Journal of Crohn's and Colitis, 2024, **18**, ii31–ii45
https://doi.org/10.1093/ecco-jcc/jjae087
Supplement Article

Considerations in Paediatric and Adolescent Inflammatory Bowel Disease

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Abstract

The incidence of inflammatory bowel disease [IBD] is rising most rapidly among children and adolescents. Paediatric-onset IBD is associated with a more extensive and severe disease course compared to adult-onset IBD. At a young age, screening for underlying genetic and immunological disorders is important and may impact treatment management. Early and effective treatment is crucial to reach disease remission and prevent complications of ongoing active disease. In children with Crohn's disease, exclusive enteral nutrition is an effective induction therapy. Other promising dietary therapies, such as the Crohn's disease exclusion diet, are emerging. Within paediatric IBD, anti-tumour necrosis factor therapy is the only approved biological thus far and additional treatment options are crucially needed. Other biological therapies, such as vedolizumab and ustekinumab, are currently prescribed off-label in this population. A specific challenge in paediatric IBD is the unacceptable and major delay in approval of drugs for children with IBD. A guided transfer period of paediatric patients to adult care is associated with improved disease outcomes and is required. Major knowledge gaps and challenges within paediatric IBD include the aetiology, diagnostics, and monitoring of disease, tailoring of treatment, and both understanding and coping with the physical and psychological consequences of living with IBD. Challenges and research gaps in paediatrics should be addressed without any delay in comparison with the adult field, in order to ensure a high quality of care for all patients with IBD, irrespective of the age of onset.

Key Words: Child; Crohn's disease; ulcerative colitis

1. Introduction

Inflammatory bowel disease [IBD] is an immune-mediated chronic disease of the gastrointestinal [GI] tract, classified into Crohn's disease [CD], ulcerative colitis [UC], and IBD-unclassified [IBD-U]. The exact pathogenesis of IBD remains unknown. The disease is considered to develop in genetically susceptible individuals who are exposed to specific environmental factors that alter the intestinal microbiome, resulting in dysbiosis and immune dysregulation.[1] Onset of disease during childhood occurs in ~10% of the IBD patients.[2,3] In this review, we discuss the current considerations, developments, and challenges in health care for children and adolescents with IBD.

2. Epidemiology and increasing incidence of IBD

The incidence and prevalence of IBD have been rapidly increasing worldwide over the last few decades, and have risen most rapidly at a young age.[2–5] Although the increase in incidence in adults might be stabilizing in Western countries,[6] the incidence of paediatric IBD is still accelerating or even emerging, especially in low- to moderate-income countries.[4]

Reasons for the increasing incidence of paediatric IBD could be improved recognition and awareness of IBD onset at younger age and better diagnostic capabilities.[5,7,8] Nevertheless, Khan *et al*. illustrate that environmental factors play the most crucial role in today's increasing incidence.[4] This is based on two observations. First, the incidence of paediatric IBD increases with increasing income of a country and, second, incidence increases when westernization of a region with previously low incidence rates takes place. People migrating from regions with low rates to regions with high rates of IBD remain at a decreased risk of developing IBD. However, when migrating at a younger age, people are at higher risk of developing IBD.

2.1. Environmental factors influencing IBD

Westernization is associated with increased consumption of processed foods, dairy and cereal products and correlates with the current increases of incidence of inflammatory diseases in general,[9] and specifically IBD. An increased risk of CD was associated with increased intake of total fat, polyunsaturated fat acids, omega-3 and omega-6 fatty acids, mono- and disaccharides, and meat.[10] High dietary fibre and fruit intake was associated with a decreased risk of developing CD.[10,11] During childhood, exposure to breast feeding, animals, and the rural environment have been shown to be associated with a decreased risk of developing IBD.[12–14] Diet and intestinal microbiota are among the environmental factors that can be influenced by the patient and treatment strategy. Recent studies showed that diet can influence downregulation of local immune function, and alter the intestinal microbiota

and mucosal barrier function.[15–17] The use of dietary therapy for reaching remission will be further discussed in a subsequent section of this review. Furthermore, an upcoming consideration is that environmental factors might also influence the type of IBD that develops.[5] For example, in children and young adolescents, nitrogen dioxide [a pollutant related to traffic] might be associated with development of CD, whilst sulphur dioxide [a pollutant related to industry] might be associated with the development of UC.[18] However, there is still a limited understanding on how environmental factors influence the microbiome and pathogenesis of IBD overall.

2.2. Burden on healthcare systems and costs

The increasing incidence of IBD imposes a high burden on healthcare systems and costs. Paediatric IBD especially contributes to a high economic burden as these patients require longer healthcare utilization and a more intensified inpatient and outpatient regimen compared to adults.[19,20] The use of biologicals has been identified to highly contribute to healthcare costs in paediatric IBD.[21] A systematic review of disease-related costs in paediatric IBD showed that comorbidities and psychiatric disorders might be predictors of high costs as well.[22] A relatively unstudied and undiscussed aspect is the indirect economic burden of paediatric IBD for families, consisting of work absenteeism of parents, out-of-pocket costs, psychological issues, and lower professional development.[23,24] Out-of-pocket costs were found to be highest in paediatric IBD families that experience frequent relapses and active disease. Specifically, for parents of lower to middle income, out-of-pocket costs related to IBD care might lead to financial stress.[25] Awareness among paediatric gastroenterologists on the indirect cost burden, and supporting friendlier IBD environments could help in reducing the economic burden on families.[24] Bridging the research gap on the indirect and out-of-pocket costs worldwide would contribute to understanding how to improve awareness, as most current studies are from North America.[22]

3. Differences between paediatric-onset and adult-onset IBD

3.1. Aetiology

There are several differences between paediatric-onset and adult-onset IBD. A selection of the most important differences is provided in Figure 1. First, genetic susceptibility is believed to play a more important role in the aetiology of paediatric IBD. Higher polygenic risk scores and multiple genetic variants are associated with disease manifestation at childhood

