Chapter

Partial Enteral Nutrition in Crohn's Disease

Evgen Benedik, Darja Urlep, Anija Orel and Rok Orel

Abstract

Exclusive enteral nutrition (EEN) has proven to be a highly effective treatment option in inducing remission in active Crohn's disease (CD) in the paediatric population. In adults with CD, the results of meta-analyses demonstrated that therapy with corticosteroids was more effective in comparison with EEN. The most important limitation of the success of EEN treatment is patients' compliance. Exclusivity of enteral nutrition and its substantial impact on the quality of life are the main reasons why EEN is not acceptable to many patients. Therefore, the treatment with partial enteral nutrition (PEN), where patients are allowed to eat some ordinary food besides enteral formulas, is becoming an important treatment option, not only in inducing, but also in maintaining remission in CD. However, strong evidence on the efficacy of PEN for induction and maintenance of CD remission is still lacking. Due to the excellent safety profile of the treatment with enteral nutrition in comparison with other treatment modalities, further well-designed, randomised, controlled studies are necessary to elucidate the exact role of PEN in inducing and maintaining of remission in CD patients. Herein, the most relevant studies on the efficacy and the role of PEN in active and quiescent CD are reviewed.

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

1. Introduction

Crohn's disease (CD) is a life-long immune-mediated inflammatory disease which may affect any part of the gastrointestinal tract. The aetiology of the disease is multifactorial and complex, with genetic and environmental factors involved. It is widely accepted that inappropriate response of the innate and adaptive immune system to the altered composition of the indigenous intestinal microbiota plays crucial role in the pathogenesis. Both the development and treatment of the disease may therefore be influenced by different factors that can affect the composition of the intestinal microbiota, the permeability of the epithelial barrier, or the functioning of the gut immune system. Each of these factors can be significantly affected by nutrition. Epidemiological studies have shown that a diet containing large quantities of red and processed meat, animal fat, and refined sugars is associated with an increased risk, and a diet containing large quantities of fruits and vegetables with a reduced risk for CD development [1–4].

Therefore, the possibilities of treating CD with nutritional therapy are particularly interesting. Close partnership between the patients, gastroenterologist and dietitian is necessary when utilising nutritional therapy to treat CD. Dietitian provides support for dietary changes and asses the actual nutrient intake, patient's nutritional status, and discuss the role of enteral nutrition as the treatment option. Dietitian should be included in patient's treatment from diagnosis onwards. The ultimate goal of CD treatment is to induce and maintain clinical remission and mucosal healing with treatment modalities with least adverse effects [5]. Compared to other treatments such as corticosteroids (CS), immunomodulators and biologic drugs, nutritional therapy has an excellent safety profile, presenting with significantly less adverse effects compared to any other type of treatment. Many adverse effects of immunosuppressive drugs (thiopurines, methotrexate) and biological drugs, especially the increased risk of infections and malignancy, have been reported and are of major concern [6–9].

Since the discovery that exclusive enteral nutrition (EEN) that provides adequate nutritional intake of all macro- and micronutrients over a sufficiently long period can not only improve the nutritional status of patients but also alleviate inflammation, such treatment has been extensively studied. There is strong evidence that EEN is as effective as CS in inducing remission in patients with CD. In paediatric patients, when it comes to the induction of mucosal healing, EEN seems to be even more effective then CS [10–15]. EEN was also found to be able to promote transmural healing [16, 17]. There are currently many different enteral formulas available on the market. Some are elemental, semi-elemental and others polymeric. They differ in flavour, energy density, osmolarity, content of dietary fibre and some other nutrients but they all provide sufficient energy and essential nutrients intake.

Patients with CD are often malnourished at the time of diagnosis and growth retardation is frequently present in paediatric patients [18–20], so a positive effect on nutritional status and growth represents an important additional benefit of EEN [21]. Therefore, consensus guidelines of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Crohn's Colitis Organisation (ECCO) recommends EEN as a first-line therapy in all children with active CD, including those with colonic involvement [22]. Although, based on some initial studies, EEN had been shown to be as effective as CS for induction of remission also in adult patients with CD [23–27], subsequent studies did not confirmed this, and their meta-analyses demonstrated that CS were more effective treatment option in adult CD patients [13, 14, 28–31].

The reason for different efficacy of EEN in paediatric and adult CD populations is not completely understood. It may be due to longer disease course, higher prevalence of more aggressive phenotypes and more permanent structural changes of the bowel in adults. In addition, EEN is probably not so strictly adhered to in adult patients, when compared to children, who are usually under supervision from their parents. Children and especially adolescents are more motivated to achieve remission through the use of EEN, as most of them decline CS treatment due to appearance related side effects such as facies lunata, acne vulgaris and increased hairiness [5, 22]. The difference may also be due to the lack of well-designed randomised controlled studies in adult CD population. It has been noted, that the conclusions of the meta-analyses on the superior efficacy of CS in adults were mainly based on an intention to treat analyses, while when only results of the patients who strictly adhered to EEN protocols were analysed, the

remission rates were comparable to those receiving CS [32]. Anyway, except for Japan, induction therapy with EEN is not common in adult patients with active CD. Japanese guidelines recommend EEN as one of the treatment options for active CD in adults [33], since a Japanese study reported that elemental EEN had a higher rate of induction of remission in CD patients compared with CS and has improved luminal lesions [34]. ECCO guidelines for medical management of adult CD from 2016 recommended the use of EEN as an adjunctive treatment to improve nutritional status and in patients who decline other drug therapy [35], while in the most recent edition of this guidelines from 2019 EEN is not mentioned at all [36]. Recent guidelines of the European Society for Clinical Nutrition and Metabolism (ESPEN) directly recommends EEN as a first line of treatment only for children and adolescents, while an option to use EEN in selected cases of adults is mentioned only in fine print [37].

