Enteral Nutrition as Treatment Option for Crohn’s Disease: In Kids Only?

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Abstract

Inflammatory bowel disorders (IBD) are characterized by chronic and recurrent inflammatory reactions of the intestinal mucosa resulting in progressing ulcerating lesions. Research over the past decade clearly identified in patients with Crohn’s disease (CD) a marked dysregulation of the intestinal microbiome (dysbiosis) as one trigger factor in these inflammatory processes, particularly in patients with a high genetic risk. When treating patients with CD, most drugs aim to control the inflammatory process (either by inhibiting inflammatory pathways or by reducing the activity of immune cells). Given the importance of the disturbed interaction between the microbiota and the host immune system, there might be a different therapeutic approach in targeting directly the intestinal microflora. There are good data to believe that the use of exclusive enteral nutrition (EEN) is one such option. Historically, enteral nutrition (EN) was used as supplemental nutritional therapy in CD patients with planned resection surgery. This treatment option showed unexpected and very powerful anti-inflammatory effects, and it was rapidly introduced as induction therapy for active CD. Several clinical trials and case series confirmed the efficacy of EN to induce remission in approximately 80% of patients equaling the potential of steroids. It is well established that EN has this strong anti-inflammatory potential only when given on an exclusive basis, without any additional food. This raises major compliance issues, probably one of the reasons why it is less used in adult patients. A recent study demonstrated that EEN has a specific effect on the intestinal microbiota, which is markedly different from steroid-induced remission, while all patients obtained complete clinical remission. These observations give a first basis for the understanding of the impact of EEN on dysbiosis in patients with CD.
Introduction

Inflammatory bowel disorders (IBD) are chronic recurrent inflammatory diseases affecting the intestinal mucosa. The inflammatory reaction is characterized by a polymorphic infiltrate causing alterations of the epithelial cell turnover and barrier with subsequent erosions and ulcerations of the intestinal mucosa. These inflammatory lesions cause symptoms such as diarrhea, intestinal bleeding and abdominal pain, as well as systemic symptoms, such as fever in some patients. The precise causes triggering this chronic inflammatory reaction are not yet completely understood; research over the past decade clearly identified in patients with Crohn’s disease (CD) a dysregulation of the intestinal microbiome (dysbiosis) as one key trigger factor [1–3]. However, up to now, it is not clear if this dysbiosis is primary and thus causative of the inflammatory reaction or if it occurs secondary once the inflammation is installed. Large prospective cohort studies in North America and Europe are underway to address this point. The disturbed microbial-immune interaction leading to chronic intestinal inflammation is more likely to occur in individuals with a particular genetic risk. Up to now, over 150 susceptibility genes were identified which confer a particular risk to develop CD or ulcerative colitis [4–7]. Therefore, we consider the distinct phenotypes of IBD as multifactorial disorders with a complex genetic background and not yet identified environmental trigger factors affecting the homeostatic interaction between intestinal microbiome and the host’s immune system.

Treatment strategies for patients with CD are based on a rationale aiming to control the inflammatory process (either by inhibiting inflammatory pathways or by reducing the activity of immune cells). Over the last decade, several new drugs, mainly biologics were tested and subsequently introduced in treatment strategies [8–10]. These drugs are highly efficient in blocking the immune system and thereby in inducing remission in patients. Their safety profile being good, there are still important side effects that can occur, even if they are rare. Mainly infectious and aberrant immune reactions have been reported; however, some cases of tumors and cancers were also attributed to the (prolonged) use of immunosuppressants [11, 12]. Given the importance of the disturbed interaction between the microbiota and the host immune system, there might be a possibility for a different therapeutic approach in targeting directly the intestinal microflora. There are good arguments to believe that the use of exclusive enteral nutrition (EEN) is one such option. The perfect safety profile of this treatment approach is an additional advantage to use it, especially in vulnerable patients, such as children.
Use of Nutritional Therapy for Crohn’s Disease

Historically, enteral nutrition (EN) was used as supplemental nutritional therapy in adult patients with CD complicated by marked malnutrition as well as in undernourished and severely growth-retarded children with CD. The idea was to improve the nutritional status of patients prior to resection surgery. This treatment option showed unexpected and very powerful anti-inflammatory effects, and some patients did not require resection surgery anymore. Thus, EN was rapidly introduced as induction therapy for active CD. It is important to use EN appropriately to obtain its anti-inflammatory effects [13]. There is evidence that supplementary EN is not efficacious enough to induce remission in CD, while when given on an exclusive basis, without any additional food, a high anti-inflammatory effect can be obtained [14] (see below).