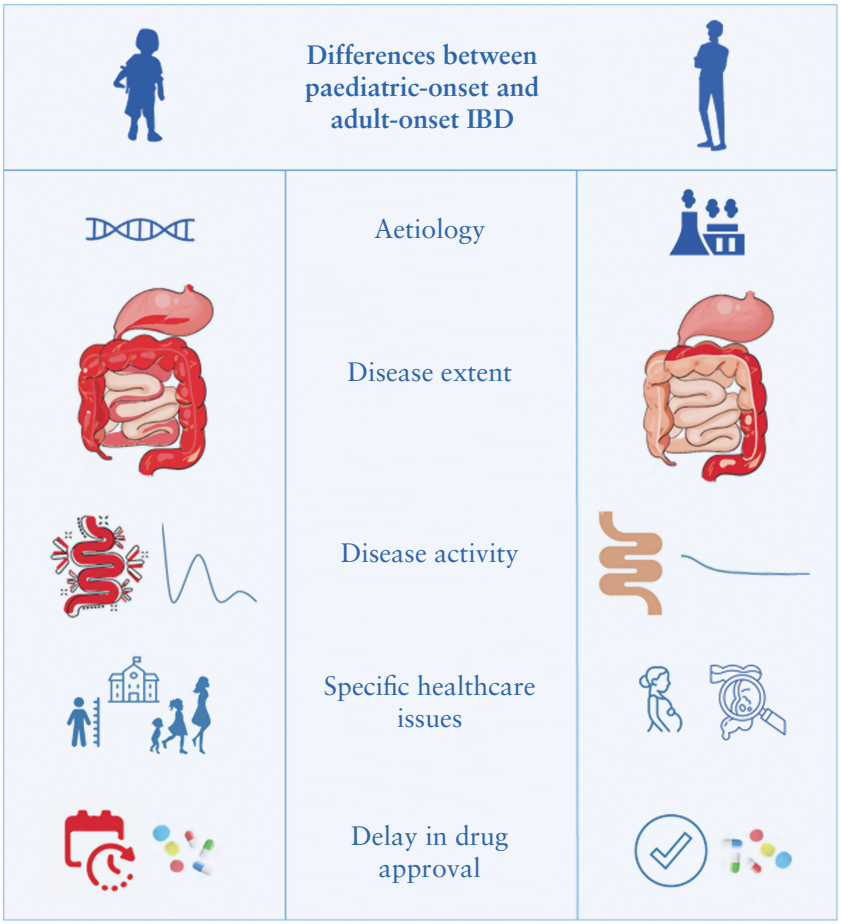

Figure 1. Overview of relevant differences between paediatric-onset and adult-onset inflammatory bowel disease [IBD]. Genetics play a bigger role in the aetiology of paediatric IBD with decreasing age. Environmental factors probably play the major role in the aetiology of adult IBD. In paediatric-onset IBD, there is more extensive, dynamic, and severe disease activity compared to adult-onset IBD. Furthermore, whilst growth, puberty, and school attendance are some of the issues discussed in paediatric IBD, pregnancy and surveillance endoscopies are topics of discussion in adult-onset IBD. Compared to adults, there is a delay in drug approval for children with IBD.

and adolescence, as well as with a severe disease course.[26,27] In children with very early onset IBD [VEO-IBD], defined as disease onset at <6 years of age, genetics play an even bigger role. At this moment, more than 100 monogenic defects for IBD have been identified.[27–29] The Porto IBD Group developed a gene panel of 75 monogenic defects for the diagnostic screening of paediatric IBD.[30] Some of these mutations can cause primary immune deficiencies [PIDs][31] or intestinal epithelial barrier dysfunction.[32,33] Mutations causing PIDs for example include defects in the signalling of interleukin [IL]-10[34–36] and X-linked inhibitor of apoptosis protein [XIAP],[37,38] which promote intestinal inflammation and lead to IBD-like disease. Furthermore, IL-10 and XIAP mutations are related to the development of extra-intestinal manifestations, such as perianal disease and arthritis.[34,35] Examples of mutations considered to dysregulate epithelial barrier function are MUC1, MUC3, MUC4, AGR2, and WNT2B.[32,33,39]

Genetic screening has become an important diagnostic tool contributing to the understanding of the aetiology of [VEO]-IBD. If a monogenic defect is the underlying cause of VEO-IBD, treatment should be tailored appropriately.[27] Recently, studies are emerging in which children with paediatric VEO-IBD with underlying PIDs are curatively treated by haematopoietic stem cell transplantation.[36,40] Additionally, genetic screening contributes to the understanding of IBD manifestation from a family perspective.[27]

3.2. Clinical features and phenotype

Children with IBD may present with more atypical complaints compared to adult-onset IBD,[41] mainly patients with CD and VEO-IBD.[42] Within paediatric patients with IBD, up to 22% initially present with extra-intestinal manifestations such as acute or chronic growth delay, anaemia, fatigue, and perianal disease without diarrhoea or other gastrointestinal complaints.[2,43–45] This atypical presentation of paediatric IBD often results in diagnostic delay.[46] Therefore, it is important to continue creating awareness and adequate diagnostic management of IBD at younger age. The family history is an important feature at presentation of paediatric IBD. A few studies have reported on the percentage with a positive family history in paediatric onset-IBD, and found that 11.1–13.7% of patients had a first-degree relative with IBD.[47–49] Paediatric-onset IBD is associated with a higher risk of positive family history compared to adult- or elderly-onset IBD.[50]

Paediatric IBD is known to be associated with a more extensive and severe disease course compared to adults, also when controlled for duration of disease and disease location at diagnosis.[19,51,52] Van Limbergen *et al*. showed that panenteric and colon-only CD, extensive UC, and dynamic disease location were more often reported in paediatric patients with IBD compared to adult-onset IBD.[53] Several studies have reported more upper GI tract involvement in paediatric IBD compared to adult-onset IBD. The question remains whether upper GI tract involvement is indeed more common in paediatric IBD or whether the standard gastroscopy in the diagnostic process of paediatric IBD explains the higher rates.[2,51,54] Additionally, more frequent periods of active disease are reported in paediatric IBD, despite a more intensified medical regimen with increased biological and immunomodulatory therapy.[52] Paediatric CD is especially known to often result in chronically active and disabling disease leading to, for example, intestinal resection.[55] Nevertheless, Pigneur *et al*. showed that in the general paediatric IBD population, surgery rates were equal to those in adults and no difference was found in rates of penetrating or stricturing disease in paediatric IBD patients compared to adult IBD.[52] This could be due to the low number with ileal involvement [which is associated with structuring or penetrating disease] within paediatric IBD patients diagnosed <8–10 years old.[51,53]

3.3. Specific healthcare issues in paediatric IBD care

Next to differences in presentation and disease course, different healthcare issues in paediatric IBD should be addressed compared to adult-onset IBD. Monitoring of age-specific complications, such as growth retardation,[56] pubertal delay, developmental delay, decreased bone age,[57] fatigue, school absenteeism,[19,58] and nutritional impairment,[7,19,56] are of utmost importance. Additionally, the need for psychological monitoring in paediatric IBD patients is becoming more evident. The impact of fatigue, not keeping up with peers, and processing a chronic disease at a young age adversely affect children emotionally.[59,60] Several studies show decreased quality of life and increased risk of psychiatric disorders, mostly depression and anxiety disorders.[61,62] Increased disease activity, low family stability, and familial psychiatric disorders are kown to correlate with the risk of psychiatric disorders in paediatric IBD patients.[60,63] Klomberg *et al*. showed that caregivers of children with IBD also experience impairment in daily life and work, mainly around time of diagnosis.[64] Given these recent findings, the need for psychological support to be implemented in standard paediatric IBD care for parents and child has been emphasized,[65,66] especially at diagnosis[64] and during transition to adult health care.[61]

4. Treatment of paediatric IBD

There are several treatment options for children with IBD.[67–69] In this review, we will discuss current developments and insights regarding dietary interventions, biological therapy, and surgical interventions.

