Use of exclusive enteral nutrition in paediatric Crohn's disease in The Netherlands

Charlotte de Bie a, Angelika Kindermann b, Johanna Escher a,*

a Department of Paediatric Gastroenterology, Erasmus MC—Sophia Children's Hospital, Dr. Molewaterplein 60, 3015 GJ, Rotterdam, The Netherlands
b Department of Paediatric Gastroenterology, Academic Medical Centre—Emma Children's Hospital, Meibergdreef 9, 1100 DD, Amsterdam, The Netherlands

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Abstract

Background and aims: A six-week course of exclusive enteral nutrition (EEN) is recommended as first treatment in active paediatric Crohn's disease (CD). We aimed to assess short-term and long-term outcome of EEN, and to identify predictive factors of treatment success.

Methods: The medical records of newly diagnosed paediatric CD patients initiating EEN as remission induction therapy between January 2008 and October 2011 were retrospectively studied. Treatment outcome was assessed using a previously described pattern recognition model.

Results: 77 CD patients (median age 13.9 years, 57% male) initiated a six-week course of EEN, combined with azathioprine maintenance treatment in 92%. Patients received EEN as either hyperosmolar sip feeds or polymeric formula by nasogastric tube. In patients completing a six-week course of EEN (n = 58), complete remission was achieved in 71%, partial remission in 26%, and no response in 3%. Complete remission rates were higher in children presenting with isolated ileal/ileocaecal disease and malnutrition. Nineteen patients discontinued EEN before the intended treatment period due to worsening of symptoms (n = 9) or adherence issues (n = 10). Non-adherence occurred more often in older children, females, children from non-Dutch parents, and patients taking hyperosmolar sip feeds compared with polymeric formula by nasogastric tube. The likelihood of relapsing disease within the first year after EEN treatment was 59%.

Conclusion: A six-week course of EEN is effective in newly diagnosed paediatric CD, with response rates that seem to be influenced by disease location and nutritional status, but not by

Abbreviations EEN, Exclusive enteral nutrition; CD, Crohn's disease; HSF, Hyperosmolar sip feeds; PF, Polymeric formula; NG tube, Nasogastric tube; IQR, Interquartile range; SDS, Standard deviation score.

* Corresponding author. Tel.: +31 10 7036076; fax: +31 10 7036811.
E-mail addresses: c.i.debie@erasmusmc.nl (C. de Bie), a.kindermann@amc.uva.nl (A. Kindermann), j.escher@erasmusmc.nl (J. Escher).

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1. Introduction

Induction of remission in paediatric patients with active Crohn’s disease (CD) can be achieved by exclusive enteral nutrition (EEN) or corticosteroids. EEN has been shown to be as effective as corticosteroid therapy in inducing remission in paediatric CD. However, EEN is more effective than corticosteroids in inducing mucosal healing, and improving nutritional status and linear growth recovery. Additionally, EEN is not associated with any side-effects, and leads to improved quality of life.

EEN usually involves a 6 to 8 weeks course of liquid formula that replaces normal diet (no other food and drinks are allowed, except water), followed by the reintroduction of a normal diet over a period of 1 to 2 weeks. In The Netherlands, a consensus-based guideline on treatment of paediatric IBD has become available since 2008. EEN for a period of 6 weeks is recommended as first treatment for active newly diagnosed CD, which is similar to the recommendations of other European guidelines on the treatment of paediatric CD. Polymeric formula (PF) is advised, but there are no clear guidelines on the type of formula. Non-adherence occurs frequently and limits the success of this treatment in everyday clinical practice.

2. Materials and methods

Newly diagnosed paediatric CD patients were selected from the databases of two tertiary referral centres in The Netherlands (Erasmus MC – Sophia Children’s Hospital, Rotterdam; Academic Medical Centre – Emma Children’s Hospital, Amsterdam). In both centres, a six-week course of EEN was offered to all newly diagnosed children with active luminal CD, but a minority of patients (10%) refused this treatment and was treated with corticosteroids instead. For this study, we included the newly diagnosed paediatric CD patients who initiated a primary induction course of EEN between January 2008 and October 2011. All patients were commenced on EEN aiming to complete 6 weeks of liquid diet therapy. Patients who were treated for relapse of disease or received prior corticosteroid treatment before initiation of EEN, were excluded from this study. The diagnosis of CD was based on endoscopic, histological, and/or radiological findings, according to the Porto criteria.