Despite the strong evidence of EEN efficiency in paediatric and potentially in adult CD patients as well and its better impact on mucosal healing in comparison with CS, EEN is not popular in many parts of the world. Its major disadvantage is the need to consume exclusively enteral formulas, while avoiding all other foods for a long period, usually 6–8 weeks. This has a substantial impact on the quality of life and is unacceptable for many patients. Although all formulas used for EEN are designed for oral use, many patients (although there are significant differences between parts of the world and between children and adults) accept them so poorly that they must be administered via a nasogastric tube. To overcome this main constraint, the idea of the use of partial enteral nutrition (PEN) instead of EEN has emerged. Compliance and adherence to enteral nutrition would likely be much better if patients could consume some ordinary food besides the enteral formula, either unrestricted or in a form of specified elimination diets (ED). The ideal candidates for PEN are therefore all patients who are not adherent to EEN and those who do not want to receive CS due to their several side effects. In addition, there is a growing body of research addressing the possibility of nutritional treatment of CD with diets containing only a limited selection of ordinary foods without the addition of enteral formulas. Although there are many such diets, objective data on their effectiveness are very limited.

Therefore, we limited our systematic review to the efficacy of therapeutic approaches using PEN in combination with either unrestricted or specified ED for induction of CD remission in adults and children, while other nutritional treatment options are presented only in the outline of the discussion.

2. Literature search

A systematic literature search was conducted using PubMed Library on April 3, 2020. The following user query was used: ("crohn disease"[MeSH Terms] OR "crohn"[Title/Abstract] OR "crohn disease"[Title/Abstract] OR "crohn's"[Title/Abstract] OR "crohn's disease"[Title/Abstract]) AND ("enteral nutrition"[MeSH Terms] OR "enteral"[Title/Abstract] OR "enteral nutrition"[Title/Abstract]) NOT "parenteral"[Title/Abstract] NOT "exclusive"[Title/Abstract] AND "english"[language].

Based on these criteria, from 399 publications identified in PubMed database using these terms, 13 key articles were selected for further analysis, first identified study being published in 1996 (only 3 articles were published before 2004). All selected articles are gathered in **Table 1**.

Ref.	Year	Country	Type of study	n	Number of patients on PEN and comparators	Route of PEN	Type of PEN	Volume taken	Remission or relapse rates (n, %)	Significant difference (P value)
ADULT STUDIES										
Verma et al. [38]	2000	UK	Prospective non-randomised cohort study	39	PEN 21 Non-PEN 18	oral	Elemental	35–50% EAR	Remission rate at 1 year: PEN 10/21 (48%) NT 4/18 (22%)	PEN vs. non-PEN: P = 0.0003
Verma et al. [39]	2001	UK	RCT	33	ED 19 PD 14	oral	Elemental / polymeric	35–50% EAR	Remission rate at 1 year: PEN 8/19 (42%) NT 6/14 (43%)	Polymeric vs. Elemental: NS
Takagi et al. [67]	2006	Japan	RCT	51	PEN 26 Non-PEN 25	Mainly Oral/ NG	Elemental (half-elemental diet)	900–1200 ml/kcal daily	Relapse rate after 1 year: PEN 9/26 (34.6%) NT 16/25 (64%)	PEN vs. non-PEN: P < 0.01
Yamamoto et al. [40]	2007	Japan	Prospective non-randomised	40	PEN 20 non-PEN 20	NG tube at night	Elemental + low fat diet	1200–1800 ml/kcal daily	Relapse rate after 1 year: PEN 5/20 (25%) non-PEN 13/20 (65%)	PEN vs. non-PEN: P = 0.03
Yamamoto et al. [41]	2010	Japan	Prospective non-randomised	56	PEN+IFX 32 IFX 24	NG tube at night	Elemental formula + low fat diet	1200–1500 ml/kcal daily	Remission rate after 56 weeks: IFX + PEN 25/32 (78%) IFX 16/24 (67%)	IFX + PEN vs. IFX: NS
Hirai et al. [42]	2013	Japan	Retrospective-cohort study	102	PEN+IFX 45 IFX 57	Oral	Elemental formula	>900 ml/kcal daily	Remission rate after 544.1 ± 26.5 days: IFX + PEN 31/45 (69%) IFX 33/57 (42%)	IFX + PEN vs. IFX: P = 0.009

Ref.	Year	Country	Type of study	n	Number of patients on PEN and comparators	Route of PEN	Type of PEN	Volume taken	Remission or relapse rates (n, %)	Significant difference (P value)
Hanai et al. [43]	2012	Japan	RCT	95	PEN 32 MP 30 CG 33 All groups on 5-ASA	Oral/NG	Elemental	≥900 kcal daily	Remission rate at 2 years: PEN 14/32 (46.9%) MP 17/30 (56.7%) CG 7/33 (21.2%)	PEN vs. CG: P = 0.034 PEN vs. MP: NS
POST-SURGERY										
Yamamoto et al. [40]	2007	Japan	Prospective, non-randomised	40	PEN 20 Non-PEN 20 Both groups on 5-ASA	NG	Elemental	1200–1800 ml/kcal daily	Relapse rate at 1 year: PEN 1 (5%) CG 7 (35%) Endoscopic relapse rate at 1 year: PEN 6 (30%) CG 14 (70%)	PEN vs. CG: P = 0.045 PEN vs. CG: P = 0.027
Yamamoto et al. [44]	2013	Japan	Prospective, non-randomised	40	PEN 20 Non-PEN 20 Both groups on 5-ASA	NG	Elemental	1200–1800 ml/kcal daily	Relapse rate during 4 years of study: PEN 6 (30%) CG 12 (60%)	PEN vs. CG: NS
PAEDIATRIC STUDIES										
Wilschanski et al. [45]	1996	Canada	Retrospective cohort study	47	PEN 28 NT 19	NG tubeNoctural enteral feeding	Semi-elemental or elemental	50–60% EAR 4 or 5 nights/week	Relapse rate at 6 months: PEN 5/28 (18%) NT 15/19 (79%) Relapse rate at 12 months: PEN 12/28 (43%) NT 15/19 (79%)	At 6 months: PEN vs. NT: P < 0.001 At 12 months: PEN vs. NT: P < 0.02