5. Dietary therapy in paediatric IBD

The main goals of paediatric IBD treatment are to induce and maintain mucosal healing, increase quality of life, and establish adequate weight gain and linear growth.[67,68] The ECCO-ESPGHAN Guidelines and NASPGHAN Guidelines recommend exclusive enteral nutrition [EEN] above corticosteroids [CS] as first-line induction therapy to reach remission in children with active low- to moderate-risk luminal CD.[68,70] EEN is a liquid diet that replaces nutritional needs over ~8 weeks.[68] EEN is a commonly used induction therapy in paediatric CD in Europe. Already in 2003, 76% of paediatric gastroenterologists in western European countries frequently prescribed nutritional therapy.[71] By contrast, 31% of Northern American responding paediatric gastroenterologists reported to have never used EEN before and 55% only sparsely used EEN as induction therapy in 2011.[72] The frequency of prescribing EEN is considered to be influenced by the extent of experience with EEN and current practice setting.[72] There is no evidence that EEN is an effective induction therapy for children with UC.[73–75]

5.1. Efficacy of EEN as induction therapy

The efficacy of an 8-week course of EEN for induction of remission in paediatric CD has been well established. Several

studies and meta-analyses have shown an equal effect of EEN compared to CS in children with mild-to-moderate CD in reaching clinical and biochemical remission. Clinical remission rates range from 71% to 92% after EEN induction therapy in children with CD.[76,77] Moreover, a meta-analysis in 2017 including eight studies showed that EEN was superior to CS in achieving mucosal healing compared (odds ratio [OR] 4.50, 95% confidence interval [CI] 1.64, 12.32).[78] Besides inducing remission and promoting healing of intestinal inflammation, EEN does not exert negative effects on bone mineral density,[79] weight gain, or linear growth as known from CS treatment.[77,80,81] Side-effects of EEN are mostly limited to GI tolerability, such as vomiting and nausea.[68] A few cases of refeeding syndrome have been reported in malnourished children with CD starting with EEN.[82]

Although EEN has a very important role in the treatment of children with CD, consuming only a liquid diet during 8 weeks is strenuous for children both socially and psychologically. In a single-centre study, half of the paediatric CD patients reported to struggle to finish EEN, with lack of flavours being the most common reason.[83] Parents might also struggle with EEN due to impact on social situations and costs.[84] Initial non-adherence can negatively influence the disease course.[81] De Bie *et al*. reported that of 77 paediatric patients, initial non-adherence was observed in 20% which resulted in lower remission rates [53%] compared to patients who completed the EEN course [71%].[81] Boneh *et al*. showed that of the non-responders to EEN induction therapy, 75% was not adherent to the diet.[85] Predictors of poor adherence are considered to be colonic involvement and faecal calprotectin >600 µg/g at diagnosis.[86] Additionally, predictors of poor clinical response to EEN induction treatment include complex disease behaviour, increasing age, specifically age >15 years, and severe clinical disease at diagnosis (defined as Pediatric Crohn's Disease Activity Index [PCDAI] ≥ 40).[86,87] It is considered that older age, and increased clinical and biochemical disease activity at start of EEN are associated with poor adherence.[81,86] Although there is a lack of conclusive data on the effectiveness of EEN in adults with CD, EEN might be effective for induction treatment in adults with CD.[88] EEN is reported to be more effective in children compared to adults, which may be due to reduced adherence of EEN in adult patients with IBD.[78,88]

The current recommendation of the paediatric IBD Porto group is to use EEN as induction therapy in active luminal mild-to-moderate CD irrespective of disease location.[73] There remains some controversy regarding whether the phenotype of paediatric CD influences the effect of EEN in achieving remission and mucosal healing. Traditionally, colonic CD is considered to respond less well to EEN compared to CD with ileal involvement.[89,90] Afzal *et al*. showed that patients with isolated colonic disease had significantly lower remission rates after an 8-week course of EEN compared to patients with isolated ileal disease [50% vs 92%, $p = 0.021$].[90] Another study showed a response rate of 88% in children with isolated ileal or ileocaecal disease vs 50% in children with colonic involvement.[81] Nevertheless, several more recent studies showed no difference in reaching clinical remission with EEN in case of only colonic involvement.[91,92] A study by Fell *et al*. showed improvements in endoscopic and histological scores in both ileal and colonic disease and, particularly, a reduction of pro-inflammatory cytokines in the terminal ileum as well as the colon confirming the anti-inflammatory properties of EEN in both mucosal locations.[17]

5.2. Mechanisms of dietary therapy

Complete elemental diet has been described since the 1970s.[93] Since then, many studies have been performed concerning enteral nutrition as induction therapy in IBD. While the exact mechanism of EEN is still not completely unraveled, it is suggested that the therapeutic properties of EEN act by altering the composition of the intestinal microbiome and reducing local pro-inflammatory cytokines leading to mucosal healing.[16,17,94–96] Several studies show decreased local pro-inflammatory cytokines, such as IL-6 and interferon gamma,[17,96–100] during EEN induction therapy. Additionally, clinical remission and healing of intestinal inflammation were associated with a decline of mucosal pro-inflammatory cytokines after EEN induction treatment in IBD.[17,98] As the role of the intestinal microbiota is becoming more clear and evident, correction of dysbiosis might arise as a major goal in the management of IBD in the future.[94]

In patients with IBD, a less diverse and stable microbiome with an abundance of Proteobacteria [associated with pro-inflammatory effects] and reduction of Firmicutes [associated with immunoregulatory effects] has been found compared to healthy controls. A higher disease activity in IBD is associated with a less diverse microbiome.[101] Surprisingly, a systematic review in 2017 concluded that EEN induction therapy resulted in a reduction of microbiota diversity.[102] Another recent prospective study in paediatric patients with IBD observed an increase in Firmicutes and decrease in Proteobacteria after 6 weeks of EEN treatment compared with healthy controls.[16]