The medical records were retrospectively reviewed by a single investigator (CdB). Baseline characteristics included age, gender, family history of IBD in first degree relatives, height and weight, laboratory parameters, disease location, and the presence or absence of perianal disease. Information on the type of formula, route of administration, duration of the liquid diet, and adherence to EEN treatment was also recorded (when available), as well as the initiation of immunomodulatory maintenance therapy.

2.1. Definitions

Disease location was categorised by a recent paediatric modification of the Montreal classification, the Paris classification: (L1) involvement of the terminal ileum only, with limited or no caecal disease; (L2) colonic involvement only; and (L3) involvement of both the terminal ileum and colon. Involvement of the terminal ileum was based on the results of ileocolonoscopy and/or small bowel imaging by MRI. Upper gastrointestinal disease (L4 disease) was separated into oesophagogastrroduodenal disease (L4A disease) and jejunum/proximal ileal disease (L4B disease). L4A disease was defined as the presence of ulcerations, erosions/aphthae, cobblestones, and/or stenosis. The presence of mucosal erythema, oedema, granularity, and/or nodularity was not sufficient to be considered evidence of involvement. Perianal disease was defined as the presence of a perianal abscess and/or fistula, and did not include the isolated presence of skin tags, fissures, or haemorrhoids.

EEN treatment outcome was retrospectively evaluated by a pattern recognition model, previously described and published by Nielsen et al. This model has also been demonstrated to be useful for the assessment of other treatments for CD. At the end or shortly after cessation of EEN treatment, patients were classified according to their clinical response as complete remission, partial remission, or no response. Complete remission was defined as ≤2 stools/day without blood, pus, or mucus, no abdominal pain, and no weight loss. Partial remission was defined as ≤4 stools/day, less than daily loss of blood, pus, or mucus with the stools, less than daily abdominal pain, or weight loss. When there was no regression of clinical symptoms, patients were classified as having no response. At the end of follow-up (minimal 3 months after cessation of EEN), the patients obtaining complete and partial remission were evaluated for relapse of disease, defined as symptoms requiring another induction course of treatment.

2.2. Statistical analysis

Data were collected and analysed in SPSS (version 17.0, SPSS, Inc., Chicago, IL). Descriptive statistics were calculated as percentages for discrete data. Continuous variables were presented as medians and interquartile ranges (IQR). Data on height, weight, and body mass index (BMI) were converted to standard deviation scores (SDS) using the 2010 Dutch standards (Growth Analyser RCT, version 4.0, Dutch Growth Foundation). For comparisons of proportions, we used Pearson’s chi-square analyses or Fisher’s exact tests, as appropriate. Quantitative data were compared using Mann–Whitney U tests, or Wilcoxon signed rank tests for paired data. To test for independent predictive factors of
EEN treatment outcome, a logistic regression model was constructed with treatment outcome (complete remission vs. partial remission/no response) as the dependent variable. Kaplan–Meier analysis was used to estimate the cumulative probability of maintaining remission over time. Time to event was analysed from the date of EEN initiation until the date of relapse, or last known follow-up. Statistical significance was defined as a two-tailed \( P \)-value < 0.05.

3. Results

3.1. Patient characteristics

During the study period, 77 newly diagnosed paediatric CD patients with active disease (median age 13.9 years, IQR 11.1–15.7 years; 57% male) initiated a six-week induction course of EEN. Most children (70%) were of Dutch origin. At start of treatment, the median height for age SDS was \(-0.79\) (IQR \([-1.5\) to \(-0.06\]), and the median weight for height SDS was \(-0.86\) (IQR \([-1.7\) to \(-0.11\)). Twenty percent of patients had a first-degree relative with IBD. Disease location could be determined in all patients but one, as there was no endoscopic or radiological examination of the terminal ileum. Isolated terminal ileal disease (±limited caecal disease, L1) was seen at presentation in 25% (19/76), isolated colonic disease (L2) in 24% (18/76), and ileocolonic disease (L3) in 51% (39/76) of paediatric CD patients. In total, 38% (29/77) of patients had oesophagogastroduodenal disease (L4A), and 29% (18/63) jejunal/proximal ileal disease (L4B). Perianal disease occurred in 10% (8/77) of patients.