Efficacy of Exclusive Enteral Nutrition as Treatment Option for Crohn’s Disease

It is now well established that EEN has a strong anti-inflammatory effect with reduction of systemic and mucosal inflammatory parameters within few days [15]. So far, no controlled RCT compared EEN to placebo in children with CD. But several studies compared EEN with steroids leading to two pediatric meta-analyses as well as a Cochrane review combining pediatric and adult data and analyzing the efficacy of EEN as induction therapy for CD [16–18]. In the RCTs that compared EEN to steroids and used remission rates as outcome parameter, an overall combined remission rate of approximately 75% for EEN at the end of exclusive treatment has be shown. There was no marked difference to the remission rates obtained with steroid medication (fig. 1) in these two meta-analyses based on a total of 11 pediatric RCTs [19–28]. A further pediatric RCT was recently published [29], and several small open-labelled studies looked on the anti-inflammatory potential of EEN. It is somewhat challenging to summarize efficacy of EEN based on these open-labelled studies since there are major differences in the way EEN is performed with regard to the duration of exclusive EN, feed type, as well as the way efficacy is measured [30, 31]. Two recent large single-center studies, each based on more than 100 pediatric CD patients, further support the results of the RCTs, and both show a remission rate of approximately 80% [32, 33]. It is interesting to pin point that in the pediatric experience EEN has the same potential to induce remission as steroids, contrasting with adult data. These excellent results for EEN occur in IBD centers that regularly use EEN as a treatment option; however, in centers that rarely or almost never use EEN,
remission rates differ significantly, indicating that the successful use requires some experience.

Many different liquid nutritional products were tested in the treatment of CD, and as demonstrated by randomized controlled trials in children and in adults, the protein source in the feed does not affect its efficacy [27–29, 34]. Efficacy does not depend on the protein nature; polymeric as well as elemental feeds have the potential to equally induce remission in CD patients. However, acceptability and cost of EN differ markedly between elemental diet and polymeric feeds. Elemental feeds are less often tolerated by mouth, and patients most often require a nasogastric tube for treatment that is less well accepted by patients. In contrast, in patients receiving polymeric feeds [32], oral use is possible, making it the first choice for patients. We recently demonstrated that there is no significant difference in the potential to induce remission between 8 weeks of oral or continuous nasogastric feeds [32]. This is in keeping with studies that have given polymeric feeds only by nasogastric feeds: results were similar between children treated with oral or a combination of oral and nasogastric feeding. Therefore, in our center, we always offer patients oral feeds with a polymeric formula, while EEN via nasogastric tube remains reserved for patients unable to achieve the desired caloric intake or who refuse oral feed due to taste or texture. Elemental feeds should only be reserved for patient intolerant to cow’s milk proteins. It is of importance to offer an appropriate energy amount. Since most patients have weight loss and often growth retardation, the estimated energy requirements are above recommended intake; we most often

![Fig. 1. Meta-analysis of clinical trials comparing EN with glucocorticosteroid-induced remission in children with CD. Modified from Heuschkel et al. [16].](image-url)
use at least 120% of normal caloric requirement adapted to the age and the estimated catch-up growth.

The most important detail in the use of EN as induction therapy is the fact to use it on an exclusive basis, without any additional foods. In their RCT (exclusive EN vs. partial EN with normal diet over 6 weeks using an elemental formula), Johnson et al. [14] showed clear superiority of full EEN over partial EN in remission rates at 6 weeks [10/24 (42%) vs. 4/26 (15%)]. It is important to point out that in this study the induction of remission by EEN is markedly lower than most other published studies, and that there was a high dropout rate in both arms [14]. As highlighted in this study, compliance is a major issue, and probably one of the reasons why EN is less used in adult patients. Compliance is a priori not better in children, but since they have most often marked growth retardation and EEN allows efficiently gaining catch-up growth, their motivation to follow a complete cycle of EEN is in most studies excellent. In our personal experience, adherence to EEN is close to 90%, probably due to the way we monitor patients on EEN. They have a regular home visit by a dietician or nurse and patients are always seen within 4 weeks from starting EEN.

