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Review

Exclusive enteral nutrition in Crohn's disease: Evidence and practicalities

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SUMMARY

Exclusive enteral nutrition (EEN) is the first line therapy for paediatric Crohn's disease, providing a complete nutritional feed whilst simultaneously inducing remission in up to 80% of cases. The effect of EEN on systemic/local intestinal immune function and subsequent inflammation (including barrier permeability, direct anti-inflammatory effects and cytokine signalling pathways), alongside changes in the microbiome (specific species and broad taxonomic shifts, functional changes) are becoming clearer, however the exact mechanism for induction of remission in Crohn's disease remains uncertain. The evidence of efficacy in paediatric Crohn's disease is strong, with selected adult populations also benefiting from EEN. However despite recommendations from all major societies (ECCO, ESPGHAN, NASPGHAN and ESPEN) first-line use of EEN is varied and Europe/Australasia/Canada show significantly more routine use than other parts of North America. Growth and nutritional status are significantly improved with EEN compared to corticosteroids but long-term outcomes are sparse. This review discusses the evidence underlying the use of EEN, highlighting the mechanisms thought to underlie how EEN induces remission in Crohn's disease, when and how to use EEN, including practical issues in both paediatric and adult practice (formulation, compliance, volumes and administration), and summarises the ongoing research priorities.

1. Introduction

Exclusive enteral nutrition (EEN) is a highly effective treatment for the induction of remission in Crohn's disease (CD). It is widely used, steroid-sparing and the first-line therapy in Paediatric CD with remission rates of 60–80% [1–3]. European and Australasian use of EEN is significantly higher than in parts of North America, despite published guidance [4,5]. In adult CD there is weaker evidence of efficacy, thought to relate to practicalities of use (compliance, tolerability etc.). It is recognised that many adult centres will use corticosteroids or biological agents as first line therapy [6]. Despite this a proportion of adults with CD will respond well to EEN and it can be used to effectively and safely induce remission [6,7]. There is no role for EEN in the treatment of ulcerative colitis [8].

EEN was first used in the 1970s and advocated as a first line therapy from the 1990s. Contemporary consensus guidance from ECCO, ESPGHAN, ESPEN and NASPGHAN directs clinicians to use EEN to induce remission wherever possible [1,3,5,9]. These guidelines reinforce the position that corticosteroids, or early immunosuppressive therapy, should be reserved for those patients where EEN is not an option [1]. Over the last 20 years the goals of treatment in CD have shifted from relief of symptoms to inducing mucosal healing, whilst continuing to maintain growth, nutritional status, quality of life and avoiding side effects [10]. EEN remains the treatment of choice to induce deep remission (mucosal healing) in paediatric patients [1,11]. Additional benefits include avoidance of the growth retarding effects of corticosteroids and providing a complete nutritional feed correcting micro- and macro-nutrient deficiencies [3,12]. In this review the evidence underlying these assertions will be discussed through a systematic approach, highlighting the evidence behind the use of EEN in CD, how EEN works, when and how to use EEN and summarise some of the ongoing research priorities.

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Search strategy

We searched the Cochrane Library, MEDLINE, Embase and relevant specialty journals for articles published between Jan 1, 1980, to September 1 2017, with the terms:

("Crohn's disease", "inflammatory bowel disease" OR "IBD") AND ("Exclusive", "only") AND ("Nutrition", "Feed", "Modulen", "Elemental", "Amino Acid", "formula" OR "enteral").

We reviewed all publications from 2007 to 2017 and prioritising those published after 2010. Commonly referenced and highly regarded older publications were also included. We searched only for articles published in English, or those translated into English. We also searched reference lists of articles identified by this strategy and selected those we judged relevant. Randomised controlled trials, observational studies, retrospective studies, meta-analyses, review articles, editorials, conference abstracts and case reports were included.

2. Mechanism of action of EEN

Over last 5–10 years some of the precise changes in immune function (including intestinal barrier permeability, cytokine signalling pathways), microbiota (specific and broad microbiome shifts) and intestinal inflammation (direct anti-inflammatory effects) seen with EEN therapy been elucidated [13–16]. See Fig. 1. Despite advances the exact mechanism of action has remained uncertain.

2.1. Systemic and local immune modulation

Systemic inflammatory markers, such as C-reactive protein and erythrocyte sedimentation rate are normalised with EEN, often correcting before any detectable change in nutritional status [17,18]. Additionally EEN has the effect of directly reducing pro-inflammatory cytokines within the intestine, reducing growth failure in CD linked to increased circulating IL-6, TNF-α and TNF-γ [19]. There is an ongoing question as to whether the improvement in growth seen with EEN is due to improved nutritional status and/or reduction in pro-inflammatory cytokines [20]. In vitro modelling of intestinal inflammation has shown a direct effect on enterocytes by EEN with down-regulation of the pro-inflammatory IL-8 and IL-6 response [20,21]. There is evidence that EEN can increase the concentrations of systemic circulating anti-inflammatory cytokines, such as transforming growth factor (TGF) beta-1 [22]. The active T-cell response seen in CD may directly be altered by EEN, allowing alternative production of regulatory T-cells which promote anti-inflammatory processes in the mucosa [22]. Another theory relates to the direct effect of molecules such as TGF β2 (which is present in some EEN) on the intestine, however the mechanism of action remains uncertain and may involve direct downregulation of inflammatory cells or promotion of healing to the epithelial barrier [22].

