Review Article

# Dietary Treatment for Crohn's Disease—Old Therapy, New Insights

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## Abstract

Crohn's disease in childhood accounts for about 25% of the overall prevalence of this condition, and compared with adult-onset disease has unique characteristics in being more likely to involve the colon, being more aggressive in behavior, and requiring early escalation of therapy. Exclusive enteral nutrition has proven to be an effective therapy, especially in children. There are various hypotheses regarding mode of action; however, the precise mechanisms are yet to be established. The aim of this paper is to provide an up-to-date review of the efficacy and mechanism of action of exclusive enteral nutrition in Crohn's disease. A PubMed search was performed using the terms 'mechanism of action', 'exclusive enteral nutrition', 'partial enteral nutrition', 'nutritional therapy', 'children', 'paediatric', 'Crohn's disease'. Relevant articles were selected from this search. In addition, the reference lists of these papers were scrutinized for further relevant publications. There is significant evidence for efficacy of exclusive enteral nutrition and some evidence for a number of mechanisms, including alteration of the gut microbiome, a direct anti-inflammatory effect at the mucosal level, and through alteration in the fat content within the diet. Exclusive enteral nutrition provides benefits beyond disease remission, especially through promoting growth; further studies are required to elucidate exactly how it works and the longer-term outcomes. This is particularly important given the lack of negative effects compared with the significant side-effect profile of biological therapies. Improving resources to minimize the psycho-social impact of exclusive enteral nutrition may open the way for wider use in adult patients through the development of solid diet alternatives to liquid feeds.

## Introduction

Exclusive enteral nutrition (EEN) is a nutritional therapy used for treatment of Crohn's disease (CD), particularly in children. In practical terms, it requires stopping all usual foods and substituting an exclusive liquid low-residue feed, using either a polymeric or an elemental formula as the sole source of nutrients for 6 to 8 weeks. Historically, use of EEN aimed at improving nutritional status of patients with inflammatory bowel disease (IBD), especially in those who were not amenable to surgical treatment. The observed reduction in symptoms with EEN was thought to be secondary to improvements in nutritional status. In the 1970's, a group of surgeons first reported efficacy of EEN in CD, when they treated 13 patients with elemental diet and showed a significant decrease in the inflammatory markers in a majority, along with nutritional improvement[1]; at that time, steroids continued to be the mainstay of treatment. In 1982, Navarro *et al*.[2] was able to show that EEN in pediatric CD induced remission and decreased steroid dependency. In addition, prolonged EEN (from two to seven months) was able to reduce or resolve stenotic bowel disease.[2] O'Morain published the first controlled trial in 21 adults in 1987,[3] wherein an elemental diet given for four weeks was compared with oral steroids and showed that the efficacy of EEN in inducing remission was similar to that of treatment with corticosteroids.

Rigaud *et al*.[4] (1991) conducted a prospective randomized clinical trial (RCT) with elemental or polymeric diet for four to six weeks in 30 steroid-unresponsive CD patients and showed significant improvement in mucosal lesions seen at colonoscopy, inflammatory markers and nutritional state on follow-up; however, the majority of patients suffered relapse within a year. In a double-blind RCT, Royall *et al*.[5] compared amino acid with peptide-based formula in adults with CD over 3 weeks and showed that the rate of clinical remission in the two groups was similar. In 1997, Zoli *et al*.[6] published a RCT showing that, in adult CD, EEN was as effective as steroids in initiating clinical remission. These authors hypothesized that the mechanism of action was probably secondary to the effects of EEN in normalizing intestinal permeability.[6] A multicenter RCT, wherein 33 children with CD were rand-

**Keywords:** Exclusive enteral nutrition**;** Crohn's disease**;** Nutritional therapy**;** Pediatric**;** Adult**;** Inflammatory bowel disease.

