Chapter 6
Enteral Nutrition in the Treatment of Inflammatory Bowel Disease

Athos Bousvaros

Introduction

For over 30 years, exclusive enteral nutrition (EEN) has been utilized to treat Crohn's disease both in children and in adults. However, while EEN has gained widespread acceptance in Europe, Canada, and Japan, EEN treatment is not widely utilized in the USA. A study by Levine et al. demonstrated that approximately 60 % of European pediatric gastroenterologists utilize EEN, compared to approximately 4 % of their American counterparts [1]. The chapter below will review the evidence that EEN is effective in both adult and pediatric Crohn's disease. I will discuss the impact of EEN on clinical disease activity, biomarkers, and endoscopic healing. The chapter will also provide instruction on how to implement an EEN program, as well as the challenges one may face. The advantages and disadvantages of this form of treatment in Crohn's disease are listed in Table 6.1. The chapter will focus almost exclusively on the treatment of Crohn's disease, as there is no evidence that EEN brings about a remission in ulcerative colitis. The reader is also referred to the excellent North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) clinical report on use of EEN to treat pediatric Crohn's disease [2].

A. Bousvaros, M.D., M.P.H. (✉)
Division of Gastroenterology and Nutrition, Harvard Medical School, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, USA
e-mail: Athos.bousvaros@childrens.harvard.edu

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Table 6.1 Advantages and disadvantages of enteral nutrition therapy in inflammatory bowel disease

Advantages
Reduces disease activity
Reduces biomarkers of inflammation (sedimentation rate, fecal calprotectin)
May induce remission
Promotes weight gain
Promotes linear growth (in children)
Corrects micronutrient deficiencies
Reduces intestinal permeability
Steroid-sparing
Not immunosuppressive
Extensive experience for over 30 years, especially outside the USA
Disadvantages
May be less effective than corticosteroids, especially in adults
Usually used as a short-term induction treatment (6–12 weeks)
Limited evidence to support the use of EN as a maintenance therapy
No evidence of efficacy in ulcerative colitis
Less efficacy (though still effective) in colonic Crohn disease
Refeeding syndrome may occur
May need to be administered through nasogastric tube
Most efficacious when the patient does not eat during the induction period
Insurance may not pay
Requires large multidisciplinary team to effectively implement (including physician, nurse, registered dietician, possibly psychologist or social worker)

History

The development of EEN to treat pediatric Crohn's disease was actually preceded by encouraging preliminary data regarding home parenteral nutrition in Crohn's disease. In 1979, Strobel et al. published a case series of 17 children, age 9–20 years, who were placed on home parenteral nutrition for severe symptomatic Crohn's disease. At that time, the only readily available maintenance therapies for Crohn disease were sulfasalazine and corticosteroids. All patients had disease of their small intestine and/or colon, and many of them had complications including enterocutaneous fistulae and growth failure. The patients were placed on home parenteral nutrition with a dosage of 60–80 kcal per kilo and a daily home in volume of 3–4 L/day. The duration of remission in patients ranged from 15 days to 539 days. Benefits included fistula closure, reduction of corticosteroid dose, increase in serum albumin, improved growth, and improved nutritional status. Complications of parenteral nutrition use in this cohort included dislodgement, catheter infections, and zinc deficiency dermatitis [3].

Based on the encouraging results from home parenteral nutrition studies, Morin and colleagues published a case series in 1980 of four children who received a 6

