Chapter 5

Exclusive and Partial Enteral Nutrition in Crohn's Disease

Darja Urlep, Evgen Benedik and Rok Orel

Additional information is available at the end of the chapter

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Abstract

Exclusive enteral nutrition (EEN) is a well-establised primary therapy in active pediatric Crohn's disease (CD). EEN promotes mucosal healing, restores bone mineral density, and improves growth. On the contrary, treatment of active CD with corticosteroids (CS) has a strong negative impact on the linear growth and bone density. Therefore, EEN is recommended as a first-line therapy in children with active CD. EEN has been evaluated in a number of clinical studies including randomized controlled trials. While meta-analyses of adult studies suggest superiority of CS, pediatric studies have shown that EEN is at least as effective as CS in inducing remission. The mechanisms by which EEN suppresses inflammation are not yet fully elucidated. Hypotheses include improvement in nutritional status, decreasing of the inflammatory cascade mechanism, limiting luminal antigen exposure, improving intestinal permeability, and modification of intestinal microbiota.

Keywords: Crohn's disease, exclusive enteral nutrition, partial enteral nutrition, children, adults

1. Introduction

Inflammatory bowel disease (IBD) is an immune-mediated condition, which includes Crohn's disease (CD), ulcerative colitis (UC), and IBD-unclassified (IBD-U) [1]. Nearly 25% of patients are diagnosed before 16 years of age. A number of studies have shown that pediatric-onset IBD presents with a more difficult phenotype when compared to adult-onset IBD and may have the consequences of growth retardation and delayed puberty as well as the psychological consequences of disease onset at a very vulnerable time of psychosocial development [2–5].

Exclusive enteral nutrition (EEN) is successful in the treatment of undernutrition. Moreover, EEN is able to induce remission in CD patients with active inflammation. The European Society of Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Crohn's Colitis Organization (ECCO) recommend EEN as a first-line therapy in children with active CD and emphasize the use of EEN over CS in all children with active inflammatory intestinal luminal disease, including colonic involvement [6].

The therapy with EEN provides all of the nutritional needs by a liquid formula either orally or through a nasogastric tube. EEN is usually recommended for 6–8 weeks, and after this period, a normal diet is gradually reintroduced. For EEN therapy, elemental, semi-elemental, or polymeric formulas may be used. Elemental formulas are based on amino acids and contain no whole proteins, while semi-elemental formulas do contain peptides of varying lengths. Polymeric formulas are based on whole proteins and are therefore more palatable [7]. In addition, polymeric formulas usually cost less. The choice of formula most frequently depends on the clinician's experience and local availability [8].

EEN is especially recommended in CD children with stunted growth and in those presenting with low weight and a catabolic state. If EEN is not tolerated orally, a nasogastric tube may be used [6].

Nevertheless, EEN therapy remains underused in clinical practice, especially in adults in whom its efficacy in achieving clinical remission is considered to be less than the standard anti-inflammatory therapies [9].

In current review, different aspects of EEN as well as partial enteral nutrition (PEN) will be addressed, including their efficacy, treatment modalities, impact on mucosal healing, mechanisms of anti-inflammatory effects, and the role of enteral nutrition in maintaining remission.

2. The history of exclusive enteral nutrition

The first report on successful use of enteral feeding was published in 1973 by Voitk et al. It demonstrated improvement in inflammatory indices and weight gain in 13 patients. Nine of them were planned for surgery and two of them were able to avoid it after a period of exclusive elemental formula treatment [10].

In 1981, Logan et al. found a decrease in the number of gut lymphocytes and diminished protein loss when elemental enteral nutrition was used in patients with extensive small bowel CD [11].

Navarro et al. studied the efficacy of continuous elemental EEN on 17 pediatric patients with active CD and demonstrated that EEN was successful in inducing clinical remission. Additionally, therapy with EEN was proven to be safe and well tolerated [12].

Five years later, O'Morain et al. found that elemental EEN was equally successful or even more effective than steroids in inducing clinical remission in adults with active CD [13]. However, in 1995, a meta-analysis by Griffiths et al. demonstrated that therapy with EEN

was significantly less effective compared to CS in a mixed population of adult and pediatric patients with CD [14]. But in 1997, in a randomized controlled trial by Zoli et al., EEN with an elemental diet was again shown to be equally effective as CS in inducing remission in a cohort of adult patients with both mild and moderately active CD [15].