All patients were untreated at the time EEN was initiated. Most patients (71, 92%) were started on azathioprine \((L4B)\). Disease location could be determined in all patients but one, as there was no endoscopic or radiological examination of the terminal ileum. Isolated terminal ileal disease (±limited caecal disease, L1) was seen at presentation in 25% (19/76), isolated colonic disease (L2) in 24% (18/76), and ileocolonic disease (L3) in 51% (39/76) of paediatric CD patients. In total, 38% (29/77) of patients had oesophagogastroduodenal disease (L4A), and 29% (18/63) jejunal/proximal ileal disease (L4B). Perianal disease occurred in 10% (8/77) of patients.

3.2. EEN treatment

Most patients received either hyperosmolar sip feeds (HSF; n = 41, 53%), or polymeric formula (PF) by nasogastric (NG) tube (n = 30, 39%). Additionally, one patient was treated with semi-elemental formula by NG tube, three patients received PF by mouth, and two patients used a combination of PF by NG tube and HSF.

Children who initiated EEN treatment administered by NG tube were always admitted to the hospital for 2–4 days, whereas most patients on HSF initiated treatment at home. The volume and caloric density of the enteral feeds were determined by the dietician on the basis of the patient's daily nutritional requirements, in general 110–120% of the recommended dietary allowance of total energy and protein. No other foods and drinks (except water) were allowed during a course of EEN. By the end of the course, the dietician discussed a two-week scheduled return to a normal diet with the child and his/her parents.

Various brands of polymeric and semi-elemental formulas were used, depending on the local preference of the treating physician and/or dietician. Information on their composition is summarised in Table 1. When receiving HSF, the patients were allowed to make a choice of the kind and combination of drinks from a test kit, taking into account the recommendations of the dietician concerning daily nutritional requirements (in general 6–10 HSF/day). Almost all patients taking HSF used a combination of flavoured drinks, depending on their own preferences in taste, which made it impossible to determine the number of patients receiving a certain brand of sip feeds. HSF were milk-based, yoghurt-based, or juice-based (Nutridrink, Nutridrink Yoghurt Style, Nutridrink Juice Style by Nutricia, Zoetermeer, The Netherlands; Ensure Plus, Ensure Plus Fresh by Abbott Nutrition, Hoofddorp, The Netherlands; Resource Energy, Resource Fruit by Nestlé Health Science, Oosterhout, The Netherlands; Fresubin Energy Drink, Fresubin Jucy Drink by Fresenius Kabi Nederland BV, Zeist, The Netherlands). The energy density of these HSF varied from 125 to 150 Kcal/100 ml, and the osmolarity varied from 455 to 750 mOsmol/l. Juice-based HSF contained no fat, while other HSF had a total amount of fat of 4.9–5.8 g/100 ml.

### Table 1: Composition of formulas used for exclusive enteral nutrition therapy in newly diagnosed paediatric Crohn's disease.