Ref.	Year	Country	Type of study	n	Number of patients on PEN and comparators	Route of PEN	Type of PEN	Volume taken	Remission or relapse rates (n, %)	Significant difference (P value)
Knight et al. [46]	2005	UK	Retrospective cohort study	40	PEN 22 NT 18	oral	Elemental or polymeric	1000 ml daily	Relapse rate at a median time of 54.5 weeks: PEN 13/22 (60%) NT 12/18 (67%)	PEN vs. NT: NS
Duncan et al. [47]	2014	UK	Retrospective cohort study	48	PEN 15 NT 13 AZA 20	Oral 14/ /NG 1	Polymeric	25% of pts. original EEN volume	PEN 9/15 (60%) NT 2/13 (15%) AZA 13/20 (65%)	PEN vs. NT: P = 0.001 PEN vs. AZA: NS
Gavin et al. [48]	2018	UK	Retrospective	102	PEN 58 NT 44	Oral	Polymeric and Elemental formula	median 30% EAR daily (range 13–65% EAR)	Relapse rate at 6 months: PEN 21/58 (36%) NT 21/44 (48%) Relapse rate within 12 months: PEN 45/58 (78%) NT 34/44 (77%) Relapse rate < 6 months EEN/PEN 14/43 (33%) CS/NT 16/29 (55%)	PEN vs. NT at 6 months: NS PEN vs. NT at 12 months: NS EEN/PEN vs. CS/NT:NS (P = 0.09)

RCT: randomised controlled trial; NS: not significant; EAR: Estimated Average Requirement; PEN: partial enteral nutrition; Non-PEN: without PEN; NT: no treatment; ED: elemental diet; PD: polymeric diet; HED: half elemental diet; MP: mercaptopurine; EEN/PEN: PEN after EEN treatment; CS/NT: no treatment (normal diet) after CS; AZA: azathioprine; CG: control group; IFX: infliximab; 5-ASA: 5-aminosalicyilic acid.

Table 1.
Summary of key studies on efficacy of partial enteral nutrition (PEN) in maintaining Crohn's disease (CD) remission.

3. Results

3.1 Partial enteral nutrition (PEN) for induction of remission in active Chron's disease (CD)

Through a systematic search, we identified 8 original articles on the use of PEN for induction of remission in active CD (**Table 1**). Of these, 5 papers presented the results of prospective controlled trials, 2 randomised and 3 non-randomised, while 3 papers described retrospective analyses of medical records of patient series. Beside to the basic methodology, research differed most in how much of a daily energy requirements patient received in the form of PEN and what they enjoyed as the rest of their daily energy requirements, unrestricted diet or special ED. In addition, we found 3 original studies using PEN simultaneously with different medical therapies for induction of remission [49–51]. It was impossible to determine how much of the effect on a disease activity could be attributed to the PEN itself from the result of these studies, so we did not include them in this review.

In 2006, Johnson et al. [52] published the results of the first prospective randomised controlled trial on the efficacy of PEN compared with EEN in inducing remission in active CD. Fifty children with active CD were randomised into two groups. In the "PEN group", children received 50% of their daily energy requirements from the elemental formula and 50% from an unrestricted diet. The control group consisted of children, treated with EEN, with 100% of their daily energy requirements provided from the elemental enteral formula. The remission rate after a 6 week-treatment period was significantly higher in EEN group (10/24, 42%) compared to the PEN group (4/26, 15%) ($P = 0.035$), pointing to a low efficacy of PEN [52]. Of note, the intention to treat remission rate in this study using elemental enteral formula was surprisingly low, even for EEN control group, in compare to majority of other studies.

In a retrospective cohort study by Gupta et al. [53] from the Children's Hospital of Philadelphia (CHOP), the remission and response rates were determined in 43 children who were treated for active CD with PEN according to the CHOP protocol, where all patients received 80–90% of their daily energy requirements from the enteral formula (elemental, semi-elemental or polymeric) and the rest from an unrestricted diet. This study showed a remission and response rate of 65% and 87%, respectively, after a mean treatment period of 2 months (1–4 months) [53]. These results are in line with the remission rates of EEN treatment reported from literature [12, 22, 54, 55]. Additionally, the study protocol with PEN was able to increase weight and improve laboratory markers in children with CD. The authors concluded that CHOP protocol, that allows patients to consume a small amount of ordinary food, has an important positive impact on treatment adherence and on the quality of life during the treatment period [53].

In a prospective cohort study, Lee et al. [56] compared clinical outcomes and mucosal healing as estimated by faecal calprotectin in 90 children with active CD receiving either PEN ($n = 16$), EEN ($n = 22$) or anti-tumour necrosis factor (TNF) therapy ($n = 52$) for induction of remission. After an 8-week treatment period, clinical response was demonstrated in 64% of patients on PEN, 88% on EEN, and 84% on anti-TNF ($P = 0.08$). EEN and anti-TNF were significantly more effective in diminishing mucosal inflammation compared to PEN. The reduction of faecal calprotectin to $\leq$250 μg/g was found in 14% of patients on PEN, 45% on EEN, and 62% on anti-TNF ($P < 0.001$) [56].