In the mouse model intestinal antigen presentation through the class 2 major histocompatibility complex has been shown to be down regulated with EEN, demonstrating an impact of diet on immune and environment interaction, this may reduce the subsequent downstream inflammation induced by an environmental trigger (such as bacteria) [23,24].

2.2. Intestinal inflammation and barrier function

The inflammation seen in active CD is linked to increased intestinal permeability with a breakdown of an effective barrier against bacteria and potential pro-inflammatory molecules [25]. Whether this increased permeability is the cause or an effect of disease is unknown, but has been demonstrated to pre-exist any active inflammation [26]. Since the 1980's it has been known that EEN has a direct anti-inflammatory effect on the intestine in CD, with improvement of the abnormal permeability after 6 weeks of EEN [27]. The effect of diet on intestinal permeability and integrity of the mucus layer has been explored, some evidence suggests specific components of diet (such as wheat, emulsifiers and some fatty acids) may have adverse effects on epithelial cell tight-junctions or impair mucus function [25]. A potential mechanism is that EEN allows restoration of a functional epithelial (and mucus) barrier by excluding foods that adversely affect barrier function [25].

Contemporary work has demonstrated normalisation of mucosal microRNAs over treatment with EEN, suggesting a possible

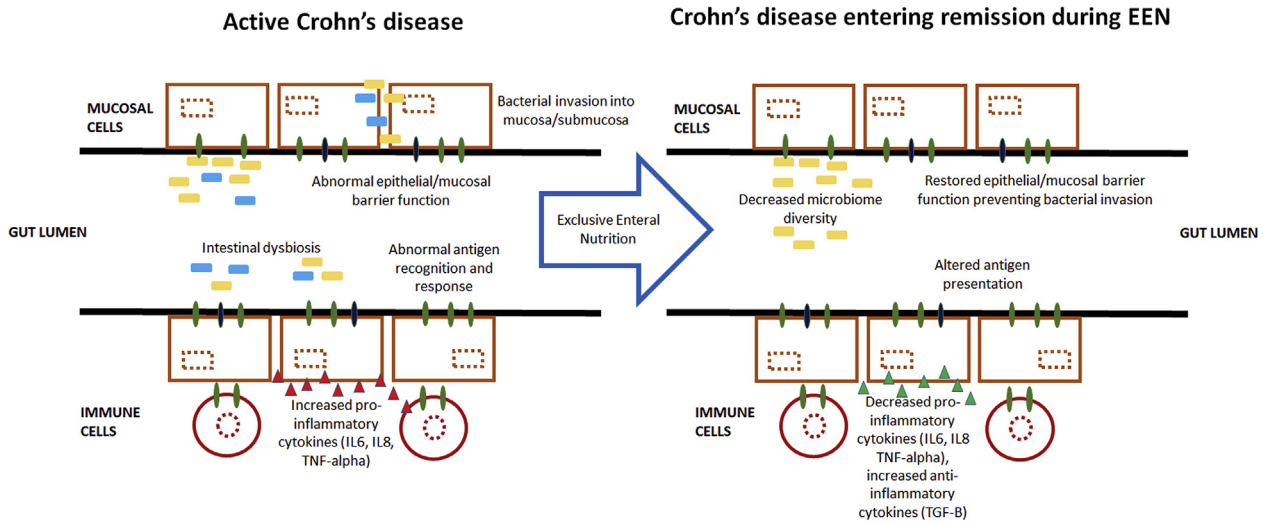

Fig. 1. Summary of mechanisms of action through which exclusive enteral nutrition induces remission in Crohn's disease. Restoration of epithelial barrier function with no invasion of bacteria into the mucosa, reduction in inflammatory response mediated through reduction of pro-inflammatory cytokines and local action of anti-inflammatory cytokines and normalisation of handling of bacteria, with alterations in the composition of the microbiome.

role in post-transcriptional regulation of gene expression [28]. In vitro modelling has shown a direct effect of polymeric formula on enterocyte differentiation and expression of molecules associated with innate response to bacteria, shaping the intestinal immune response to the microbiome [29].

Some short chain fatty acids (SCFAs), such as butyrate, have been shown to have some local anti-inflammatory properties, with changes in metabolic activity and concentration reported during treatment with EEN [30,31]. Diet can have a significant impact on relative SCFA concentrations (additional role of the microbiome) and these alterations have been demonstrated overtime with EEN, with a possible anti-inflammatory role [32,33].