week period of continuous enteral alimentation with elemental formula, and no concomitant treatment. Children were given approximately 80 cal per kilogram of body weight. One patient developed symptoms of bowel obstruction and underwent an ileocecectomy during the period of treatment. All children gained weight and height during treatment, and also developed reductions in the Crohn disease activity index. These children gained a mean of only 1.7 cm of height in the 2 years prior to the enteral nutrition therapy. After 6 weeks of EEN, they gained a mean of approximately 5 kg in weight and 3 cm of height over the following 6 months. There was also improvement in mid-arm circumference and triceps skin fold thickness [4]. Subsequently, O'Morain and colleagues performed a randomized 4 week trial of exclusive enteral therapy with elemental formula vs. prednisolone (0.75 mg/kg/day) in 21 patients (mostly adults: age range 15–60), with active CD (mostly small and large bowel). The investigators reported comparable changes in clinical disease activity and sedimentation rate. Patients treated with steroids exhibited greater weight gain by 3 months, while those treated with elemental diet exhibited more improvement in hemoglobin and albumin [5]. Many additional open-label and randomized trials performed in the following decade continued to demonstrate efficacy of this enteral therapy. In 1995, Griffiths and colleagues performed a meta-analysis comprising 8 randomized trials, and including 413 patients. These trials included studies comparing one type of formula with another (e.g., elemental vs. polymeric), and formula compared to corticosteroids. All trials were small or medium sized, the largest being 107 patients [6]. The rates of clinical remission in the EEN groups ranged from 22 to 82 %, whereas in the corticosteroid group the rates of clinical remission ranged from 50 to 90 %. The meta-analysis concluded that enteral nutrition was inferior to corticosteroids at inducing remission (pooled odds ratio 0.35, 95 % confidence interval 0.23–0.53), but there was no difference between elemental and polymeric formula [7]. A subsequent meta-analysis suggested that EEN may be more effective in children than adults [8].

Biological Effects of Exclusive Enteral Nutrition Treatment

Reduced Intestinal Permeability

Intestinal permeability in inflammatory bowel disease can be assessed utilizing a number of assays. Most commonly, permeability is assayed by asking a patient to ingest a compound that is only partially absorbed across the epithelial barrier, and assessing absorption of that compound by measuring levels in the blood or urine. Compounds utilized to assess permeability include lactulose, polyethylene glycol, and chromium-labeled EDTA. Studies consistently demonstrate increased permeability (a.k.a. "leaky gut") in patients with active Crohn disease, but some studies also suggest increased permeability in inactive CD, as well as unaffected family members [9, 10]. In vitro, enteral nutrition may improve epithelial cell adhesion,

reduce intestinal permeability to macromolecules by restoring epithelial cell continuity, and increase epithelial monolayer integrity [11, 12]. In vivo, CD patients treated with elemental diet demonstrate reduced intestinal permeability after 4 weeks of EEN [13].

Alteration of Intestinal Microbiota

Current evidence regarding the pathogenesis of inflammatory bowel disease suggests that IBD occurs when a genetically predisposed individual is exposed to potential environmental triggers, resulting in poorly controlled intestinal inflammation. Over 140 genes have been identified that either increase or decrease the risk of inflammatory bowel disease. The lack of a clear monogenic etiology in the majority of our patients suggests that environmental causes are central in the pathogenesis of IBD. Diet is an obvious environmental factor that is an ongoing and active topic of study with respect to the pathogenesis of IBD. Current studies suggest that breastfeeding may protect against the development of IBD. In addition, patients who consume greater amounts of meat fats, polyunsaturated fatty acids, and omega-6 fatty acids may have a higher incidence of inflammatory bowel disease. There are many animal models where modification of the diet may result in the development of inflammation in a genetically predisposed post [14, 15].

An underlying common pathway by which diet might affect the development of IBD in both animals and humans is via alteration of the intestinal microbiota [16]. Through high throughput sequencing methods, we are now able to analyze the microbiota of patients with chronic illness. Published data suggests that the microbial populations are significantly different in patients with and without IBD, both at the time of disease onset, and also during subsequent time periods. The microbiota can change rapidly, and alterations in diet (such as the institution of exclusive elemental nutrition) may result in the generation of a more beneficial, less inflammatory commensal flora [17]. Interestingly, one recent study suggests that EEN may actually reduce the levels of certain supposedly "protective" microbiota such as *Faecalibacterium prausnitzii* [18]. In summary, the research on how EEN affects intestinal microbiota is in its infancy. While changes in microbiota do correlate with changes in disease activity in IBD patients, it is unclear whether the microbial alterations precede the reduction of inflammation, or occur because of the reduction in inflammation.