5.3. Role of EEN in maintenance treatment

Unfortunately, the beneficial changes to the microbiome due to EEN are reduced after re-introducing a normal diet.[16,102] A study by Levine *et al*. showed that patients with a rebound after EEN induction therapy shift to pre-treatment dysbiosis when re-introducing a normal diet.[95] Complete restoration of the microbiome and metabolome with beneficial microbes might be required to maintain remission and prevent relapse in the longer term.[16] Several studies report relapse rates after re-introducing a free diet ranging from 42% to 67% in paediatric patients with CD after 1 year.[73,76] EEN might be considered for a second induction course with reported remission rates being >55%.[73] Nevertheless, this is controversial because another study showed decreased efficacy of a repetitive course of EEN.[76]

The exclusion of certain food products is suggested to be required to maintain remission.[16,95] Supplementary enteral nutrition, in addition to unrestricted diet, as additional maintenance treatment after the initial induction is also considered to beneficially affect duration of remission.[16,98,103,104] To achieve and maintain remission by extending nutritional therapy, it has to be feasible to incorporate nutritional therapy in daily life. Due to low adherence, EEN is not feasible as maintenance treatment. Therefore, more patient-friendly diets have been studied which we will discuss in the following section. Additionally, more research is required on the strategy of re-introducing a free diet to support continuous restoration of the microbiome and maintain remission.

5.4. Other nutritional diets

The CD exclusion diet [CDED] is a whole-food diet that excludes certain foods known to negatively affect the intestinal microbiome, intestinal barrier, and inflammation,[105] such as red meat, gluten, and processed food. Two randomized

controlled trials examined the CDED coupled with partial enteral nutrition [PEN] as induction therapy compared to EEN followed by PEN with gradual introduction to free diet in paediatric patients with mild-to-moderate CD.[16,95] Levine *et al*. showed that at week 6, equal efficacy was reported in both nutritional therapies in altering the microbiome and inducing clinical and biochemical remission.[95] Additionally, improved adherence was shown in the CDED with PEN groups. After 12 weeks, sustained remission, continuous alterations of the microbiome, maintaining normal C-reactive protein [CRP] levels, and further decrease of faecal calprotectin were significantly better in the CDED with PEN group.[95] Verburgt *et al*. showed that CDED with PEN was associated with a continuous reduction of Proteobacteria and increase of Firmicutes after 12 weeks compared to baseline.[16] The improved adherence of CDED with PEN compared to EEN is considered to contribute to the improved remission rates.[95] More prospective studies are required including mucosal healing as an outcome measurement in coupled CDED with PEN therapy to evaluate its role in future treatment of children with active luminal CD.[68]

A pilot study assessed the anti-inflammatory diet [AID] combined with PEN in children.[106] This diet mainly excludes certain carbohydrates that stimulate proliferation of inflammatory bacteria in the microbiome, such as refined sugar, and promotes the use of probiotic products and unsaturated fats, such as omega-3.[107] Twenty-five paediatric patients with CD received either EEN or 75% PEN with one meal per day of the AID as induction treatment and showed equal effectiveness in achieving mucosal healing, and endoscopic and clinical remission after 6 weeks.[106] Lastly, a novel patient-friendly personalized diet suggested as induction therapy in CD is the CD-treatment-with-eating diet [CD-TREAT]. CD-TREAT is an 8-week AID designed to replace EEN with whole foods. It excludes dietary components such as gluten and lactose, while promoting components such as vitamins, minerals, and fibre.[108] Svolos *et al*. examined the effect of an 8-week CD-TREAT diet in healthy adult volunteers, rats with and without IBD, and in five children with CD. Of the children, 2/5 reached clinical remission and 4/5 showed decreased faecal calprotectin levels. One child did not complete the diet.[108] The adult healthy volunteers were randomly assigned to an 8-week CD-TREAT or EEN diet. Similar changes in the microbiome were observed in both groups. These studies suggest that CD-TREAT and AID are promising feasible nutritional therapies for the induction of remission in mild-to-moderate luminal CD deserving further examination.

6. Anti-TNF treatment in paediatric patients with IBD

Besides dietary interventions, the use of biologicals has a pivotal role in the management of paediatric IBD. Anti-tumour necrosis factor [TNF] therapies have emerged as a significant advancement in the treatment landscape of IBD, substantially enhancing therapeutic outcomes. Only two biological [both anti-TNF] therapies, infliximab and adalimumab, are currently approved by the European Medicines Agency [EMA] for children with CD since, respectively, 2006 and 2014, and for children with UC in 2011 and 2021.[109] Since then, the utilization of anti-TNF has been rapidly rising. In the UK, the prevalence of anti-TNF use in paediatric IBD increased from 5.1% in 2007 to 27.1% in 2017.[110] Current paediatric IBD guidelines recommend starting anti-TNF treatment in children with CD when conventional treatment has failed, or as first-line treatment when a patient is at high risk of a complicated disease course. Predictors of a complicated disease course are, for example, presence of perianal disease or growth delay.[68] For children with UC, anti-TNF treatment is recommended when conventional treatment (5-aminosalicylic acid [5-ASA] or thiopurines) is insufficient to induce or maintain disease remission.[69]

In paediatric IBD, the approved route of administration for infliximab is intravenous, while adalimumab is prescribed subcutaneously. Subcutaneous infliximab has already been approved in adult-onset IBD since 2020, as it was demonstrated that subcutaneous infliximab is not inferior to intravenous infliximab in adults.[111,112] To date, only one small study has reported on the use of subcutaneous infliximab in children with CD.[113] In this retrospective observational study, seven children electively switched from intravenous to subcutaneous infliximab. All patients remained in clinical remission and no differences were found in infliximab trough levels or antibody formation after switching to subcutaneous infliximab. Specifically for young patients, subcutaneous administration of infliximab might have several advantages. For example, subcutaneous administration may be beneficial for children with fear of intravenous needle placement and results in less travel and hospitalization time, thereby benefiting school attendance. Additional studies are crucially warranted to assess effectiveness, feasibility, and pharmacokinetics [including area under the curve instead of solely serum trough levels in order to better compare intravenous and subcutaneous therapy] in children with IBD.[114]

6.1. Anti-TNF therapy and pharmacokinetics and pharmacodynamics

European guidelines recommend combining infliximab with an immunomodulator (methotrexate [MTX] or azathioprine [AZA]) for the first 6–12 months of therapy to improve infliximab trough levels, prevent the reduction of anti-drug antibodies, and improve the durability of infliximab.[68,115,116] In the current ECCO-ESPGHAN guideline for paediatric patients with CD, no recommendation is provided on whether AZA or MTX is the preferred immunomodulator to combine with infliximab. For children with UC, the guideline recommends to start infliximab combination therapy with AZA.[69] There is no clear significant benefit of adding an immunomodulator during adalimumab treatment.[68,117,118]