<table>
<thead>
<tr>
<th>Type of formula</th>
<th>Nutrison Standard ( ^a )</th>
<th>Nutrison Energy ( ^a )</th>
<th>Nutrini Max ( ^a )</th>
<th>Nutrini Max Energy ( ^a )</th>
<th>Osmolite HiCal ( ^b )</th>
<th>Isosource Energy ( ^c )</th>
<th>Peptisorb ( ^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>4</td>
<td>14</td>
<td>2</td>
<td>12</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Type of formula</td>
<td>Polymeric</td>
<td>Polymeric</td>
<td>Polymeric</td>
<td>Polymeric</td>
<td>Polymeric</td>
<td>Polymeric</td>
<td>Semi-elemental</td>
</tr>
<tr>
<td>Energy density (Kcal/100 ml)</td>
<td>100</td>
<td>150</td>
<td>100</td>
<td>150</td>
<td>151</td>
<td>160</td>
<td>100</td>
</tr>
<tr>
<td>Osmolarity (mOsmol/l)</td>
<td>265</td>
<td>385</td>
<td>225</td>
<td>330</td>
<td>392</td>
<td>298</td>
<td>455</td>
</tr>
<tr>
<td>Total protein (g/100 ml)</td>
<td>4</td>
<td>6</td>
<td>3.3</td>
<td>4.9</td>
<td>6.3</td>
<td>5.7</td>
<td>4</td>
</tr>
<tr>
<td>Total fat (g/100 ml)</td>
<td>3.9</td>
<td>5.8</td>
<td>4.2</td>
<td>6.3</td>
<td>4.9</td>
<td>6.2</td>
<td>1.7</td>
</tr>
<tr>
<td>Polyunsaturated (PUFA) (g)</td>
<td>1.2</td>
<td>1.8</td>
<td>1.3</td>
<td>1.9</td>
<td>0.7</td>
<td>2.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Monounsaturated (MUFA) (g)</td>
<td>2.3</td>
<td>3.5</td>
<td>2.4</td>
<td>3.7</td>
<td>2.9</td>
<td>2.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Total saturated fatty acids (g)</td>
<td>0.4</td>
<td>0.6</td>
<td>0.5</td>
<td>0.8</td>
<td>1.2</td>
<td>1.7</td>
<td>1</td>
</tr>
<tr>
<td>Total carbohydrate (g/100 ml)</td>
<td>12.3</td>
<td>18.5</td>
<td>12.3</td>
<td>18.5</td>
<td>20.4</td>
<td>20</td>
<td>17.6</td>
</tr>
</tbody>
</table>

All but three patients received the formulas by nasogastric tube. Two patients received both Nutrison Standard and Nutrison Energy. In one patient, the type of polymeric formula was missing.

\( ^a \) Nutricia Nederland BV, Zoetermeer, The Netherlands.

\( ^b \) Abbott Nutrition, Hoofddorp, The Netherlands.

\( ^c \) Nestlé Health Science, Oosterhout, The Netherlands.

3.3. Efficacy of EEN induction therapy

Treatment outcome of EEN is displayed in Fig. 1. A six-week course of EEN was completed in 58 patients (75%), of which 41
(71%) achieved complete remission, and 15 (26%) partial remission. Two patients (3%) had no response after 6 weeks of EEN treatment, and were subsequently treated with corticosteroids. Withdrawal from EEN before the intended treatment period due to worsening of symptoms was necessary in nine patients (12%), who were all switched to corticosteroids. When treatment outcome was based on all initiated courses of EEN, complete remission was achieved in 53% (41/77) of patients, partial remission in 20% (15/77), and no response was seen in 14% (11/77). The remaining ten patients (13%) were not able to consume the prescribed volume of tube feeding (n=2) or HSF (n=8), and were subsequently treated with corticosteroids.

In patients achieving complete remission (n=41), both median weight for height SDS (−1.4 vs. −0.69) and BMI for age SDS (−1.6 vs. −0.69) improved significantly between the start and end of treatment with EEN (both P<0.001). When available, laboratory parameters before and after EEN treatment were compared in patients achieving complete remission. During treatment, there was a significant improvement in ESR (n=25, median −19 mm/h, P<0.001), CRP (n=27, median −42 mg/L, P<0.001), albumin (n=25, median +8 g/l, P<0.001), and platelet levels (n=34, median −108 ×10^9/l, P<0.001). Haemoglobin levels did not significantly change during EEN treatment.

Baseline characteristics of the patients achieving complete remission (n=41) were compared with those of the partial responders and non-responders (n=26, Table 2). Patients who did not complete a six-week course of EEN due to intolerance of or non-adherence to EEN were excluded from these analyses. Complete remission rates were not affected by age, gender, or type of formula (PF by NG tube versus HSF). Complete remission rates were higher in children from Dutch parents (69% vs. 42%), but this difference did not reach statistical significance (P=0.06). Patients with L1 disease had higher complete remission rates (88%) than patients with L2 disease (53%) or L3 disease (51%, P=0.04). Baseline weight for height SDS and BMI for age SDS also differed significantly between the two patient groups: patients who achieved complete remission had significantly lower median weight for height SDS (−1.4 vs. −0.06, P<0.001) and BMI for age SDS (−1.6 vs. −0.24, P<0.001) at start of EEN treatment compared with the other patient group. In a logistic regression model consisting of age, gender, nationality, disease location and weight for height SDS (or BMI for age SDS) as explanatory variables, both disease location and nutritional status remained significantly associated with treatment outcome.