**Abbreviations:** CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; ECCO, European Crohn's and Colitis Organization; EEN, exclusive enteral nutrition; FODMAP, fermentable oligo-, di- and monosaccharides and polyols; IBD, inflammatory bowel disease; IFX, infliximab; IP, intestinal permeability; OR, odds ratio; PCDAI, pediatric Crohn's disease activity index; PEN, partial enteral nutrition; RCT, randomized clinical trial; SCD, specific carbohydrate diet; SFD, solid food diet; TNFα, tumor necrosis factor alpha.

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omized to receive either elemental or polymeric formula, showed no significant differences in remission rates of the two groups.[7] A Cochrane meta-analysis in 2007, which included six studies with 192 patients receiving EEN and 160 patients receiving steroids, showed that steroids were superior to EEN in inducing remission (with an odds ratio (OR) of 0.33 and 95% confidence interval (CI) of 0.21 to 0.53).[8]

## EEN in current management of CD

There is clearly some variation in clinical practice as far as EEN management is concerned. An international survey in childhood CD found that 23 different liquid feed formulas were being used among the units that responded.[9] There were also variations in the length of therapy, with some centers prescribing EEN for four to six weeks and others for six to eight weeks. Not only did the liquid feeds differ but some centers used polymeric and other elemental formulas also, and some preferred nasogastric to oral feeding. There are no specific controlled trials comparing the efficacy of EEN that have been based on types of formula feed or duration of treatment. In some centers, semi-elemental diets are used[10]; although, these have been largely superseded by polymeric feeds, which are more palatable and more likely to be taken by mouth. The period of EEN is followed by a gradual introduction and escalation of a low-residue diet (*i.e.* low-fiber diet, limiting foods like raw fruits and vegetables), usually over a few days; however, the literature regarding reintroduction of foods is very limited, and speed of return to usual diet varies from a few days to several weeks. The optimal method of food reintroduction has yet to be established.[7] There is some evidence to suggest a beneficial effect in CD from combining partial EEN together with usual diet and immunosuppressive medications.[11]

## Efficacy of EEN in CD

### *Induction of remission at new diagnosis*

There are no RCTs comparing EEN with placebo in pediatric CD. EEN, when compared to steroids in multiple clinical trials subjected to meta-analysis, has shown an overall induction of remission rate of around 75%. Pediatric trials and two meta-analyses also demonstrate similar efficacy of both EEN and corticosteroids in inducing remission.[12–15] Schwab *et al*.[14] performed a meta-analysis of 15 studies which included 571 patients receiving EEN and concluded that there was no difference in the remission rates between EEN and corticosteroid-treated groups. In addition, the meta-analysis showed that the efficacy of elemental and polymeric diets was similar.[16] A further pediatric meta-analysis, which included five pediatric trials involving 147 children, showed that EEN and corticosteroids had similar efficacy. In children, better compliance was found with elemental and semi-elemental diets compared to adults, who had a high drop-out rate of 40%.[17]

Dziechciarz *et al*.[13] analyzed four RCTs involving 144 pediatric patients and showed the remission rates in the EEN and corticosteroid groups were similar (relative risk of 0.97, 95%CI: 0.7–1.4). In contrast, the 2007 Cochrane meta-analysis by Zachos *et al*.,[8] which included both pediatric and adult trials comparing EEN to corticosteroids with 192 patients receiving EEN and 160 receiving corticosteroids, demonstrated a pooled OR of 0.33 (CI 0.21–0.53), favoring corticosteroid therapy. The same meta-analysis also looked at 10 trials involving 334 patients, and showed no difference in the efficacy of elemental versus non-elemental formula (OR of 1.10; 95% CI: 0.69–1.75). A North American Pediatric Gastroenterology, Hepatology and Nutrition working group on IBD has examined this meta-analysis and raised questions over-interpretation. They found that many of the pediatric trials that had been excluded for methodological reasons showed that EEN had similar or higher efficacy than the steroids. The difference in the results from trials in adult patients showing lower rates of remission compared to pediatric studies are probably due to lower compliance rates with EEN and possibly less experience among adult gastroenterology teams with supporting the use of this treatment.[10]