Interestingly, in contrast to clinical practice in Europe, a combination of AZA and infliximab is seldom used in the USA.[119] There are several disadvantages concerning the use of AZA, including the risk of leukopenia, pancreatitis, and, although very rare, an increased risk of developing lymphoma.[68,120] A recent study compared infliximab trough levels and clearance in a cohort of children with CD within the USA, who received optimized infliximab due to proactive therapeutic drug monitoring, and a cohort of children with CD in Europe who received infliximab combined with AZA. Optimized infliximab dosing [of patients with a measured trough level <5 µg/mL at the fourth infusion, 54% of patients received intensified infliximab dosing] vs infliximab plus AZA combination therapy showed no difference in infliximab trough levels or clearance during the first 22 weeks after starting infliximab.[121] In future practice, further optimization of infliximab dosing [e.g. using pharmacokinetic dashboards]

is likely to reduce the likelihood of antibody formation and increase durability of infliximab. This might possibly replace the need for adding an immunomodulator when starting infliximab.

In paediatric IBD, high infliximab and adalimumab trough levels are associated with improved clinical outcomes.[116,122] Because of the clear exposure–response relationship for anti-TNF, it is important to monitor anti-TNF trough levels. Therapeutic drug monitoring [TDM] of anti-TNF trough levels can be either reactive, when determined in case of loss of response, or proactive, when determined irrespective of disease status. A recent comprehensive review on TDM in paediatric IBD stated that the benefit of reactive TDM has been widely accepted, while data on proactive TDM in paediatric IBD are scarce.[123] Several large trials in adults with IBD have not shown a benefit of proactive TDM, emphasizing the need for paediatric trials. However, two studies in paediatric patients with CD (one prospective randomized control trial [RCT] and one retrospective study) have shown benefit of proactive TDM.[123–125] According to the current ECCO-ESPGHAN guidelines, it is recommended to obtain a trough level before the fourth infliximab infusion or before the third adalimumab injection.[68] In case anti-drug antibodies are detected, these may be resolved by intensifying the dose or adding an immunomodulator.[126,127]

6.2. Timing of anti-TNF treatment

Starting effective treatment from diagnosis onwards is crucial to minimize complications in paediatric IBD.[128] A shift towards earlier use of biological treatment in the disease course of children with CD has occurred in the past few years. A systematic review, including five studies on paediatric CD, showed that early initiation of anti-TNF treatment had a beneficial effect on clinical remission, relapse rate, and mucosal healing in paediatric CD.[129] Additionally, an RCT showed that in children with moderate-to-severe CD, first-line infliximab [consisting of five infusions of infliximab with AZA maintenance therapy] was more effective compared to conventional treatment [EEN or prednisolone with AZA maintenance]. After 52 weeks, 19/46 patients treated with first-line infliximab were in clinical remission without treatment intensification compared to 7/48 patients with conventional treatment [$p = 0.004$].[130] Furthermore, a recent prospective observational study which included 331 children with CD showed that early anti-TNF [initiated <90 days from diagnosis] resulted in higher rates of sustained steroid-free remission without treatment intensification at 1 year compared to patients not receiving early anti-TNF treatment.[131] In children with UC, no clear advantage of early anti-TNF treatment has been shown. However, there are limited paediatric data on early vs late anti-TNF therapy in UC.[132]

7. Non-anti-TNF biologicals, small molecules, and dual targeted therapy

Of paediatric patients starting anti-TNF therapy, more than 50% continued anti-TNF treatment after 3 years.[133] In case of inadequate or loss of response to anti-TNF treatment, despite dose optimization, subsequent treatment options are vedolizumab and ustekinumab for both UC and CD.[68,69] For children with UC, tofacitinib is another treatment option.[69] None of the three aforementioned drugs has yet been approved for children with IBD by the EMA and are, thus, prescribed off-label.

7.1. Non-anti-TNF biologicals

Ustekinumab is an IL-12 and IL-23 inhibitor.[68] A systematic review showed that for both paediatric CD [based on three studies, 96 patients] and UC/IBD-U [based on two studies, 35 patients] ~45% of patients achieved CS-free clinical remission at 1 year when receiving ustekinumab. Almost all patients were treated with biologicals before starting ustekinumab.[134]

Vedolizumab is an α4β7 integrin antibody and inhibits the adhesion of the gut-homing subset of T lymphocytes to the mucosa.[135] A systematic review showed that the pooled clinical remission at 1 year was 46% in children with CD [based on three studies, 92 patients] and 45% in children with UC/IBD-U [based on three studies, 112 patients] receiving vedolizumab.[135] The largest prospective cohort study assessing the effectiveness of vedolizumab in children with IBD to date is the VEDOKIDS study. This study reported clinical remission rates without steroids or EEN at week 14 of 32% [21/65] in children with CD and 42% [32/77] in children with UC. Furthermore, vedolizumab was more effective in biologic-naïve children and children with UC showed numerically improved disease outcomes compared to children with CD.[136]

The clinical utility of TDM in ustekinumab and vedolizumab treatment is currently being studied. Although there seems to be an exposure–response relationship for ustekinumab in adults with CD, this has not yet been clearly established in children.[137] It remains unclear whether an exposure–response relationship is present for vedolizumab.[138] Hyams *et al*. suggested an exposure–response relationship for vedolizumab in children with UC, but not for children with CD.[139] By contrast, Colman *et al*. showed that in children with CD, patients achieving steroid-free clinical remission at the fourth infusion had higher trough levels compared to patients not in steroid-free clinical remission.[140] Atia *et al*. only showed an exposure–response relationship in paediatric patients with CD <30 kg at week 6.[136]

7.2. Small molecules

Tofacitinib is a Janus kinase [JAK] inhibitor. Recent literature reports promising results for tofacitinib in children with refractory UC. Although prospective and RCTs regarding tofacitinib are lacking in the paediatric field, several retrospective cohort studies stress the importance of tofacitinib in reaching rapid clinical remission and preventing surgery in this group.[141–143] A single-centre retrospective cohort study, including 21 patients <21 years old with UC and IBD-U, showed a clinical response in 43% of patients after 12 weeks of induction therapy with tofacitinib.[142] Furthermore, at week 52, 33% were still on tofacitinib with good clinical response and were steroid-free. There were no thrombi, zoster reactivation, or clinically significant hyperlipidaemia, which are the most important adverse events reported in adult cohorts.[142] One case report showed endoscopic remission after 36 weeks in a child with IBD after exhausting all therapeutic options.[144] Rapid clinical improvement [3 days] is also reported in children suffering from acute severe colitis with conventional treatment failure preventing surgery.[145]

Other upcoming JAK inhibitors in the adult field, such as upadacitinib and filgotinib, are currently rarely used, and only off-label, in the treatment of children with IBD. Nonetheless,

a recent retrospective study including 20 adolescents with CD and UC showed that in 11 patients who started upadacitinib monotherapy, 7/11 achieved steroid-free clinical remission at 6 months. Adverse events were reported in 2/20 patients [cytomegalovirus colitis and hyperlipidaemia requiring treatment].[146] To our knowledge, no studies have yet been published on the efficacy and safety of filgotinib in children with IBD. While awaiting large prospective or RCTs on JAK inhibitors in paediatric IBD, optimal use of real-world data collection in children and adolescents starting these treatment options is required.

