due to test criteria 1–6.	1. Infection susceptibility in the presence of abnormal laboratory tests—immunodeficiency. 2. Inflammatory features—inborn error of immunity (IPEX syndrome or haemophagocytic lymphohistiocytosis). 3. Congenital multiple intestinal atresias or congenital diarrhoea. 4. Early-onset malignancy (<25 years of age). 5. Family history of suspected monogenic IBD (criteria 1–5). 6. In advance of interventions and/or therapies.

If patients meet the criteria in the UK then the R15 panel should be requested through the local Genomic Medicine Service.
IBD, inflammatory bowel disease; IPEC, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome.

therapeutic options including medication or haemopoietic stem cell transplantation. Genetic counselling for future pregnancy and screening for associated risks (including lymphoproliferative disorders) are important considerations.

OPTIMAL MANAGEMENT STRATEGIES

Providing optimal outcomes requires optimal management strategies. This is best delivered across clinical care networks with careful monitoring of outcomes in order that processes and treatments can be reviewed, updated and improved to enhance clinical care. Multidisciplinary working, including specialist nursing, dietetics, psychology and specialist pharmacy input, is at the core of good practice. Figure 1 summarises the contemporary aspects of IBD management in children, alongside recent and future developments. Typically, maintenance therapy will follow ECCO-ESPGHAN (European Crohn's and Colitis Organisation-European Society of Paediatric Gastroenterology, Hepatology And Nutrition) Crohn's and colitis guidelines with the potential for either rapid escalation to biologics from immunomodulators in treatment refractory patients or top-down therapy in patients with high-risk disease.[17] Defining optimal strategies for an individual is difficult and prediction tools are urgently needed.

Referral and management networks

Over the last 20 years there has been a centralisation of care for IBD services. Many acute and chronic paediatric conditions have seen a similar shift, with specialist centres providing the lead for a referral and management network across a number of hospitals. In paediatric gastroenterology, there has been a formal recommendation for working in established networks, with evidence of potential improvement in outcomes.[18] Patient-centred care, provided closer to home, allows general paediatric referrals to be expedited to a known specialist centre, and for subsequent treatment, such as monoclonal infusions, to be provided at the local hospital.

Impact on services and planning

The rapid increase in paediatric IBD incidence has significant impacts on services and workforce planning. While the prevalence is increasing, the real impact centres on diagnostic services (including endoscopy), treating the early stages of extensive and severe disease and ensuring nutrition, growth and education
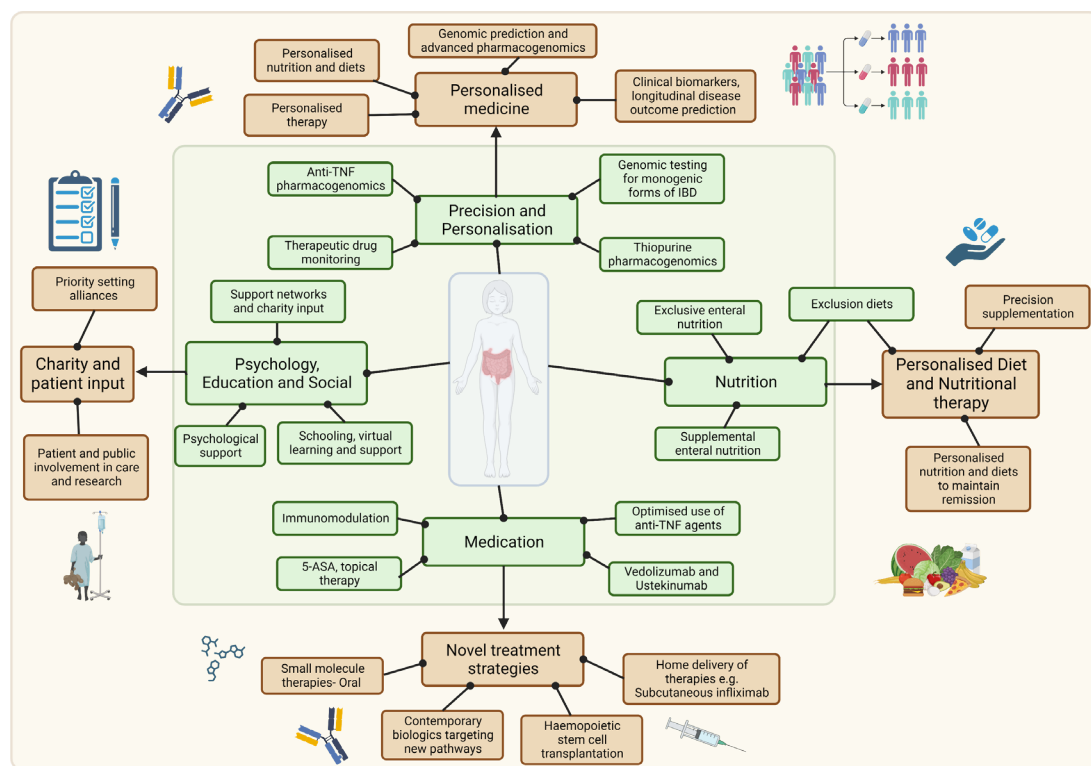