2.3. Microbiome

There has been an explosion of interest in the role of the microbiome in disease pathogenesis of CD over the last 5 years [34]. The impact of EEN on the microbiome, including alterations of specific bacterial species, broad shifts in bacterial taxa and potential functional changes are beginning to be elucidated [14,33,35,36]. A recent systematic review of the effects of EEN on the microbiome concluded that despite huge variation between studies/patients, bacterial shifts, alterations in diversity and metabolomics changes over treatment were very likely to play a role in achieving remission [37].

Intestinal dysbiosis is well documented, although the exact microbial disturbances in an individual patient vary hugely [14]. The advent of 16S rDNA sequencing and more recently metagenomic sequencing (shotgun sequencing) has allowed for identification of bacteria at a scale not previously possible [34]. Typing of bacteria to a species level and inference of functional capability of the microbiome is realistic in both individuals and in groups of patients.

The largest study to date, from the RISK inception cohort (2014), reported significant differences in mucosal bacterial abundances (in classes such as *Enterobacteriaceae*, *Bacteroides* and *Clostridiales)* between patients and controls but did not follow patients over time [35]. Longitudinal studies have looked at the changes in microbiome diversity alongside specific bacterial species with EEN and shown a general trend towards decreased bacterial diversity during treatment [13,31,38,39]. Despite this several studies have demonstrated an increased abundance during the treatment phase returning to a diversity more similar to healthy controls as they enter remission [33,40]. Bacterial changes within specific taxa are reported in each study, with huge variations in the changes observed; normal gut commensal bacteria (*Bacteriodes, Prevotella*, *Enterobacteriaceae* etc.) have been shown to both increase and decrease in relative abundances [38,39,41]. The role of specific bacteria has been explored, with early studies reporting *Faecalibacterium prausnitzii* as an anti-inflammatory commensal, however more recent reports have demonstrated a reduction in abundance over treatment with EEN [42,43]. This has been replicated and the anti-inflammatory role of this bacteria has been discredited [31].

The metabolic and functional role of the microbiome in CD is of interest, with evidence suggesting disruption of normal homoeostatic metabolic functions in active disease [35,44]. To date two studies have looked at the effect of EEN on the functional potential of the microbiome during treatment, both Quince et al. and Ashton et al. demonstrate significant functional differences in the microbiome between CD and healthy controls, returning to normal over treatment [33,36]. Interestingly Walton et al. demonstrated reduction in concentrations of faecal microbial products (including potentially toxic chemicals) over treatment with EEN [45]. This evidence points to a potential role of EEN in normalising intestinal microbiome function, reducing pro-inflammatory bacterial products, leading to healing.

A major limitation of current studies detailing changes in the microbiome over treatment with EEN is that they are typically conducted on faecal samples. Mucosal dysbiosis (including interaction with the host immune system) is likely to be weakly reflected in stool and therefore more subtle dysbiotic signatures and altered functional potential may not have been observed, even if it was present [35]. Understanding causality regarding the microbiome and reduction in inflammation is difficult. Further work including serial mucosal sampling is required. MacLellan et al. provide further appraisal of the evidence of EEN and the microbiome [14].

3. EEN induces remission in paediatric Crohn's disease

European and North American guidelines recommend EEN as the first line agent in active luminal CD, diagnosed <17 years of age [1,5]. Early data indicated that EEN was more likely to be effective in patients with small bowel involvement; however, subsequent meta-analysis has demonstrated effectiveness regardless of site of luminal involvement [46–48]. There is a paucity of data regarding the effectiveness of EEN in CD with isolated severe pancolitis, however the limited evidence appears to indicate that EEN remains an effective treatment option in selected patients [47,49]. There is limited evidence to suggest that isolated perianal CD should be treated with EEN and consensus opinion indicates that alternative therapy is used in these patients (although EEN may still be of benefit) [1,50]. No substantial evidence exists for the use of EEN in patients with extra-articular manifestations (arthritis, uveitis etc.) although there have been several reports of patients with juvenile idiopathic arthritis being effectively treated with EEN [51,52] and successful treatment of scleritis and psoriasis in CD using only EEN [53]. EEN is equally as effective as corticosteroids in induction of remission at diagnosis [47,48,54–57]. Data focussed on induction of remission in paediatric patients with recurrent disease has shown >50% remission rates with significantly decreased disease activity in those not reaching full remission [58].

