Exclusive enteral nutrition in pediatric inflammatory bowel disease

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Purpose of review
Nutritional interventions play a central role in the treatment and management of inflammatory bowel disease (IBD) in children. Although malnutrition is a common presenting sign of IBD, nutritional interventions have focused not only on correction of the malnourished state but also on treatment of the primary disease.

Recent findings
Exclusive enteral nutrition (EEN) has been the primary therapy utilized in pediatric IBD specifically, Crohn's disease. This intervention provides total calories from formula meeting complete macronutrient and micronutrient needs for a patient. EEN has been shown to improve growth and correct micronutrient deficiencies as well as improve comorbid conditions like osteopenia and anemia. EEN has also been shown to be equally as efficacious as steroids in inducing remission with better mucosal healing.

Summary
EEN is a primary therapy in IBD. Both the North American and European Societies of Pediatric Gastroenterology, Hepatology and Nutrition consider EEN as first line therapy for inducing remission in Crohn's disease.

Keywords
Crohn's disease, exclusive enteral nutrition, inflammatory bowel disease, nutrition, pediatrics, ulcerative colitis

INTRODUCTION

Nutritional interventions play a central role in the treatment and management of inflammatory bowel disease (IBD) in children. Although malnutrition is a common presenting sign of IBD, nutritional interventions have focused not only on correction of the malnourished state but also on treatment of the primary disease. Exclusive enteral nutrition (EEN) has been the primary therapy utilized in pediatric IBD specifically, Crohn's disease. This intervention provides total calories from formula meeting complete macronutrient and micronutrient needs for a patient. EEN has been shown to improve growth and correct micronutrient deficiencies as well as improve comorbid conditions like osteopenia and anemia. EEN has also been shown to be equally as efficacious as steroids in inducing remission with better mucosal healing. Currently, the North American and European Societies of Pediatric Gastroenterology, Hepatology and Nutrition consider EEN as first-line therapy for inducing remission in Crohn's disease.

EXCLUSIVE ENTERAL NUTRITION IN CROHN'S DISEASE

EEN provides a means of inducing remission and optimizing nutritional status. It requires that a patient stop eating and receive all dietary energy as elemental and/or polymeric formula. A number of randomized trials show that primary EEN therapy achieves remission rates comparable with corticosteroids in children. In addition, there is improvement in growth as compared with patients on corticosteroids. EEN has been shown to be effective also in maintaining remission [1–4,5▪▪].

Induction of remission

Since the initial report of EEN in Crohn's disease in 1982, there have been over 200 publications on EEN with multiple meta-analyses showing that the use of enteral nutrition in children is as effective as corticosteroids in inducing remission [3,5▪▪,6]. Generally,

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KEY POINTS

- EEN is recommended by the North American and European Societies of Pediatric Gastroenterology, Hepatology and Nutrition as first line therapy for inducing remission in Crohn's disease.
- EEN is associated with clinical remission as well as improved anthropometrics in pediatric Crohn's disease.
- EEN is associated with increased mucosal healing in Crohn's disease as compared with steroids.

EEN leads to the induction of remission in approximately 80–85% of patients.

Many studies show efficacy of EEN. Day *et al.* reported that 12 of 15 (80%) newly diagnosed Crohn's disease patients, and seven of 12 (58%) with long-standing disease entered remission on a polymeric formula. In a study by Navas-López *et al.* [7], the outcomes of 40 children with Crohn's treated with EEN revealed 80% remission rate after 6–8 weeks of EEN on an intention to treat basis. When the investigators evaluated the outcomes in the 34 children who had completed the full period of EEN, 32 (92%) entered remission.