Figure 1 Current (green) and future (orange) management aspects in paediatric-onset inflammatory bowel disease (IBD). Holistic care is important to improve outcomes, considering all aspects of the patient including psychological, education and social. 5-ASA, 5-aminosalicylic acid Figure created with biorender.com

are maintained during key phases of biological and psychosocial development. The doubling of patient numbers in a short timeframe requires rapid development of training posts, consultant jobs, allied health professionals and provision of space in hospital. Consideration of home delivery of monoclonal therapy, through initiatives such as subcutaneous infliximab, must also be considered.[19]

Stratifying patients and impacting on outcome

The concept of early biological therapy in Crohn's disease leading to longer term quiescent disease remains largely theoretical, but the possibility of improving inflammation and preventing complications still requires prompt diagnosis and early referral. Not all patients will require biological, immunomodulator or small molecule therapy to achieve long-term remission. Other individuals will require tailored therapy due to underlying genomic variation. Achieving the ability to predict and personalise management will have a huge impact on medical and quality of life outcomes.

NEW DEVELOPMENTS IN DIETETIC MANAGEMENT

Exclusive enteral nutrition has a long-standing and significant evidence base of efficacy at inducing (and maintaining) remission in Crohn's disease.[20] It works to induce remission in up to 80% of paediatric patients with Crohn's disease, but the focus is widening in diet and IBD, both in terms of aetiology and treatment.

New diets and partial enteral nutrition

Despite the interest in diet and dietary manipulation in IBD, no 'normal' food diet has significant evidence of efficacy in inducing remission, including FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols), Mediterranean, vegetarian and other exclusion diets (such as wheat or dairy).[21] The newer Crohn's disease exclusion diet and CD-TREAT, diets specifically developed to induce remission in Crohn's disease through exclusions of specific foods, are beginning to amass small amount of evidence, although the role of partial enteral nutrition as part of these regimens is unclear.[22] At this point, the evidence to recommend a specific food diet, volume or percentage of calories as partial enteral nutrition, or specific exclusions, as a treatment to induce, or maintain remission is conflicted or lacking. However, this does not equate to dietary therapy being an unviable future option for treatment. This should not be confused with nutritional supplementation, providing personalised nutritional advice and care to malnourished patients to replenish macronutrients and micronutrients and facilitate high-quality growth. Prevention of adiposity in children with IBD is now as important as prevention of long-term undernourishment.[23]

