MINIREVIEWS

Use of exclusive enteral nutrition in adults with Crohn's disease: A review

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Abstract

Exclusive enteral nutrition (EEN) is well-established as a first line therapy instead of corticosteroid (CS) therapy to treat active Crohn's disease (CD) in children. It also has been shown to have benefits over and above induction of disease remission in paediatric populations. However, other than in Japanese populations, this intervention is not routinely utilised in adults. To investigate potential reasons for variation in response between adult studies of EEN and CS therapy. The Ovid database was searched over a 6-mo period. Articles directly comparing EEN and CS therapy in adults were included. Eleven articles were identified. EEN therapy remission rates varied considerably. Poor compliance with EEN therapy due to unpalatable formula was an issue in half of the studies. Remission rates of studies that only included patients with previously untreated/new CD were higher than studies including patients with both existing and new disease. There was limited evidence to determine if disease location, duration of disease or age of diagnosis affected EEN therapy outcomes. There is some evidence to support the use of EEN as a treatment option for a select group of adults, namely those motivated to adhere to an EEN regimen and possibly those newly diagnosed with CD. In addition, the use of more palatable formulas could improve treatment compliance.

Core tip: Exclusive enteral nutrition (EEN) is established treatment for children with active Crohn's disease (CD). At present, this therapy is used sparingly in adult patients outside of Japan. In reviewing the published literature regarding the use of EEN in adult patients, this article highlights evidence supporting the use of EEN as a treatment option for selected patients: namely those motivated to adhere to an EEN regimen and those newly diagnosed with CD. The role of EEN in adult patients with CD should now be re-examined, with particular regard to treatment protocols and the use of more palatable polymeric formulae that may enhance compliance.

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INTRODUCTION

Crohn's disease (CD) is an incurable inflammatory bowel disease (IBD) characterised by inflammation of the gastrointestinal tract, which leads to chronic symptoms such as diarrhoea, abdominal pain and rectal bleeding[1]. The peak age of diagnosis is between 15 and 30 years of age,

leading to many years of disease and associated morbidity. Standard first line treatment in adults newly diagnosed with CD is corticosteroid (CS) therapy, which is effective at inducing remission or response in approximately 85% of patients[2]. However, CS therapy has many well documented acute side-effects: furthermore there are numerous long term adverse effects due to repeated or continual use of CS[3]. Also, CS resistance can occur in 8%-22% of patients and CS dependency occurs in 15%-36% of patients[4]. Alternative therapies that can effectively induce and maintain disease remission without short and long term side effects are desirable.

Exclusive enteral nutrition (EEN) is the provision of 100% of a person's nutritional requirements from a liquid nutrition formula either orally or *via* a feeding tube. EEN is usually provided for 6-8 wk and then usual diet is gradually reintroduced[5]. In children with CD, EEN has been shown to be an effective and feasible alternative to CS[6]. In addition to avoiding the adverse effects of CS exposure, EEN provides additional benefits over and above those provided by CS. EEN therapy is associated with higher rates of mucosal healing[7], altered intestinal flora[8], greater weight gain[9], improved vitamin D status[10], enhanced bone turnover[11], an early rise in Insulin-like growth factor 1[12], and better quality of life after treatment[13]. There are few long term follow up studies post EEN, but those that have been conducted in children indicate that EEN may improve time to relapse[14]. The administration of supplementary enteral nutrition (SEN) once disease remission is achieved has been shown to be beneficial in maintaining remission compared with a free diet in Japanese adults[15] and children[16].

However, in adult CD populations, EEN is generally not seen as a first line therapy for newly diagnosed or those with a flare of pre-existing CD. European[2] and North American[17] clinical guidelines only recommend EEN if a patient declines drug therapy or as an adjunctive therapy to support nutrition, rather than as a primary therapy. These recommendations are primarily based on the results of a Cochrane systematic review of six randomised controlled trials including 192 patients treated with EEN and 160 patients treated with CS[18]. The review found a pooled OR of 0.33 (95%CI: 0.21-0.53) in favour of CS and concluded that CS were superior to EEN in the induction of remission of disease. In contrast to these guidelines, recent Japanese experience demonstrates efficacy in that setting[15].

It is not clear why the benefits of EEN therapy seen in paediatric populations are not achieved in adults. We aimed to review the published literature reporting the use of EEN as a primary therapy for active CD in adults and examine potential reasons for this apparent discrepancy.

SEARCH

The Ovid database was searched from September 2012 to March 2013 for articles published between 1946 and now. Key search terms were: "CD", "Crohn disease",
"EEN" and "enteral nutrition". Abstracts were scanned and articles in English that compared enteral nutrition with CS treatment in adults were considered relevant. Studies were excluded if enteral nutrition was not the sole source of nutrition, enteral nutrition was provided as well as other medication (for example, antibiotics), the study included children, or the study did not compare CS and EEN. A manual search was also completed of reference lists of articles retrieved, relevant review articles and meta-analyses on the topic.

RESEARCH

Study characteristics

Eleven studies published between 1984 and 2002 were identified that compared EEN with CS treatment in adults (Table 1). Two were abstracts[19,20] and the rest were full articles. The studies were conducted in Europe, North America and Asia: three in England[19,21,22], one in Spain[23], one in Greece[20], one in Italy[24], one in the United States[25], one in Japan[26] and three[27-29] were multi-centre European trials. All but two studies enrolled a mix of patients with newly diagnosed CD (naïve to prior treatment) and existing CD. All but one study compared one enteral nutrition formula with CS therapy.