3. Elemental versus polymeric enteral feeds

In the 1990s, both elemental and polymeric enteral nutrition were used in the largest pediatric inflammatory centers in United Kingdom as a first line of treatment of active CD. Clinical studies were then conducted to compare elemental versus polymeric enteral formulas [16]. In a randomized controlled trial by Rigaud et al., no significant difference was found in inducing clinical remission in adult CD patients between elemental and polymeric enteral formulas [17]. Ludvigsson et al. conducted a multicentre randomized control trial to compare the efficacy of elemental and polymeric formulas in children with active CD. The efficacy in inducing remission was found not to be different between elemental (E028E; Nutricia) and polymeric formulas (Nutrison Standard; Nutricia). However, patients who were receiving polymeric formula had better weight gain [18].

In a meta-analysis by Griffits et al., the efficacy of EEN therapy with elemental versus nonelemental formulas was compared. They demonstrated that there was no significant difference in the efficacy between the elemental and nonelemental formulas [14].

4. The efficacy of exclusive enteral nutrition versus corticosteroids

EEN has been evaluated in a number of clinical studies including randomized controlled trials (RCTs) that compared EEN with CS in adult and pediatric populations of patients with active CD. To date, eight meta-analyses have been published on the efficacy of EEN versus CS. Among these meta-analyses, three of them were performed exclusively on the pediatric population, whereas others included adult patients as well. While meta-analyses of adult studies have suggested better efficacy of CS, pediatric studies have shown that EEN is at least as effective as CS in inducing remission and is superior to CS in improving nutritional status and growth recovery without adverse side effects [19].

4.1. Efficacy of EEN versus CS in adult and mixed population of CD patients

In the first meta-analysis by Fernandez-Banares et al., the therapy with EEN was significantly less effective compared to CS. The meta-analysis included nine trials with mostly adult CD populations. The overall remission rate was 57.7% for EEN and 79.4% for CS [20]. A meta-analysis by Messori et al. included studies exclusively on the adult CD population which compared the effectiveness of EEN versus CS. The patient-specific end-point of the meta-analysis was occurrence of treatment failure. CS were more effective than EEN for inducing remission in adult active CD. In fact, the relative risk of treatment failure (RTF) was significantly lower in the steroid

group than in the EEN group. They concluded that the data examined in this meta-analysis do not support the use of EEN as primary treatment for acute exacerbations of CD in adults [21]. In 1995, Griffiths et al. included eight RCTs (mixed adult and pediatric CD of 413 patients) comparing EEN with CS. Odds ratios (OR) for likelihood of clinical response were calculated. They found that EEN was inferior to CS (OR 0.35; 95% CI 0.23–0.53) [14]. A similar meta-analysis was performed in 2001 by the same team of authors from Toronto. In accordance with the stricter inclusion criteria, only four RCTs were included (130 patients treated with EEN and 123 treated with CS). The meta-analysis yielded a pooled OR for remission of 0.30 favoring CS therapy (95% CI 0.17–0.52) [22]. This meta-analysis was updated in 2007 and included six clinical trials with 192 patients treated with EEN and 160 treated with CS. The pooled OR for remission, after combining all type of enteral diets and comparing them with CS therapy, was 0.33 favoring steroid therapy (95% CI: 0.21–0.53) [23].

4.2. Efficacy of EEN versus CS in pediatric CD population

The first meta-analysis on pediatric population was published in 2000 by Heuschkel et al. The meta-analysis included five RCTs and was composed of 147 pediatric patients with active CD, and it demonstrated that EEN was equally effective as CS in inducing remission (relative risk (RR) = 0.95; 95% CI: 0.67–1.34). EEN was, however, superior in improving growth and pubertal development. Additionally, EEN seemed to be without the side effects. According to the results of this meta-analysis, EEN was then recommended as a first-line therapy in children with active CD [24]. The same results were demonstrated 7 years later in a meta-analysis by Dziechciarz et al. Only four RCTs (144 pediatric CD patients) met the inclusion criteria. No significant difference in remission rates between the patients receiving EEN and CS was found [25].

In the most recent published meta-analysis by Swaminath et al., eight clinical studies (451 pediatric CD patients) were included based on the inclusion criteria and availability of data that could be abstracted into meta-analysis. The efficacy in inducing remission was not different between EEN and CS (OR = 1.26; 95% CI 0.77–2.05). The authors also compared the efficacy between EEN and CS treatment in newly diagnosed CD patients (OR = 1.61; 95% CI 0.87–2.98) with relapsed patients (OR = 0.76; 95% CI 0.29–1.98) [26].

5. Recommendations on exclusive enteral nutrition in adult patients with Crohn's disease

To date, according to the results of meta-analyses on the adult CD population, EEN appears to be less effective than CS. Therefore, therapy with EEN is used as a first-line treatment in active CD only when therapy with CS is contraindicated [27].