NEW AND OLD DRUGS, NEW APPROACHES

The pharmacological landscape of IBD is a rapidly developing area, which slowly trickles down to paediatric practice. Despite the seismic shift that was seen with anti-tumour necrosis factor (TNF) agents in the 2000s, additional therapeutic options have been slow to emerge but are now much more available. Understanding of the best ways
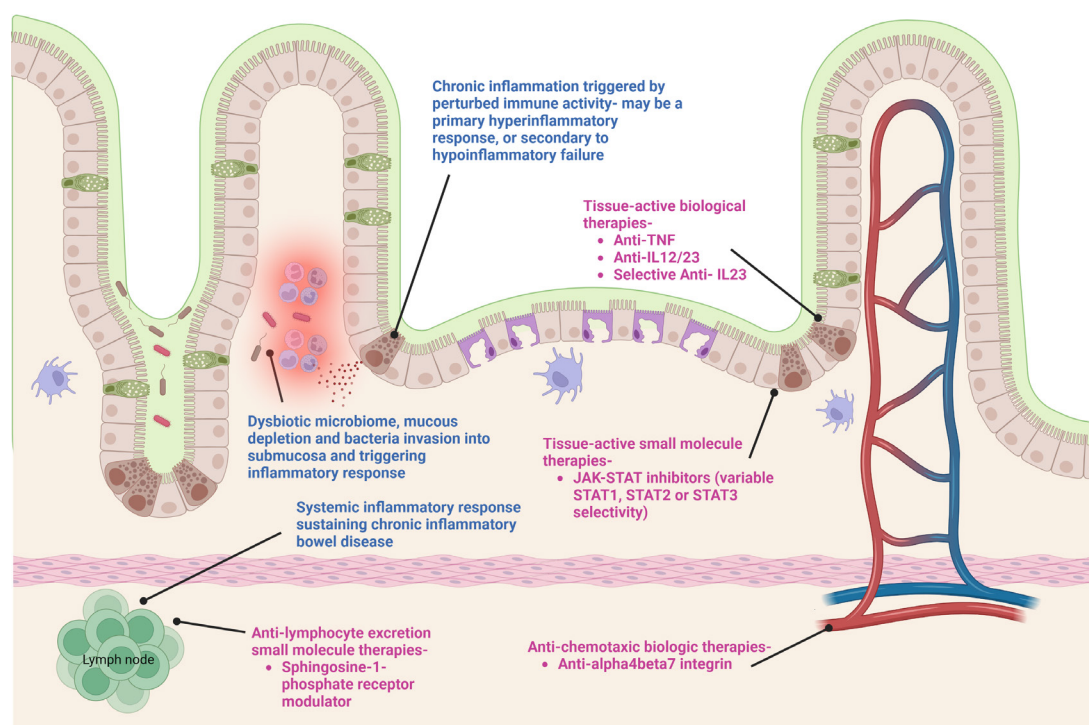

Figure 2 Disease aetiology in inflammatory bowel disease (IBD) is highly heterogenous—factors including genomic, epithelial function, bacterial and immunological function lead to significant heterogeneity in pathogenesis. There are likely to be numerous mechanisms at play within individuals, often leading to similar or related pathogenic phenotypes (represented by the blue text). There are now numerous therapeutic options for patients, although not all are available in paediatric practice yet. We have pointed to the mechanism of action of biologics and small molecule drugs (purple text). Figure created with biorender.com. IL, interleukin; TNF, tumour necrosis factor.

Table 2 Potential therapeutic drug monitoring strategies for biologics in patients with inflammatory bowel disease[36]