The impact of disease location upon outcomes has been variable in reported studies. Afzal *et al.* [8] showed a marked disparity between colonic disease (50% response rate) and ileal or ileocolonic disease (remission rate between 92 and 83%, respectively). In contrast, a subsequent report from Buchanan *et al.* [9] involving 114 children showed that those with isolated terminal ileal disease ($n = 4$) had a lower remission rate, but that location did not otherwise influence outcome. A retrospective study conducted by de Bie *et al.* assessed the outcomes of EEN in 77 children. They noted that ileal or ileocolonic disease location and poor nutritional status at baseline were important factors with regard to outcome [10]. With the aforementioned studies noted, a recent Cochrane analysis notes inadequate data from full publications to perform further subgroup analyses by age, disease duration or disease location [5▪▪].

In regards to types of formula, multiple studies have shown no difference in formula type and outcomes. Berni Canani *et al.* evaluated polymeric formula versus semielemental formula versus elemental formula versus corticosteroids in 47 patients. 86.5% of children receiving nutritional therapy versus 90% of patients treated with corticosteroids went into remission by 8 weeks. Similar rates of remission were seen in all formula groups [11]. In addition, a randomized, multicenter study by Ludvigsson *et al.* [12] showed no statistical difference between the effect of elemental and polymeric formula, with 11/16 (69%) and 14/17 (82%) of pediatric patients achieving remission, respectively.

For adults with IBD, EEN has shown conflicting results. A 2007 Cochrane Database Systematic Review comparing EEN versus steroids favored steroids based on intent-to-treat [odds ratio (OR) 0.33, 95% confidence interval (CI): 0.21–0.53] [13]. It is unclear whether the perceived difference between efficacy in pediatric EEN studies and adult EEN studies are related to disease or compliance with therapy. Two studies in adults with Crohn's show similar efficacy with EEN when delivered via nasogastric tube [14,15].

Mucosal healing

Although clinical remission is an important outcome for patients with IBD, in recent years there has been an additional emphasis on the importance of mucosal healing as a primary outcome measure in IBD. This is related to the role of mucosal healing as a predictor for long-term outcomes in Crohn's disease.

A number of studies have shown early mucosal healing with EEN at 8–10 weeks following commencement of therapy. In addition, EEN has consistently outperformed corticosteroids in achieving mucosal healing in cases of active Crohn's disease when the two different therapies have been directly compared. Borrelli *et al.* [16] found 26 of 37 patients in the EEN group achieved mucosal healing, in which only four of 10 in the steroid group achieved the same end point. Berni Canani *et al.* [11] found 14 of 19 patients induced with EEN achieved mucosal healing, whereas only six of 18 patients treated with corticosteroids achieved the same endpoint. Overall, patients who received EEN were 4.5 times more likely to demonstrate mucosal healing (OR 4.50, 95% CI: 1.64, 12.32); compared with those who received corticosteroids [17▪▪].

In addition to mucosal healing, there is evidence that EEN can lead to resolution of transmural inflammation. In a prospective study by Grover *et al.* involving 34 children with Crohn's disease, clinical remission was reported in 84% of patients with 58% having early endoscopic response. A subset of this group also had magnetic resonance enterography before and after EEN, which demonstrated complete transmural healing in three of 14 children [18].

Perhaps most encouraging, early mucosal healing as a result of EEN has been shown to result in sustained remission at 3 years [19]. A prospective study of early mucosal healing with EEN in newly diagnosed children with luminal Crohn's disease revealed complete mucosal healing at 1 year predicted more favorable sustained remission for up to

3 years. A total of 54 eligible children (33 males) completing EEN induction were analyzed. The median duration between pre-EEN and post-EEN assessments was 60.5 days. In the post-EEN group, clinical remission was observed in 45/54 (83%), and biochemical remission was observed in 39/54 (72%) of patients. Complete mucosal healing was observed in 18/54 (33%) and near complete in 10/54 (19%) of participants. Sustained remission was superior in those with complete mucosal healing versus those with active endoscopic disease 13/18 (72%) versus 10/36 (28%), $P = 0.003$ at 1 year, 8/16 (50%) versus 3/24 (8%), $P = 0.008$ at 2 years and 8/16 (50%) versus 1/19 (6%), $P = 0.005$ at 3 years [19].