In the current ECCO consensus guidelines for medical management of adult CD, therapy with enteral nutrition is regarded as a complementary treatment to improve nutrition and not as a primary therapy. It is still considered appropriate to use EEN in patients who decline all other drug therapies [28]. Further studies on EEN use as a primary therapy to induce remission in adult CD patients are needed to clarify the efficacy of EEN. The reasons for the difference

in the efficacy of EEN between the pediatric and adult CD population have still not been elucidated. In adult IBD patients, who have a longer disease course and more frequent complications, EEN may be less effective. EEN may not be so strictly adhered to in adult patients, when compared to children, who are supervised by their parents. Furthermore, children and especially adolescents are generally more motivated to achieve success through this therapy. Most of them refuse CS treatment due to the unpleasant side effects related to appearance such as facies lunata, acne vulgaris, and increased hairiness.

6. Exclusive enteral nutrition and mucosal healing

Mucosal healing is an important therapeutic endpoint that, when achieved early, is associated with fewer hospitalizations, reduced surgical resections, lower risk of fistulizing disease, and less use of biologic drugs [29–32]. It is well established that treatment with EEN is capable of achieving mucosal healing in CD. On the contrary, CS have poor ability to induce mucosal healing. A study made in 1990, on the effects of prednisolone on mucosal healing in patients with active CD, found that 27% of patients still had minor lesions and only 12% achieved complete mucosal healing after 4–7 weeks of CS therapy [33]. Similarly, none out of eight patients with CD, treated with prednisolone for postoperative recurrence, showed mucosal healing after 6–9 weeks, based on the overall endoscopic assessment of the mucosa rather than a detailed endoscopic score [34]. These findings suggest that CS have little or no positive effects on induction of mucosal healing in CD. In a RCT in children with active CD, Borrelli et al. compared not only the efficacy of EEN versus CS in inducing clinical remission but also in achieving mucosal healing. The therapy with EEN was superior in achieving mucosal healing compared to CS. Mucosal healing was found in 14 of 19 CD patients (74%) in the EEN group and in 6 of 18 patients in the CS group (33%, $p < 0.05$) [35]. In a retrospective study by Berni Canani et al., 65% of pediatric CD patients on EEN therapy and 40% on CS ($p < 0.05$) achieved improvement in mucosal inflammation. Seven patients on EEN and none on CS were found to have complete mucosal healing ($p < 0.005$) at the end of treatment. In addition, the duration of clinical remission was longer in the EEN group when compared with the CS group [36]. Recently, Grover et al. had used the Simple Endoscopic Score for CD (SES-CD) to define endoscopic mucosal lesions in 26 children with active CD receiving EEN for 8 weeks. At the end of the EEN therapy, 42% of patients had complete mucosal healing (SES-CD = 0) and the other 58% had complete or near-complete mucosal healing (SES-CD < 3) [37]. Mucosal healing after EEN therapy was also demonstrated in the adult population of active CD patients. In a study by Yamamoto et al., a 4-week therapy with EEN has shown a complete endoscopic remission rate of 44% in the terminal ileum and 39% in the colon [38]. In a recent pediatric meta-analysis by Swaminath et al., two pediatric studies provided data on mucosal healing at the end of induction therapy with EEN versus CS [35, 36]. The occurrence of mucosal healing was significantly more likely in the group of CD children, who were receiving EEN, compared to those receiving CS (OR = 4.5; 95% CI 1.64–12.32) [26]. Furthermore, Rubio et al. compared fractionated oral versus continuous enteral feeding in terms of clinical and mucosal healing and have demonstrated similar rates of mucosal healing in patients receiving ether fractionated or continuous enteral feeding [39].

7. Disease location and efficacy of exclusive enteral nutrition

In the early 2000s, EEN was especially used in CD patients with small bowel disease. That was in accordance with the results of a clinical trial by Afzal et al. which have shown that EEN was less effective in CD patients with colonic disease in comparison with those who had only small bowel involvement or small and large bowel disease [40]. However, recent studies and meta-analyses have not confirmed this negative association [23, 25]. Buchanan et al. found no significant differences in remission rates in terms of disease location [41]. Similar findings were reported in a study by Rubio et al. where the site of disease activity had no impact on response to nutritional therapy [39]. The same results were demonstrated in a study by Gupta et al. where the location of the inflammation in CD did not affect the efficacy of EEN [42].

