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Review

Exclusive Enteral Nutrition as an Effective Treatment in Inflammatory Bowel Disease

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Abstract

In recent years, the incidence of Inflammatory Bowel Disease (IBD) has risen significantly in the Western population, pointing toward the potential influence of environmental and dietary factors. In order to explain this, some research on nutritional therapy identifies exclusive enteral nutrition (EEN) as a highly effective approach for managing IBD in children. This treatment achieves high remission rates; more specifically, some clinical trials have reported remission rates from 70% to 100%. EEN not only facilitates mucosal healing but also exhibits a safer profile than corticosteroids (CS) and supports improved nutritional outcomes. After understanding the role of the microbiota in IBD, it has been discovered that EEN plays a fundamental role in modulating the microbiota and, consequently, the inflammatory response, reducing pro-inflammatory microbiota. Despite these promising effects, the implementation of EEN in clinical settings remains inconsistent across different regions and clinical guidelines. This narrative review seeks to gather and analyze the current literature on EEN and its impact on IBD, clarifying its mechanisms of action and examining its potential roles

in different scenarios, such as pediatric Crohn's disease, adult treatment regimens, preoperative care, and ulcerative colitis (UC) management.

Keywords
Exclusive enteral nutrition; inflammatory bowel disease; Crohn's disease; ulcerative colitis; gut microbiome; nutrition

1. Introduction

IBD is a chronic, systemic and immune-mediated condition characterized by metabolic alterations in the intestinal microbiota, leading to dysbiosis, which is defined as a reduction in gut microbial diversity [1]. Short-chain fatty acids, including acetate, propionate, and butyrate, are anti-inflammatory compounds produced through the breakdown of soluble fiber by particular microbiota species such as *Faecalibacterium prausnitzii*, *Clostridium leptum*, and *Bacteroides* at the intestinal level [2]. The rising incidence of IBD in Western populations indicates that diet and the intestinal microbiota play a role in the pathogenesis of IBD [3, 4].

Preclinical animal studies demonstrated that a diet rich in fats and sugars exacerbates intestinal inflammation by promoting an overgrowth of harmful bacteria (e.g., Proteobacteria) and depleting short-chain fatty acids-producing microbes [5].

The balance of gut bacteria is crucial in preventing IBD. In patients with IBD, there is a decrease in beneficial bacteria such as Firmicutes and Bacteroidetes, and an increase in harmful bacteria like Actinobacteria and Proteobacteria [6, 7]. In this regard, it has been observed that a diet high in calories and low in nutrient quality may disrupt gut microbiota homeostasis. Moreover, diets rich in processed and refined foods have been associated with IBD [8-11]. This disruption in gut microbiota homeostasis leads to an impairment of the intestinal barrier. It facilitates the translocation of bacteria and toxins, thereby activating immune response via triggering an inflammatory cascade response, directly influencing Farnesoid X receptor (FXR) signaling or via Toll-like receptors (TLRs) and NOD-like receptors (NLRs). These pathways, in turn, activate NF-κB, leading to the secretion of pro-inflammatory cytokines and type 1 T helper (TH1) cell activation, mechanisms that are dysregulated in patients with IBD [1, 12-14].

Although a causal relationship remains difficult to establish, emerging evidence points to a complex interplay between diet, microbiota, and immune dysregulation.

Furthermore, malnutrition, irrespective of IBD status, is associated with an immature gut microbiome dominated by facultative anaerobes and Gram-negative bacteria such as Enterobacteriaceae, which contribute to endotoxemia and systemic inflammation through lipopolysaccharide release [14, 15].

Given this imbalance, many studies have investigated the role of diet in managing IBD and even inducing remission. ESPEN guidelines [8] support EEN as the first line of treatment for mild to moderate Crohn's disease in children.

However, the effectiveness of other diets, including specific carbohydrate, Paleolithic, gluten-free, low FODMAP, anti-inflammatory, carrageenan-free, milk-free, red meat-restricted or -

enriched, vegetarian, and n-3 PUFA-rich diets, on intestinal inflammation and disease remission continues to be evaluated [8, 9, 12].