Growth and nutrition in inflammatory bowel disease

Growth failure is seen in about 30% of children with Crohn's disease from 9 years of age into their adolescence [20,21]. In a study by Kanof *et al.* [22], up to 88% of children with Crohn's disease had some degree of linear growth impairment prior to their diagnosis. The cause of growth failure is multifactorial with many nutritional obstacles existing for patients with IBD. During active disease patients are often faced with anorexia, early satiety and pain with eating which limit oral intake and therefore overall caloric intake. Although nutritional intervention can improve growth, permanent growth impairment is not uncommon in pediatric Crohn's disease, occurring in 19–35% of patients [23–25].

EEN has been used in pediatric IBD to improve growth and nutritional status. Long-term refeeding studies in undernourished children with Crohn's disease show catch-up growth, with average height and weight gains of 7–9 cm/year and 7 kg/year, respectively, with daily dietary energy intakes approximating 133% of recommended values for ideal body weight, or 60–75 kcal/kg actual body weight [26,27]. EEN is able to deliver these nutritional needs by a standardized means. Gerasimidis *et al.* [28] evaluated the influence of EEN upon body composition parameters in 17 children. Body impedance analysis demonstrated marked improvement in lean mass but not fat mass with 8 weeks of EEN. In addition, Khoshoo *et al.* [29] showed improved weight, lean body mass and skin fold thickness measurements after 6 weeks of EEN. Similarly, a study from Azcue *et al.* [30] showed improvements in weight and lean body mass subsequent to EEN, as well as improved linear growth in comparison with children treated with corticosteroids.

In addition to improved nutritional status, bone health has been shown to be improved with EEN in IBD. In a study by Whitten *et al.* [31], newly diagnosed children with IBD who went onto an 8-week course of EEN showed normalization of bone markers suggesting improved bone formation. In addition, Soo *et al.* [32] found a 6-week course of EEN followed by a 2-week course of partial enteral nutrition (PEN) resulted in better improvements in *z*-scores on Dual-energy X-ray Absorptiometry scans when compared with children treated with corticosteroids.

Exclusive enteral nutrition protocols

There is variation in the use and implementation of EEN. Variation includes type, duration of formula, use of nasogastric tubes and inclusion of other food for taste. Currently, there is little evidence to suggest differences in outcome based upon type of formula: elemental, semielemental, polymeric enteral formula or contents of formula. A typical regimen involves the use of a polymeric formula administered exclusively over 8–12 weeks, although some studies have looked at 6 weeks as well.

Exclusive enteral nutrition side effects

Few significant side effects are seen with EEN. Nausea, loose bowel movements and constipation have been associated with formula feeds. In addition, refeeding syndrome has been reported following EEN [33,34]. These patients often present with moderate/severe malnutrition which placed them at increased risk of refeeding syndrome. The most impactful potential side effect on routine clinical care is the association of EEN with formula fatigue. These patients are unable to continue drinking formula and often require nasogastric feeds or alternative therapy for their IBD. Given these concerns, close follow-up with patients are required to assure proper intake of formula.

Variations on a theme: partial enteral nutrition

Although PEN does appear to improve clinical symptoms, EEN is more effective for decreasing mucosal inflammation and getting patients into clinical remission. Johnson *et al.* randomized 50 children with active Crohn's disease to receive 50 or 100% of their energy requirement as elemental formula for 6 weeks. The primary outcome was achievement of remission. Remission rate with PEN was lower than with total enteral nutrition (15 versus 42%). In addition, only EEN increased hemoglobin and albumin, and was associated with improvement in sedimentation rate. In addition, Lee *et al.* prospectively compared EEN with PEN in 90 children with Crohn's disease. Clinical response

was achieved by 64% of patients on PEN compared with 88% of patients on EEN. Fecal calprotectin also improved in a greater percentage of patients in the EEN group with 14% of PEN patients getting to less than 250 mg/dl as opposed to 45% of patients on EEN [35].