	Conventional dosing schedule	Accelerated/increased dosing schedule	First level/ antidrug antibodies	Frequency of levels/antidrug antibodies		Steady-state target levels	Insufficient response or specific clinical scenario target level
				Unstable patient or not in remission	Stable patient in remission		
Infliximab (intravenous)	5 mg/kg induction at 0, 2, 6 weeks 5 m/kg 8 weekly for maintenance	10 mg/kg at 0, 2, 6 weeks and then 8 weekly and/or reduce dosing interval	Pre-4th dose (trough level)	2 monthly (trough level)	6 monthly (trough level)	3–7 mg/L (some evidence >10 mg/L may be helpful)	>10 mg/L but may be higher (up to 15 mg/L)
Infliximab (subcutaneous)	**All induction dosing=intravenous** 4 weeks after previous intravenous administration 120 mg 2 weekly (body weight >50 kg only)	**All induction dosing=intravenous** 4 weeks after previous intravenous administration 120 mg weekly (body weight >50 kg only)	Pre-4th dose (trough level)	2 monthly (as close to trough level)	6 monthly (as close to trough level)	3–7 mg/L (some evidence >10 mg/L may be helpful)	>10 mg/L but may be higher (up to 15 mg/L)
Adalimumab	>40 kg = 80 mg+40 mg for induction at 0, 2 weeks and 40 mg 2 weekly for maintenance <40 kg, induction dosing is 40 mg+20 mg at 0, 2 weeks and 20 mg 2 weekly maintenance	>40 kg = 160 mg+80 mg for induction at 0, 2 weeks <40 kg, induction dosing is 80 mg+40 mg at 0, 2 weeks Double dose to 80 mg or 40 mg depending on body weight and/or reduce dosing interval to weekly	Pre-4th dose (trough level)	2 monthly (as close to trough level)	6 monthly (as close to trough level)	5–10 mg/L	>10 mg/L
Ustekinumab	<40 kg=6 mg/kg intravenous infusion for induction followed by 45 mg subcutaneous every 8 weeks for maintenance in children >40 kg=390 mg intravenous infusion for induction followed by 90 mg subcutaneous every 8 weeks	Increase dose and/or reduce dosing interval	Pre-4th dose (trough level)	2 monthly (trough level)	6 monthly (trough level)	Aim for 1.1–1.4 mg/L	Aim for 3 mg/L
Vedolizumab	6 mg/kg, max dose of 300 mg Induction given at 0, 2 and 6 weeks Maintenance every 8 weeks Subcutaneous dosing may be considered (2 mg/kg subcutaneous 2 weekly after intravenous)	Increase dose and/or reduce dosing interval	Pre-4th dose (trough level)	2 monthly (trough level)	6 monthly (trough level)	Aim for ~12.5 mg/L	Unknown

For specific references to ranges please refer to Exeter laboratory (https://www.exeterlaboratory.com/test/anti-tnf-drug-and-antibody-testing-at-exeter-clinical-laboratory/). For children with very low weight, abnormal body composition or abnormal renal/liver function doses may need to be adjusted.

to use current drugs, including therapeutic drug monitoring (TDM), is also having patient impact. Selecting the best drug for a patient, based on clinical and 'omic data, will further improve efficacy and outcome. A summary of different contemporary treatments targeting basic disease pathogenesis can be seen in figure 2.

Therapeutic drug monitoring

The use of drug monitoring to optimise outcomes is not new. We have been aware of the formation of antidrug antibodies against infliximab for decades and measuring drug levels has guided therapy. The ability to interpret these values and tailor therapy to a patient through TDM is increasing. While there continues to be equipoise between proactive and reactive drug monitoring, the use of any TDM does appear to have benefits to patients.[24] We have summarised current data and pragmatic recommendations for dosing and monitoring biologics in children in table 2.

Top-down management

Top-down therapy, especially in patients with a Crohn's disease phenotype, is now commonplace, with paediatric evidence of comparable 1-year outcomes and potentially reduced treatment failure when compared with step-up therapy.[25] Evidence of long-term impact of this strategy in Crohn's disease is still lacking, including in paediatric populations, and while early remission rates are often superior in first-line biological treatment, the effect appears to taper overtime, and longitudinal superiority compared with conventional therapy is uncertain.[26] Despite this, differentiating top-down from aggressive therapy in moderate to severe disease is very important, with top-down therapy focusing on treating all patients with biologics at disease onset to prevent complications, and aiming to 'turn off' the inflammatory process.[27] Aggressive therapy in refractory disease, or with severe disease, may also necessitate introduction of biological

therapy at or shortly after diagnosis, treating to a target, but does not ubiquitously use this as a treatment strategy in all patients.