In 2007 the Cochrane review of both adult and paediatric data by Zachos et al. concluded that corticosteroids were more effective than EEN at inducing remission, however acknowledgement of many confounding factors must be made (tolerability to adults, adherence to regimens, unable to double-blind studies etc.) [47]. When restricting to only high quality studies the Cochrane authors found no difference between corticosteroids and EEN. Focused meta-analysis of paediatric data by Dziechciarz et al. (including 4 trials and 144 patients) did not show a difference between EEN and corticosteroids (RR 0.97, 95% CI 0.68–1.40) [48]. The most contemporary paediatric meta-analysis, by Swaminath et al. (2017), included 8 studies and 451 patients and demonstrated no difference between corticosteroids and EEN (OR 1.26, 95% CI 0.77–2.05) [57]. The summary of all meta-analyses can be seen in Table 1. Cohort studies in paediatric populations have demonstrated a clinical remission rate of 60–80%, comparable to steroids [49,59]. The most contemporary data (from the last 5 years) continues to show the effectiveness of EEN. Studies from Levine et al., Grover et al. (two studies) and de Bie et al. demonstrated clinical remission rates of 73%, 84%, 83% and 71% respectively [17,60–62]. There are fewer recent adult data, although Yang et al., studying patients with stricturing or penetrating disease, demonstrated EEN inducing full clinical remission within 12 weeks in 80.5% of patients [63].

A further study by Grover et al. (2015) retrospectively analysed 89 paediatric patients over 2 years. Data demonstrated superiority of EEN over corticosteroids as initial induction therapy when comparing 2 year corticosteroid-dependency (EEN, 7% vs CS, 43%)

Table 1
Summary of four meta-analyses comparing exclusive enteral nutrition to corticosteroids for induction of remission in Crohn's disease.

Author	Year	Total patients	EEN remission rates of included studies	Comparison to corticosteroids	Comments and additional findings
Griffiths [104]	1995	413 paediatric patients	22–82%	EEN was Inferior to CS, OR 0.35; 95% CI 0.23–0.53	No difference in elemental versus polymeric formulas, OR 0.87; 95% CI 0.41–1.83
Zachos [47]	2007	315 adult patients, 37 paediatric patients	20–84%	EEN was inferior to CS, OR 0.33; 95% CI 0.21–0.53	No difference in elemental versus polymeric formulas, OR 1.10; 95% CI 0.69–1.75
Dziechciarz [48]	2007	144 paediatric patients	60–90%	There was no difference between EEN and CS, RR 0.96, 95% CI 0.6–1.14	Polymeric formula resulted in significantly greater weight gain than elemental formula, mean difference 2.5 kg, 95% CI 0.9–4.1, p = 0.004
Swaminath [57]	2017	451 paediatric patients	46–90%	There was no difference between EEN and CS, OR 1.26; 95% CI 0.77–2.05	No difference between EEN and CS efficacy when comparing newly diagnosed (OR 1.61; 95% CI 0.87–2.98) or relapsed Crohn's disease (OR 0.76; 95% CI 0.29–1.98). Mucosal healing was associated with treatment with EEN compared to corticosteroids (OR 4.5; 95% CI 1.64–12.32).

and primary response to anti-TNF therapy (EEN, 86% vs CS, 68%) [64]. Whilst there is limited data on longer term remission rates in EEN, Berni et al. followed up patients for 12 months after induction and observed lower relapse rates with EEN vs corticosteroids [65]. The most contemporary data is summarised in Table 2.

3.1. Markers of inflammation

EEN leads to rapid normalisation of markers of systemic inflammation with no significant difference between EEN and corticosteroids in meta-analysis or single centre study [57,60]. Lower faecal calprotectin levels have been associated with corticosteroid use compared to EEN, Levine et al. reported only 3/23 (13%) patients treated with EEN had a faecal calprotectin <300 μg/g at 8 weeks, compared to 22/72 (30.5) of those treated with corticosteroids [60].

3.2. Nutritional status and growth

EEN as induction therapy leads to improved nutritional status when compared to corticosteroids [15]. Objective measurement has demonstrated improvement in lean mass and weight over the EEN induction period [66–69] with additional improvements in serum markers of growth such as insulin-like growth factor 1 (IGF-1) [18]. Biochemical measures of nutritional status including iron and albumin levels also improve [65]. Over 8 weeks of treatment with EEN Gerasimidis et al. demonstrated a significant reduction in anaemia (32%–9%) and increase in haemoglobin by 0.75 g/dL [70]. Measurement of several micronutrients also demonstrated significant increases over time [66].

There is reduced incidence of linear growth failure with EEN compared to corticosteroids (7% vs 26%) [64]. Berni et al. demonstrated EEN increased height by over 1% over 8 weeks compared to <0.3% increase with corticosteroids, similarly Borelli et al. showed an increase in height gained in those treated with EEN compared to corticosteroids (+0.8 cm) [11,65]. Several historical RCTs have demonstrated superiority of EEN over corticosteroids when looking at height standard-deviation scores (SDS) with height velocity (SDS 0.32) and mean height (SDS 0.3) both significantly higher with EEN than corticosteroids (SDS −3.1 and −2.8 respectively) at 6 months [71,72]. Interestingly a meta-analysis has demonstrated that those treated with a polymeric diet gained significantly more weight

Table 2
Summary of studies on exclusive enteral nutrition from last 5 years detailing remission rates, duration of treatment, patient numbers and type of feed.