Immunologic Effects

Enteral nutrition contains many micronutrients that may influence the development of the mucosal immune system. In particular, retinoic acid (derived from vitamin A) may play a critical role in the development of oral tolerance, and in the maintenance of the IgA mucosal barrier [19]. Vitamin D may also play a key role in the

perpetuation of certain T-cell subsets that may mediate intestinal immune tolerance [19, 20]. However, given that vitamin supplementation alone does not appear to reduce IBD disease activity, there are probably other mechanisms by which EEN more directly affects the intestinal immune system. Experiments by Sanderson and colleagues suggest that EEN may both reduce antigen presentation by MHC class II cells and also reduce production of IL-6 by epithelial cell lines [21]. The precise molecular mechanisms by which EEN impacts inflammation at the cellular level have yet to be delineated.

Clinical Benefits of Exclusive Enteral Nutrition Therapy

Induction of Remission in Active Crohn Disease

Studies in both children and adults suggest that patients with active Crohn disease treated with EEN for 6–10 weeks may achieve remission from 60 to 80 % of the time [2, 22]. A Cochrane review comparing randomized trials of EEN to some other treatment (usually corticosteroids) demonstrated an odds ratio of 0.33 favoring EEN [23]. In the single most conclusive pediatric study, Borelli et al. randomized 37 children to receive either EEN therapy (exclusive polymeric diet, no other foods allowed) or a course of tapering corticosteroids for a 10 week period. Assessments performed at the beginning and the end of the trial included history, examination, assessment of clinical disease activity, blood sampling, and ileocolonoscopy. Both groups demonstrated similar improvements in the Pediatric Crohn disease activity index (from over 35 down to 10 points), C-reactive protein (from 10 to 3 mg/dL), and ESR (from 40 to 20 mm/h). However, at the end of the 10 weeks, the proportion of children with endoscopic improvement was greater in the EEN group (74 %) compared to the steroid group (33 %) [24].

Evidence suggests that EEN may not be as effective if children are allowed to eat during the induction period. In a study by Johnson and colleagues, 50 children were randomized to receive either EEN, or 50 % EN in addition to an unrestricted regular diet. While both groups reported improved well-being, 42 % of children in the EEN group entered remission, compared to only 15 % in the partial enteral nutrition group [25]. In contrast, Levine and colleagues performed an open-label intervention in 47 children and young adults consisting of 6 weeks of enteral nutrition in conjunction with a restricted diet. The restrictive diet excluded gluten, casein, and high fat foods, but allowed limited amounts of rice-based products, fresh chicken breast, carrots, tomatoes, and water. Packaged snacks, sodas, and candies were excluded. On this dietary intervention, remission rates (as measured by Harvey Bradshaw index and PCDAI) were obtained in approximately 70 % of children and adults. Between weeks 6 and 12, the diet was liberalized in a limited manner, and 80 % of the group in remission at 6 weeks was able to stay in remission. This study suggests that limited amounts of certain types of food may not impair the efficacy of EEN [26].

Maintenance of Remission in Crohn Disease

While the evidence supporting induction of remission in both children and adults with active Crohn disease is strong, the data supporting its use in maintenance therapy is far weaker. One of the limitations of using EEN as enteral treatment is the adherence to the medical recommendation. It is challenging for an adult, let alone a child, to forego eating for prolonged periods of time. For this reason, many centers utilize EEN as a steroid sparing "bridge" to some other maintenance treatment such as immunomodulators. In adults, Takagi et al. randomized 51 adult patients with CD in remission to either an unrestricted diet, or to a diet consisting of 50 % of required calories as EN + 50 % unrestricted diet. After 1 year, 64 % of patients in the unrestricted diet group had relapsed, compared to 35 % of the 50 % EN group [27].

A retrospective analysis of a protocol utilized at the Children's Hospital of Philadelphia also suggests that partial enteral nutrition may assist in maintaining remission in a subset of patients. Forty three children underwent induction with EN via nasogastric tube with continuous feedings given over 10–12 h, and for a period ranging from 8 to 12 weeks. Unlike EEN protocols, these patients were allowed to consume 10–20% of their calories as food on any given week. Clinicians utilized either polymeric, partially hydrolyzed, or elemental formulas depending on physician preference. Concomitant therapies, including immunomodulators, biologics, and aminosalicylates, were allowed. After the induction period, 65 % of patients had achieved clinical remission. Over a 6 month period, 29 children elected to continue with the nutritional therapy. Adverse effects included nausea, vomiting, diarrhea, difficulty sleeping with the nasogastric tube, and increased urination [28].