EXCLUSIVE ENTERAL NUTRITION IN ULCERATIVE COLITIS

There is limited knowledge on the use of EEN in ulcerative colitis. There does exist growing evidence from animal models suggesting EEN may be beneficial in colitis [36–38]. Three clinical reports have shown a positive effect from EEN on ulcerative colitis disease activity; however, two of these reports did not subanalyze the patients with Crohn's verses ulcerative colitis [39,40]. In the third report, consisting of a single uclerative colitis patient with primary sclerosis cholangitis, the patient went onto EEN and transitioned to the specific carbohydrate diet (SCD). The patient went into remission on EEN with improvement in markers of inflammation and liver enzymes, and subsequent normalization of labs on the SCD. In addition, this patient had normalization of endoscopic findings of colitis 1 year after initial therapy [41].

MECHANISM OF ACTION

The current IBD paradigm focuses on three main areas: first, the microbiome; second, the mucosal barrier and third, the immune system. The effects of EEN impact all three of these areas. Diet has a profound effect on the microbiome composition, and EEN has been shown to alter the microbiome in distinct ways [42,43]. Leach *et al.* examined changes in the microbiome throughout the duration of treatment with EEN in children. They showed marked and prolonged reduction of bacterial diversity across all bacterial groups with the use of EEN. In particular, variations in the composition of the *Bacteroides* group correlated closely with reducing disease activity and inflammatory proteins [43]. In another study which again showed reduction in diversity during EEN, the concentrations of *Faecalibacterium prausnitzii* species, a putative protective species, decreased after EEN [44]. A more recent study looking at the number of operational taxonomic units (OTUs) in the fecal microbiome showed a reduced OTU with initiating EEN. This reduction in OTU was correlated with successful induction of remission. Furthermore, subsequent flare of disease occurred in concert with an increase in OTUs [45].

The intestinal mucosa and mucus layer play an important role in the pathogenesis of IBD as the primary barrier to the fecal microbiome. Breakdown of the mucus layer and/or intestinal epithelial layer allows for increases in intestinal permeability. This increases the interaction between the host immune system and the fecal microbiome.

Nahidi *et al.* [46] showed that a polymeric formula *in vitro* resulted in normalization of altered permeability and migration of key tight junction proteins back to the cell membrane. In addition, in murine models, polymeric formula in IL-$10^{-/-}$ mice with intestinal inflammation was able to reverse impaired intestinal permeability and altered tight junction protein localization, in conjunction with normalization of inflammatory changes [38].

A third effect of EEN is a direct immunomodulatory effect. This may be a result of components of the formula or because of reduced antigenic load with the removal of a whole food diet. Many studies have shown that EEN results in decrease in mucosal levels of proinflammatory cytokines. Meister *et al.* [47] used ex-vivo mucosal biopsies to demonstrate that an elemental formula resulted in an increased ratio of IL-1Ra to IL-1β compared with the ratio in control samples. In addition, using an in-vitro model of inflammation de Jong *et al.* [48] showed that polymeric formula led to a reduction in cellular production of IL-8 following stimulation with TNF-α.

CONCLUSION

Historically, the focus of nutrition in pediatrics has been for the correction of a malnourished presenting state, rather than as primary therapy for a chronic medical condition outside of allergy, celiac and inborn errors of metabolism. In IBD, a condition of chronic immune dysregulation, nutrition not only corrects the malnourished state but also treats the primary disease. The literature illustrates a promising future for nutritional/dietary modification as treatment for IBD. Already EEN is recommended as first-line therapy to induce remission in pediatric Crohn's disease. With the success of EEN in IBD as well as the knowledge of the complex interactions among the intestines, microbiome and immune system, the potential for other nutritional/dietary therapies to play an integral role in IBD exists [49▪▪,50,51]. Further investigation of nutrition and diet in IBD are required to further understand the pathogenesis and cause of IBD as well as to further develop better therapies for IBD.

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Conflicts of interest

None of the authors have a conflict of interest in regards to this article except for David Suskind who has written/published Nutrition in Immune Balance (NIMBAL).

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