Author	Year of publication	Type of study	Patients included	Newly diagnosed or relapse	Duration of treatment	Type of feed	Remission rate	Comments
Lambert et al. [108]	2012	Retrospective	57	Newly diagnosed	4–8 weeks	Polymeric	84%	Improved outcomes at 6 months compared to CS
Saadah [109]	2012	Retrospective	50	Newly diagnosed	6 weeks	Polymeric	32%	No comparison to CS
Soo et al. [110]	2013	Retrospective	105	Newly diagnosed	6 weeks	33 polymeric; 3 semi-elemental	88.9%	No difference between EEN and CS
Hojsak et al. [111]	2014	Retrospective	74	Relapse	6–8 weeks	Polymeric	84.2%	Significantly longer to relapse in those treated with EEN vs CS
Levine et al. [60]	2014	Prospective cohort	201	Newly diagnosed	6–8 weeks	Polymeric	79%	No difference between EEN and CS
Lee et al. [80]	2015	Prospective cohort	90	Newly diagnosed and Relapse	8 weeks	Unknown	88%	Partial enteral nutrition induced remission in 64% of patients
Luo et al. [112]	2015	Retrospective	28	Newly diagnosed	8 weeks	Polymeric	90%	Significantly improved remission rates compared to CS
Connors et al. [113]	2017	Retrospective	111	Newly diagnosed	6–16 weeks	Unknown	86.6%	Induction with EEN was significantly associated with reduced risk of exposure to CS over 2 years

(+2.5 kg) than those treated with an elemental diet [48]. Further studies are required with longer follow-up periods, whilst corticosteroids suppress short-term growth, if improved long-term remission is achieved then overall growth may be better. Future work must detail growth outcomes at >1 year to truly assess the impact of EEN/corticosteroids.

3.3. Mucosal healing

Mucosal healing is now seen by many as the objective treatment goal in CD [61,73]. Limited high quality data is available on the effects of EEN on mucosal healing; 2 paediatric studies (RCT and retrospective cohort) from 2006 appear to demonstrate superiority of EEN over corticosteroids at induction of mucosal healing (pooled OR 4.5, CI 95% 1.64–12.32) [11,57,65]. Fell et al. (2000) demonstrated high rates of mucosal healing with EEN, with complete remission in up to 79% of patients [74]. Grover et al. demonstrated improvement in endoscopy assessment with EEN in 2014, with 43% of children achieving mucosal healing and 21% achieving transmural healing [17]. Grover et al. (2016) showed complete mucosal healing in 33% with near complete mucosal healing in 19% of patients, complete mucosal healing was associated with sustained remission over 3 year follow-up [61].

4. Practical issues

4.1. Elemental or polymeric feeds

EEN can be delivered as either a polymeric (such as Modulen, Nestle) or elemental (such as Elemental O28, Nutricia) feed (see Table 3). Polymeric or elemental refers to the protein source in the feed. There is no difference in efficacy between polymeric and elemental regimens for the induction of remission in either CD (odds ratio 1.10, 95% CI 0.69–1.75%) [47]. Direct comparison of clinical remission rates by RCT has been performed on limited adult (polymeric 59%, elemental 80%) and paediatric patients (polymeric 82%, elemental 69%) with no statistical differences reported [69,75].

Table 3
Nutritional comparison of a polymeric (Modulen, Nestle) and elemental (EO28 Nutricia) exclusive enteral nutrition feed.

Nutrients	Modulen IBD (per 100 g powder)	Elemental 028 Extra (per 100 g powder)
Energy (kcals)	500	443
Carbohydrate (g)	54 (43% kcals)	59 (53% kcals)
Protein (g)	18 (15% kcals)	12.5 (11% kcals)
Fat (g)	23 (42% kcals)	17.5 (36% kcals)
Sodium (mg)	170	305
Chloride (mg)	365	333
Potassium (mg)	600	466
Calcium (mg)	445	245
Phosphorus (mg)	300	200
Magnesium (mg)	100	82
Iron (mg)	5.4	4.2
Zinc (mg)	4.7	4.2
Copper (mg)	0.5	0.4
Iodine (μg)	49	33
Selenium (μg)	17	15
Manganese (mg)	0.9	0.6
Chromium (μg)	25	15
Molybdenum (μg)	37	33
Vitamin A (μg)	410	330
Vitamin D (μg)	4.9	2.5
Vitamin K (μg)	27	25
Vitamin C (mg)	47	28
Vitamin B1 (mg)	0.6	0.6
Vitamin B2 (mg)	0.6	0.6
Vitamin B6 (mg)	0.8	0.8
Niacin (mg)	5.8	4.2
Folic acid (μg)	120	83
Vitamin B12 (μg)	1.6	1.7
Pantothenic acid (μg)	2.4	2
Biotin (μg)	16	18
Vitamin E αTE (mg)	6.5	6.1

For several reasons (including similar efficacy data) polymeric feed regimens are more commonly used than an elemental formulations, the most recent international survey indicated >90% of centres used a polymeric feed [76,77]. Polymeric formulations are relatively palatable and lower in cost compared to elemental formulations [69,78]. There is wide variation in practice regarding the addition of flavouring to feeds and leniency regarding a small proportion of normal diet in addition to EEN [76,77]. Guidance on this is clear and recommends that feed should be exclusive with total elimination of normal diet, however addition of flavourings, sugar free sweets/chewing gum are widely used [1,5].