Improvement of Nutritional Status and Growth

Treatment with corticosteroids is associated with reduction of inflammation and an improved sense of well-being, but at a cost. As mentioned previously, mucosal inflammation persists despite corticosteroid treatment. Patients receiving steroids may gain weight and fat mass, but do not exhibit gains in muscle mass, bone density, and height velocity [29, 30]. For this reason, corticosteroid sparing agents (immunomodulators and biologics) are essential in the long-term treatment of most Crohn disease patients. Studies of medical therapy suggest that anti-TNF agents are most likely superior to thiopurines and methotrexate as maintenance agents, and might do a better job of promoting linear growth, acquisition of bone density and muscle mass [31, 32]. Enteral nutrition may also play a crucial role in treating growth failure, even if given periodically. In a study performed prior to the routine use of immunomodulators for treating Crohn disease, Belli et al. administered a continuous nasogastric infusion of an elemental formula to a group of adolescents with CD and growth failure. Patients were given 50 % of their caloric requirement as EN for 1 out of every 4 months for a period of 1 year. Patients grew 7 cm/year

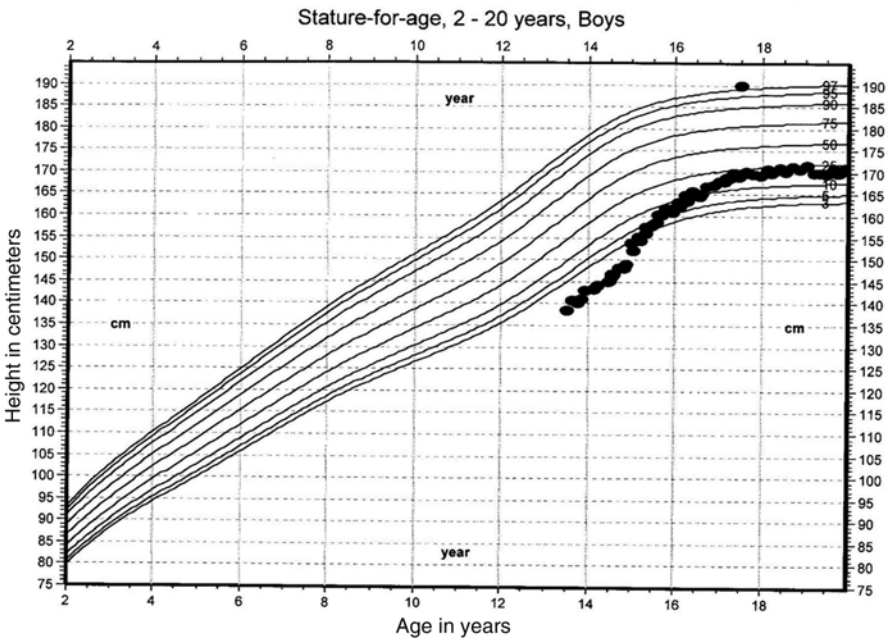

Fig. 6.1 Growth curve of a child treated with supplemental EN and biologics. The x axis represents age in years, and the y axis height in centimeters. The supplemental treatment was begun at the age of 14 years, 6 months, with increase in the patient's stature from below the third percentile to the 25 % by age 18 years

during their treatment year, compared to 2.9 cm/year in the year prior to their treatment. A comparison age matched control group only grew 1.7 cm during the period of observation [33]. Figure 6.1 demonstrates the impact of combined enteral nutrition and biologic treatment in a teenager who was not growing despite the use of immunomodulators as steroid sparing agents.

Improvement in Bone Health

Children and adults with IBD are at risk for osteopenia and osteoporosis. The causes of reduced bone density are multifactorial, and include: inflammation, reduced bone formation, increased bone resorption, hypovitaminosis D, prolonged corticosteroid therapy malnutrition, and physical inactivity [34]. Enteral nutrition therapy has been shown to improve bone formation and reduce bone resorption (as measured by C-terminal telopeptides of type 1 collagen) [35]. In addition to reducing disease activity, EN may improve bone mass by providing supplemental calcium and vitamin D [36].