Of additional interest is the study by Sigall-Boneh *et al*.[16] showing that partial enteral nutrition (PEN) can also lead to high remission rates in both children and adults with CD. Forty-seven patients (34 children, 13 young adults) with mild to moderate CD were treated with a 6-week structured CD exclusion diet, wherein they had access to certain solid foods and restricted exposure to other foods, and derived 50% of their caloric intake from a polymeric formula (*i.e.* the PEN). Response was seen in 78% and remission in 70% of these patients, as measured by decrease in the Harvey-Bradshaw index and pediatric Crohn's disease activity index (PCDAI), in addition to normalization of C-reactive protein (CRP). There was no significant difference in remission rates for the groups of pediatric and young adult patients.[18]

Based on the above evidence, the current European Crohn's and Colitis Organisation (ECCO) and European Society of Paediatric Gastroenterology, Hepatology and Nutrition consensus guideline from 2014 recommends the use of EEN as first-line therapy to induce remission in children with active luminal CD, and against using PEN.[19] For adult CD, the ECCO evidence-based consensus from 2017 recommends using systemic corticosteroids as first-line therapy.[20] The European Society of Parenteral and Enteral Nutrition currently also considers that EEN is not proven to be effective in inducing remission in adults with CD. The more limited data from adult CD patients on inducing remission is different from pediatric experience, probably due to lesser experience and expertise in EEN use, and lower compliance rates–problems that will require significant resources, such as more dietetic support, to address.[21]

### *Re-induction of remission in patients with relapsed disease or disease flare-ups*

The relapse rates in patients treated with EEN at initial diagnosis and going into remission are between 60–70% within the first year.[15,22] Seidman *et al*.[21] and Day *et al*.[22] performed studies including children with relapsing CD; the results showed that efficacy of EEN in inducing remission during a relapse was 50%, with five out of 10 and seven out of 12 patients, respectively, responding. Both studies noted that even in children who were non-responders to EEN the disease activity decreased and nutritional status improved. A randomized trial involving 32 adult patients with active CD showed similar remission rates for the patients receiving EEN and those receiving corticosteroids. However, after follow-up for one year, there was a higher relapse rate in patients who received EEN, as compared to the steroid-treated group.[23] Grogan *et al*.[15] performed a double-blind RCT of EEN in 34 children with CD, with the treatment given over a six week period; patients with large bowel disease alone were excluded from the study. The authors compared the efficacy of polymeric to elemental enteral feed, with a 2-year follow up period. There were no significant differences in the clinical and biochemical remission rates between the

**Table 1. Practice points on exclusive enteral nutrition in Crohn's disease**

| | |
|---|---|
| Choice of formula | Polymeric |
| Route of administration | Oral/nasogastric tube or combination |
| Duration of feeds | 6 to 8 weeks |
| Markers of efficacy | Symptom reduction, weight gain, normalization of CRP and fecal calprotectin |
| Reintroduction of regular food | 1 to 4 weeks |
| Partial enteral nutrition in remission | Preferable |

Abbreviation: CRP, C-reactive protein.

two groups. Two-thirds of children in both groups relapsed within a year; the majority of children (82%) who relapsed used EEN as treatment for relapse. There are no studies showing EEN efficacy during flare-ups in patients who did not receive EEN during initial presentation or who are EEN-naïve. Other issues for investigation are whether EEN-exposed patients naturally perform worse on EEN therapy after a second or a third flare-up and whether this is secondary to poor compliance or mucosal changes with chronic disease.