This review aims to provide a comprehensive overview of EEN in IBD, based on a literature search of PUBMED and MEDLINE databases from February 1987 to April 2024. Search terms included: ("Crohn's disease", "CD", "inflammatory bowel disease" OR "IBD") AND ("Exclusive", "only") AND ("Nutrition", "Feed", "Elemental", "formula", "enteral nutrition" OR "enteral"). The most relevant studies were selected based on their contribution to the understanding of EEN in pediatric patients with IBD.

2. Exclusive Enteral Nutrition

CS are often used to induce remission in IBD. Still, their use in children is associated with notable side effects, including growth delays with low bone mineral density and adrenal suppression [16, 17].

Since the initial success of EEN in treating Crohn's disease, numerous studies have shown that EEN is as effective as CS in inducing remission in children [18-21]. This has led to its growing adoption by gastroenterologists as a safer alternative to CS, particularly because EEN's side effects are generally mild and limited to gastrointestinal tolerability.

In 2014, the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Crohn's and Colitis Organization (ECCO) [13] recommended EEN as the first-line induction therapy for children with luminal Crohn's disease, citing its effectiveness and safety.

3. Exclusive Enteral Nutrition Formulas

EEN therapy is a short-term dietary intervention that involves consuming a complete nutritional formula as the only source of nutrition for 6-8 weeks, via oral route or nasogastric tube feeding. No other food or drink is allowed during this time. After this period, a regular diet is gradually reintroduced. Long-term EEN therapy is not feasible.

There are three major categories of enteral nutrition formulas, differentiated by the structure of their protein content; elemental diets with only amino acids, semi-elemental diets with peptides of varying length and polymeric diets with intact proteins which are more palatable and do not always require feeding tube to administer.

Enteral nutrition formulas are categorized into three groups based on their protein source: Elemental formulas contain only amino acids, semi-elemental formulas contain peptides, and polymeric formulas are made of intact proteins. The last one is often more palatable and can be consumed orally.

No specific type of enteral formula has been proven more effective than others in inducing remission in CD.

Berni Canani et al. [15] compared every type of formula versus each other and CS in 47 patients and demonstrated that they have similar efficacy in achieving remission. However, given the limited sample size and the fact that this effect has only been observed in this study, these findings should be interpreted cautiously when translating them into routine clinical practice.

Narula et al. [21] in their meta-analysis of 11 trials (378 participants) performed a subgroup analysis to evaluate the different types of elemental and non-elemental diets (elemental, semi-

elemental, and polymeric), and it showed no differences in remission rates. There was no difference between elemental and non-elemental diets in side event rates (RR 1.00, 95% CI 0.63 to 1.60) or withdrawals due to side events (RR 1.29, 95% CI, 0.80 to 2.09). Elemental formulas are unnecessary; intact protein formulas can be equally effective [21].

4. Mechanisms of Action

While the exact mechanisms of how EEN works are not fully elucidated, current hypotheses focus on the removal of dietary antigens and modulation of gut microbiota. This may involve altering the gut microbiome, immune response, and intestinal lining [22, 23]. The removal of food antigens prevents immune cells from reaching the gut mucosa, which lowers the inflammatory response [24].

Some theories suggest that EEN may work by reducing the synthesis of pro-inflammatory cytokines. In vitro studies have shown that EEN has a direct anti-inflammatory effect on enterocytes, where adding a polymeric formula resulted in lower levels of IL-8 and IL-6 in response to a pro-inflammatory stimulus [25]. Additionally, EEN may increase the concentration of other systemic circulating anti-inflammatory cytokines, such as transforming growth factor (TGF) beta-1, and modulate the response of regulatory T cells that promote anti-inflammatory processes in the mucosa [26].

Breese et al. [27, 28] also demonstrated that EEN can decrease the levels of various inflammatory cytokines, such as interleukin-2, interferon *γ* and tumor necrosis factor *α,* which was correlated with histological healing.

Additionally, EEN may help to promote tissue repair by increasing the production of healing factors like TGF-beta1 and decreasing the levels of vascular endothelial growth factor (VEGF), achieving clinical remission [29, 30].