The studies utilised a range of nutritional products, in varying regimens, as summarised in Table 2. Eight of the studies used elemental formula and three studies used polymeric formula. Most formulas were a 1 kcal/mL concentration apart from one which used a 1.5 kcal/mL formula. Duration of EEN treatment ranged from 2-6 weeks but most studies used EEN therapy for four weeks. Mode of delivery of the EN formula was either orally, or *via* a nasogastric tube (NGT) if not tolerated orally, or continuous feeding *via* an NGT or nasoduodenal tube. Nutritional composition of the formulas was quite different depending on the type and brand of formula used. All formulas had relatively similar amounts of protein (14%-22% of total energy), whereas fat content varied considerably (1%-35% of total energy). Carbohydrate content varied relative to fat content (49%-82% of total energy).

The only study that compared two different enteral formulas and CS was published by Gassull *et al*[27] They compared two EEN formulas that were the same except for the predominant type of fat: one was high in oleic acid and the other was high in linoleic acid. Study recruitment was ended prematurely because less than 33% of the high oleic acid formula group had achieved disease remission and the remission rate was significantly different from that of the other treatments.

CS protocols also ranged between the evaluated studies. Usual initial CS dosage was between 0.5 mg/kg per day and 1.0 mg/kg per day, with subsequent weaning courses. CS were given orally in two studies[23,27] but the route of administration was not published in the majority of studies. Two studies administered CS and sulfasalazine concurrently[28,29].

Table 1 Studies of adults that compared exclusive enteral nutrition with corticosteroid therapy

Ref.	Year	Country	Age (SD or range)	Received no previous CD treatment (% of EEN group)	Number of participants		% that achieved remission (intention to treat)		Significant difference (*P* value)	Remission criteria	Number that did not complete EEN intervention, *n* (%)		% that achieved remission (treatment completed)	
					EEN	CS	EEN	CS			Formula un-palatable	Other reason	EEN	CS
Engelman *et al*[19]	1993	England	23-54	Not stated	7	4	100%	100%	NS	HBI < 6.0	0 (0)	0	100%	100%
Gassull *et al*[27]1	2002	Europe	31.3 (3.3)	50%	20	19	20%	79%	0.0005	VHAI < 120	5 (25)	0	27%	79%
Gassull *et al*[27]2	2002	Europe	30.8 (4.1)	43.50%	23	19	52%	79%	NS	VHAI < 120	4 (17)	0	63%	79%
González-Huix *et al*[23]	1993	Spain	31.1 (4.1)	47%	15	17	8%	88%	NS	VHAI < 120	0 (0)	0	80%	88%
Gorard *et al*[21]	1993	England	31.6 (3.0)	50%	22	20	45%	85%	< 0.05	HBI - remission not defined, mean < 2	9 (41)	2	91%	89%
Lindor *et al*[25]	1992	United States	34.7 (26-64)	33%	9	10	50%	33%	NS	CDAI decrease > 100 points	3 (33)	1	60%	63%
Lochs *et al*[28]	1991	Europe	27.5 (1.5)	Not stated	55	52	53%	79%	< 0.01	CDAI decrease > 100 points or > 40%	7 (13)	0	60%	85%
Malchow *et al*[29]	1990	Europe	30.1 (11.5)	20%	51	44	41%	71%	< 0.05	CDAI decrease > 100 points or > 40%	20 (39)	0	71%	91%
Mantzaris *et al*[20]	1996	Greece	Not stated	20%	10	10	40%	70%	NS	CDAI <150 or decrease > 100 points	0 (0)	0	40%	70%
Okada *et al*[26]	1990	Japan	21.0 (3.3)	100%	10	10	80%	30%	< 0.01	HBI < 1	0 (0)	0	80%	30%
O'Moráin *et al*[22]	1984	England	31.9 (15-60)	100%	11	10	82%	80%	NS	HBI - remission not defined. Mean < 3	2 (18)	0	100%	100%
Zoli *et al*[24]	1997	Italy	33.5 (15.9)	Not stated	12	10	67%	50%	NS	HBI < 3	1 (8)	1	80%	50%

[1,2]Gassull *et al* had two EEN arms: [1]High oleic fatty acid formula; [2]High linoleic fatty acid formula. CD: Crohn's disease; CDAI: Crohn's disease activity index; CS: Corticosteroids; EEN: Exclusive enteral nutrition; HBI: Harvey Bradshaw Index; NS: Non-significant; VHAI: Van Hees activity index.

Disease remission criteria

Three remission criteria were used across the 11 studies - the CD Activity Index (CDAI), the Harvey Bradshaw Index (HBI), and the Van Hees Activity Index (VHAI). The CDAI score uses a seven day history of general well-being, abdominal pain, loose stools, presence of abdominal mass and CD complications, anti-diarrhoeal use, haematocrit and weight[30]. The HBI is based on a one day history of general well-being, abdominal pain, loose stools and presence of abdominal mass and CD complications[30]. It correlates well with the CDAI ($r = 0.8$)[30]. Clinical remission is usually defined as a CDAI of less than or equal to 150 points or a HBI of less than or equal to 4 points[30]. Of the four studies that used the CDAI to define remission one used this criteria, one used a decrease of more than 100 points and two used either a CDAI of less than 150 or a decrease of 40% or more. Five studies used the HBI to define disease remission, the cut-offs used by each study were different.

The VHAI is calculated using serum albumin and erythrocyte sedimentation rate, body mass index, abdominal mass, gender, fever, loose stools, bowel resection and CD complications. The VHAI correlates moderately ($r = 0.67$) with the CDAI[31]. Both studies that used the VHAI used the same cut-off of less than 120 to define disease remission.