Partial enteral nutrition (PEN) is not recommended for the induction of remission in CD [1]; the largest study to date demonstrated paediatric patients treated with EEN reached remission in 42% compared to those treated with PEN who reached remission in only 15% [79]. In a study of 90 children Lee et al. demonstrated clinical remission in 64% of patients treated with PEN, compared to 88% treated with EEN and 84% treated with anti-TNF [80].

4.2. Disease site

Early data suggested that EEN was more effective if there was small bowel involvement. Afzal et al. (2005) supported this hypothesis; 84% patients with ileal involvement achieved remission compared to only 50% with isolated colonic disease [46]. However a meta-analyses and several single centre cohort studies have failed to make the same conclusions, with similar rates of remission observed regardless of disease location [47,49,59,81]. This has led to the decision from ECCO/ESPGHAN/NASPGHAN to recommend EEN regardless of the site of luminal CD [1,5]. Isolated colitis/isolated small bowel disease may be different phenotypic/genotypic manifestations of disease and future work on personalised therapy may reveal groups of patients more likely to respond to EEN [82].

4.3. Duration of treatment

Current recommendations are that EEN is given over a period of 6–8 weeks, either orally or by a nasogastric tube [1]. Although inflammatory markers begin to fall within the first 2 weeks of EEN they continue to improve over the 6–8-week treatment period. There is considerable variation in practice. An international survey of practice by Whitten et al. observed large variation in EEN duration (<6 weeks–>12 weeks) with the most common practice to continue EEN for 6–8 weeks prior to food reintroduction [57,77]. There are no controlled trials looking at the appropriate length of treatment, current practice is based on consensus [1,5].

4.4. How much should be given?

The correct volume of EEN considers several patient factors. The main determinant of total fluid requirement is patient body weight (see Table 1). Estimated average requirement (EAR) for energy (based on age) is used to calculate the daily calorific content of the volume of EEN required for each patient. Standard concentrations of formulae are 0.86–1 kcal/ml but can be concentrated as necessary over the 6–8-week treatment period to meet satiety (and fulfil fluid/calorific requirements). Longitudinal studies have shown resting energy requirements are not increased in active CD therefore predictive energy expenditure equations are suitable for estimating requirements at all stages of disease (see Table 4) [3,83,84]. Whilst

Table 4
Daily Estimated Average Requirement (EAR) for energy and fluid requirements in children aged 10–18 [114].

Age (years)	EAR (kcals/day)
Boys	
10	2032
11	2127
12	2247
13	2414
14	2629
15	2820
16	2964
17	3083
18	3155
Girls	
10	1936
11	2032
12	2103
13	2223
14	2342
15	2390
16	2414
17	2462
18	2462

Standard growth rate is an additional 5 kcals/kg body weight/day.
Fluid requirement-
10–20 kg – 1000 mL + 50 mL per kg body weight above 10 kg.
20–70 kg – 1500 mL + 20 mL per kg body weight above 20 kg.
Over 70 kg – 2500 mL.

resting energy expenditure (REE) is unchanged throughout disease there is an alteration in total energy expenditure (TEE); initially TEE decreases in comparison to healthy children due to a decrease in physical activity, during recovery there is increased physical activity with a corresponding increase in TEE with the final phase also resulting in increased TEE due to an additional energy cost of 'catch-up' growth once remission is achieved [83,84]. It is important to note that energy expenditure equations are only a guide [3]. Daily estimated average requirement for protein follows a slightly different pattern. In active inflammation the proteolytic, catabolic response justifies an increase in protein provision to 1.2–1.5 g/kg body weight returning to 1 g/kg body weight in remission, similar to healthy subjects [3]. An additional consideration in the final few weeks of treatment with EEN is patient satiety. Avoiding overfeeding is important in this stage of management [85].

5. Food reintroduction

There is currently no strong evidence to guide reintroduction of food at the end of the period of EEN. As normal diet is gradually reintroduced EEN should be weaned in a proportional manner, many survey respondents adopted a method of gradually reintroducing food groups every 2–3 days over a period of 2–3 weeks whilst simultaneously decreasing EEN [1,77]. A single centre study demonstrated no difference in relapse rate between rapid food reintroduction and gradual reintroduction over 5 weeks in 39 newly diagnosed patients but this has not been replicated [86]. The type of food to reintroduce remains contentious with some centres favouring a low fibre diet in the initial period [77]. There are a lack of prospective, controlled, studies and insufficient evidence to recommend a specific diet. Further work is required to identify any food components that contribute to relapses or unsuccessful food reintroduction [87]. The current guidance states no specific diet needs to be followed during remission [3].