8. The long-term efficacy of exclusive enteral nutrition

The long-term efficacy of the induction therapy with EEN is not yet well established. Studies comparing the long-term outcomes of EEN versus CS treatment are limited. In a retrospective study by Lambert et al., a lower 1-year (61 versus 77%) and 2-year relapse rate (61 versus 89%) was demonstrated in CD children who were treated with EEN in comparison with those receiving CS [43]. Grover et al. have shown that induction therapy with EEN was superior to CS in reducing growth failure, CS dependency, and loss of response to infliximab over the first 2 years [44]. In a retrospective German study, most of the pediatric patients with active CD, treated with EEN, relapsed during the first year. Fortunately, 66% of them responded to a second course of EEN with remission [45]. In a recent study by Connors et al., both short- and long-term outcomes of EEN and CS induction therapy were examined. Out of 127 patients reviewed, a total of 111 propensity score-matched CD patients receiving EEN (n = 76) or CS (n = 35) were analyzed. Their data showed that clinical remission after EEN was superior to that after CS treatment, with 86.6 versus 58.1% of patients reaching remission within 4–12 weeks of starting treatment. This study supports a more optimistic view toward EEN as an approach to CS avoidance: over 40% of EEN-treated patients in their cohort remained steroid naive for at least 4 years. In addition, patients treated with EEN exhibited significantly greater improvement in height z-scores than patients treated with CS, at 1-year follow-up. The therapy with EEN over CS for induction of remission was associated with avoidance of CS over a 6-year follow-up period. This study showed that long-term steroid avoidance via EEN therapy is feasible without an increased need for escalation to anti-tumor necrosis factor alpha (anti-TNF-α). Most of the patients in the EEN-treated group who remained steroid-naive for 2 and 4 years had also not been exposed to anti-TNF-α, indicating that early anti-TNF-α use could account for only a minor portion of steroid avoidance in this group. They concluded that EEN induction therapy is more effective in achieving early remission and is associated with long-term steroid avoidance without increased use of biologics or need for surgery [46].

9. Current practice

Despite the reported benefits, EEN is not universally used in pediatric centers. Wide differences have been noted in the use of EEN between pediatric gastroenterologists in Europe and North America [47, 48]. A questionnaire-based study by Whitten et al. has shown wide variations in EEN protocols used in different areas of the world. Thirty-five centers were included in the study. The most centers recommend a 6–8 week therapy with polymeric formula and the gradual introduction of food quantity over 4–6 weeks [49].

10. The role of exclusive enteral nutrition in improvement of nutritional status and linear growth

Patients with IBD and especially children and adolescents often present with symptoms of undernutrition [50]. Both inflammation and undernutrition contribute to decreased height velocity [5]. Linear growth patterns correlate with disease activity, and there is strong pathophysiological evidence that inflammation interferes with the growth hormone axis [51, 52]. EEN decreases proinflammatory cytokines, including IL-6 and TNF-α, after which an increase in growth hormones (IGF-1 and IGFBP-3) is observed within 2 weeks of treatment [53]. It is not only that EEN decreases inflammation, it improves malnutrition and other specific nutritional deficiencies as well. Nutritional supplementation plays an important role in linear growth improvement. Importantly, EEN may also influence growth recovery in pediatric CD patients by limiting chronic corticosteroid exposure, which is a significant contributing factor toward growth failure [46, 54].

11. The role of preoperative exclusive enteral nutrition

To date, few experiences have been reported on the role of preoperative EEN in diminishing postoperative complications after bowel resections or other surgical interventions in patients with IBD. Li et al. investigated the influence of preoperative 3-month EEN on the incidence of postoperative intra-abdominal septic complications in CD patients with enterocutaneous fistulas. A retrospective study on 123 CD patients suffering from enterocutaneous fistulas was performed. The patients were divided into an EEN or a non-EEN group. A significantly lower rate of postoperative intra-abdominal septic complications was demonstrated in the EEN group versus the non-EEN group (3.6 versus 17.6%, $p < 0.05$). The results of this study have shown that preoperative EEN is an important factor for reduced risk of postoperative intra-abdominal septic complications [55]. The authors from the same IBD centre conducted another study to evaluate the impact of EEN on the perioperative outcome in CD patients following immunosuppressive therapy. There was a significant difference observed in the incidence of postoperative complications between the groups of CD patients who received and those who did not receive EEN ($p < 0.05$). In addition, the use of EEN decreased the need for urgent surgery and reoperation [56].

12. Mechanisms of action of exclusive enteral nutrition

Therapy with EEN substantially attenuates intestinal inflammation in CD patients. However, the mechanisms by which EEN suppresses inflammation are not yet fully understood. Hypotheses include improvement in nutritional intake and nutritional status, decreasing of the inflammatory cascade mechanism, limiting luminal antigen exposure, improving intestinal permeability, and modification of the intestinal microbiota [57]. Significant progress has been made in understanding mechanisms of how EEN suppresses inflammation. Basic research has demonstrated that EEN has direct anti-inflammatory properties, can correct localization of tight junction proteins and has other important impacts on intestinal permeability, alters micro RNAs expression, and profoundly affects the intestinal microbiota [58].