7.3. Dual targeted therapy

In case paediatric patients do not respond to any of the aforementioned drugs, another treatment option is to combine advanced treatments. A few studies have been investigating dual targeted therapy in children with IBD.[147] The largest study is a retrospective multicentre study from the paediatric IBD Porto Group. Sixty-two children with IBD who were previously treated with biologicals were included. They received the following combinations of biological therapy: anti-TNF plus vedolizumab or ustekinumab, vedolizumab combined with ustekinumab, or tofacitinib combined with another biological. The clinical remission rate 12 months after the start of dual biological therapy was 63%. In 13% of patients severe adverse events were reported.[148] Additionally, upcoming drugs, such as upadacitinib, can be used as dual therapy as well: favourable outcomes were shown in nine patients using a combination of upadacitinib and ustekinumab or vedolizumab.[146] Dual targeted therapy may be feasible in children with refractory IBD. Nevertheless, this must always be weighed against the risk of combining two strong immunosuppressors.[148]

8. Surgery in paediatric patients with IBD

Besides dietary and biological treatment, abdominal surgery has an important role in the treatment of a selected group of paediatric patients with IBD. Specifically in children, several factors need to be considered to evaluate surgery as the right treatment option, including for example restoration of growth, avoiding courses of corticosteroids, but also psychological consequences, such as distress about stoma and fear.[149] The estimated risk of undergoing abdominal surgery during childhood in patients with CD has been reported to be 58/286 [20%] and 19/220 [9%] in children with UC.[150,151] Data collection for these studies was mainly before the implementation of biological therapy [2002–2012 and 1997–2014, respectively]. The risk of surgery may have decreased since the introduction of biological therapy.[110] However, there is contradictory evidence to this finding suggesting that biologicals may only cause a delay in surgery instead of actually preventing it.[152]

Multiple indications for performing surgery have been previously established. Except for several acute indications [such as large abdominal abscesses, obstruction, or perforation], most surgeries are performed in an semi-elective setting.[149] Generally, surgery is advised when patients still have active disease after optimized drug treatment.[69,153] Interestingly, retrospective and prospective data in adults with CD suggest that an ileocaecal resection may be an option before starting anti-TNF treatment.[154,155] Surgery may be curative for UC, but not for CD. No clear recommendations exist on post-operative treatment in patients with UC. In low-risk patients with CD, not restarting treatment after surgery may be considered, or starting of 5-ASA in case of colonic involvement, or maintenance enteral nutrition or thiopurines. In high-risk patients, it is recommended to start with anti-TNF after surgery.[153] Although abdominal surgery rates are fortunately low, it remains an important treatment option for children with IBD.

9. Transition from paediatric to adult care

As IBD is a chronic and lifelong disease, paediatric patients require transfer to adult care at a certain point in their life. At that moment, patients will encounter a difference in care, including different physicians, location, responsibilities, and expectations. Paediatric care usually is more family focused, is multidisciplinary, and requires parental guidance.[156,157] In adult care, patients are required to be more independent.[156,157] Additionally, other treatment targets are addressed in paediatric care, such as growth and pubertal development, compared to adult care, where for example fertility and cancer screening are issues of concern.[157]

If the transfer from paediatric to adult care is unguided, patient-related problems [such as adherence] can occur and negatively affect the control of the disease and therapeutic relationship. To smoothly guide the actual transfer to adult care, transition of care could be implemented. Transition of care is defined as the period of time in which planned purposeful movement of children with chronic diseases to adult care is organized.[157] Several studies have compared outcomes of patients who transferred from paediatric to adult care with and without a transition process.[158] Patients with transition of care had lower hospital admissions, fewer no-shows, required less surgical intervention, were more likely to be steroid free, used fewer biologicals, had more disease knowledge, and were more likely to adhere to their medication compared to patients without a transition process.[158] These findings have an important message: transition of care should be considered as an essential part of an effective disease management strategy.

Despite the current insights, a survey taken in 2015 showed that 40% of respondents did not apply a formalized transition process.[159] The ECCO-ESPGHAN published a review on organizing transition of care, formulating several practice points. Timing of transition is dependent on regulations by the countries, but is ideally initiated in early adolescence. Furthermore, it is advised to arrange joint paediatric and adult appointments, in both the paediatric environment and the adult care environment. The actual moment of transfer to adult care preferably occurs during stable remission.[159]

Patient readiness is also important for the actual transfer to adult care. For a smooth transition, patients need to acquire various competencies, such as sufficient knowledge about their disease, self-management, and decision-making.[157,159] A top-ten list of the most important factors for a successful transition was formulated through a Delphi procedure involving IBD nurses, patients, and adult and paediatric gastroenterologists. The most important factor for successful transition was decision-making regarding IBD, followed by independent communication by the patient and patient satisfaction.[160] To measure readiness for transition in practice, multiple checklists have been developed. The Transition Readiness Assessment Questionnaire [TRAQ] was identified as the most effective tool to assess transition readiness in a systematic review conducted in 2014.[161] The TRAQ is a questionnaire for patients incorporating questions about self-management and