Wall et al. [57] performed a prospective non-randomised study including 38 adolescent and young adult patients with active CD. All patients were treated with EEN for the first two weeks, six (16%) of them discontinued this treatment in a

few days because of personal decision or intolerance to polymeric enteral formula. After this initial period 21 patients were treated with EEN and 11 patients with PEN allowing one meal of ordinary food per day for another 6 weeks. Seven (33%) patients from EEN group and 2 (18%) patients from PEN did not complete the treatment, predominantly because of complications and worsening of disease. There was no significant difference between the groups (P = 0.5). During the initial two weeks of treatment with EEN, clinical Harvey–Bradshaw Index (HBI), serum C-reactive protein (CRP) and faecal calprotectin concentrations significantly decreased (P = 0.003; P = 0.005, P = 0.028). The authors observed further clinical improvement in patients who continued with EEN with significant decrease of HBI (P = 0.031), while markers of inflammation remained stable. In the PEN group, clinical condition and markers of inflammation did not significantly change during 6-week therapy. The authors concluded that there were no significant differences in disease activity or inflammatory markers at week 8 between patients who used EEN for 8 weeks compared with patients who used 2 weeks of EEN followed by 6 weeks of PEN [57].

In contrast with aforementioned studies allowing to eat a certain proportion of unrestricted ordinary food along with enteral formulas, other researchers combined PEN with specially designed diets.

A group of investigators from Israel led by Arie Levine developed a special diet named Crohn's disease elimination diet (CDED), based on the exclusion of dietary components hypothesised to affect either the microbiome, intestinal permeability, or innate immune system involved in CD pathogenesis. It excludes animal fats, milk and dairy, gluten and all processed and canned foods that contain additives (especially emulsifiers and maltodextrin) [58–60]. According to the authors' hypothesis, the major mechanism leading to response to EEN, is the exclusion of specific deleterious dietary factors which may impair the barrier function of the intestinal mucus layer and epithelium that allows adherence and invasion of non-pathogenic bacteria or bacterial antigens. The adherence of bacteria to the intestinal epithelium, their penetration and replication within the cells of the innate immune system such as epithelial cells, macrophages and dendritic cells can lead to continuous triggering of the adaptive immune system and therefore to the chronic inflammation [59, 61].

In 2014 the group published a retrospective report on cohort of children (n = 34) and young adults (n = 13) with active mild to moderate luminal CD who had been treated with their PEN protocol for 12 weeks. The protocol consisted of two stages. During the first 6 weeks, CDED was more restrictive and 50% of the daily energy requirements was provided in the form of polymeric enteral formula. In the second 6-week period, polymeric enteral formula was continued to supply only 25% of daily energy requirements, while small amounts of whole grain bread, and free intake of nuts, fruits, and vegetables were allowed. By week 6, a remission and response rate were 70.2% and 78.7%, respectively. The remission rates were similar in children and adults. In paediatric patients mean Paediatrics Crohn's Disease Activity Index decreased from 27.7 ± 9.4 to 5.4 ± 8.0 (P < 0.001). Similarly, HBI decreased from 6.4 ± 2.7 to 1.9 ± 2.9 in adults (P < 0.001). At week 12, 27/32 (84%) patients, that were in remission at week 6, were still in remission after the step-down phase. Normalisation in CRP was observed in 21/30 (70%) patients. Surprisingly, 6/7 (86%) patients who were treated with only CDED, without additional enteral formula, achieved remission as well [58].

In another retrospective analysis, same group reported their experience with 21 patients (11 adults and 10 children) who had lost response to biologic drugs despite dose escalation or combination therapy and were treated with PEN by a polymeric enteral formula and the CDED, 50% of daily energy requirements from each, for the first 6 weeks, followed by 6-week step-down phase as described above.

Paediatric patients with severe flares received 2 weeks of EEN followed by PEN and CDED. Clinical response was obtained in 19/21 (90.4%) patients, and remission in 13/21 (62%). Mean HBI decreased from 9.4 ± 4.2 to 2.6 ± 3.8 ($P < 0.001$). Three out of the four (75%) patients who used the CDED alone without any enteral formula supplementation, entered clinical remission. Significant decrease in CRP ($P < 0.001$) and increase in albumin concentrations ($P < 0.005$) were observed. The authors concluded that dietary treatment combining PEN and CDED may be a useful salvage regimen in CD patients failing biological therapy [62].

In 2019, Levine et al. [63] published the results of the multicentre prospective randomised controlled trial comparing the efficacy of standard EEN with CDED coupled with PEN for the induction of remission of CD. Seventy-eight children with mild to moderate active luminal CD were randomised either to EEN for 6 weeks followed by 25% of daily energy requirements intake with PEN and gradual introduction of ordinary foods during next 6 weeks or to CDED 50% and PEN 50% for the first 6 weeks followed by step-down phase CDED 75% (as explained before) with PEN 25% for the second 6 weeks. The primary endpoint of the study was patients' tolerance to both treatment regimens. The secondary endpoints were clinical response, normalisation of laboratory markers, including calprotectin as a surrogate marker for mucosal inflammation and changes in faecal microbiota. The combination of CDED and PEN was tolerated by significantly more participants (97.5%) than EEN (73.6%) ($P = 0.002$). At week 6, the remission rate in both groups did not differ significantly ($P = 0.38$). Thirty of 40 (75%) patients treated by CDEC and PEN achieved remission in compare with 20/38 (59%) treated by EEN. However, at week 12, significantly more patients given CDED and PEN group (75.6%) were in remission compared with children given EEN and then PEN without dietary restrictions (45.1%) ($P = 0.01$) [63].