12.1. Anti-inflammatory effect of EEN

It is clear that EEN suppresses intestinal inflammation. In 1981, Logan et al. found a decrease in the number of gut lymphocytes and diminished protein loss when elemental enteral nutrition was used in patients with extensive small bowel CD [11]. In 1995, Breese et al. demonstrated that therapy with EEN reduced the number of lymphokine-secreting cells in the gut mucosa in CD [59]. Three years later, Beattie et al. reported on different mechanisms of action of EEN in CD. EEN was shown to be able to reduce the number of cytokine-producing cells in the inflamed mucosa of CD patients [16]. In a study by Fell et al., a decline in ileal and colonic interleukin-1beta mRNA was observed after 8 weeks of oral polymeric diet. In addition, a decrease of interferon gamma mRNA with a rise of transforming growth factor beta1 mRNA was demonstrated in the ileum and a fall of interleukin-8 mRNA in the colon [60]. Yamamoto et al. successfully managed acute duodenal CD with a low-speed elemental diet infusion via nasogastric tube in a 28-year-old female and also demonstrated that the duodenal mucosal cytokine levels remarkably decreased compared with those before the treatment [38]. Recently, Nahidi et al. cocultured heat tolerance (HT)-29 colonic epithelial cells with TNF-α in the presence or absence of polymeric formula, as used for EEN. Microarray analysis showed that polymeric formula modulated the expression of genes involved in the nuclear factor kB pathway with consequent downregulation of IL-6 and IL-8 proteins [61]. Alhagamhmad et al. wanted to find out whether the specific components in the polymeric formula drive the demonstrated attenuation of the nuclear factor kB cascade. They used tumor necrosis factor-α-exposed HT-29 colonic epithelial cells to investigate the immunosuppressive activity of the glutamine, arginine, vitamin D3, and α-linolenic acid (ALA), present in polymeric formula, along with curcumin. They found out that glutamine, arginine, and vitamin D3, but not ALA, significantly attenuated IL-8 production. Glutamine and arginine led to a phosphorylation blockade of the signaling components in NF-κB and P38 pathways, reduction in kinase activity, and enhancement in NO production. They concluded that glutamine, arginine, and vitamin D3 can suppress inflammation at concentrations equivalent to those used in polymeric formula. According to these findings, glutamine and arginine-fortified polymeric formulas might be a promising option to enhance the effectiveness of EEN therapy in CD treatment [57]. There is accumulating evidence that microRNAs play an important role in CD pathogenic processes, including regulation of pro and anti-inflammatory pathways. Guo et al. performed a microarray analysis in 25 adult CD patients and 10 healthy individuals treated with EEN. The microarray analysis showed that the

mucosal micro RNAs expression profile is significantly altered after EEN therapy compared with the one in inflamed mucosa before EEN treatment [62]. The Australian investigators demonstrated that polymeric formula had a direct anti-inflammatory effect on colonic enterocytes. Polymeric formula was able to reduce interleukin (IL)-8 response to proinflammatory stimuli when it was added to the culture medium. The authors concluded that polymeric formula may modulate gut inflammation by directly reducing the inflammatory response of the intestinal epithelium [63]. Recently, the same team of investigators found that the incubation of human cells (Caco-2 human adenocarcinoma cell line) with a polymeric formula resulted in a dose-dependent increase in the expression of intestinal alkaline phosphatase, which is a recognized marker of enterocyte differentiation. Intestinal alkaline phosphatase is implicated in the innate gut immune response to enteric pathogens. This finding suggests that cell surface-associated intestinal alkaline phosphatase may be an aspect of the gut's innate immune response to pathogenic bacteria that is strengthened by polymeric formula [64].

12.2. Reduction in dietary antigen exposure

In the first years, only elemental formulas were used for the treatment of active CD. It was believed that the effect of EEN was based on exclusion of the dietary antigens which might have a role in inducing and promoting the inflammatory cascade. However, later research has shown that whole protein polymeric formulas were also as effective in inducing remission in patients with active CD [14, 18, 22, 65, 66].