EEN has been shown to reduce systemic markers of inflammation. A prospective study involving thirty-two patients with active Crohn's disease found that two weeks of EEN led to significant improvements in disease symptoms ($p = 0.003$), as well as decreases in blood markers of inflammation, such as insulin-like growth factor-1 ($p = 0.006$), serum c-reactive protein (CRP) ($p = 0.005$), and fecal markers of inflammation, such as calprotectin ($p = 0.028$) [31].

In addition to reducing these pro-inflammatory cytokines, EEN reduces growth failure in CD linked to increased circulating IL-6, TNF-α and TNF-γ [32]. There is an ongoing question as to whether the improvement in growth seen with EEN is due to improved nutritional status and/or reduction in pro-inflammatory cytokines. In this regard, malnutrition has been associated with a pro-inflammatory state. In patients with IBD, there is a chronic inflammation and an increase in the cytokines above, which leads to decreased appetite, weight loss, and muscle wasting, ultimately resulting in protein-energy malnutrition. Moreover, chronic malnutrition further aggravates muscle degradation, reduces protein synthesis, and lowers albumin levels, worsening the negative nitrogen balance already present in IBD. In cases of severe malnutrition, mitochondrial impairment weakens energy production, making the inflammatory process more metabolically demanding and depleting vital nutrients necessary for immune function. This creates a cycle in which inflammation and malnutrition perpetuate each other, delaying tissue healing and increasing the risk of further metabolic decline, especially during disease relapses [14, 15].

Other theories suggest that certain foods in the diet (such as wheat, emulsifiers, and some fatty acids) cause damage to the epithelial cell tight junctions or mucus function, disrupting the intestinal

barrier. By eliminating these compounds from the diet through EEN, intestinal barrier integrity and mucus function would be restored, contributing to an improvement in the disease [33].

5. Clinical Remission Rates

This treatment can effectively induce biochemical and clinical remission in up to 80% of children [18, 21]. It is more effective than CS in reducing short-term inflammation in the gut lining and improving the Pediatric Crohn's Disease Activity Index (PCDAI) [19, 20, 34]. A study by Navas-López et al. [35] found that 80% of 40 children treated with EEN achieved remission after 6-8 weeks, and an even higher percentage (92%) achieved remission among those who completed the full course of treatment. Table 1 summarizes 7 studies comparing EEN to CS for the induction of clinical remission in Crohn's disease. Among the predictive factors associated with a better response are mild to moderate disease (wPCDAI < 57.5), fecal calprotectin (FC) < 500 μg/g, ileal involvement, and CRP > 15 mg/L [36, 37]. On the other hand, poor adherence is one of the main predictive factors for failure. While adherence in children exceeds 80%, it does not reach more than 60% in adults, which may explain a significant part of the differences observed between children and adults [38-40].

Table 1 EEN vs CS for the induction of clinical remission in Crohn's disease.

Author	Year	Type of study	Total patients	Type of EEN used and dose	Duration of treatment	EEN remission rates
Berni Canani et al. [15]	2005	Retrospective	37	Elemental (475 kcal/100 g) Semi-elemental (497 kcal/100 g) Polymeric (500 kcal/100 g)	8 weeks	86.5%
Borreli et al. [41]	2017	Open-label, randomized, prospective, controlled trial	19	Oral polymeric diet 14% protein content, 44% carbohydrate and 42% fat. 1 kcal/mL calorie density.	10 weeks	79%
Lamber et al. [42]	2021	Retrospective	60	Extensively hydrolyzed formula 50–60 kcal/kg/d	4-8 weeks	85%
Luo Y et al. [43]	2015	Retrospective	10	Oral polymeric 117.9 ± 4.2 kcal	9.2 weeks	90%
Levine et al. [44]	2014	Prospective	43	Polymeric formula	8-12 weeks	83%
Pigneur et al. [45]	2019	Randomized controlled trial	13	MODULEN IBD® 100 kcal 3.6 g protein 11 g carbohydrate 4.6 g fat	8 weeks	100%
Grover et al. [46]	2013	Prospective, single-center and open-label	26	Nutrison (1 kcal/ml, Nutricia UK, 40 g protein, 39 g fat/1000 ml) or resource protein (1.25 kcal/ml, Nestle, 18.8 g protein, 7 g fat/200 ml)	8 weeks	84%

6. Preoperative Exclusive Enteral Nutrition

Surgical intervention in Crohn's disease is often reserved for complications or refractory cases. This often leads to higher risks of post-operative complications due to factors such as compromised immune function, infection, and malnutrition [47]. Therefore, pre-surgical optimization plays a key role in patients with IBD.