Remission of disease

Remission was achieved with EEN therapy on an intention to treat basis in 20%-100% of patients and 30%-100% of patient on CS therapy (Table 1). Seven of the 11 studies found no significant difference between EEN and CS treatment to induce disease remission[19,20,22-25,27]. Of those patients who completed the course of EEN therapy disease remission was achieved in 23%-100% of patients and in 30%-100% of patients that completed CS treatment[19-29]. Those that did not complete the course of EEN therapy were

Table 2 Characteristics of exclusive enteral nutrition regimens used in studies of adults that compared exclusive enteral nutrition with corticosteroid therapy

Ref.	Nutritional product	Type of feed	Duration of EEN (wk)	Calorie density (kcal/mL)	Nutritional composition (% TE)	Mode of delivery	Calorie intake per day
Engelman *et al*[19]	Peptamen	Peptide based elemental	2	1	Pro 16, CHO 51, Fat 33	Orally	30-35 kcal/kg per day
Gassull *et al*[27]	High oleic acid	Polymeric (powder)	4	1	Pro 22, CHO 46, Fat 32	Orally and NGT	Not stated
Gassull *et al*[27]	High linoleic acid	Polymeric (powder)	4	1	Pro 22, CHO 46, Fat 32	Orally and NGT	Not stated
González-Huix *et al*[23]	Edanec HN	Polymeric	4	1	Pro 22, CHO 46, Fat 32	NGT	Not stated
Gorard *et al*[21]	Vivonex TEN	Elemental	4	1	Pro 15, CHO 82, Fat 3	Orally, or NGT	2100 kcal per day
Lindor *et al*[25]	Vital HN	Peptide based elemental	4	1	Pro 17, CHO 74, Fat 9	Orally	40 kcal/kg per day
Lochs *et al*[28]	Peptisorb	Peptide based elemental	4-6	1	Pro 16, CHO 69, Fat 15	NGT or NDT	35 kcal/kg per day
Malchow *et al*[29]	Survimed	Peptide based elemental	3-6	1	Pro 14, CHO 76, Fat 10	Orally	33 kcal/kg per day
Mantzaris *et al*[20]	Nutrison HE	Polymeric	4	1.5	Pro 16, CHO 49, Fat 35	NDT	2250 kcal per day
Okada *et al*[26]	Elental	Elemental	6	1	Pro 19, CHO 81, Fat 1	NDT	40-60 kcal/kg per day
O'Moráin *et al*[22]	Vivonex	Elemental	4	1	Pro 15, CHO 82, Fat 3	Orally, or NGT	40-60 kcal/kg per day
Zoli *et al*[24]	Peptamen	Peptide based elemental	2	1	Pro 16, CHO 51, Fat 33	Orally	Not stated

CHO: Carbohydrate; EEN: Exclusive enteral nutrition; NDT: Nasoduodenal tube; NGT: Nasogastric tube; Pro: Protein; % TE: Percentage of total energy.

usually started on CS therapy.

Withdrawal from treatment
Withdrawals from treatment varied between studies. EEN study group withdrawals were mostly due to unpalatable enteral nutrition formula. The number of withdrawals for this reason was as high as 41% of the EEN group in one study but 0% in other EEN study groups. Occasionally patients had to withdraw as they required urgent surgery. Withdrawals from CS groups were much lower. Common reasons cited for withdrawing were side effects, non-compliance with treatment or the patient needing urgent surgery.

Disease location
All 11 of the studies recorded the disease location of patients. The majority of patients had ileocolonic disease and smaller numbers had ileal or isolated colonic disease. No studies found disease location to be associated with the likelihood of achieving disease remission using EEN or CS therapy.

Age of participants
The age of the participants was recorded differently across the 11 studies. The mean age of patients enrolled in the studies was 27.5-34.7 years old. Inclusion of older adults aged more than 50 years of age was not uncommon. Only one study included mostly younger adults (mean 21.0 ± 3.3 years)[26].

DISCUSSION
EEN is rarely used in adults with active CD, apart from in Japan. Its use is usually reserved for those patients who do not want to use CS therapy, as an adjunctive therapy or where other treatment options have failed. Since the first studies with adults in the 1980s and 1990s much more is known about the way in which EEN therapy induces disease remission in children and how SEN therapy can assist in maintenance of disease remission. It is timely to readdress the possible reasons for the discrepancy between results from adult and paediatric studies that have compared EEN and CS therapy.

Disease remission criteria
The disease remission criteria used by researchers can have a profound impact on the study results. Comparison of disease remission rates between studies is challenging when disease remission is not universally defined. Five of the 11 studies used the HBI to measure disease remission[19,21,22,24,26]. Two of the studies that used the HBI did not describe their remission criteria[21,22]; however the mean HBI of participants after the EEN intervention was less than 4, which corresponds with standard interpretations of clinical remission. Another study used a HBI cut off of less than six points with 100% of participants in both the EEN and CS therapy groups achieving remission in this study[19]. The fourth study to use the HBI used a cut-off of 0-1 points to define disease remission[26]. Only 30% of patients in the CS group achieved remission using this criterion compared with 80% of the EEN group. It is unknown if a more liberal cut-off would have increased the number of patients achieving disease remission in the CS group. Regardless of the HBI cut-off used at least 80% of the EEN group participants (that completed the course of EEN) in each of the five studies achieved disease remission.