Relapse rates were first determined in 37 CD patients who achieved complete remission by the end of EEN treatment and had a follow-up of at least 3 months after cessation of EEN. After a median follow-up of 1.5 years (IQR 0.7–2.5), 62% (n=23) of these patients had relapse of disease. Three patients did not receive immunomodulatory maintenance therapy when relapse of disease occurred. The median time to relapse of disease was 20.6 weeks (IQR 10–39 weeks, range 2–169 weeks). Kaplan–Meier analysis showed that the cumulative probability of relapsing disease within the first year after EEN treatment was 59% (Fig. 2). In the partial remission group, 12 of 15 children had a follow-up of at least 3 months after cessation of EEN treatment. All these patients had initiated azathioprine maintenance therapy within the first weeks of EEN treatment. Nine patients had relapse of disease within 4 months, while one patient relapsed after 2 years. In the remaining two patients, partial remission was followed by a prolonged response with a follow-up of 2.2 and 1.4 years, respectively. Following relapse of disease, treatment consisted of a second course of EEN (n=4), corticosteroids (n=18), ileocaecal resection (n=2), anti-TNF treatment (n=6), optimisation of the azathioprine dosage (n=2), and switch of azathioprine to methotrexate (n=1).

### 3.4. Adherence to EEN treatment

As was mentioned earlier, ten children discontinued EEN treatment due to non-adherence to the prescribed volume of EEN. In one of these patients, there was an unsuccessful attempt to switch from HSF to tube feeding.

<table>
<thead>
<tr>
<th>Table 2 Characteristics of 67 newly diagnosed paediatric Crohn’s disease patients according to exclusive enteral nutrition treatment outcome.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment outcome</td>
</tr>
<tr>
<td>Age at diagnosis (year)</td>
</tr>
<tr>
<td>Gender (male)</td>
</tr>
<tr>
<td>Nationality (Dutch)</td>
</tr>
<tr>
<td>Height for age SD score</td>
</tr>
<tr>
<td>Weight for height SD score</td>
</tr>
<tr>
<td>BMI for age SD score</td>
</tr>
<tr>
<td>Positive family history</td>
</tr>
<tr>
<td>Disease location</td>
</tr>
<tr>
<td>L1</td>
</tr>
<tr>
<td>L2</td>
</tr>
<tr>
<td>L3</td>
</tr>
<tr>
<td>L4A disease</td>
</tr>
<tr>
<td>L4B disease</td>
</tr>
<tr>
<td>Perianal disease</td>
</tr>
<tr>
<td>Type of formula</td>
</tr>
<tr>
<td>Polymeric formula by nasogastric tube</td>
</tr>
<tr>
<td>Hyperosmolar sip feeds</td>
</tr>
</tbody>
</table>


* Patients who were treated with polymeric formula by mouth (n=2), semi-elemental formula (n=1), or a combination of polymeric formula and hyperosmolar sip feeds (n=2) were excluded from this analysis.
In the 58 patients completing a six-week course of EEN, at least five patients (9%) experienced difficulties with adherence to EEN treatment. Two patients (one complete remission; one partial remission) did not comply with the exclusivity principle, as they admitted to have eaten other foods besides the treatment with HSF or tube feeding. In two patients (both partial remission), there were temporary difficulties with drinking the prescribed volume of HSF at the initiation of treatment. The fifth patient (non-responder) initially tolerated the volume of HSF well, but failed to drink the adequate volume after 5 weeks of EEN treatment due to nausea and continuing IBD symptoms.

Characteristics of children with established non-adherence were compared with those of the other patients. Children with established non-adherence were significantly older than the other patients (15.5 years vs. 13.4 years, \(P=0.04\)). Additionally, non-adherence was more often reported in females (36% vs. 7%, \(P=0.003\)), in patients from non-Dutch parents (35% vs. 13%, \(P=0.06\)), and in patients receiving oral treatment, i.e. HSF or PF by mouth (27% vs. 10%, \(P=0.08\)).

### 4. Discussion

Our study has demonstrated that a six-week course of EEN was effective for induction of remission in newly diagnosed children with CD, but non-adherence occurred frequently and limited the success of this treatment in everyday clinical practice. Different types of formula were used as EEN treatment, but there was no significant difference between HSF and PF on treatment outcome. We found a significant variation in treatment response based on disease location and nutritional status at start of EEN treatment.

