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UPDATES IN THE MANAGEMENT OF PEDIATRIC INFLAMMATORY BOWEL DISEASE

Introduction

Canada has one of the highest rates of childhood-onset inflammatory bowel disease (IBD) in the world, with the recent Crohn's and Colitis Canada's 2023 Impact of Inflammatory Bowel Disease in Canada Report[1] demonstrating that approximately 6,158 children and youth under 18 years are living with IBD, along with 600-650 new diagnoses under age 16 per year. This number is expected to rise to 8,079 by 2035.[2] This represents approximately 10-20% of newly diagnosed patients.[3] Concerningly, although still relatively uncommon compared with adolescent onset IBD, the incidence has increased most significantly in children under 5 years old. Recent health administrative data demonstrated the national incidence of IBD, overall, to be 29.9 per 100,000 (95%CI: 28.3, 31.5) in 2023, with increasing incidence in pediatrics (AAPC:1.27%; 95%CI:0.82, 1.67), despite stable incidence in adults (AAPC:0.26%; 95%CI: -0.42, 0.82).[4] **Figure 1** demonstrates that this increase in pediatric incidence is a worldwide phenomenon. Current IBD care in pediatrics is moving toward a precision medicine approach, with unique and standardized approaches to genetics, risk stratification and disease phenotype, nutritional and advanced therapies, and specialized multidisciplinary clinics with knowledge of the unique challenges pediatric patients and their families face with a diagnosis of IBD.[5]

Pediatric Inflammatory Bowel Disease is Becoming Increasingly Common Around the World

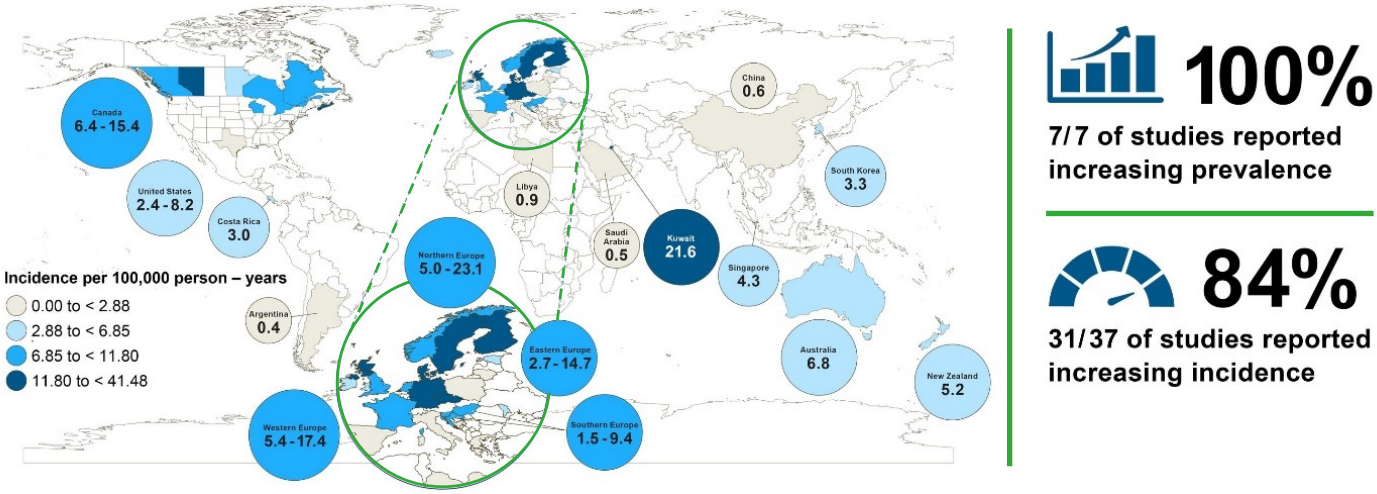

Figure 1. Map depicting global increasing incidence of pediatric IBD; Adapted from - Kuenzig ME, Fung SG, Marderfeld L, et al; InsightScope Pediatric IBD Epidemiology Group; Benchimol EI. Twenty-first century trends in the global epidemiology of pediatric-onset inflammatory bowel disease: systematic review. Gastroenterology. 2022 Apr;162(4):1147-1159.e4

Genetics

Genetic factors, microbial dysbiosis and aberrant immune responses associated with environmental factors are thought to be the main influencing factors in the development of IBD,[6] with likely varying contributions of these depending on age. With advances in next generation DNA sequencing, it is possible to genetically diagnose children with IBD or IBD-like disease, labelled 'monogenic IBD'. These patients typically are rare, severe and refractory to conventional therapies.[7] These were recently examined in a systematic review of monogenic IBD to collect established cases,[8] where the most commonly reported monogenic defect was interleukin (IL)-10-signalling colitis, followed by chronic granulomatous colitis (CGD), and X-linked inhibitor of apoptosis (XIAP) deficiency. **Figure 2a** shows the commonly seen genetic mutations,