The duration of EEN treatment in clinical studies varies considerably (2–12 weeks), but the majority of clinical centers routinely use cycles of 6–8 weeks. As already mentioned, inflammatory parameters drop within days of starting EEN [15, 35, 36], but weight gain and catch-up growth require a longer treatment period. In addition, there is some evidence that use of at least 8 weeks of EEN allows to induce mucosal healing. Six different studies analyzed the potential of EEN to induce mucosal healing, with healing rates from 19 to 75% [15, 26, 32, 36–38]. There are clear differences between these studies in terms of definition of mucosal healing which make them difficult to compare. The rate of mucosal healing was markedly higher in patients on EEN compared to steroid-induced remission [26, 37]. One RCT included mucosal healing as outcome parameter, indicating a clear superiority of 10 weeks’ EEN compared to steroids, with mucosal healing rates of 74 versus 33% for EEN and steroids, respectively [26].

Recent studies measuring fecal calprotectin during EEN noted reduction in values continues up to 8 weeks. At the end point, many patients still have not achieved normal values, despite being in clinical remission with normalization of CRP, providing proxy evidence that longer courses may be more advantageous [29, 39].

**Who Are Optimal Candidates for Exclusive Enteral Nutrition?**

Initially, EEN was thought to work only in CD patients with small bowel disease, with some studies showing differential healing rates between ileal and colonic lesions [15, 40]. However, when cumulating all available stud-
ies, there is evidence supporting EEN as induction therapy for all CD patients with luminal disease regardless of site, which is further supported by the Cochrane meta-analysis. Indeed some recent studies specifically looking at patients with isolated colonic disease confirmed that remission rates are not different in this subgroup of patients from children with small bowel involvement \([17, 32, 33]\). There are no clear data regarding isolated perianal (and also oral) lesions; in some patients, these lesions tend to improve, but no study analyzed this adequately. It is important to mention that so far no study showed improvement of fistula with EEN. It seems that in CD luminal inflammatory lesions respond to EEN, while penetrating lesions do not. There are no data to support the use of EEN in patients with ulcerative colitis.

**Mode of Action**

While there is no doubt about the efficacy and the potential of EEN to treat CD, many questions arise regarding its mode of action. It was discussed that the reduced allergenic load, nucleotide-free diet, no addition of food additives, and anti-inflammatory lipid composition explain its efficacy. These might all be relevant factors in the anti-inflammatory reaction by the immune system which manifests within few days. A new hypothesis was developed recently in that EEN has a specific effect on the intestinal microbiota potentially correcting the observed dysbiosis in CD patients. First studies analyzed changes in the microbiome during and after EEN \([41–43]\). A recent study compared the composition of the intestinal flora of a CD patient with EEN-induced remission with that of a CD patient with steroid-induced remission \([43]\). This study showed that the microbiota is significantly different in patients with EEN-induced remission from that in patients with steroid-induced remission, while all patients were in complete clinical remission. These observations give a first basis for the understanding of the impact of EEN on dysbiosis in patients with CD.

In conclusion, EEN is a very safe and potent strategy to induce remission in patients with luminal active CD. Clinical trials showed that it works in pediatric and adult CD patients, but not in ulcerative colitis. The acceptability and compliance with the exclusivity principle of EN is the major obstacle of this strategy. As it became clear that oral use is as efficacious as the enteral route via nasogastric tube, the use of EEN might increase in the future. Growth retardation is a major indication for the use of EEN; therefore, it is more common in pediatric IBD centers, but there is no reason not to use EEN for treating adult patients.
with luminal CD. It constitutes a real alternative to immunosuppressive therapy for the treatment of CD due to its excellent safety profile and probably also its mode on action on top of the inflammatory cascade.

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**References**