### *Maintenance of remission*

The role of EEN as maintenance therapy is unclear. There have been multiple studies examining the use of PEN as a possible way of prolonging remission. Verma *et al*.[24] concluded from their study of 30 adult CD patients that PEN is safe, well-tolerated and effective in quiescent CD, and showed significant reduction in relapse rates based on disease activity scores. A prospective study in 2010 highlighted that concomitant PEN during infliximab (IFX) maintenance therapy does not significantly increase the maintenance rates of clinical remission.[25] A multicenter trial in Japan recruiting 102 patients showed that PEN combined with IFX maintenance use was associated with significantly reduced relapse rates, as compared to IFX alone.[26]

Esaki *et al*.[27] performed a single-center retrospective study in adult CD patients who had entered remission after parenteral nutrition. One group received more than 1200 kcal per day from supplementary nutrition (the 'enteral nutrition' group), and another group received less than 1200 kcal per day from supplementary enteral nutrition (the 'non-enteral nutrition' group). The authors concluded that clinical remission can be prolonged by supplementary nutrition (with relapse rates higher in the 'non-enteral nutrition' group), and that the risk of relapse in the 'enteral nutrition' group was significantly increased if they had penetrating CD or had undergone previous surgery.

A recent systematic review of 12 studies including 1,169 patients (95 of them children) with inactive CD concluded that PEN was more effective than a regular diet and that PEN used in combination with standard immunosuppression produced results either better than or as effective as the comparator group without the PEN.[28] Sigall Boneh *et al*.[29] reported on 21 children and adults with CD who had lost response to biologics and were treated with PEN using a polymeric formula after two weeks of EEN. The study subjects were allowed an oral diet based on fruit, vegetables, meats and complex and simple carbohydrates (termed the Crohn's Disease Exclusion Diet) (Table 1), which was hypothesized to modify the microbiome or intestinal permeability. Clinical remission, as measured by the Harvey-Bradshaw index, occurred in 62% of the children, along with decreased inflammation, as shown by biochemical evidence (*i.e.* reduction in CRP and increase in mean serum albumin concentration). The authors concluded that nutritional treatment, which combines an exclusion diet based on a range of solid foods together with PEN, might be an effective salvage therapy in some patients.

These studies collectively suggest that the quantity of enteral formula feed used is important. The higher the calories provided by the enteral formula, the higher were the remission rates[29]; however, large RCTs are necessary to define the role of manipulation of enteral nutrition for the maintenance of remission in CD. In contrast, Johnson *et al*.,[30] who looked at 50 children with active CD based on PCDAI >20, showed that long-term PEN does not suppress bowel inflammation and is unlikely to prevent disease relapse. The authors randomly recruited patients to receive total caloric requirements from either 50% PEN from elemental formula with unrestricted regular diet or 100% of calories from EEN with an elemental formula. At follow-up, clinical disease scores (*i.e.* PCDAI) and biochemical parameters (*i.e.* CRP, serum albumin, platelet count, erythrocyte sedimentation rate) of disease remission were recorded in both groups for comparison. The remission rate with PEN was significantly lower than that with EEN (15% *vs*. 42%, $p = 0.035$). While the PCDAI fell in both groups, the reduction was significantly greater in the EEN group. The authors concluded that the benefits in the PEN group were secondary to symptomatic and nutritional improvements and not to anti-inflammatory effects.

## Solid food-based diets

### *Specific carbohydrate diet (SCD)*

The SCD is a grain-free diet, which is low in sugar. Its design is based on the hypothesis that complex carbohydrates (polysaccharides and oligosaccharides) are poorly absorbed and promote gut bacterial overgrowth, which then acts as an inflammatory signal causing mucosal damage, worsening the carbohydrate malabsorption and perpetuating an inflammatory cascade. The SCD restricts carbohydrate intake, and a gluten-free diet would be one example of such a diet.[31] Suskind *et al*.[31] performed a retrospective review of 26 children (20 CD, 6 ulcerative colitis) attending an IBD center where patients followed a SCD for between three and 48 months. There was a significant decrease in the disease activity scores (PCDAI and the Pediatric Ulcerative Colitis Activity Index) at 6 months. Mutlu *et al*.[32] reported a case series of 50 adult IBD patients who went into remission when following a SCD over a mean time-period of 35 months and who were able to maintain remission. However, symptom reduction was not correlated with objective markers of gut inflammation, like fecal calprotectin or mucosal healing, and symptomatic response by itself was found to be clearly not adequate for assessment of an anti-inflammatory

effect of diet.