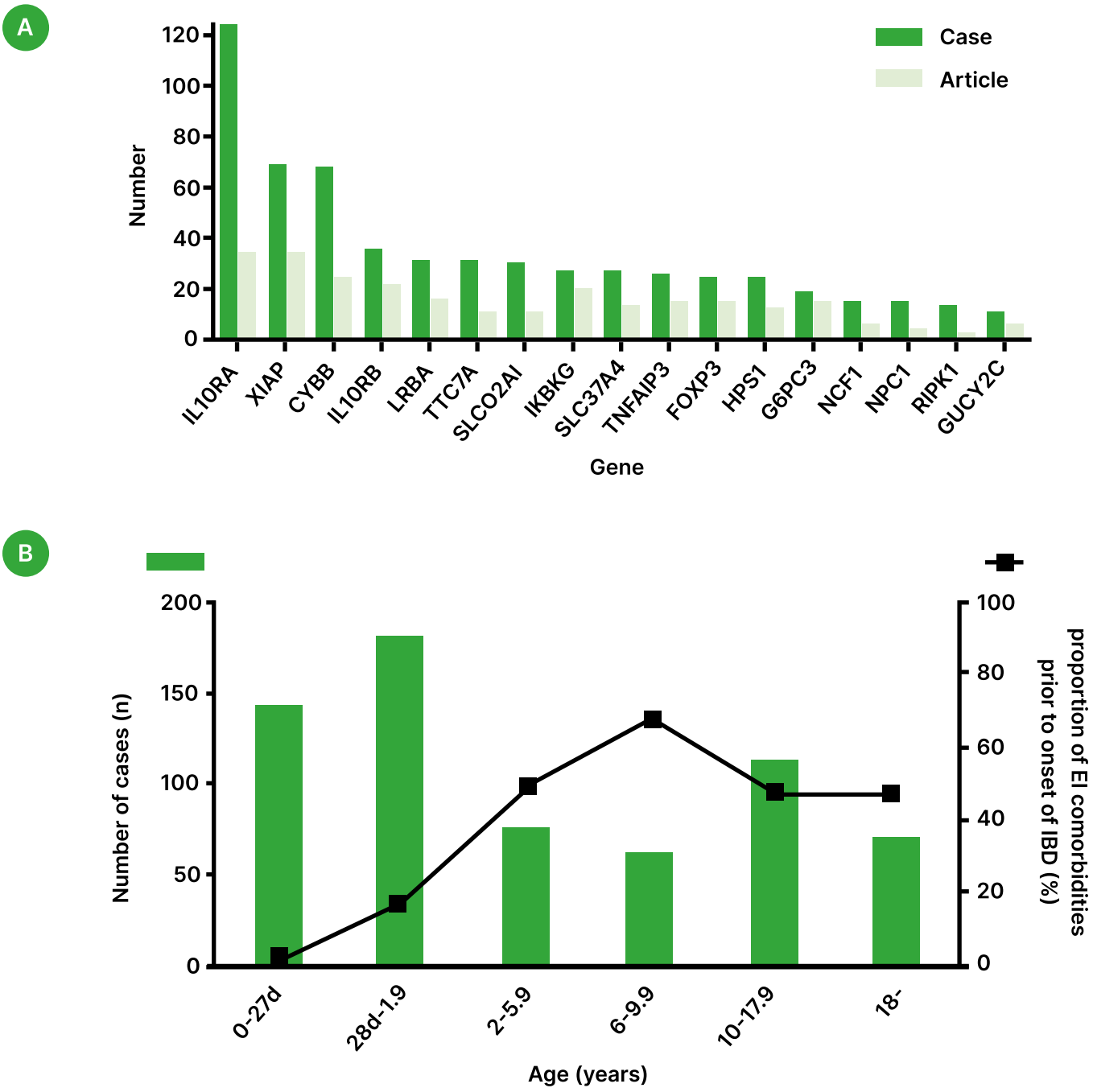

Figure 2. Common genes and age at onset of monogenic inflammatory bowel disease (IBD). **A** - Number of reported monogenic IBD cases and articles stratified by gene. Only genes that have 10 or more cases are listed. Dark orange bars, number of cases; light orange bars, number of articles. **B** - Distribution of IBD onset age. Orange bar (left y-axis) is the number of cases in each age group. The line graph (right y-axis) is the proportion of patients with extraintestinal (EI) manifestations before onset of IBD.
Image adapted from - Nambu R, Warner N, Mulder DJ, et al. A systematic review of monogenic inflammatory bowel disease. Clin Gastroenterol Hepatol. 2022 Apr;20(4):e653-e663.

and **Figure 2b** shows distribution by age, where more than 10% of cases were identified in adult age groups. Seventy-six percent of patients developed at least one extraintestinal issue during their disease course, with treatments including surgery (27.1%), hematopoietic stem cell transplantation (23.1%) and biological therapies (32.9%). These data highlight the diverse nature of monogenic disease, and it should be considered in all patients if there is an unusual phenotype, significant extraintestinal disease, or they are refractory to therapy.