A retrospective case–control study comparing patients with structuring or penetrating CD who received pre-operative EEN to those who underwent surgery without pre-operative optimization found that 25% of patients treated with EEN (Modulen IBD™), with a mean duration of 6.3 weeks and oral volumes determined by energy requirements and individual tolerance, avoided surgery and were able to receive alternative therapies. Patients who were under EEN treatment also had shorter surgeries and significantly fewer post-operative complications compared to those who did not (8% vs 32%, $p < 0.001$). A significant decrease in CRP was also observed in the EEN group. The control group had a ninefold increase in post-operative abscesses and/or anastomotic leaks (OR 9.1; 95% CI 1.2-71.2, $p = 0.04$) [48].

Evidence suggests that nutritional "prehabilitation" using EEN before surgery can be beneficial. Studies conducted in adult patients with CD and malnutrition showed that pre-operative EEN improved disease activity, reduced CRP levels and improved nutritional status [49-52]. Furthermore, patients with CD and malnutrition who received preoperative EEN had low postoperative complication rates, similar to CD patients with good physical condition [30]. EEN before surgery is an independent protective factor against various postoperative complications [50, 52].

EEN response is higher when the patient meets some conditions, such as younger age, male sex, serum albumin >3.5 mg/L, and milder disease activity [51, 53]. On the contrary, the factors associated with adverse outcomes are disease location (L3 vs L1), high CRP, and operative time [52, 54]. Regarding the phenotype of Crohn's disease, most studies include patients with penetrating disease. However, those that include patients with both penetrating and stricturing phenotypes do not perform a subgroup analysis to determine whether one group responds better than the other to EEN.

A study by Zhen Guo et al. [55] demonstrated that pre-operative EEN using a polymeric formula (Nutricia™) with a goal calorie intake of 20–25 kcal/kg body weight per day can reduce post-operative complications in IBD surgery. Patients who received pre-operative nutritional therapy had lower rates of anastomotic leakage (2.3% vs 17.9%, $p = 0.023$) and temporary diverting stomas (22.8% vs 40.9%, $p = 0.036$) compared to those without preoperative optimization, findings consistent with those reported in other studies [51, 56]. Low serum albumin levels before surgery and pre-operative nutritional therapy were identified as independent risk factors for anastomotic leakage.

High levels of inflammation and malnutrition have been linked to increased rates of postoperative complications in CD [52, 57, 58].

However, as highlighted by some systematic reviews, these data should be interpreted cautiously, as the current evidence is generally of medium to poor quality and is retrospective, with inadequate controls. The improvement observed in these studies may be overestimated, as the benefits of EEN could be attributed to the improvement in the nutritional status of patients with malnutrition rather than to any specific advantage over other forms of nutrition. Additionally, multiple other factors that could be acting as confounding factors and could impact nutritional markers, stoma creation,

and infectious complications, such as frailty, comorbidity, steroid and immunosuppressant use, smoking status, and surgeon-related factors such as decision-making around the timing of surgery [51, 59]. Therefore, high-quality randomized controlled trials are warranted to validate these findings.

7. Mucosal Healing

A systematic review performed by Swaminath et al. [18] compared the effectiveness of CS and EEN in children with CD.

While both treatments were found to be equally effective in terms of inducing remission (OR = 1.26 [95% CI 0.77, 2.05]), mucosal healing was higher among patients receiving EEN compared to CS (OR = 4.5 [95% CI 1.64-12.32]).

This meta-analysis includes eight trials with 226 children with CD treated with EEN and 225 children with CD treated with CS for newly diagnosed or relapsed disease. To investigate whether treatment efficacy varied between patients with newly diagnosed CD and those with relapsed disease, the studies were analyzed separately.