### *Fermentable oligo-, di- and monosaccharides and polyols (FODMAP) diet*

The FODMAP diet is based on the hypothesis that a low FODMAP diet would result in reduction of bowel bacterial overgrowth, and thus prevent secondary mucosal damage.[33] The FODMAP diet restricts ingestion of vegetables and certain fruits, while the SCD allows for unrestricted fruit and vegetables, with the exception of potatoes and yams. The literature supporting the use of the FODMAP diet in IBD is very limited. A retrospective study involving 72 adult patients with IBD showed a decrease in gastrointestinal symptoms, namely abdominal pain, bloating and stool frequency, after starting a FODMAP diet.[34] A prospective study concluded that a FODMAP diet was an effective strategy in IBD, in the main, by improving symptoms secondary to superimposed irritable bowel syndrome.[35] They showed that 50% of patients (52 CD, 20 ulcerative colitis) on low FODMAP intake responded with significant reduction in abdominal symptoms, abdominal pain, bloating, wind and diarrhea, and the response showed a direct correlation with dietary adherence in CD patients.[36]

### *IgG4-guided exclusion diet*

IgG1 and IgG4 are dominating subclasses of antibodies to food antigens, and IgG4 is produced following chronic exposure to the antigen. Patients with CD have significantly higher levels of IgG4 responses to food antigens.[37] It has been hypothesized that targeted IgG4-based exclusion diet may reduce the inflammatory response in CD patients and may present a method of personalizing an exclusion diet. A sham-controlled randomized trial recruited 145 active CD patients and showed that those who received an IgG4-guided exclusion diet for four weeks, based on exclusion of four food types with highest antibody titers, had significant improvement in their quality of life scores, as compared to the sham diet control group.[38]

### *Paleolithic diet*

This diet is based on the hypothesis that current diseases are a consequence of exposure to processed foods produced by modern agricultural advances and, therefore, dietary treatment should involve increasing intakes of lean, non-domesticated meats and non-cereal plant-based foods, like roots, nuts, legumes and fruits. There is no data on use of such a diet in IBD.

## Family perceptions of diets

A recent study in a pediatric gastroenterology center looked at the experience of families and children around EEN and their thoughts about potential solid food diet (SFD) alternatives. The majority of families (59%) with experience of EEN were happy to use this treatment again, in the event of a future relapse of CD. This most likely reflects their experience of the efficacy of EEN, improved palatability of polymeric feeds, and the expertise of the pediatric healthcare professionals involved in providing support.[39] Many families had already experimented with dietary modification of some sort, as a way of controlling symptoms. The survey supports previously published literature, that, if effective, most families would prefer to use a SFD than liquid formula for EEN.[40]

## Mechanism of action of EEN

In children with CD, EEN is as effective as corticosteroid therapy but without the side effects. Although the precise mechanism of action remains unknown, there are various hypotheses based on what is known about the pathophysiology of CD. The pathogenesis involves an interaction between a genetic susceptibility, immunology of the host and its mediation in causing tissue injury or tissue healing, and environmental factors. The hypotheses are: restoration of cytokine balance between pro- and anti-inflammatory cytokines; a direct effect on gut mucosa; modification of gut flora; change in fat composition of diet influencing the pro- and anti-inflammatory mediators; and, enhancement of nutritional status and 'bowel rest' (including avoidance of multiple food antigens found in normal diet). Here, we review the evidence behind the above postulates on mechanisms of action.