5.1. Maintenance enteral nutrition

A detailed appraisal of the role of maintenance enteral nutrition (MEN) in maintaining remission is beyond the scope of this review. ESPEN guidelines suggested maintenance enteral nutrition in the form of oral nutritional supplements may be beneficial to nutritional status and anthropometry and in doing so may influence length of remission; however the evidence is not strong enough to make a recommendation [3]. There is some evidence suggesting that MEN may prolong remission and be steroid-sparing [88–90] although a 2017 study by Gavin et al. did not show a reduction in relapse rates at 12 months [91]. Further prospective studies are required before MEN can be recommended as an effective maintenance treatment.

5.2. Combination with other therapy

There is no role for EEN in combination with corticosteroids for induction of remission in CD and failure to respond to EEN within 2 weeks should trigger alternative treatment [1]. Maintenance therapy (such as thiopurines/5-aminosalicylate) can be started during the period of EEN, however optimal timing of starting is controversial and is largely determined by patient's needs and clinician preference [1,5].

Several studies have focussed on combination of EN (Enteral Nutrition) with other maintenance medication, reporting improved remission rates in children treated with EN alongside normal diet [92,93]. Adult data from a systematic review of 10 studies concluded that there was benefit from EN alongside maintenance medications in prolonging remission in CD and two additional studies focused on anti-TNF therapy have demonstrated benefit [89,90,94]. Nguyen et al. demonstrated 45% of patients remaining in remission on anti-TNF monotherapy compared to 75% on both anti-TNF therapy and EN at 1 year [95]. Yamamoto et al. failed to demonstrate any improvement in patients remaining in remission between those on EN (76%) and those on normal diet (67%), $P = 0.51$ [96].

6. Use of EEN in adult disease

The basic premise of EEN as an effective treatment in adult CD remains the same as in paediatric practice; however the evidence of efficacy in adults is significantly less than in children. This is likely to be related to practical issues (disruption to normal life, poor palatability, less multi-disciplinary team support, lack of experience, lack of guidance) rather than mechanistic differences (how EEN works) [97]. Consensus clinical guidelines in Europe and North America do not recommend EEN as first line therapy to induce remission [98,99]. In contrast Japanese clinicians recommend EEN for routine use [100]. A recent review on adult disease found evidence from 7 studies demonstrating no difference between EEN and corticosteroids in inducing remission (remission rates varied hugely from 20 to 100%) [101]. The same review identified the main barrier to successful treatment with EEN was adherence, with up to 41% of patients dropping out of EEN treatment, rates much higher than with steroid therapy [101]. Overcoming obstacles to treatment (such as with use of NGT) and focussing on specific patient groups who may benefit from therapy (newly diagnosed, possibly small bowel involvement) may allow the nutritional benefits and similar efficacy to paediatric disease [101].

7. Essential role of the dietitian and multi-disciplinary team

A dietitian with an interest in IBD should undertake a full nutritional assessment at diagnosis prior to commencing EEN (Fig. 2) [3]. This assessment should include:

- Anthropometric measures e.g. weight, height, BMI and body composition measures (skinfold thickness or mid upper arm circumference).