Four of the 11 studies used the CDAI to measure dis-

ease remission[20,25,28,29]. The remission rates of the EEN therapy group in all four studies were low (40%-53%), with the two larger studies concluding that, on an intention to treat basis, CS therapy induces disease remission in significantly more patients that EEN therapy[28,29]. In two of the studies at least one third of the patients withdrew from the EEN group due to unpalatable formula[25,29]. Withdrawals from the CS groups were much lower (20% or less). Of those that did complete the course of EEN therapy only 40%-71% of patients achieved disease remission, whereas remission was achieved in 62%-98% of those that completed the course of CS therapy.

The disease remission rates of the two studies that used the VHAI to define disease remission were quite different. Gassull *et al*[27] hypothesised that the formula high in linoleic acid, an n-6 polyunsaturated fat, would be less effective than a high monounsaturated fatty acid formula because n-6 fatty acids are pro-inflammatory precursors. Of the 20 patients enrolled in the high oleic acid EEN group only 20% achieved disease remission after 4 wk of therapy, compared with 52% of the high linoleic acid group and 79% of those using CS therapy. It seems that the fat content of EEN formulae may affect the efficacy of EEN therapy. The other study that used the VHAI to define disease remission found that EEN therapy was as effective as CS therapy: 80% of those on EEN therapy achieved disease remission compared with 88% of those using CS therapy[23].

The criteria used to define disease remission should not impact greatly on the results of the study; however, in this case, the studies can be grouped into three categories based on the remission criteria applied. The studies that used the HBI found that EEN therapy was at least as effective as CS therapy in inducing disease remission. The two larger studies that used the CDAI found that CS therapy was superior to EEN therapy while two studies with small participant numbers found no significant difference. There may be differences in study protocols between studies with higher and lower patient numbers that could influence patient outcomes. Finally, the two studies that used the VHAI found that there was no significant difference between a high, or a moderate, polyunsaturated polymeric formula and CS therapy, but that a high monounsaturated formula was significantly less effective ($P < 0.001$) than CS therapy at inducing disease remission.

Newly diagnosed CD
There is some evidence to suggest that EEN therapy is more effective in newly diagnosed CD patients compared with patients who have existing CD. Differences in treatment response rates according to time since diagnosis are not limited to EEN therapy. Response and remission rates achieved with biologic therapy are greater in children than adults[32] which may, in part, be due to the duration of disease prior to initiation of the treatment. Similarly, adults with a shorter duration of CD are more likely to respond and achieve remission with biologic

therapy[32]. Also the use of immune-modulators early in the disease course in adults and children has been shown to reduce the probability of long term CS and intestinal surgeries[33].

Two adult studies have compared EEN with CS therapy in treatment-naïve patients[22,26]. In both studies, 80% of those treated with EEN achieved disease remission after 4-6 wk of an elemental diet (comparable to remission rates in those treated with CS). Other adult studies comparing EEN with CS have not differentiated between patients with newly diagnosed CD and existing CD in their analyses. One study mentioned that both of the newly diagnosed CD patients responded to EEN treatment[20], but the numbers enrolled in the study were too small to show if there was a statistically significant difference in response to treatment between the two groups. A study of 22 patients treated with EEN found that EEN therapy was as effective in newly diagnosed patients as those with existing disease[21], although 40% of patients did not complete the course of EEN. The authors do not indicate how many of those that completed EEN treatment had existing or newly diagnosed disease. The two larger multi-centre European trials did not differentiate between those that had and not had received previous CD treatment[28,29].

Paediatric research suggests that EEN is more effective in treating newly diagnosed CD than existing CD[9]. Day *et al*[9] showed that, of 15 newly diagnosed CD patients, 12 (80%) entered remission after eight weeks of EEN, whereas only seven of the 12 (58%) children with long-standing disease entered remission ($P > 0.05$ by fishers exact test). In other paediatric studies with newly diagnosed CD patients disease remission was achieved in 79%-93% of those that completed EEN treatment and 70%-79% on an intention to treat basis[7,34].

Duration of CD
Longer duration of CD is associated with more complications including tissue scaring, fistulae, abscess, strictures, perianal disease and bowel resections[35]. EEN therapy has been shown to induce disease remission by reducing mucosal inflammation[36-38]. Complications of CD are often non-inflammatory in nature; therefore, EEN may be less effective in treating these patients. Interestingly, a case series of three children with perianal disease at diagnosis found that EEN (used in combination with surgery and antibiotics) was effective at inducing disease remission and assisted in the healing of perianal disease[39]. EEN was used as a maintenance therapy in all three children without return of perianal disease. A clinical trial has not been conducted to further investigate the potential role of EEN in the management of perianal CD.

Overall, studies in adult patients of EEN compared with CS therapy have not excluded patients with complicated disease. Usual exclusions included imminent surgery, intestinal perforation, ileus, abscesses, massive bleeding, short bowel syndrome with ileostomy and, in

some cases, previous surgery. The presence of other complications of existing CD such as scaring, perianal disease or previous bowel surgery is not detailed in the adult literature. It is impossible to ascertain whether those who did not respond to EEN therapy had more or less complications than those who did respond. Furthermore, the studies had only small numbers of patients within each disease sub-group and were unable to conduct in-depth statistical analysis of these sub-groups.

Adherence

Non-adherence with EEN treatment was a limiting factor in the success of EEN therapy in many studies. A number of reasons for non-adherence of adult CD patients with EEN therapy have been postulated including poor taste of the formula, lack of support and poor motivation to complete the treatment.