Diet and Nutritional Therapies

Diet has been implicated in both the pathogenesis and relapsing/remitting nature of IBD, with a wealth of past and ongoing research into diet and its role in IBD. Numerous studies of nutritional epidemiology research demonstrating harmful associations with western diet and protective benefits from a Mediterranean diet and animal studies implicating ultra-processed and industrialized food in the development of inflammation have been examined for many years. There have also been small clinical trials showing degrees of benefit utilizing exclusive enteral nutrition and other dietary interventions.[9] Diet research has, however, been slow to progress, with mechanistic relationships difficult to understand, and diet interventions complicated and restrictive. The mainstay of nutritional therapy in pediatric IBD has been exclusive enteral nutrition (EEN) for Crohn's disease (CD), and it is the primary induction agent in many countries around the world for mild-to-moderate disease.[10] In Canada, rates of EEN use are similar to that of corticosteroids for induction according to data from the Canadian Children IBD Network (CIDsCaNN). EEN has demonstrated efficacy across a number of studies to induce remission and mucosal healing, and for nutritional rehabilitation.[11] It also has demonstrated adjunct benefit in children with stricturing/penetrating disease or with inflammatory masses.[11] Patient selection remains important for EEN success, and is best served when supported by a dietitian in an IBD centre with EEN experience and adequate follow-up. Data evaluating disease severity and phenotype as predictors of success are conflicting, but those with predominantly distal ileal disease and mild-to-moderate disease severity have been shown to be more likely to be responsive.[13,14] Exploration of microbiome signatures[15] and genetic markers[16] related to EEN success are ongoing.

There have been multiple dietary therapies proposed as IBD 'treatment diets', with a recent literature review suggesting more than 24 identified in the management of IBD.[17] These have had varying methodologies and outcome assessments, with no convincing evidence to support the use of a single diet over another. The most robustly assessed is the Crohn's Disease Exclusion Diet (CDED),[18] which combined a restricted diet with partial enteral nutrition (PEN) across several phases of decreasing restriction. Diet restrictions were based on animal data where food products impacted inflammation, dysbiosis or intestinal permeability. This combination was similar to EEN in inducing remission at week 6 (75% in the CDED plus PEN group vs 59% in the EEN group; P = 0.38), but has had limited success in patients with severe disease, or in the setting of loss of response to biologics.[19] Across Canadian pediatric centres there remains significant variation in standard diet recommendations and uptake of diet therapies until more robust data on therapeutic diets emerge, which continues to be a source of frustration for patients and families.

Drug Therapies

The number of approved available drug therapies for IBD in adult patients has increased rapidly over recent years. However, the unavailability of these drugs for children has been an increasing problem for pediatric IBD practitioners. There is a significant lag time prior to pediatric randomized controlled trial completion and regulatory approval, leading to prolonged off-label use of new therapies. Traditional induction therapies like corticosteroids and EEN have continued to be used, but the use of immunomodulators as maintenance monotherapy, especially in CD, has decreased significantly as we move to a focus on 'early effective therapies' as part of our treat-to-target approach, especially as most pediatric patients present with moderate-to-severe and extensive disease. In ulcerative colitis (UC), the PROTECT study demonstrated a reasonable proportion of steroid responsive children respond to standard 5-ASA therapies, but at 52 weeks, only 40% of patients were able to maintain 5-ASA therapy without requiring escalation.[20] Anti-tumour necrosis factor (TNF) therapies continue to be the most utilized maintenance therapies in pediatrics given their prolonged period of availability and ongoing effectiveness, with infliximab and adalimumab the only licensed biologics for children. However, approximately one-third of IBD patients are non-responders to anti-TNF therapy,[21] and another 20-30% will develop secondary loss of response, with or without development of anti-drug antibodies. The use of body surface area (BSA)-based dosing for young children[22] and proactive therapeutic drug monitoring[23] has shown some benefit in children compared to adults, potentially related to differences in drug clearance and body composition, as well as a non-linear relationship between body weight and BSA in young/light children. The latter point makes it such that the youngest/lightest children require the most drug per kilogram to achieve comparable drug exposure to older children/adults. Regardless, a significant proportion of children will lose response to first line anti-TNF therapy. Therefore, readily available alternatives are of the utmost importance.