Studies focusing on newly diagnosed patients (Borrelli et al. [41], Lambert et al. [42], Lou et al. [43], and Levine et al. [44]) found no significant differences between EEN and CS in inducing remission (OR 1.61, 95% CI 0.87-2.98). Similarly, a subanalysis of studies on relapsed patients (Sanderson et al., Kierkus et al., and Hojsak et al.) showed no significant differences between EEN and CS in inducing remission (OR 0.76, 95% CI 0.29-1.98).

Studies by Borrelli et al. [41] and Berni Canani et al. [15] demonstrated that EEN was significantly more effective than CS in achieving mucosal healing. Patients receiving EEN were 4.5 times more likely to achieve mucosal healing than those receiving CS (OR 4.50, 95% CI 1.64-12.32), being statistically significant.

The higher rate of mucosal healing proven in patients treated with EEN is associated with a change in the gut microbiota composition. Bénédicte Pigneur et al. [45] designed an RCT in children with CD in search of knowing if the microbial composition changed if the patient achieves mucosal healing or not. Nineteen patients were included in their trial, six with CS and thirteen with EEN. All EEN patients and five out of six steroid patients experienced clinical remission (HBI < 5) at eight weeks; the EEN group's mucosal healing rate was higher at 89% than the steroid group's (17%). Regarding the gut microbiome composition, patients who obtained remission had a higher proportion of Clostridium and Ruminococcus bacteria.

Furthermore, transmural inflammation may resolve as a result of EEN. Thirty-four children with CD had an 84% remission rate, and 58% of them had an early endoscopic response, according to Grover et al. Before and after EEN, they conducted magnetic resonance enterography, which showed that three out of fourteen patients had fully healed transmurally [46].

8. EEN in Nutritional Status

Children with CD often experience malnutrition due to poor intake, malabsorption, and chronic inflammation.

Malnutrition is associated with increased in-hospital mortality and length of stay among inpatients with IBD [60].

In children with active CD, EEN has a positive impact on their nutritional status, growth rate, and skeletal system condition [61, 62]. Conversely, CS causes a decrease in bone density and growth delay.

According to a retrospective pediatric study, EEN considerably decreased linear growth failure and corticosteroid reliance [63].

In another prospective study where participants were randomized to receive only medication treatment or a short-peptide plus medication treatment, the Z-scores for weight-for-age, body mass index, and albumin levels were higher in the short-peptide plus medication treatment group than in the medication treatment group ($p < 0.05$).

The short-peptide plus medication treatment group's total protein levels were considerably greater than the medication treatment group's ($p < 0.05$) in individuals with moderate to severe CD [64].

Twenty kids with active CD who were given an EEN with polymeric industrial food for six weeks had their nutritional status results analyzed by Malgorzata Matuszcyk et al. [61]. Thirty percent of patients were malnourished at baseline, and two-thirds of them had a BMI score within the normal range following treatment. Before the introduction of EEN, a growth deficiency was noted in 25% of patients. In general, 55% of children and 80% of those with initial growth failure experienced a gain in body height.

9. EEN as a Therapy in Adults

EEN demonstrates greater effectiveness in children than adults; however, the underlying reasons for this disparity are not fully elucidated [31]. Current clinical guidelines for adults do not include recommendations for EEN, with the notable exception of Japan, where EEN is endorsed as a first-line treatment, achieving reported remission rates of approximately 80% [65, 66].

Some studies have shown lower efficacy of EEN in the adult population and, in some cases, lower efficacy than CS [21]. The meta-analysis by Schwab et al. [67] analysed results from 571 patients on elemental, oligopeptide, and polymeric EEN, showing clinical remission rates from 55% to 66% on an intention-to-treat basis, but on per-protocol analysis, clinical remission rates were from 67% to 73%.

A narrative review encompassing seven studies comparing EEN and CS in adults with CD suggests that EEN may be equally effective to CS when adherence is achieved, with remission rates ranging from 23% to 100% for EEN and 30% to 100% for CS [68].