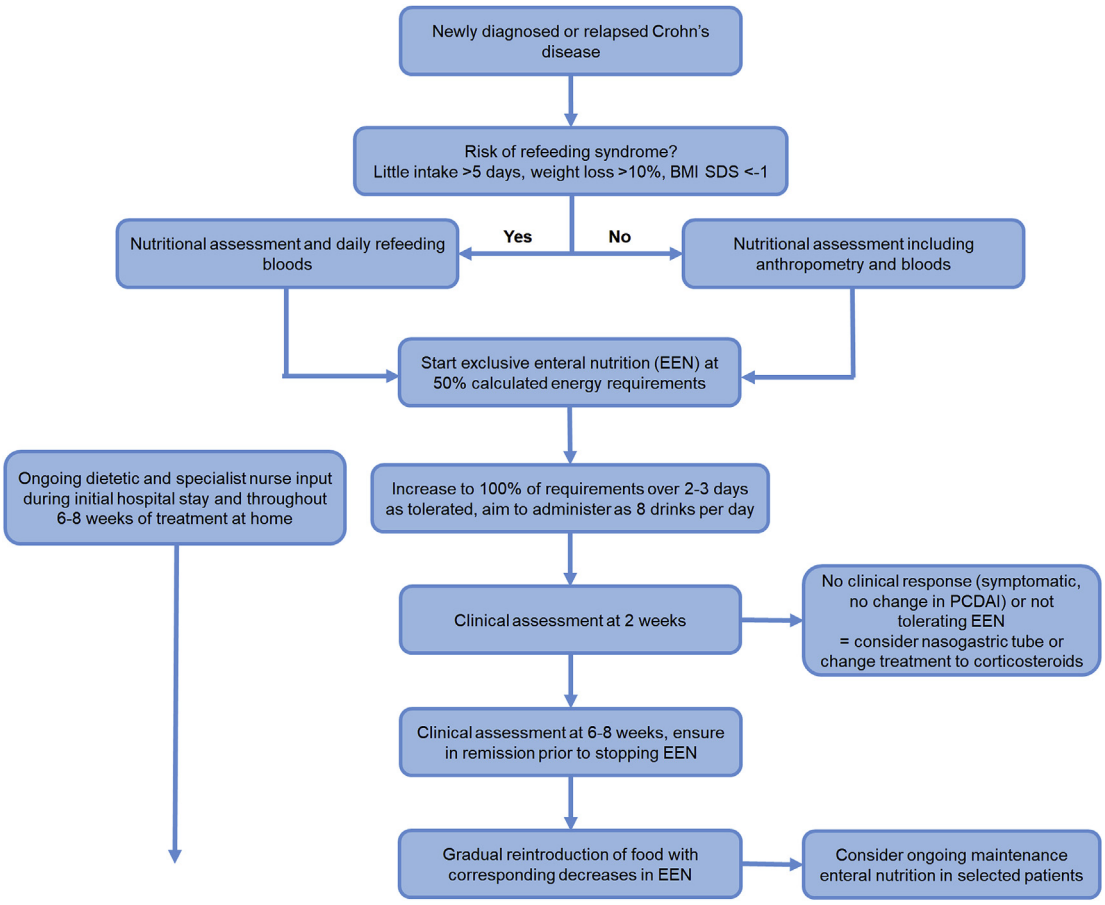

Fig. 2. Treatment algorithm for use of exclusive enteral nutrition as induction therapy in paediatric Crohn's disease.

- Assessment of refeeding risk; for patients who have eaten little over the past 5 days, had unintentional weight loss >10% over the last 3–6 months or who are malnourished (BMISDS < −1) should have no more than 50% of energy requirements as EEN initially. There should be a plan to increase to full requirements within 4–7 days if refeeding changes are not detected on clinical and biochemical monitoring [102].
- Calculation of protein and energy requirements throughout the EEN period, with consideration to the change in requirements during recovery.

Advice on the practical aspects of incorporating EEN into daily life including how to reconstitute the feed correctly should all be discussed at diagnosis. Regular contact between the dietitian and patient should take place throughout the EEN feeding period to aid compliance and to ensure satiety. A full nutritional assessment should be undertaken again at the end of the EEN period to assess the need for ongoing nutritional support [103].

Monitoring of compliance to treatment is important and patients failing to tolerate full volumes should be considered for an alternative route of administration [1]. There is a role for nasogastric tubes (NGT) in selected patients. Importantly there are no reported differences in efficacy of induction of remission when comparing fractionated oral feeds to continuous feeds [59]. Where patients are unable to tolerate due to palatability a NGT may be considered. Comparison of compliance of oral to NGT administration is variable, older data from Griffiths et al in 1995 that demonstrated compliance improved to 87–100% when feeds were administered by nasogastric tube [104]. More contemporary data has shown that between 56 and 93% of patients will tolerate EEN orally for the duration of their treatment, with the impact of multidisciplinary support being key in increasing compliance [77,85].

Identification of patients and physician barriers to effective treatment with EEN (including tolerance/compliance and psychological problems), with subsequent MDT support (dietetic, specialist nursing and psychological support) is important in improving EEN compliance [105]. Quality of life data in patients treated with EEN do show improvement in line with decreasing disease activity scores, often equal or better than with corticosteroid therapy, however disruption of normal diet and additional difficulties with daily routines must be addressed [106,107].

8. Future research priorities

The efficacy of EEN in induction of remission in paediatric CD is clear, however questions remain as to the exact mechanism through which EEN acts and which patients are likely to respond best. Stratification of patients to guide treatment, through merging of clinical and multi-omic data by machine learning is a research priority. Understanding the exact mechanisms including prospective and longitudinal assessment of changes in the microbiome and alterations immune response may lead to improved application of EEN in both children and adults. Additionally preventing relapse through maintenance enteral nutrition and the potential of an alternative to EEN through an exclusion diet presents further interesting avenues for research.

9. Conclusions

EEN is an effective, low risk and steroid-sparing treatment for induction of remission in paediatric CD, with some evidence-suggesting efficacy in adult disease, where EEN is underused. Modulation of intestinal microbiota, direct gut anti-inflammatory effects and systemic immune changes act to induce remission in newly-diagnosed and relapsed CD.

Conflict of interest

The authors have no conflicts of interest to declare.

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Contributorship

RMB and JJA conceived the article. JJA conducted the searches for articles in conjunction with JG and RMB. JJA wrote the article in conjunction with JG and RMB. JG had specific input on dietetic sections. All authors approved the manuscript prior to final submission.

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