### *Restoration of cytokine balance*

There is evidence that in CD, EEN decreases intestinal permeability (IP), and that increased IP precedes relapse of CD symptoms and may represent ongoing disease.[41–43] Wyatt *et al*.[41] showed that patients who had normal IP could maintain a prolonged remission. The authors measured IP in 72 patients with CD who were in remission, using the lactulose-mannitol test, and found that the permeability index was significantly higher in CD patients than in controls. These patients were followed-up for 1 year. It was found that 70% of those with increased IP relapsed, while only 17% with normal IP did so, suggesting that raised IP represents subclinical disease. These studies did not investigate the relationship between IP and objective markers of inflammation.

Teahon *et al*.[42] showed that 26 out of 37 CD patients with high IP relapsed within a year; however, only a very small proportion of patients with normal IP suffered a clinical relapse. Tumor necrosis factor alpha (TNFα) has previously been shown to be involved in disruption of cellular tight junctions, and thereby to increase IP.[44,45] Nahidi *et al*.[44] demonstrated that the TNF-exposed intestinal CaCo-2 monolayers with increased IP showed a complete reversal of the changes induced by TNF when treated with EEN and biologic agents like IFX, including restoration of IP. A similar experiment with corticosteroids showed only partial reversibility of the changes caused by TNF.[44]

There is now increasing evidence that various proinflammatory cytokines, such as interleukin-1β, interleukin-8 and interleukin-γ, are down-regulated by EEN. An *in vitro* model used by de Jong *et al*.[46] showed that EEN had a direct action on colonic enterocytes and reduced production of TNF and interleukin-8 when enterocytes were exposed to proinflammatory cytokines. These anti-inflammatory effects were not affected by boiling or freeze-thawing of the EEN formula, demonstrating that exposing EEN to the above conditions does not alter its effect.

### *EEN and mucosal healing*

There is emerging evidence that mucosal healing improves both short-term and long-term outcomes in CD and may change the natural history of the disease. In the short term, mucosal healing has been associated with reductions in CDAI and reduced steroid use. In the medium and long terms, mucosal healing has been shown to be as-

**Table 2. Gut microbiome changes induced by exclusive enteral nutrition**

| Increased during EEN | Decreased during EEN |
|---|---|
| Firmicutes | |
| Relative abundance of Firmicutes[58] | Concentration of *F. prausnitzii*[56] |
| Bacteroidetes | |
| Concentration of *Alistipes*[59] | Concentration of *Bacteroides/Prevotella*[56] |
| Actinobacteria | |
| Concentration of *Bifidobacterium*[59] | Concentration of *Bifidobacteria*[56] |

Abbreviation: EEN, exclusive enteral nutrition.

sociated with longer periods of remission, a reduced complication rate and a decrease in hospitalizations and surgical interventions.[47,48]

A prospective 10-week randomized, open-label trial in 37 pediatric patients comparing polymeric formula ($n$ = 18) with steroids ($n$ = 19) showed reduction in CDAI scores in both groups, with no significant difference in clinical remission rates; however, the number of patients showing mucosal healing was significantly higher in the EEN group (74%) compared to the steroid group (33%).[14] Another study looking at the mechanism of action of a specific polymeric formula (rich in transforming growth factor-β2) on mucosal healing demonstrated endoscopic improvement after 8 weeks of EEN in 29 children. Cytokine mRNA in mucosal biopsies before and after treatment with EEN indicated that 79% of children were in remission after 8 weeks of treatment, with macroscopic and histological healing in the terminal ileum and colon. This was associated with a significant reduction in mucosal interleukin-1β mRNA and TNF-α. The ileal mucosa also showed a significant reduction in interferon-γ mRNA, with an increase in transforming growth factor-β1 mRNA.[49]

An open label prospective study recruited 34 children using EEN for a minimum of 6 weeks with a clinical, biochemical and endoscopic assessment before and after completion.[50] The assessment also included disease outcomes at 1 year. The results showed that clinical and biochemical remission was achieved in 84% and 76%, respectively; moreover, 58% had good endoscopic scores and 21% achieved remission of ileal CD on magnetic resonance enterography. The children with good endoscopic scores were found to have reduced rates of disease relapse, anti-TNF use and hospitalizations when they were followed-up at 1 year. This is likely to be a secondary effect that occurs via its effect on cytokine balance or on gut microbiome.