Un-palatability of the EN formula was the most common reason for non-adherence in the studies performed to date. Many early studies that compared EEN with CS treatment used elemental formulas. The difference between polymeric and elemental formulas is that the protein fraction in polymeric formula is in its whole form rather than as individual amino acids or peptides in semi-elemental formulas and elemental formulas tend to have a low total fat content Polymeric formula has been shown to be as effective as elemental at inducing disease remission[40,41]. Elemental formulas have a distinctive smell and flavour mainly due to the presence of amino acids, which have a bitter flavour. Bitterness is negatively correlated with palatability, whereas sweetness and sourness are positively correlated with palatability[42]. Fat content may also affect the palatability of the formula[43]. The elemental formulas used in the studies were low fat (1%-3% TE) compared with semi-elemental (9%-33% TE) and polymeric (32%-35% TE) formulas. Hence polymeric formulas are thought to be more palatable. However, there is limited research comparing the palatability of the two formula types. A retrospective study of children who received elemental formula from 1992-2001 and children who received polymeric formula from 2000-2004 found that adherence to treatment did not differ between the two groups but that those receiving polymeric formula were less likely to need a nasogastric tubes (NGT) inserted to deliver the feed[44].

The mode of delivery of the formula may also play a role in patient compliance. Many studies with high adherence rates administered elemental formulas *via* NG or nasoduodenal tubes rather than orally. More recent paediatric studies have encouraged oral intake of polymeric formula and use of NGT only if needed[7,9,34]. For free living (non-hospitalised) patients, taking the formula orally may be more socially acceptable. Elemental and polymeric formulas have been shown to be as equally effective at inducing remission of disease in children[40] and adults[18].

Studies that used elemental formulas given exclusively *via* NG or nasoduodenal tubes had low rates of non-adherence (0%-13%)[26,28]. Whereas studies that reported high rates of non-adherence (33%-41%) used elemental or semi-elemental formulas given orally and if a patient did not tolerate EEN orally a NGT was placed.[21,25,29] However, three of the six studies using elemental or semi-elemental diet orally reported higher adherence rates[19,22,24]. Two of these studies[19,24] only used EEN for 2 wk and patients were given a peptide based semi-elemental formula (Peptamen) orally rather than an amino acid-based elemental formula. Of the 19 patients using EEN in these two trials, only 1 patient was non-adherent with the treatment. The third study, by O'Moráin *et al*[22] was one of the first to compare EEN to CS treatment. Patients were asked to take the elemental formula orally for four weeks and if they could not tolerate it a NGT was placed. Of the 11 patients in the EEN group, two (18%) could not tolerate the formula orally or *via* a NGT.

Of the three adult studies that used polymeric formula, two administered it *via* NG or nasoduodenal tubes with 100% adherence[20,23]. The third study used a polymeric powder (a high oleic and high linoleic acid formulation) given orally or *via* NGT if not tolerated orally[27]. Non-adherence with the treatment was 17%-25%. No published adult studies have used a ready-to-drink polymeric formula given orally. There are, however, various studies with children that have shown that polymeric formulas are palatable orally. Borrelli *et al*[7] studied 19 children with CD who drank an isocaloric polymeric formula (Modulen) as their sole source of nutrition for 10 wk. Thirteen children took the formula orally; four required overnight feeding *via* a NGT, in addition to taking it orally during the day, to meet their nutritional requirements and two children could not manage to take the required volume of formula orally or *via* a NGT. Of the 17 children that successfully completed the 10 wk intervention 15 (88%) achieved disease remission. Day *et al*[9] studied 27 children with CD who were prescribed EEN with isocaloric polymeric formula (Modulen or Osmolite) for up to 8 wk. Nineteen children managed the required volume of formula orally, five needed to take some of the formula *via* a NGT and three could not tolerate the required volume orally or *via* a NGT. Of the 24 children who completed at least 8 wk of EEN, 19 entered remission (79%).

Both of these paediatric studies used an isocaloric polymeric formula. It appears that the major reason for non-adherence in these cohorts was difficulty tolerating the volume required for nutritional requirements rather than un-palatability. It is not clear whether the volume required to meet an adult's nutritional requirements (*e.g.*, 1600-2400 mL of ready-to-drink isocaloric polymeric formula per day) may lead to poor adherence. The use of a concentrated polymeric formula, (*e.g.*, 1.5 kcal/mL formula), may help alleviate this issue.

If adherence with and response to EEN treatment of 90% and 80%, respectively, can be achieved in adults EEN may be aviable treatment option. Ready-to-drink polymeric formula, which may be more palatable orally

than elemental or semi-elemental formulas and more convenient and portable than powdered options, could provide an option for adults with CD wishing to reduce their exposure to CS, induce disease remission and potentially attain the benefits associated with EEN therapy that have been confirmed in children.

Disease location

Disease location is thought to affect the efficacy of EEN therapy. In particular, colonic disease may be more refractory to treatment than disease with ileal involvement. However, due to the small participant numbers in most adult EEN studies there has been insufficient statistical power for subgroup analyses. A pooled meta-analysis of mainly adult studies from the 1980s and 1990s found that there was insufficient data to perform subgroup analyses by disease location[18].

Some paediatric studies have specifically investigated the impact of disease location on response to EEN therapy. Afzal *et al*[13] studied 65 children aged 8-17 years old with newly diagnosed CD of which 12 had ileal disease, 39 had ileocolonic disease and 14 had isolated colonic disease. They found that disease remission was harder to induce with EEN therapy in patients with colonic disease - remission achieved in 50% compared with 82% in those with ileocolonic disease and 92% in those with ileal CD ($P = 0.02$). They also used colonoscopy to assess mucosal healing after EEN therapy and found that there was no improvement in colonic mucosal inflammation in those with colonic or ileocolonic disease.