12.3. The role of fats in EN formulas

The influence of the lipid source within the enteral feeds has been examined, but how the lipids composition of enteral nutrition affects its efficacy remains to be elucidated. In a meta-analysis by Zahos et al., the efficacy between the elemental formulas with low fat content (< 20 g/1000 kcal) versus high fat content (> 20 g/1000 kcal) was compared. This meta-analysis did not demonstrate a significant difference in efficacy of the two types of elemental formulas [23]. In the last decades, the impact of the use of fatty acids as potential immune-modulating agents in an inflammatory condition such as CD has been studied [67]. Recently, in a double-blind RCT by Grogan et al., a modest effect on the blood fatty acid composition was seen with both nutritional interventions (with Alicalm and Emsogen). After an intervention with a 6-week therapy with Alicalm, an increase of eicosapentaenoic acid (EPA) and alpha linolenic acid (ALA) was demonstrated with an inverse decrease in arachidonic acid (AA). Arachidonic acid is an important precursor to eicosanoids, which are second messengers in numerous signal transduction processes and have proinflammatory properties. The authors of this study concluded that there may be an advantage of using enteral formula that contains increased levels of ALA, as it is a precursor of anti-inflammatory eicosanoids [68].

12.4. Glutamin and arginine in EN formulas

Glutamine and arginine are conditionally essential amino acids with immunomodulatory properties. Glutamine may be essential in patients with catabolic conditions where the intervention with glutamine-supplements is able to prevent the deterioration of gut permeability and development of intestinal mucosal atrophy [69–71]. Akobeng et al. conducted a RCT,

which included 18 pediatric patients with active CD, who were randomly assigned to receive a 4-week course of either: standard polymeric formula with low glutamine content (4% of amino acid composition) or a glutamine-enriched polymeric diet (42% of amino acid composition). They found no significant difference between these two types of formula in terms of clinical efficacy [72]. In a recent meta-analysis of the same authors, only two small RCTs (total 42 patients) met the inclusion criteria. The first study is the aforementioned pediatric study by Akobeng et al. [72]. In the second study, 24 adult CD patients with acute exacerbation of IBD were treated either with glutamine-supplemented or non-supplemented total parenteral nutrition. In both included studies, no statistically significant changes in intestinal permeability were found between patients, who received glutamine supplementation and those who did not [73]. Further randomized controlled clinical studies on the efficacy and safety of glutamin supplementation in patients with active CD are needed.

12.5. The impact of EEN on gut microbiota

While all the pathogenetic mechanisms of action of EEN have not yet been elucidated, EEN is known to cause profound changes in the gut microbiome. Understanding how EEN modifies the gut microbiome to induce remission could provide insight into CD etiopathogenesis and consequently guide the development of microbiome-targeted interventions [74]. In 2005, Lionetti et al. assessed clinical remission and the fecal microbiota in nine children with active CD treated with EEN. Clinical remission was observed in eight of nine children. In all these patients, significant modification of the fecal microbiota was found after EEN therapy. In contrast, control healthy children showed a host-specific and stable microbiota over time [75]. Similarly, Leach et al. demonstrated a significantly different composition of intestinal microbiota in patients with CD treated with EEN in comparison with the microbiota of control subjects. The effect of modificated microbiota remained present for 4 months after EEN [76]. EEN was shown to promote protective species and increase the production of butyrate [77]. Surprisingly, in a Scottish study which included 15 pediatric patients with CD before and after remission with EEN and 21 control subjects, the therapy with EEN was associated with a decrease in diversity of microbiota and not vice versa as was expected. A decrease in specific 'protective' species including *F. prausnitzii* was found as well as a fall in butyrate in fecal samples. These results have challenged the current perception of a protective role of *F. prausnitzii* in CD [78]. Quince et al. have analyzed microbiota in 23 CD children and in 21 healthy controls before, during, and after EEN treatment. They demonstrated lower microbial diversity in CD patients compared with controls before EEN. During the therapy with EEN, the microbial diversity in CD children further decreased and the structure of microbiota became even more dissimilar in comparison with the healthy controls [79]. In another small study, similar results were shown. Fecal microbiota of five children with CD, before, during, and after EEN treatment was analyzed and compared with five healthy controls. It showed a dramatic decrease in the number of operational taxonomic units (OTUs) after therapy with EEN. Inversely, recurrence of inflammation corresponded with an increase in OTUs [80]. In an extension study by Lee et al., fecal samples from patients (n = 86) treated with either PEN, EEN, or anti-TNF-α were analyzed using shotgun metagenomics analysis at four points of time during treatment and compared with healthy controls. After 1 week of treatment, the microbiota composition among the EEN-treated group drifted significantly farther from centroid of the healthy controls compared to anti-TNF-α treated patients who moved closer to the centroid. However,

at the end of the study, responders (those with clinical remission and reduction in fecal calprotectin) were closer to the centroid of the healthy controls than nonresponders, regardless of treatment, suggesting that at treatment initiation, the treatment modality is the major determinant affecting gut microbiota, whereas later on, the resolution of inflammation becomes the dominant factor. Still, the resolution of dysbiosis was not complete even among responders at 8 weeks [81].