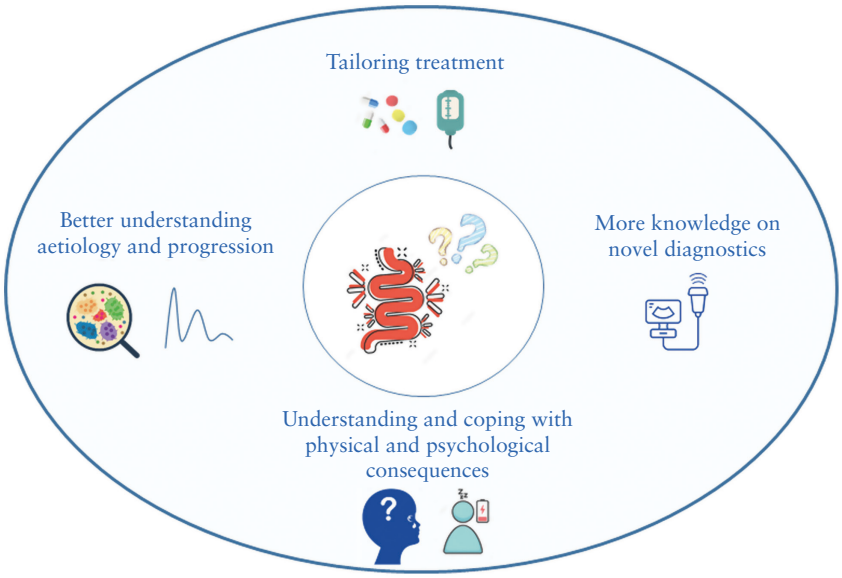

Figure 2. Overview of current research gaps in paediatric inflammatory bowel disease.

self-advocacy.[162] A higher score indicates a better transition readiness. It must be noted that this questionnaire is self-reported by the patient and could over- or underestimate its own readiness. Factors associated with higher TRAQ scores and therefore better transition readiness were older age, no concomitant, and more visits to the transition clinic.[162,163]

In summary, transition is essential for providing good quality of care and should be organized within each centre. Awareness among both paediatric and adult gastroenterologists regarding the urgency and added value of a guided transition process is needed for the organization.

10. Challenges in research and research gaps in paediatric IBD

Although care for children with IBD has improved considerably over the past decades, there are still major knowledge gaps and challenges. In 2019, a comprehensive overview was published on research gaps and challenges within IBD research. Authors stated five topics of interest, which included preclinical human IBD mechanisms, environmental triggers, novel technologies, precision medicine, and pragmatic clinical research.[164] Additionally, Jagt *et al.* formulated a top 10 research priorities in children and young adults with IBD. The priorities were selected based on input from a panel which included patients, their caregivers, and healthcare professionals. Priorities included [1] improved understanding of the aetiology and progression of IBD, [2] tailoring treatment to the individual paediatric IBD patient, [3] more knowledge on novel diagnostics of IBD, and [4] better understanding of and coping with psychological and physical consequences of IBD, such as fatigue.[165] Several solutions and ideas to reduce these research gaps and hurdles within IBD research have been identified and are discussed below.[166,167] Figure 2 graphically represents an overview of the research gaps within paediatric IBD.

(1) To obtain more knowledge on the aetiology of IBD, one promising option that researchers have proposed is exploring disease models that reflect human IBD in addition to animal models. Two novel *in vitro* disease models are organoids and gut-on-a-chip.[166] An organoid is a 3D tissue that is self-organized, and most often derived from stem cells. Organoids partially mimic the key functions and structure of a specific organ.[168] Unfortunately, they lack the complexity of the *in vivo* intestine. For example, organoids do not have blood vessels, and none of the organoids fully represent the entire function of the gut.[168,169] Another recent advancement in technology is 'gut-on-a-chip'. This is a microfluidic cell culture device and better enables mimicking the gut physiology compared to organoids.[169] Both organoids and gut-on-a-chip are promising *in vitro* models that can be used for future research.[169,170]

(2) Within the last few decades of paediatric IBD care, an important goal is to achieve more tailored treatment. The heterogeneity of IBD hampers the prediction of individual treatment response and disease course. Effective treatment at an early stage is essential to prevent development of disease complications.[128] As there are limited treatment options in paediatric IBD, it is important to optimize those treatments to increase durability of the therapy. In two systematic reviews within the paediatric IBD-ahead programme, several predictors for poor outcomes have been assessed for both paediatric CD and UC.[55,171] These predictors include demographic features [age, ethnicity], growth, clinical disease activity scores, laboratory results [including anti-microbial serology, such as ASCA/ANCA, CBir1 and OMpC], disease location, and gene polymorphisms [such as NOD2]. Nonetheless, these factors do not fully capture the heterogeneity of the disease. The exposome [environmental factors], genome, microbiome, and 'immunome' have been studied extensively and are known to play a large role in the aetiology of IBD.[172–174] Additionally, components possibly contributing to the development of IBD are increasingly studied, such as the epigenome, transcriptome, proteome, and metabolome.[173,174] Combining these fields of research [the -omes] is considered to be multi-omics. Research including multi-omic analyses is essential to obtain a better understanding of the

pathogenesis and, subsequently, the heterogeneity of the disease and to be able to predict disease and treatment outcomes.[174] Of note, Atia *et al*. showed that several predictive models of disease outcomes in children with CD achieved insufficient accuracy when applied to another cohort.[175] Therefore, predictive models should be internally and externally validated before being implemented in clinical practice.

(3) Further research on novel technologies for diagnosing and monitoring IBD is required. Treatment goals of IBD include clinical and biochemical remission, restoration of quality of life, and mucosal and transmural healing.[67] Available and frequently used methods for monitoring disease activity of IBD are clinical disease activity, laboratory tests (including CRP, erythrocyte sedimentation rate [ESR] and albumin), faecal calprotectin, and magnetic resonance imaging [MRI] enterography or endoscopy. Each of these tests has several disadvantages. Clinical disease activity poorly correlates with ongoing inflammation in the mucosa, especially in patients with CD.[67] Furthermore, although calprotectin correlates well with endoscopy, no linear correlation exists with mucosal inflammation.[68] A disadvantage of MRI enterography and endoscopy, especially for children, is that these are invasive diagnostic and monitoring tools.

An upcoming modality to monitor disease activity is the intestinal ultrasound [IUS].[68] This is a non-invasive, non-painful, and fast measurement to assess disease activity and might, therefore, even be more beneficial in children than in adults. A systematic review [based on four studies] assessing the diagnostic accuracy of IUS in detecting intestinal inflammation in children with IBD showed that the sensitivity and specificity of IUS in comparison with ileocolonoscopy was 48–93% and 83–93%, respectively.[176] IUS may play a major role in the future of monitoring IBD disease activity in children. However, as stated by the expert consensus of the International Bowel Ultrasound Group Paediatric committee, more research is required to obtain standardized measures.[177]

Lastly, models combining outcome measures could improve monitoring of IBD.[67] A recent study showed that combing faecal calprotectin, abdominal ultrasound, and colon capsule endoscopy had high diagnostic accuracy in comparison with ileocolonoscopy.[178]