Studies of adults with CD on EEN induction of remission have shown overall less efficacy, and CS have been more effective than EEN. Among the proposed factors that could explain these differences between pediatric and adult patients with CD are: disease localization, as pediatric cases are more commonly ileal, a phenotype that demonstrates a better therapeutic response to EEN, and the shorter disease duration at the time of diagnosis in pediatric patients, that may enhance treatment responsiveness. However, the most critical determinant is likely patient adherence, which is generally higher in the pediatric population, thereby improving the overall effectiveness of EEN in this group [38, 40, 68].

The poor adherence in adults is often attributed to the unpalatable nature of enteral nutrition formulas. Notably, studies involving nasogastric tube administration of EEN in adults have reported efficacy comparable to that observed in pediatric populations [69, 70].

Emerging evidence suggests that EEN may be particularly effective in adults with newly diagnosed CD and those with ileal involvement. However, additional research is needed better to define its role in adult care [68]. A prospective non-randomized pilot study of adults demonstrated that two weeks of EEN significantly improved clinical symptoms, inflammatory markers and nutritional status [31].

10. EEN in UC

Currently, there is no scientific evidence supporting the routine use of EEN for inducing remission in UC. However, EEN may benefit UC patients by improving symptoms and nutritional status [71].

In a study conducted by Pabitra Sahu et al. [72], the efficacy of EEN as an adjunctive therapy to intravenous CS was evaluated in patients with acute severe UC. Participants were randomized in a 1:1 ratio to receive either EEN or standard of care (SOC). The primary endpoint was corticosteroid failure, defined as the need for salvage medical therapy or colectomy. Results showed a lower corticosteroid failure rate in the EEN group compared to SOC, both in the intention-to-treat analysis (25% vs 43%, $p = 0.051$) and the per-protocol analysis (19% vs 43%, $p = 0.04$). However, there was no significant difference in colectomy rates between the groups (9% vs 13%; $p = 0.41$).

Aditya Bajaj et al. [73] further demonstrated the potential of EEN-supplemented corticosteroid therapy in enhancing clinical responses. Their analysis of stool samples from patients with active UC, who received either EEN-conjugated SOC or SOC alone, revealed notable microbiota changes. In the EEN group, there was an increased abundance of beneficial bacterial genera, including *Faecalibacterium* and *Veillonella*, and a reduction in *Sphingomonas*. These changes were accompanied by improvements in analytical parameters, such as serum albumin and CRP levels, which were not observed in the SOC group.

Other types of dietary interventions show promising results in UC; however, the available evidence on these interventions is still minimal. Various diets rich in fruits, vegetables, legumes, and whole grains, such as the Mediterranean diet, have been studied with favorable results, based on the premise that they can modify the microbiota and address dysbiosis [74]. Some studies have shown that the Mediterranean diet can lower calprotectin levels in the pediatric population and in patients after reconstructive proctocolectomy with ileo-rectal anastomosis and a created intestinal reservoir [75, 76].

Other, less conventional diets, such as the Ulcerative Colitis Exclusion Diet (UCED), have also been evaluated. The goal of this diet is to reduce exposure to sulfur-containing amino acids, limit the intake of animal fats, saturated fatty acids, polyunsaturated fatty acids, heme, and food additives, while increasing fiber and monounsaturated fat consumption. After 6 weeks of treatment in the pediatric population, this diet achieved clinical remission in 37% of patients and 50% when combined with pharmacotherapy, along with a reduction in calprotectin levels from 818 μg/g to 592 μg/g. However, its efficacy has only been assessed in a prospective, multicenter pilot study with a small sample size ($n = 24$) [77].

11. Conclusion

The rising incidence of IBD highlights the need for effective and well-tolerated therapies.

Understanding the pathogenesis of IBD and knowing that gut microbiota plays a key role in this, it is necessary to integrate dietary interventions into IBD treatments.

EEN has been demonstrated to be a safe and effective therapy, achieving clinical and biochemical remission rates of up to 80%. Compared to CS, EEN may offer superior benefits in promoting mucosal healing with fewer adverse events.

Therefore, EEN should be considered as a first-line therapy in pediatric settings.

Nevertheless, we need further investigation to prove these positive outcomes in adults conducting multicentric trials.

Author Contributions

APG: Study concept and design, writing – original draft, writing – editing and review. IE: Study concept and design, writing – original draft, writing – editing and review.

Competing Interests

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