Effects on Quality of Life

While the effects of EN on physical health are apparent (including reduction of inflammation, reduction of steroids dosage, and improved linear growth), the effects of quality of life in children and adults with IBD are less well studied. Quality of life is a holistic measure, encompassing not only physical but also psychological measures of well-being. Approximately 25 % of adolescents with IBD have symptoms of anxiety or depression, and may benefit from psychological interventions like cognitive behavioral therapy [37–39]. Psychological well-being has not been well studied in children receiving EN. In one study, children and adolescents receiving EEN related concerns about "feeling different" and disruption in daily activities [40]. Other studies have similarly given mixed results on the effects of EN on quality of life, with some suggesting improvement and others suggesting deterioration [41, 42]. While additional studies are needed, the current data suggests that some psychological support may be needed for children embarking on an enteral nutrition protocol. In addition, other potential contributors to reduced quality of life, such as parental stress, should be assessed before embarking on this labor-intensive treatment [43].

Infrastructure Needed for a Successful Enteral Nutrition Regimen

After a diagnosis of Crohn disease is made in a child, the physician, patient, and family typically have a meeting to plan an induction and maintenance strategy. The most common two options offered for induction of moderate disease are corticosteroids and EEN (though anti-TNF agents are increasingly being utilized earlier in the course of treatment). For the patient, the choice may initially come down to "do I take a pill once a day, or do I stop eating and have a tube down my nose for 8 weeks"? Unless the provider takes the time to explain the benefits of enteral nutrition, and has an infrastructure in place to ensure the EEN regimen is successful, prednisone becomes the default treatment. Benefits of EEN include promoting growth and controlling disease activity, while avoiding the cosmetic, immunosuppressive, and mood-altering effects of corticosteroids. While educating the family, it is also important to communicate with the patient's insurance on the benefits of treatment.

Assuming the child and family agree to proceed with EEN therapy, and the insurance approves the regimen, the next step is to meet with a registered dietician (RD). The RD can calculate the calories required by the child, and also work with the family to determine the most palatable formula. There are a number of formulas to calculate resting energy expenditure, but the Schofield equation is the one most commonly utilized [2, 44]. Some children can drink the formula by mouth, especially polymeric formulas which are more palatable. Many, however, will be unable to drink the large volumes of liquid required (often 1.5–2.5 L), and will prefer to receive a portion of

the formula while asleep through a nasogastric tube. These patients often benefit from a 1 to 2 night hospitalization, so they can learn to place the tube, utilize the feeding pump, and make sure they do not develop symptoms of GE reflux of nausea. We usually start at a slow rate (75–100 mL/h, given over 10 h), then advance gradually to full volume over several days. For children who are active and can't receive all the formula overnight, there are small pumps that can be hidden in backpacks and allow administration of formula without impairment of ambulation. The choice of formula is determined by the provider and patient. The primary factor determining which formula to use is if the patient is willing to drink it. Our center has utilized both polymeric formulas (e.g. Ensure®) and partially hydrolyzed formulas (e.g. Peptomen®).

During this period, support of the patient is required in order to prevent them from abandoning the therapy. Generally speaking, phone follow-up is the main method of support, but for many patients in person visits with the nutritionist, nurse, social worker, and physician are important. In addition to optimizing the induction regiment, the physician must develop a maintenance regimen with the family. Such regimens may involve addition of a medication (immunomodulator or biologic), while others (usually in milder cases of CD) may involve some form of partial EN and dietary therapy. Whatever the maintenance regimen chosen, the efficacy of the treatment needs to be ascertained through frequent follow-up, clinical and laboratory monitoring, and possibly follow-up colonoscopy. To quote the NASPGHAN Working Group on Enteral Nutrition, "the optimal components of a successful EEN program have not been determined. …programs involving the coordinated services of a nurse and dietitian in addition to medical staff have a greater chance of success [2]".

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