Conversely, Buchman *et al*[3] investigated the effect of disease location on remission rates after EEN therapy and found that colonic CD responded just as well as ileocolonic disease. Their study included 114 children (median age 11.6 years), all with recently diagnosed CD. Nineteen patients had colonic disease, four had ileal disease, 29 had ileocolonic disease, 49 had upper gastrointestinal tract disease and 9 had disease that could be not be classified using the Vienna classification. Of those with colonic disease 79% went into remission after eight weeks of EEN therapy compared with 86% with ileocolonic disease, 88% with upper gastrointestinal disease and only 25% with ileal disease. It should be noted that there were only 4 patients with ileal disease compared with at least 20 in the other three groups. Further evidence is needed to confirm whether CD location affects the efficacy of EEN.

Age of patient

Current guidelines suggest that EEN therapy is more appropriate to use in paediatric rather than adult patients[6,18]. There are no studies in adults that have assessed whether age affects response to EEN therapy. Although the mean age of adults included in the 11 studies evaluated here was approximately 30 years, the age range varied substantially and was not always published. Of those that did publish the age range of patients it was common to include patients aged 20 up to 50 or 60[19,22,25].

It is unknown if age affects response to EEN therapy or compliance with treatment.

CONCLUSION

Initial reports demonstrated that EEN was effective in inducing remission in adults with active CD and proposed this intervention as an alternative to CS therapy. However, subsequent larger studies failed to reproduce these results. Since then many studies have been conducted in paediatric populations and numerous benefits over and above achieving disease remission have become apparent. It appears that non-compliance with EEN treatment in early studies adversely affected the efficacy of EEN compared with CS therapy. There is also evidence to support a possible role of EEN with a specific group of adult patients - those newly diagnosed disease and, possibly, those with ileal involvement. Further research with this group is warranted. The use of polymeric formulas provided orally, which has not previously been studied in adult patients, may improve treatment compliance and allow adult patients to reap the many other benefits of EEN that have been shown in children over and above achieving disease remission and improving nutritional status.

REFERENCES

1   **Baumgart DC**, Sandborn WJ. Crohn's disease. *Lancet* 2012; **380**: 1590-1605 [PMID: 22914295 DOI: 10.1016/s0140-6736(12)60026-9]

2   **Dignass A**, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, Danese S, D'Hoore A, Gassull M, Gomollón F, Hommes DW, Michetti P, O'Morain C, Oresland T, Windsor A, Stange EF, Travis SP. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. *J Crohns Colitis* 2010; **4**: 28-62 [PMID: 21122489 DOI: 10.1016/j.crohns.2010.07.001]

3   **Buchman AL**. Side effects of corticosteroid therapy. *J Clin Gastroenterol* 2001; **33**: 289-294 [PMID: 11588541 DOI: 10.1097/00004836-200110000-00006]

4   **Gelbmann CM**, Rogler G, Gross V, Gierend M, Bregenzer N, Andus T, Schölmerich J. Prior bowel resections, perianal disease, and a high initial Crohn's disease activity index are associated with corticosteroid resistance in active Crohn's disease. *Am J Gastroenterol* 2002; **97**: 1438-1445 [PMID: 12094862]

5   **Whitten KE**, Rogers P, Ooi CY, Day AS. International survey of enteral nutrition protocols used in children with Crohn's disease. *J Dig Dis* 2012; **13**: 107-112 [PMID: 22257479 DOI: 10.1111/j.1751-2980.2011.00558.x]

6   **Heuschkel RB**. Enteral nutrition in children with Crohn's disease. *J Pediatr Gastroenterol Nutr* 2000; **31**: 575 [PMID: 11144448 DOI: 10.1097/00005176-200011000-00024]

7   **Borrelli O**, Cordischi L, Cirulli M, Paganelli M, Labalestra V, Uccini S, Russo PM, Cucchiara S. Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. *Clin Gastroenterol Hepatol* 2006; **4**: 744-753 [PMID: 16682258 DOI: 10.1016/j.cgh.2006.03.010]

8   **Andoh A**, Tsujikawa T, Sasaki M, Mitsuyama K, Suzuki Y, Matsui T, Matsumoto T, Benno Y, Fujiyama Y. Faecal microbiota profile of Crohn's disease determined by terminal restriction fragment length polymorphism analysis. *Aliment Pharmacol Ther* 2009; **29**: 75-82 [PMID: 18945264 DOI: 10.1111/j.1365-2036.2008.03860.x]

9   **Day AS**, Whitten KE, Lemberg DA, Clarkson C, Vitug-Sales M, Jackson R, Bohane TD. Exclusive enteral feeding as primary therapy for Crohn's disease in Australian children and adolescents: a feasible and effective approach. *J Gastroenterol Hepatol* 2006; **21**: 1609-1614 [PMID: 16928225 DOI: 10.1111/j.1440-1746.2006.04294.x]

10 **Levin AD**, Wadhera V, Leach ST, Woodhead HJ, Lemberg DA, Mendoza-Cruz AC, Day AS. Vitamin D deficiency in children with inflammatory bowel disease. *Dig Dis Sci* 2011; **56**: 830-836 [PMID: 21222159 DOI: 10.1007/s10620-010-1544-3]

11 **Whitten KE**, Leach ST, Bohane TD, Woodhead HJ, Day AS. Effect of exclusive enteral nutrition on bone turnover in children with Crohn's disease. *J Gastroenterol* 2010; **45**: 399-405 [PMID: 19957194 DOI: 10.1007/s00535-009-0165-0]