### *Modification of gut microbiome*

Multiple studies have shown that the gut microbiome is different in patients with IBD compared with healthy subjects and is less diverse, especially in relation to the Firmicutes phylum. In addition, there are higher concentrations of certain bacterial species, such as the adherent/invasive strains of *Escherichia coli*, and these changes may be implicated in the pathogenesis of IBD.[51–53] Hansen *et al*.[54] have shown that in mucosal samples from children with CD there is increased *Faecalibacterium prausnitzii* and reduced bacterial diversity, indicating dysbiosis. The dysbiosis hypothesis suggests that in IBD, there is an alteration of the balance between the beneficial and harmful microbiota in the gut contributing to gut inflammation.[54]

The literature has, however, been quite conflicting, especially regarding the type of change in gut microbiota in CD. Leach *et al*.[55] demonstrated that gut bacterial diversity in children with CD at diagnosis was similar to that of healthy controls, and that changes occurred in bacterial species like *Eubacteria, Bacteroides, Clostridium coccoides, Clostridium leptum* and *Bifidobacterium* during and after eight weeks of EEN, proving that EEN can modify the gut microbiome. This change was associated with decrease in the gut mucosal inflammation and was sustained for 4 months after stopping EEN.[55] Gerasimidis *et al*.[56] compared stool microbiome in 15 children with CD and 21 healthy subjects showing that the global bacterial diversity and *F. prausnitzii* concentration both significantly decreased during EEN; the greatest changes were seen in children who responded clinically to treatment with EEN. All these changes reverted to pre-treatment levels after the regular diet was recommenced. The authors concluded that these results challenge the current perception of a protective role for *F. prausnitzii*.[56]

Further publication by the Gerasimidis group confirmed that in pediatric CD, despite improvement in disease activity, EEN made the gut microbiome more dysbiotic, reducing gut microbiome diversity and decreasing the relative abundance of more than half of the bacterial taxonomic units during EEN (Table 2).[56–59] Schwerd *et al*.,[58] in contrast, described an increase in the relative abundance of *Firmicutes* after EEN therapy. Guinet-Charpentier *et al*.[59] recently demonstrated that patients who respond to EEN and in clinical remission showed a reduction in *Dialister*, *Blautia*, unclassified *Ruminococcaceae* and *Coprococcus* compared with patients in remission with other treatments, such as anti-TNF and PEN.

The limitations of some of these studies are that the analysis had been performed on serial stool samples and emphasizes the importance of studying both mucosal adherent bacteria and stool microbiota together.

### *Change in fat composition of diet*

Use of high or moderate fat feeds, when comprised of predominantly monounsaturated fats in EEN, previously showed a favorable outcome.[60] The hypothesis was that depletion of linoleic acid reduces substrate for production of proinflammatory eicosanoids, like leukotreines and prostaglandin E2. A Cochrane meta-analysis of a subgroup in 2007 including 209 patients treated with EEN formula of differing fat content (low fat: <20 g/1000 kCal *vs*. high fat: >20 g/1000 kCal) found no significant difference in efficacy (OR: 1.13; 95% CI: 0.63–2.01). The use of very low fat content (<3 g/1000 kCal) or the type of fat (long-chain triglycerides) also did not show a difference in efficacy in the treatment of active CD; although, a nonsignificant trend favoring very low fat and very low long-chain triglyceride content was observed. The authors advised that this result should be interpreted with caution, due to significant heterogeneity and small sample size.[5,8,61–64]