[4] Another knowledge gap in paediatric IBD is the understanding of and coping with physical and psychological consequences of IBD. Fatigue has been found to be an important predictive factor for a low quality of life in children with IBD[179,180] and is considered to be multifactorial. Sleep, physical activity, disease activity, and behavioural and psychological characteristics play a role. Limited research has been conducted regarding these domains specifically.[179] Marcus *et al*. stated that paediatric IBD patients might have significantly higher sleep disturbance rates, also during inactive disease.[180] Several studies report a correlation between disease activity and complaints of fatigue whilst other studies do not find this association.[59,180] In general, active inflammation and immune activation are known to cause fatigue in autoimmune disorders.[181] Furthermore, family support and psychosocial factors influence fatigue and vice versa. The influence of behavioural and lifestyle factors is supported by a small but interesting study of Scheffers *et al*.[182] In a 12-week intervention programme, including healthy diet and physical activity, in 15 children with IBD, the fatigue score and quality of life were significantly improved.[182]

Lastly, an important challenge in paediatric IBD research that needs to be addressed is the major delay in approval of drugs for children with IBD compared to adults. As mentioned before, infliximab and adalimumab were approved with a 6- to 8-year delay for paediatric IBD compared to adult-onset IBD. Vedolizumab, ustekinumab, and tofacitinib/JAK inhibitors are not yet approved by the EMA for paediatric IBD.[109] Croft *et al*. showed that there is an average delay of 7 years between approval for drugs in adults and children with IBD, and stated this delay to be unacceptable.[109] Delay in approval increases the off-label use of these drugs which is potentially dangerous, and associated with an increased occurrence of adverse drug reactions.[183] Also, in some countries it is difficult or not possible to prescribe drugs off-label, which further minimizes treatment options for children with IBD.[109] One of the identified barriers contributing to the delay in approval is the relatively small pool of paediatric patients with IBD. The pool of patients to be included for research is even further reduced since patients who are not therapy-naïve or are treated with the current off-label drug are often excluded.[109] Since it is generally accepted that the mechanism of treatment is similar in adults and children, future studies should focus especially on pharmacokinetic features in children,[184] including dose and frequency. Trials comparing new drugs with placebo are generally considered to be unethical in children with IBD, as placebo is not an equipoise of current available treatment.[184] Several actions have been proposed to shorten the delay in drug approval, including discussing extrapolation from adult data in paediatric IBD, expanding the paediatric pool by international cohort studies, and prioritizing investigational drugs in new clinical trials.[109]

11. Conclusion

Paediatric IBD is a lifelong disease and often presents with a more extensive and severe disease course compared to adults. The incidence of paediatric IBD is rising, and is accompanied by an increased healthcare and cost burden. Early and effective treatment is essential to obtain and maintain disease remission and increase quality of life. Transition of paediatric to adult care is required for continuation of good quality of care and adherence. Therapy needs to be individualized taking into account the stages of life passed in paediatric IBD. Ongoing research incorporating various -omics is upcoming to identify more reliable predictors of disease course and treatment response. These research gaps should be addressed without delay as in adults, so all patients with IBD will receive the highest quality of care.

Funding

This paper was published as part of a supplement supported by an independent education grant from Pfizer.

Conflict of Interest

L. de Ridder has received institutional research support from Pfizer, Medtronic, Abbvie, Janssen, Eli Lilly, Takeda, Crocokids, and Kiddy Goodpills, all unrelated to content of this paper. S.A. Vuijk report grants from Pfizer, Crocokids, and

Kiddy Goodpills, all unrelated to content of this paper. A.E. Camman report grants from PIBD-NET, Stichting Vrienden van Sophia, and Stichting Autoimmuun Onderzoek, all unrelated to content of this paper.

Acknowledgments

The figures have been created or edited based on figures of PNG tree and the noun project. Figures can be found at: elderly PNG Designed By 58pic from https://pngtree.com/freepng/elderly-child-disabled-silhouette_4383628.html?sol=downref&id=bef, human organ intestine PNG Designed By 58pic from https://pngtree.com/freepng/human-organ-intestine-illustration_5456036.html?sol=downref&id=bef, flathuman PNG Designed By dwizkyindra from https://pngtree.com/freepng/flat-adult-people-hand-drawing-illustration_5424776.html?sol=downref&id=bef, DNA created by Soba Mustache from Noun Project from https://thenounproject.com/icon/dna-2029312/, pollution created by callorine from Noun Project from https://thenounproject.com/icon/pollution-2950364/, school created by Shashank Singh from Noun Project from https://thenounproject.com/icon/school-3233076/, growth icons PNG Designed By hublot90 from https://pngtree.com/freepng/development-icon-child-growth-stages-toddler-milestones-of_3641257.html?sol=downref&id=bef, length created by Adrien Coquet from Noun project from https://thenounproject.com/icon/tall-2636088/, growth icons PNG Designed by hublot90 from https://pngtree.com/freepng/development-icon-child-growth-stages-toddler-milestones-of_3641257.html?sol=downref&id=bef, pregnant woman created by icronfield from Noun Project from https://thenounproject.com/icon/pregnant-4504538/, colon cancer screening created by Amethyst Studio from Noun Project from https://thenounproject.com/icon/colon-cancer-screening-5873697/, delay created by Adrien Coquet from Noun Project from https://thenounproject.com/icon/delay-3734223/, check mark created by Icons By Alfredo from Noun Project from https://thenounproject.com/icon/check-mark-3600091/, take medicine PNG designed by Jason from https://pngtree.com/freepng/tablet-treatment_3220036.html?sol=downref&id=bef, ultrasound created by N. Style from Noun Project from https://thenounproject.com/icon/ultrasound-3340045/, fatigue PNG designed by artsbyfanny from https://pngtree.com/freepng/fatigue-tiredness-covid-19-symptoms-vector-icon_6275547.html?sol=downref&id=bef, bacteria clipart PNG designed by 588ku from https://pngtree.com/freepng/magnified-cartoon-bacteria-illustration_4524950.html?sol=downref&id=bef, and question mark PNG designed by 588ku from https://pngtree.com/freepng/tricolor-minimalist-style-question-mark_4488723.html?sol=downref&id=bef. Premium figure of gut and psychological consequences can be found at: https://pngtree.com/freepng/comicstyle-icon-of-gut-constipation-and-colitis-on-white-background-vector_12384103.html, https://pngtree.com/freepng/child-and-career-mom-symbol_14411142.html, https://pngtree.com/freepng/bowel-ache-body-irritable-vector_10552264.html.

Author Contributions

SAV, AEC: concept of review, literature search, writing first draft of the paper, reviewing, figures, critical revision of the manuscript for important intellectual content, final approval of the version to be submitted. LdR: concept of review, writing, reviewing, critical revision of the manuscript for important intellectual content, final approval of the version to be submitted.

Data Availability

No new data were generated or analysed in support of this research.

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