Recently, Urlep et al. [64] published a prospective cohort study on efficacy of PEN combined with ED, a diet resembling CDED and based on basic foods, compared with EEN for inducing a remission in children with active CD. Twenty-five patients were allocated to a 6-week nutritional therapy with either EEN or PEN combined with one meal per day consisted of food from ED (approximately 25% of daily energy requirements). In addition to clinical evaluation and laboratory tests, ileocolonoscopy was performed before and after 6 weeks of treatment to directly assess the mucosal inflammation by using Simple Endoscopic Score (SES-CD). Clinical remission rates were similar in EEN and PEN with ED group (69,2% and 75%, respectively; $P = 0.999$). The endoscopic remission rates were 45.5% in both groups, and mucosal healing rates were also 45.5% in EEN group and 27.3% in PEN with ED group ($P = 0.659$). The study revealed that PEN in combination with relatively easy-to-keep ED was as effective as EEN for induction of both clinical and endoscopic remission [64]. However, current ECCO/ESPGHAN guidelines on medical management of paediatric CD do not recommend using PEN for the induction of remission [22].

3.2 Partial enteral nutrition (PEN) as maintenance therapy in Chron's disease (CD)

Summary of key studies on efficacy of PEN in maintaining CD remission in adult and paediatric CD patients is presented in **Table 1**.

3.2.1 PEN for maintenance therapy in adult CD

Already, in the year 1983, Harries et al. [65] reported a beneficial effect of additional enteral supplementation on the maintenance of CD remission. They

conducted a controlled cross-over study in a cohort of 28 malnourished adult CD patients. For a two-month period (control period) the patients were on an unrestricted diet and for the next two-month period they received supplementary polymeric enteral formula (treatment period). The study demonstrated that the addition of enteral formula had a beneficial effect not only on the nutritional status, but also on the disease activity [65].

Ten years later, Hirakawa et al. [66] conducted a prospective controlled study in 61 CD patients who achieved remission with EEN. They were divided into 4 groups and followed-up for 1, 2 and 4 years. For maintenance of remission the first group of patients was receiving PEN in a form of elemental enteral formula in addition to their unrestricted diet. In the second group the same nutritional regimen was combined with standard medications. In the third group, only medical therapy was used, while the fourth group stayed on an unrestricted diet and without any medicines. The cumulative remission rates after 1, 2, and 4 years were significantly better in the elemental hyperalimentation group, compared with all other groups. It was concluded, that therapy with enteral nutrition has a role not only in inducing remission, but also for the maintenance of remission in CD patients [66].

In a non-randomised cohort study by Verma et al. [38], PEN was found to be more effective than an unrestricted diet for remission maintenance at 1-year follow-up. Adult patients with CD remission (n = 39) were divided into two groups according to their choice. Twenty-one out of 39 patients received elemental enteral formula (35–50% of daily energy requirements) in addition to their unrestricted diet, while the remaining 18 patients chose to have an unrestricted diet. On an intention to treat basis, 10 patients (48%) in the first group and 4 patients (22%) in the second group were still in remission at 12 months of follow-up ($P < 0.000$) [38].

In 2001, the same authors studied 33 CD patients with CS-dependent disease who were all in remission at the start of the study. They all received enteral formula in an amount that provided 35–50% of their daily energy requirements. Patients were randomised to receive either an elemental formula (n = 19) or a polymeric formula (n = 14) and were followed up for 12 months. Failure of maintenance therapy was defined by an increase in the Crohn's Disease Activity Index, inability to cessate CS or the need for surgery. According to the per-protocol data analysis, the success rate of PEN in CS-dependent patients was 14/27 (52%). The response was not significantly different between elemental (42%) and polymeric (43%) groups [39].

In a study by Takagi et al. [67], CD patients in remission, achieved with different treatment modalities (with CS, 6–8 weeks EEN, surgery, infliximab (IFX)), were randomly assigned to two groups. In the "half elemental diet group« (n = 26) patients received half of their daily energy requirements from an elemental enteral formula (900–1200 ml daily) and half from an unrestricted diet. Patients in the second group (n = 25) were on an unrestricted diet. The relapse rate was significantly lower in the half elemental group (9/26; 34.6%) in comparison with the unrestricted diet group (16/25; 64%) ($P < 0.01$), after a mean follow-up of 11.9 months. According to the results of this randomised controlled trial, with a low risk of bias, PEN seems to be a promising maintenance therapy in CD [67].

In 2006 Esaki et al. [68], conduct a retrospective study which was designed to determine risk factors for recurrence of CD under enteral nutrition. They include 145 patients with CD, who were primarily induced into remission by total parenteral nutrition. The patients were classified into two groups: enteral nutrition group (n = 98; 1200 kcal/day of enteral nutrition), or non-enteral nutrition group (n = 47; < 1200 kcal/day of enteral nutrition) according to the amount of their daily elemental or polymeric diet. Contributions of enteral nutrition and other clinical variables to the recurrence were analysed retrospectively. They conclude that among patients with CD under maintenance enteral nutrition, the risk of recurrence differs

according to the disease type and the site of involvement. The maintenance treatment by enteral nutrition alone seems insufficient for patients with penetrating type or with colonic involvement [68].