12 **Beattie RM**, Schiffrin EJ, Donnet-Hughes A, Huggett AC, Domizio P, MacDonald TT, Walker-Smith JA. Polymeric nutrition as the primary therapy in children with small bowel Crohn's disease. *Aliment Pharmacol Ther* 1994; **8**: 609-615 [PMID: 7696450]

13 **Afzal NA**, Van Der Zaag-Loonen HJ, Arnaud-Battandier F, Davies S, Murch S, Derkx B, Heuschkel R, Fell JM. Improvement in quality of life of children with acute Crohn's disease does not parallel mucosal healing after treatment with exclusive enteral nutrition. *Aliment Pharmacol Ther* 2004; **20**: 167-172 [PMID: 15233696 DOI: 10.1111/j.1365-2036.2004.02002.x]

14 **Day AS**, Whitten KE, Sidler M, Lemberg DA. Systematic review: nutritional therapy in paediatric Crohn's disease. *Aliment Pharmacol Ther* 2008; **27**: 293-307 [PMID: 18045244 DOI: 10.1111/j.1365-2036.2007.03578.x]

15 **Takagi S**, Utsunomiya K, Kuriyama S, Yokoyama H, Takahashi S, Iwabuchi M, Takahashi H, Takahashi S, Kinouchi Y, Hiwatashi N, Funayama Y, Sasaki I, Tsuji I, Shimosegawa T. Effectiveness of an 'half elemental diet' as maintenance therapy for Crohn's disease: A randomized-controlled trial. *Aliment Pharmacol Ther* 2006; **24**: 1333-1340 [PMID: 17059514 DOI: 10.1111/j.1365-2036.2006.03120.x]

16 **Critch J**, Day AS, Otley A, King-Moore C, Teitelbaum JE, Shashidhar H. Use of enteral nutrition for the control of intestinal inflammation in pediatric Crohn disease. *J Pediatr Gastroenterol Nutr* 2012; **54**: 298-305 [PMID: 22002478 DOI: 10.1097/MPG.0b013e318235b397]

17 **Lichtenstein GR**, Hanauer SB, Sandborn WJ. Management of Crohn's disease in adults. *Am J Gastroenterol* 2009; **104**: 465-83; quiz 464, 484 [PMID: 19174807 DOI: 10.1038/ajg.2008.168]

18 **Zachos M**, Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2007; (**1**): CD000542 [PMID: 17253452]

19 **Engelman JL**, Black L, Murphy GM, Sladen GE. Comparison of a semi elemental diet (Peptamen) with prednisolone in the primary-treatment of active ileal Crohn's disease. *Gastroenterology* 1993; **104**: A697-A697

20 **Mantzaris GJ**, Archavlis E, Amperiadis P, Kourtessas D, Triantafyllou G. A randomized prospective trial in active Crohn's disease comparing a polymeric diet, prednisolone, and a polymeric diet plus prednisolone. *Gastroenterology* 1996; **110**: A955-A955

21 **Gorard DA**, Hunt JB, Payne-James JJ, Palmer KR, Rees RG, Clark ML, Farthing MJ, Misiewicz JJ, Silk DB. Initial response and subsequent course of Crohn's disease treated with elemental diet or prednisolone. *Gut* 1993; **34**: 1198-1202 [PMID: 8406153 DOI: 10.1136/gut.34.9.1198]

22 **O'Moráin C**, Segal AW, Levi AJ. Elemental diet as primary treatment of acute Crohn's disease: a controlled trial. *Br Med J* (Clin Res Ed) 1984; **288**: 1859-1862 [PMID: 6428577]

23 **González-Huix F**, de León R, Fernández-Bañares F, Esteve M, Cabré E, Acero D, Abad-Lacruz A, Figa M, Guilera M, Planas R. Polymeric enteral diets as primary treatment of active Crohn's disease: a prospective steroid controlled trial. *Gut* 1993; **34**: 778-782 [PMID: 8314510 DOI: 10.1136/gut.34.6.778]

24 **Zoli G**, Carè M, Parazza M, Spanò C, Biagi PL, Bernardi M, Gasbarrini G. A randomized controlled study comparing elemental diet and steroid treatment in Crohn's disease. *Aliment Pharmacol Ther* 1997; **11**: 735-740 [PMID: 9305483 DOI: 10.1046/j.1365-2036.1997.t01-1-00192.x]

25 **Lindor KD**, Fleming CR, Burnes JU, Nelson JK, Ilstrup DM. A randomized prospective trial comparing a defined formula diet, corticosteroids, and a defined formula diet plus corticosteroids in active Crohn's disease. *Mayo Clin Proc* 1992; **67**: 328-333 [PMID: 1548947]

26 **Okada M**, Yao T, Yamamoto T, Takenaka K, Imamura K, Maeda K, Fujita K. Controlled trial comparing an elemental diet with prednisolone in the treatment of active Crohn's disease. *Hepatogastroenterology* 1990; **37**: 72-80 [PMID: 2179093]

27 **Gassull MA**, Fernández-Bañares F, Cabré E, Papo M, Giaffer MH, Sánchez-Lombraña JL, Richart C, Malchow H, González-Huix F, Esteve M. Fat composition may be a clue to explain the primary therapeutic effect of enteral nutrition in Crohn's disease: results of a double blind randomised multicentre European trial. *Gut* 2002; **51**: 164-168 [PMID: 12117873 DOI: 10.1136/gut.51.2.164]

28 **Lochs H**, Steinhardt HJ, Klaus-Wentz B, Zeitz M, Vogelsang H, Sommer H, Fleig WE, Bauer P, Schirrmeister J, Malchow H. Comparison of enteral nutrition and drug treatment in active Crohn's disease. Results of the European Cooperative Crohn's Disease Study. IV. *Gastroenterology* 1991; **101**: 881-888 [PMID: 1679736]