***Improvement in growth and nutrition***

The conventional therapies for IBD (especially combination immunosuppressive treatment) are generally effective; however, there are significant concerns regarding the impact of disease activity and treatment on growth in children. EEN has been proven to have significant growth and nutritional benefits apart from its use in inducing remission. Prolonged use of corticosteroids is known to negatively impact linear growth via osteocyte and osteoblast apoptosis, increased osteoclastogenesis, decreased osteoblastogenesis, increased autophagy in osteocytes and osteoclasts, and reduced gastrointestinal calcium absorption, resulting in reduced bone formation.

Griffiths *et al*.[65] reviewed mechanisms of impaired growth in CD, such as proinflammatory cytokines, causing direct interference with insulin like growth factor-I and mediation of linear growth, cytokine-mediated anorexia, and mucosal damage leading to protein-losing enteropathy. EEN has been shown to reverse the growth hormone-resistant state induced by proinflammatory cytokines.[65] Whitten *et al*.[66] investigated 23 children with a new diagnosis of CD before and after six weeks of EEN. They reported normalization of inflammatory markers, serum markers of bone turnover and bone-specific alkaline phosphatase, concluding that these findings indicated an improvement in bone health. Denne *et al*.[67] showed that in inactive CD, EEN promoted anabolism by suppressing proteolysis and increasing protein synthesis to rates that were similar to those of healthy children.

There is limited literature on micronutrient status in CD patients. A Japanese study that evaluated zinc and selenium status in 31 patients on long-term EEN found these patients to be deficient and recommended zinc and selenium supplementation.[68] However, Akobeng *et al*.[69] found low plasma concentrations of vitamins C and E in childhood CD patients after four weeks of EEN and an increase in selenium concentrations. It is difficult to make any specific recommendations based on the limited literature and contrasting findings.

## Future research directions/perspective

EEN is a simple, safe and effective therapy in pediatric CD. EEN improves nutritional status, growth and bone health. It is associated with mucosal healing, is inexpensive and has no serious side effects, but demands healthcare resources (specifically, dietitians and specialist nurses) and currently there is no agreed exit diet strategy. Although a major advance, anti-TNF therapy is not effective in a significant number of patients. The current treatment strategies in CD are limited and usually linked to ways of increasing immunosuppression with newer monoclonal antibodies, all associated with potentially significant side effects. There is increasing evidence that IFX appears to be more effective with EEN, as compared to IFX alone, in maintaining remission.[70] PEN and SFD are showing promise in management of gastrointestinal symptoms, and RCTs exploring this further are needed. If the mechanisms of action of EEN were fully elucidated, there may be scope for designing more effective EEN formulas or solid food-based diets that would be acceptable across the age range of patients with CD and might be tailored to phenotype.

## Conclusions

In children with CD, EEN is a highly effective treatment and induces remission in more than two-thirds of newly diagnosed patients; the efficacy is better than that of corticosteroids. EEN is also efficacious in inducing remission in relapsing CD. There is evidence to support on-going use of PEN to maintain remission in the long-term, and there is limited evidence to support the use of PEN in conjunction with modified solid food-based diet at diagnosis of CD to induce remission. In adults, limited evidence suggests that corticosteroids are superior to EEN in inducing remission. Solid food-based diets may be used to decrease concurrent gastrointestinal symptoms. There is evidence to support a mechanism of action of EEN via restoration of cytokine homeostasis and its effect on mucosal healing. The data on the mechanism of action via modification of the gut microbiome and alteration of fat content of the diet is limited and conflicting. There is robust data, however, on a direct effect of EEN on promotion of growth and improving nutrition and bone health.

## Conflict of interest

The authors have no conflict of interests related to this publication.

## Author contributions

Drafting the manuscript with the opportunity to revise or question its contents (RV, JWLP).

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