In 2007 Yamamoto et al. [40] confirmed the positive impact of PEN in maintaining CD remission. They conducted a prospective controlled non-randomised study in 40 CD patients in remission. Patients in the enteral nutrition group (EN group; n = 25) received elemental enteral formula (1200–1800 ml daily) via a nasogastric tube at night and a low-fat diet during the day. Non-EN group (n = 20) was on an unrestricted diet. On an intention to treat basis, 5 patients (25%) in the EN group and 13 patients (65%) in the non-EN group relapsed during the 1-year follow-up period (P = 0.03). Furthermore, they demonstrated that the mucosal tissue levels of interleukin (IL) 1 beta, IL-6 and TNF-alpha significantly increased in the non-EN group during 1 year of follow-up, while the levels of these cytokines in the EN group did not change significantly. Similarly, the mucosal inflammation seen by ileocolonoscopies was significantly increased in the non-EN group. The researchers concluded that PEN is effective in diminishing clinical relapse rates and in suppressing cytokine production and mucosal inflammation in CD patients who entered clinical remission. Limitations of the study are its relatively small number of patients and a non-randomised design. Only patients with good compliance were assigned to the EN group, therefore, the bias of the study is high. Nevertheless, this study clearly shows that PEN has a positive effect not only on clinical activity but also on inflammation of the gut mucosa [40].

In 2009, Takagi et al. [69] investigated the quality of life of patients on PEN for maintenance of remission and the medical cost of this treatment regimen. This is an extension study of their previous randomised controlled trial [67], which showed that quality of life did not significantly differ between the two groups of patients; the PEN and the non-PEN group. Interestingly, there was also no statistically significant difference in the medical costs between these two groups of CD patients [69].

Yamamoto et al. [41] conducted a prospective study to examine the efficacy of combined PEN and IFX maintenance treatment. Patients who achieved remission with IFX and were treated with regular IFX infusions to maintain remission (5 mg/kg every 8 weeks) were divided into two groups. In the first group patients received IFX with concomitant PEN (1200–1500 ml of elemental enteral formula at night and low-fat diet during the day). The second group was treated only with maintenance IFX without PEN. Surprisingly, there was no statistically significant difference observed in remission rates between the two groups at the end of the 56-week follow-up (P = 0.51) [41]. However, this study was not randomised, and it involved only a small cohort of patients.

On the contrary, other studies demonstrated the beneficial effect of combined PEN and IFX maintenance treatment. In a retrospective study by Hirai et al. [42], 45 patients on maintenance therapy with IFX received concomitant PEN (elemental formula; > 900 kcal daily) and 57 patients were administered only IFX without PEN. The patients were followed for 544 ± 27 days. The cumulative remission rate was significantly higher in the combined PEN and IFX group in comparison to the non-combined group (P = 0.009) [42]. The authors hypothesised that PEN contributed to the positive effect of maintenance IFX due to its anti-inflammatory effect [70–73], the effect on cytokine production and the beneficial effect on gut microbiota [74–77].

Similar findings were observed in a multicentric retrospective study by Kamata et al. [78]. They found that concomitant PEN (≥ 900 kcal daily) during IFX maintenance therapy significantly prolonged the remission period. The group of CD patients treated with combined PEN and IFX therapy showed significantly

lower cumulative loss of response rate in comparison with the non-combined group ($P < 0.049$). The authors believe that PEN may decrease intestinal inflammation, therefore less serum IFX levels may be effective for controlling the disease [78].

In a meta-analysis by Nguyen et al. [79], the effect of concomitant PEN therapy with IFX in comparison with IFX monotherapy was assessed for maintenance of CD remission. Four studies met the inclusion criteria [41, 42, 80, 81]. In the group of patients on the combined PEN and IFX therapy, significantly higher percentage of patients (74.5%) remained in clinical remission in comparison with the IFX monotherapy group (49.2%) after 1 year of follow-up period ($P < 0.01$) [79].

Hanai et al. [43] conducted the only adult randomised controlled study comparing the efficacy of PEN with 6-mercaptopurine (6-MP) in maintaining CD remission. They studied 95 patients with CD in remission who were split into 3 groups. All patients took 5-aminosalicylic acid (2250–3000 mg per day). In the first group ($n = 30$) they received 6-MP (0.5–1.5 mg/day), in the second group ($n = 32$) they were on PEN (elemental enteral formula; ≥ 900 kcal daily and intake of 3.5–4.0 kcal/kg/day from food in line with the recommendation of a qualified dietician), in the third group ($n = 33$) patients received only 5-aminosalicylic acid (control group). The percentage of patients who were still in remission after 2 years of follow-up were 56.7% (MP group), 46.9% (PEN group) and 21.2% (control group), respectively. There was a significantly higher remission rate in the PEN group versus the control group ($P < 0.034$). Furthermore, the remission rates between PEN and MP group did not differ significantly ($P = 0.273$) [43]. Although this is a prospective randomised controlled study, its limitation is relatively small sample size. Therefore, further larger studies should be conducted to confirm these results. As thiopurines are drugs with many side effects [82], results of such studies would be desirable to decide upon an appropriate maintenance therapy, that should have a high ratio between efficiency and adverse effects.

3.2.2 PEN for maintenance therapy after surgery in CD patients

Some smaller retrospective studies demonstrated that therapy with enteral nutrition had reduced relapse rate after surgery in CD patients [83, 84].

In Ikeuchi et al. [83], they examined the effects of postoperative nutritional therapy in patients with perforating and non-perforating type of CD. They retrospectively reviewed the records for 218 patients who underwent surgical interventions for CD between 1974 and 2001. Patients were divided into four groups: 92 patients in the non-perforating type group had received an elemental diet, 22 patients in the non-perforating type had received an unrestricted diet, 88 patients in the perforating type had received an elemental diet and 16 patients in perforated type had received an unrestricted diet. They conclude that in patients with CD postoperative elemental diet and nutritional education is effective in reducing the incidence of second resection. It appears that postoperative elemental diet and nutritional education is more important in patients with perforated type CD [83].