12.6. Exclusion of specific dietary components

During the 6- to 8-week therapy with EEN, the patients with active CD should not eat any food, and their 100% daily caloric requirements are covered by liquid formula. Therefore, the therapy with EEN automatically involves exclusion of many common dietary components which might have a deleterious effect on the intestinal mucosa. The avoidance of these potentially harmful dietary components might present another potential anti-inflammatory mechanism of EEN [82].

13. Partial enteral nutrition for maintaining remission in Crohn's disease

There are some studies suggesting that nutritional supplementation with liquid formulas may prolong remission in patients with quiescent CD [83–85]. However, the efficacy of partial enteral nutrition (PEN) for maintaining remission in inactive CD has not yet been fully evaluated. On the contrary, the use of immunomodulators and biological medications for maintaining remission in CD is well established. The adverse events of these medications, such as the increased risk of infection and malignancy, have always been concerning [86, 87]. Therefore, we should aim for a safer maintenance regimen, especially in children. Maintenance enteral nutrition (MEN) could be an attractive option for maintaining remission of inactive CD, as it will eliminate serious adverse events associated with the use of immunosuppressive medications and biologics. In 1987, Jones et al. reported their experience with 77 (16–65 years) CD patients in clinical remission who tried to maintain remission by personalized food exclusion diets along with a supplementary elemental diet. Twenty six of 77 (33.7%) patients remained in remission for 2 years and 18 (23.4%) patients for at least 3 years [88]. In a study by Wilschanski et al., pediatric patients with active CD who were successfully treated with EEN were assessed retrospectively according to whether they continued supplementary enteral nutrition or not. Time to relapse and linear growth were compared between the two cohorts. Patients who continued nasogastric supplementary feeding ($n = 28$) after reintroduction of their otherwise normal diet remained in remission longer than those who discontinued nocturnal supplementation ($n = 19$) ($p < 0.02$). Furthermore, continued use of nasogastric supplements before completion of puberty was associated with improved linear growth [85]. In 2000, Verma et al. studied a series of 39 consecutive patients with CD in clinical remission over 12 months. Patients in group 1 ($n = 21$) received oral nutritional supplementation along with their normal diet and patients in group 2 ($n = 18$) had a normal unrestricted diet without the nutritional supplementation. Forty-eight percent of patients in group 1 remained in remission for 12 months compared to the 22% of patients in group 2 ($p < 0.0003$) [89]. In 2007, Akonbeng et al. conducted a systematic review on the efficacy of enteral nutrition for maintenance of remission in CD. Only two studies were included based on the inclusion criteria

[90]. In the first study, a significant lower relapse rate was found in CD patients who received half of their daily nutritional needs from an elemental formula and the remaining half by normal diet compared to patients who only received a normal diet [90]. In the second study, the comparison between elemental and polymeric formulas (providing between 35 and 50% of patients' caloric intake in addition to normal diet) was assessed in terms of maintenance of remission. Both type of formulas were equally effective in maintaining remission and allowing withdrawal of steroid therapy [91, 92]. Recently, Nakahigashi et al. have reviewed the efficacy of EN for the maintenance of remission in patients with quiescent CD. Seven prospective cohort studies were included and three of them were RCTs. In all studies, patients used EN as a supplement or as a nocturnal tube feeding in addition to their normal food. The maintained clinical remission rate at 1 year was significantly higher in patients treated with EN in four of the six studies [93]. Although some studies suggest that PEN may be helpful for the maintenance of remission in the pediatric population [84, 85], data on the long-term usage of PEN for remission maintenance in pediatric CD patients are still lacking. A recent retrospective study by Schulman et al. investigated the efficacy of PEN treatment in the maintenance of remission in the pediatric CD population. In their centre, this approach has been in practice for the last several years. They assessed 42 pediatric CD patients who entered clinical remission on 4–12 weeks of EEN and were maintained on PEN as a supplementary diet (50% of total calories obtained as polymeric formula). The control group consisted of patients who refused PEN. They found that the decrease in the disease activity was greater in the PEN group than in the control group, as was the total increase in body mass index between the time of diagnosis and 8 months after. Laboratory parameters, such as albumin and CRP, also showed better improvement in the PEN group than in the control group. Although PEN was able to maintain short remission in patients initially treated with EEN, most of the patients required concomitant medication at some point after PEN initiation. They conclude that PEN treatment was partially effective in maintaining remission in patients who were initially treated with EEN. To better assess the efficacy of PEN for maintaining remission in children with CD, further prospective studies are required. Recently, El-Matary et al. have published a systematic review on the efficacy of MEN in adult and pediatric patients with CD. Twelve studies (1169 patients, including 95 children) fulfilled the inclusion criteria. As the included studies were significantly heterogeneous, a meta-analysis was not performed. Eleven studies showed that EN was either better than or as effective as its comparator in maintaining remission in patients with inactive CD. Only one adult RCT (n = 51), with low risk of bias, compared EN with a regular diet and found a relapse rate of 34% in the EN group versus 64% in the control group ($p < 0.01$) after a mean follow-up of 11.9 months. The authors concluded that EN is more effective than a regular diet and as effective as some medications in maintaining remission for patients with inactive CD. Large, properly designed RCTs of sufficient duration are, however, still required to confirm this outcome regarding EN versus individual medications [94].