In 2014 vedolizumab became the first anti-integrin designed specifically for gastrointestinal disease in adults, targeting α4β7; it was established

through the GEMINI program.[24] It has been used off label in pediatrics, initially in anti-TNF refractory patients, but more recently in bio-naïve patients, especially in UC. There are multiple pediatric observational studies demonstrating its safety and efficacy, the largest of which is the VEDOKIDS study[25] demonstrating 42% steroid-free remission rates at Week 14 in UC and 32% in CD, with some benefit in bio-naïve patients. Durability data are sparse, with small series demonstrating some benefit with early dose optimization and proactive therapeutic drug monitoring.[26] To this point safety data are excellent, which make this drug an attractive therapy for pediatric patients. Additional studies are needed to explore the role of other anti-integrin therapies in pediatrics.

Ustekinumab, a monoclonal antibody that binds to the p40 sub-unit of IL-12 and IL-23, is approved in adults, with established efficacy through the UNITI and UNIFI trials.[27,28] The drug has been used off-label in Canada since 2016 in children, again initially in anti-TNF refractory patients. CIDsCaNN published the early Canadian experience in anti-TNF refractory UC,[29] demonstrating 44% steroid-free remission at Week 52. In CD, Canadian data by Chavannes et al[30] demonstrated 38.6% of patients achieving clinical remission at Week 52. Both studies reported good safety profiles. Data regarding the utility of proactive therapeutic drug monitoring and dose optimization are sparse in pediatrics, so far only presented in abstract form, demonstrating some association between higher proactively measured week 8 ustekinumab levels and favourable clinical outcomes.[31] Recently, newer molecules targeting p19 found only on IL-23, including risankizumab, mirikizumab and guselkumab, have been undergoing clinical trials in adult patients demonstrating efficacy with encouraging data. Pediatric clinical trials are ongoing. Early off-label use for risankizumab was recently made available, but published data of the pediatric experience are not yet available.

JAK-STAT inhibitors, which inhibit the activity of one or more JAK enzymes interrupting intracellular STAT pathway phosphorylation, were the first family of targeted small molecules utilized in IBD, with tofacitinib the first licensed for use in adults. The OCTAVE clinical trials demonstrated safety and efficacy in adults for UC,[32] and there is currently an active clinical trial in pediatric patients with moderate-to-severe UC in both bio-naïve and anti-TNF failed patients. Pediatric off-label use has been available, predominantly for anti-TNF failed patients, with published series demonstrating efficacy and early safety data. Up to 41.2% of patients had clinical response and steroid-free remission at 52 weeks.[33] A second small study showed improvements in colectomy rates in hospitalized patients who were steroid and anti-TNF refractory.[34] Upadacitinib, an oral selective JAK1 inhibitor, is undergoing a Phase 3 clinical trial in moderate-to-severe pediatric UC in both bio-naïve and experienced patients, and has had encouraging off-label use to date presented in abstract form.[35] Other JAK inhibitors are currently under investigation. Most intriguing to this group of drugs is rapidity of onset, which in future could potentially obviate the need for corticosteroids in select patient; therefore, more robust safety and efficacy data are eagerly awaited.

Finally, sphingosine-1-phophate (S1P) receptor modulators bind to, and indirectly antagonize, the S1P receptors on lymphocytes trapping them within lymph nodes, reducing immune response. Multiple S1P receptors are undergoing clinical trials in IBD (ozanimod, fingolimod and etrasimod), with ozanimod currently undergoing a clinical trial in pediatric CD, with off-label use recently available.

With a number of new drugs and pathways available, pediatric IBD specialists will have more treatments available for our patients. Data regarding sequencing and positioning will become of paramount importance. In addition, data evaluating safety and efficacy of so called 'multi-modal' therapy combining dual biologics or biologics and small molecules are starting to emerge for refractory pediatric patients,[36-38] expanding our treatment armamentarium for patients with difficult to control disease.

Conclusions

Goals of care in pediatric IBD are initially similar to those of adults. These include achieving long-term, steroid-free clinical remission and achieving mucosal healing, to prevent long-term disease-related complications. Children have unique additional goals, including optimizing physical, pubertal and psychological growth, maintaining nutrition and quality of life through school and adolescence, and consideration of the potential treatment toxicities given extended periods of time on medications. This is especially true as our patient population at disease onset continues to get younger and treatments more complicated. Given this, it is increasingly recognized that children with IBD should be treated in specialized, multidisciplinary centres with access to physicians, specialized nurses, dietitians, and mental health professionals with expertise in IBD[1] to try and enable children and families to access the highest quality care for their IBD.

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Financial Disclosures:

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