Therefore, Yamamoto et al. [85] conducted the first prospective non-randomised study in 40 consecutive adult patients after resection for ileal or ileocolonic CD. Patients were assigned either to the PEN group ($n = 20$) or to the control group ($n = 20$) with an unrestricted diet. In the PEN group, patients received elemental enteral formula (1200–1800 ml daily) at night, through a nasogastric tube, and a low-fat diet during the day. Patients from both groups additionally took 5-aminosalicyilic acid 3000 mg daily. Ileocolonoscopy was performed at 6 and 12 months after surgery. One patient from the PEN group (5%) and 7 patients (35%) from the control group relapsed during the 1-year follow-up period ($P = 0.048$). Furthermore,

6 patients (30%) in the PEN group and 14 patients (70%) in the control group developed endoscopic recurrence by 12 months after surgery (P = 0.027) [85].

In 2013 the same authors published an extension study on the long-term efficacy of PEN as a maintenance therapy in CD patients who underwent surgery. Twenty patients were on PEN, delivered as a continuous elemental enteral formula during the night-time, and on a low-fat diet during the day. Twenty control group CD patients were given an unrestricted diet without therapy until disease recurrence. Recurrence rates after 5-year-follow-up were significantly lower in the PEN group compared to the control group (P = 0.02). This study confirmed the results of the previous study and showed that PEN may be effective in maintaining remission in CD patients after surgery [44]. However, both studies included a small number of patients and only the highly compliant ones were assigned to PEN group, so the risk of bias was high.

3.2.3 PEN for maintenance therapy in paediatric CD patients

In 1982 Navarro et al. [86] first reported the use of prolonged constant rate elemental enteral nutrition (CREN) in CD. It has been used in 17 paediatric patients with CD. Exclusive CREN was maintained from 2 to 7 months and progressively reduced to assure fractioned oral intakes from 12 to 22 months. From this preliminary study, CREN appeared to be as effective as CS therapy in initiating remission of active CD and was able to supress CS dependence. In some cases, with prolonged CREN, reduction or disappearance of stenotic lesions of the bowel was observed. Two other positive points must be emphasised: the favourable psychological impact of the method and the ability to avoid growth suppression secondary to CS. The long-term effects and longer remission must be confirmed by a multicentre study in a larger group of patients [86].

In 1988 Belli et al. [87] demonstrated decreased activity of CD and improvement in growth in a group of 8 children who had received elemental enteral formula at cyclical periods of time (one out of 4 months) for 1 year [87]. Although this was a small study, it encouraged further investigations on maintenance therapy with enteral nutrition.

Wilschanski et al. [45] conducted a retrospective study on 47 children and adolescents with CD who achieved clinical remission after EEN induction therapy. Twenty-eight patients continued with nocturnal PEN through a nasogastric tube and 19 patients consumed an unrestricted diet without enteral supplementation. The relapse rate was significantly higher in patients on an unrestricted diet in comparison with those who were treated with PEN at 6 ($P < 0.001$) and 12 months ($P < 0.02$), respectively. Furthermore, the group of patients on nocturnal PEN who had not yet completed puberty had improved linear growth compared to similar patients who were on an unrestricted diet [45].

On the contrary, Knight et al. [46] did not confirm the better outcome in patients receiving PEN. They retrospectively studied the short and long-term outcomes of using enteral nutrition for induction and maintenance of remission in paediatric CD patients. Out of 79 newly diagnosed CD patients, 44 (55%) chose EEN as the primary induction therapy and 40 (90%) of those responded to treatment. These 40 patients were then encouraged to continue with maintenance PEN (1000 ml of elemental or polymeric enteral formula daily) in addition to an unrestricted diet, but only 22 (55%) were able to accept the PEN treatment protocol. The authors did not find a statistically significant difference in the remission rates between the two groups [46]. However, the consumed volume of enteral formula was not carefully recorded, this could have affected the results and may have led to the higher rate of treatment failure [46].

A study by Duncan et al. [47] showed completely opposite results. In this retrospective study, 48 CD patients who entered clinical remission or responded to an eight-week treatment with EEN, were encouraged to continue a maintenance therapy with 25% of the volume of the previously used elemental or polymeric enteral formula. Only 15 out of 48 (31%) patients chose PEN, for a mean time of 11 months (range 4–14 months). Twenty (42%) patients took azathioprine and 13 (27%) patients had no maintenance treatment. Remission rates at one year were 60% in the PEN group, 65% in the azathioprine group and 15% in the control group. There was a significantly higher remission rate in the PEN group versus the control group (P = 0.001). Furthermore, remission rates between PEN and azathioprine group were not significantly different (P = 0.14) [47].

In 2015 Konno et al. [88], reported their real-life data on the long-term outcome of maintenance treatment with PEN in a consecutive cohort of 58 paediatric CD patients who entered remission with different treatment regimens. All 58 patients received PEN with a least 30 kcal/kg/day of elemental enteral formula in conjunction with a low-fat diet (< 20 g fat/day). In addition, they were treated only with 5-ASA, until first relapse. Fifty-two out of 58 patients took enteral formula orally and the remaining 6 through a nasogastric tube. The relapse rates were 12% at 1 year, 27% at 2 years, and 48% at 5 years, respectively [88]. This study surprisingly showed that approximately half of the children who received PEN as a maintenance therapy were able to sustain remission for 5 years without taking other medication such as immunosuppressives.

Schulman et al. [89] studied 42 CD paediatric patients who entered clinical remission after EEN and received PEN as a supplementary diet (50% of daily energy requirements as polymeric enteral formula). The control group consisted of patients who refused PEN. They found that the total increase in body mass index (BMI) and the total decrease in the mean weighted Paediatric Crohn's Disease Activity Index between the time of diagnosis and eight months after diagnosis were greater in the PEN group compared to the control group. Furthermore, in the PEN group there was better improvement in albumin and CRP levels in comparison with the control group. However, more than 50% of patients required concomitant maintenance therapy within two weeks of PEN initiation and most of patients required concomitant immunosuppressive therapy at some point after initiation of PEN [89].