14. Partial enteral nutrition in the treatment of active Crohn's disease

In 2006, Jones et al. have published the first RCT on partial enteral nutrition (PEN). Fifty children with active CD (PCDAI >20) were randomly assigned in PEN or EEN group. Children in PEN group had obtained 50% of their caloric requirements from elemental formula and 50% from

unrestricted diet, while children in EEN had received 100% of their energy requirements from elemental formula for 6 weeks. This study showed that the conventional treatment with EEN was associated with a significantly higher remission rate in comparison with PEN (42 versus 15%) [95]. The next study on the efficacy of PEN was conducted at The Children's Hospital of Philadelphia (CHOP). The authors retrospectively studied the efficacy of their CHOP protocol of PEN, which allowed patients to consume 10–20% of their daily caloric needs from a normal diet and 80–90% from enteral nutrition. In this study, a remission rate of 65% and response rate of 87% were demonstrated, which is comparable with the remission rate of EEN from literature. The authors concluded that the use of the CHOP protocol may increase compliance in the population of pediatric CD patients by improving quality of life [42]. Recently, Sigall-Boneh et al. treated 47 patients (34 children and 13 young adults) with early mild-to-moderate luminal CD with PEN. Their approach allowed patients to consume 50% of dietary calories from a polymeric formula and remaining calories from a special Crohn's disease exclusion diet (CDED). In the study, a clinical response and remission were achieved in 78.7 and 70.2% patients, respectively. Surprisingly, in six of seven patients who refused PEN and used only the specific exclusion diet for CD, clinical remission was observed. This study has shown for the first time that a combination of PEN with the exclusion diet was successful and led to high remission rates in early mild-to-moderate luminal CD, in children and young adults [96]. Furthermore, the findings of this study suggest that specific dietary products may play a role in the promotion of intestinal mucosal inflammation. The authors of this study hypothesize that the major mechanism leading to response to EEN used in children with active CD is exclusion of specific dietary factors which may have negative impact on the innate immune mechanisms of intestinal mucosa such as the mucous layer, intestinal permeability, or colonization and adherence with adherent-invasive *E. coli* (AIEC). They suggest that specific dietary components such as additives may impair the barrier function of the intestinal epithelium and allow adherence and invasion of nonpathogenic bacteria or bacterial antigens. Adherence of bacteria to the intestinal epithelium, penetration, and replication within epithelial cells, dendritic cells, and macrophages leads to continuous triggering of the adaptive immune system, resulting in inflammation [97]. According to the results of recent epidemiological and animal model studies, they developed CDED based on exclusion of dietary components hypothesized to affect the microbiome or intestinal permeability or other elements of innate immune system involved in CD pathogenesis [82, 97]. CDED is a structured diet that excludes animal fats, milk and dairy, gluten, and all processed and canned foods, which contain additives (especially emulsifiers and maltodextrin) [96]. Although the authors from CHOP and Israel did show that PEN may be effective in inducing the remission in active CD, this approach of treatment is not recommended according to the ESPGHAN/ECCO guidelines on the treatment of active CD in pediatric population [6]. Further studies on the efficacy of PEN are warranted to elucidate the efficacy of this treatment approach.

15. Conclusion

EEN is recommended as a first-line therapy for remission induction in pediatric luminal Crohn's disease. Despite the inconsistent evidence regarding long-term efficacy, EEN has an established advantage over corticosteroids with comparable clinical efficacy but superior

mucosal healing effect as well as better safety profile. The exact mechanism by which EEN exerts its beneficial impact is still not established, particularly, whether exclusion of specific potentially harmful dietary components plays an important role. Nevertheless, accumulating evidence suggest a direct anti-inflammatory effect and an effect on the intestinal microbiota. The relationships between these effects and the specific triggers for the observed changes are yet to be elucidated.

Conflict of interest

The authors have no conflicts of interest.

Author details

Darja Urlep*, Evgen Benedik and Rok Orel

*Address all correspondence to: darja.urlep@kclj.si

University Children's Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia

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