Better use of traditional monoclonals

Infliximab (2000s) and adalimumab (2010s) have been licensed in paediatric practice for many years; however, we are only now beginning to optimise their use, deliver personalised treatment schedules and understand pharmacodynamics in younger children. Perhaps the best example of this is infliximab dosing. The humanised murine monoclonal antibody against TNF-α has been a mainstay of IBD treatment, initially in Crohn's disease and then ulcerative colitis. Conventional dosing has focused on 5 mg/kg, given at 0, 2 and 6 weeks and then maintenance dosing every 8 weeks, but this is now outdated (table 1). Frequently, induction is accelerated through reduced dosing interval, and initial dosing is often with 10 mg/kg.[28] Guided by TDM, maintenance dosing is tailored to patients to ensure adequate drug levels and reduced markers of inflammation (C-reactive protein, erythrocyte sedimentation rate, FCp), and minimise the risk of antidrug antibody formation.[29]

Concurrent immunomodulation with thiopurines or methotrexate has been a mainstay of therapy, aiming to reduce immunogenicity of monoclonal therapy.[17] Although routine use is widely debated in view of the potential toxicity and small long-term risk of lymphoma. Adalimumab appears to be less immunogenic than infliximab, although whether this represents its subcutaneous delivery route is uncertain. Contemporary genetic evidence has identified the human leucocyte antigen (HLA) genotype HLA DQA1*05 as a major risk factor for development of antidrug antibodies.[30] Administration of drug via a subcutaneous route appears to be less immunogenic, with subcutaneous infliximab on the horizon for paediatric practice, to complement adalimumab.[19 30] We are increasingly looking at the potential to better use the drugs available and thereby better stratify patients by risk of loss of response, with evidence also emerging of the ability to withdraw concurrent immunomodulation after 12 months of dual therapy with an anti-TNF agent.[31]

Newer monoclonals and small molecules

Ustekinumab (anti-interleukin (IL)-12/23) and vedolizumab (anti-α4β7) are in routine use in paediatric practice but remain unfunded for prepubescent children (table 1). Efficacy and safety are established, and these agents provide a useful alternative to anti-TNF therapy, with specific benefits for treatment of concurrent pathologies including psoriasis (ustekinumab).[32 33]

New therapies are coming, with the biological risankizumab (selective anti-IL-23), likely to be available within the coming year for patients aged 16 and over. Additional p19 inhibitors (such as mirikizumab) are also on the horizon of adult practice. Similarly, the small molecule class of drugs is filtering into the paediatric therapeutic arsenal, with JAK-STAT inhibitors (filgotinib, tofacitinib, upadacitinib) and sphingosine-1-phosphate inhibitors (ozanimod) also emerging as potent, oral options in specific cases, such as acute severe colitis.[34] The routine adoption of these agents is likely to take some time, but the direction of travel is clear. Efficacy of these newer agents varies by indication, although when used as a first agent they remain more effective (at a population level) then in patients with loss of response to another agent. Similar to anti-TNF agents, trial data reflect a clinical response in only up to ~50% of patients, reflecting a significant primary non-response rate for all therapeutic options.[35]

LINKING WITH ADULT SERVICES

Learning from adult practice has huge benefits, but the relationship is bidirectional. Paediatric services have more expertise in genetics, more focus on nutrition and have more time for transition. Early and consistent collaborative working is not a recent development but has become more important. Facing challenges such as exhaustion of therapeutic options, complex surgery, adolescent health issues (sexual health, smoking, alcohol) and genetic diagnoses requires paediatric–adult joint working, which goes beyond the traditional model of transition. While transition remains important, evidence suggests a lack of knowledge and engagement from patients and clinicians has determinantal impacts on long-term outcomes.[35]

CONCLUSIONS

Paediatric IBD is an exciting and dynamic field, with advances in basic and translational science beginning to have clinical impact. In this narrative review we have covered some of the recent and significant developments in practice and pointed towards some of the future advancements we envisage. Personalisation of all aspects of care is still not a routine reality but we are making progress and the next 10 years will see further advances.

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