29 **Malchow H**, Steinhardt HJ, Lorenz-Meyer H, Strohm WD, Rasmussen S, Sommer H, Jarnum S, Brandes JW, Leonhardt H, Ewe K. Feasibility and effectiveness of a defined-formula diet regimen in treating active Crohn's disease. European Cooperative Crohn's Disease Study III. *Scand J Gastroenterol* 1990; **25**: 235-244 [PMID: 1969678]

30 **Vermeire S**, Schreiber S, Sandborn WJ, Dubois C, Rutgeerts P. Correlation between the Crohn's disease activity and Harvey-Bradshaw indices in assessing Crohn's disease severity. *Clin Gastroenterol Hepatol* 2010; **8**: 357-363 [PMID: 20096379 DOI: 10.1016/j.cgh.2010.01.001]

31 **van Hees PA**, van Elteren PH, van Lier HJ, van Tongeren JH. An index of inflammatory activity in patients with Crohn's disease. *Gut* 1980; **21**: 279-286 [PMID: 7429289 DOI: 10.1136/gut.21.4.279]

32 **Panaccione R**, Ghosh S. Optimal use of biologics in the management of Crohn's disease. *Therap Adv Gastroenterol* 2010; **3**: 179-189 [PMID: 21180600 DOI: 10.1177/1756283X09357579]

33 **Fascì Spurio F**, Aratari A, Margagnoni G, Doddato MT, Papi C. Early treatment in Crohn's disease: do we have enough evidence to reverse the therapeutic pyramid? *J Gastrointestin Liver Dis* 2012; **21**: 67-73 [PMID: 22457862]

34 **Grogan JL**, Casson DH, Terry A, Burdge GC, El-Matary W, Dalzell AM. Enteral feeding therapy for newly diagnosed pediatric Crohn's disease: a double-blind randomized controlled trial with two years follow-up. *Inflamm Bowel Dis* 2012; **18**: 246-253 [PMID: 21425210 DOI: 10.1002/ibd.21690]

35 **Tarrant KM**, Barclay ML, Frampton CM, Gearry RB. Perianal disease predicts changes in Crohn's disease phenotype-results of a population-based study of inflammatory bowel disease phenotype. *Am J Gastroenterol* 2008; **103**: 3082-3093 [PMID: 19086959 DOI: 10.1111/j.1572-0241.2008.02212.x]

36 **Baert F**, Moortgat L, Van Assche G, Caenepeel P, Vergauwe P, De Vos M, Stokkers P, Hommes D, Rutgeerts P, Vermeire S, D'Haens G. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. *Gastroenterology* 2010; **138**: 463-48; quiz 463-48 [PMID: 19818785 DOI: 10.1053/j.gastro.2009.09.056]

37 **Berni Canani R**, Terrin G, Borrelli O, Romano MT, Man-

guso F, Coruzzo A, D'Armiento F, Romeo EF, Cucchiara S. Short- and long-term therapeutic efficacy of nutritional therapy and corticosteroids in paediatric Crohn's disease. *Dig Liver Dis* 2006; **38**: 381-387 [PMID: 16301010 DOI: 10.1016/j.dld.2005.10.005]

38   **Rubio A**, Pigneur B, Garnier-Lengliné H, Talbotec C, Schmitz J, Canioni D, Goulet O, Ruemmele FM. The efficacy of exclusive nutritional therapy in paediatric Crohn's disease, comparing fractionated oral vs. continuous enteral feeding. *Aliment Pharmacol Ther* 2011; **33**: 1332-1339 [PMID: 21507029 DOI: 10.1111/j.1365-2036.2011.04662.x]

39   **Wong S**, Lemberg DA, Day AS. Exclusive enteral nutrition in the management of perianal Crohn's disease in children. *J Dig Dis* 2010; **11**: 185-188 [PMID: 20579222 DOI: 10.1111/j.1751-2980.2010.00434.x]

40   **Verma S**, Brown S, Kirkwood B, Giaffer MH. Polymeric versus elemental diet as primary treatment in active Crohn's disease: a randomized, double-blind trial. *Am J Gastroenterol* 2000; **95**: 735-739 [PMID: 10710067 DOI: 10.1016/s0002-9270(99)00586-9]

41   **Sakurai T**, Matsui T, Yao T, Takagi Y, Hirai F, Aoyagi K, Okada M. Short-term efficacy of enteral nutrition in the treatment of active Crohn's disease: a randomized, controlled trial comparing nutrient formulas. *JPEN J Parenter Enteral Nutr* 2002; **26**: 98-103 [PMID: 11871742 DOI: 10.1177/014860710202600298]

42   **Mukai J**, Miyanaga Y, Ishizaka T, Asaka K, Nakai Y, Tsuji E, Uchida T. Quantitative taste evaluation of total enteral nutrients. *Chem Pharm Bull* (Tokyo) 2004; **52**: 1416-1421 [PMID: 15577236 DOI: 10.1248/cpb.52.1416]

43   **De Araujo IE**, Rolls ET. Representation in the human brain of food texture and oral fat. *J Neurosci* 2004; **24**: 3086-3093 [PMID: 15044548 DOI: 10.1523/jneurosci.0130-04.2004]

44   **Rodrigues AF**, Johnson T, Davies P, Murphy MS. Does polymeric formula improve adherence to liquid diet therapy in children with active Crohn's disease? *Arch Dis Child* 2007; **92**: 767-770 [PMID: 17475695 DOI: 10.1136/adc.2006.103416]

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9 771007 932045