Gavin et al. [48], reported real-life data on their experience with EEN as induction therapy and PEN as a maintenance therapy. 102 newly diagnosed paediatric CD patients were included. Seventy-seven (75%) patients were treated with a 6–8-week course of EEN and the remaining 25 with CS (25%). The remission rate in the EEN group was 76% and in the CS group 75% respectively. Following induction treatment, 58 out of 102 (57%) patients received PEN as a maintenance therapy (median 30% of daily energy needs; range from 13 to 65% of daily energy requirements of polymeric or elemental formula) and rest as an unrestricted diet. Forty-four out of 102 (43%) patients consumed an unrestricted diet for a median duration of 4 months (range 1–12 months). The increase of BMI z-score was significantly higher in the PEN group in comparison with the unrestricted diet group. However, relapse rates were similar in both groups at 6 and 12 months [48].

El-Matary et al. [90], published a systematic review on the efficacy of maintenance PEN. Databases were searched to April 2015. Twelve studies met the inclusion criteria; however, a meta-analysis was not performed due to the excessive heterogeneity of the studies. Out of these 12 studies, 11 of them had shown a beneficial effect of PEN in maintaining remission, therefore, authors concluded that PEN was more effective than unrestricted diet in maintaining CD remission [90].

Gavin et al. [91] conduct a survey including patients, parents and UK dietitians regarding their experience with maintenance enteral nutrition (MEN) which is

often routinely used in paediatric CD to prolong remission although there is limited evidence for efficacy and a lack of formal guidelines. They identified a different perspective between patients, families and professionals on the use of MEN. Young people and parents reported difficulties with adherence to MEN especially due to the taste and they stated a preference for dietary advice. This study advocates that the extensive use of MEN in clinical practice is limited to comply with ESPGHAN recommendations. Patient led care promotes the use of dietary advice as a mode of nutritional support during inactive disease [91].

In Kim et al. study [92], they determine the abilities of EEN and PEN to induce and maintain clinical remission in paediatric patients with CD, respectively. All paediatric patients with CD who received EEN at a single centre in 2000–2014 were identified retrospectively. Remission rates of the EEN and PEN during the 2 years study period were determined. Risk factors for EEN and PEN failure were also identified. They conclude that EEN and PEN effectively induced and maintained remission in a paediatric population. However, non-adherence was a limiting factor in the success of therapy, especially in females [92].

In Watanabe et al. [93], they investigate the effectiveness of enteral nutrition with an elemental diet regarding the avoidance of hospitalisation. Altogether 268 patients with CD who visited hospital from 2003 to 2008 were enrolled. The relationship between the proportion of energy consumed with an elemental diet and hospitalisation as an endpoint was examined retrospectively. They conclude that the use of an elemental diet of 900 kcal/day may be effective in avoiding hospitalisation in CD patients with ileal lesions. However, this diet may be useful in improving the long-term convalescence of these patients [93].

According to the current ECCO/ESPGHAN clinical guidelines on CD, in children with low-risk CD who achieved clinical remission, monotherapy with maintenance enteral nutrition (at least 50% of daily energy requirements) can prolong remission [22].

4. Conclusions

Despite the evidence that EEN is an effective and safe therapeutic option in inducing remission in paediatric and potentially in adult active CD and it is substantially more effective in promoting mucosal healing compared to CS, it is still underused in clinical practice. Its biggest disadvantage is patients' compliance. Taste fatigue due to the poor palatability and the subsequent negative impact on the quality of life remain the most important reasons why EEN therapy is not acceptable to many patients. Thus, the use of PEN, where some ordinary food, besides enteral formulas, can be consumed, is rapidly becoming an interesting therapeutic option. Unfortunately, the first well designed, prospective randomised controlled trial on PEN did not confirm PEN efficacy in inducing remission in active CD [52]. However, some recent small and retrospective studies pointed to the possible beneficial effect of PEN in active CD. Larger prospective randomised studies are needed to examine the possible role of PEN in inducing remission in paediatric and adult CD.

While EEN is not an acceptable therapeutic option for maintenance of CD remission in clinical practice, several studies examined the efficacy and the usefulness of PEN in maintaining remission in adult and paediatric CD (**Table 1**). The results were conflicting. Most of these studies were non-randomised, with only a small number of patients included. However, the results of some recent studies, including the Japanese randomised controlled trials with a large enough sample size and a sufficiently low risk of bias [67], were promising and indicated that PEN might be effective in maintaining CD remission.

Due to the excellent safety profile of enteral nutrition, treatment with PEN in inducing and maintaining remission in CD patients merits further investigation. Larger, well-designed, randomised controlled studies on the efficacy of PEN as a monotherapy or in combination with other medications and/or ED are needed in adults and the paediatric CD population.

Conflict of interest

The authors declare no conflict of interest.

Author details

Evgen Benedik[1,2*], Darja Urlep[1], Anija Orel[1,3] and Rok Orel[1]

1 Division of Paediatrics, Department of Gastroenterology, Hepatology and Nutrition, University Medical Centre Ljubljana, Ljubljana, Slovenia

2 Human Nutrition Group, Department of Food Science and Technology, Biotechnical Faculty, University of Ljubljana, Ljubljana, Slovenia

3 Division of Paediatrics, Unit of Diet Therapy and Hospital Nutrition Care Services, University Medical Centre Ljubljana, Ljubljana, Slovenia

*Address all correspondence to: evgen.benedik@kclj.si

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