The complete remission rate of 71% in children completing a six-week course of EEN was similar to the rate reported in the Danish study that used the same definitions for EEN treatment outcome (i.e. 67%).\(^{14}\) However, these remission rates are based on completed courses of EEN only. When all courses of EEN would have been included in the analyses, the complete remission rate had been 53% (41/77) in our study and 54% (25/46) in the Danish study. This rate is relatively low in comparison with other studies on the efficacy of EEN,\(^8\) which could be explained by the frequently observed difficulties to fully comply with EEN in our study. At least 15 of 77 (20%) patients could not adhere to the prescribed volume of EEN or the exclusivity principle, resulting in early discontinuation of EEN treatment in ten patients. Other studies on EEN treatment have reported non-adherence rates of 5–20%,\(^{18-21}\) which negatively affects the clinical response to EEN.\(^{19,20}\)

Adherence to treatment is a complex process, where a multitude of interacting variables (patient, family, treatment, and health-professional related factors) seems to play a role.\(^{22}\) In our study, a significant patient-related factor affecting adherence was age, which is in accordance with previous data suggesting that non-adherence is more common among adolescent patients than in younger patients.\(^{23}\) Additionally, we found that female CD patients experienced more difficulties with EEN treatment than male patients. Previous adult IBD literature has reported contradictory results on the association between gender and adherence.\(^{24}\) Treatment-related factors that could affect adherence to EEN are the type of formula and/or route of administration. We found a trend toward higher non-adherence rates in children receiving oral EEN treatment (mostly HSF), which is in contrast with the study of Rubio et al. who reported similar adherence rates between children receiving PF by NG tube and orally.\(^{25}\) It is also possible that the formula composition has affected the compliance rate in our study. HSF have a relatively high osmolarity, which can cause fullness and nausea, thereby negatively affecting adherence. Finally, health-professional related factors affecting adherence might be the intensity of monitoring a patient during EEN treatment. In general, our patients had one or two clinic visits with the paediatric gastroenterologist and two visits with the dietician during a course of EEN (at initiation, and at the end of a six-week course.
of EEN). This monitoring frequency is modest when compared with other studies, in which a weekly home visit of a clinical nutritionist was provided during the course of EEN, or patients were regularly phoned by the dietitian and IBD nurse specialist during the first weeks of treatment. Taken together, there are multiple factors possibly affecting adherence, which requires further investigation.

Length of EEN treatment and composition of the formulas might also have had an effect on the treatment outcome in our study, but data on the importance of these aspects are still limited. In most clinical studies on EEN treatment in paediatric CD, EEN is administered during a period of 6 to 8 weeks. Several patients in our study achieved partial remission at the end of their six-week treatment period, but experienced further improvement of their symptoms in the weeks following cessation of EEN, suggesting a potential benefit from a longer treatment course. Previous research on the importance of formula composition on EEN treatment outcome has shown that the nitrogen source of the diet (elemental, semi-elemental, polymeric) does not affect remission rates in paediatric CD. However, the importance of fat content and composition, the potential advantage of using TGF-beta (an anti-inflammatory cytokine) enriched formulas, and the effect of using commercially available flavoured drinks on treatment outcome are yet to be determined. Although our results should be interpreted with caution due to heterogeneity of the HSF, we did not find a difference between HSF and PF by NG tube on treatment outcome.

Despite the increasing data on the positive effects of EEN in paediatric CD, there are still limited data on the way in which EEN reduces intestinal inflammation. Traditionally, reduction of antigenic pressure (‘bowel rest’) was considered an important working mechanism of EEN. However, this hypothesis is probably not the primary factor, as formulas with different protein sources achieve similar remission rates. Recent data suggest that EEN modulates bacterial flora within the gut lumen, thereby reducing intestinal inflammation. A third explanation may be that EEN has direct anti-inflammatory effects on intestinal epithelial cells by down-regulation of mucosal pro-inflammatory cytokines. Finally, improvement of the nutritional status by repletion of nutritional deficiencies is likely to contribute to the benefits seen with EEN. This latter hypothesis is strengthened by our observation that nutritional status at start of treatment was associated with treatment outcome: complete remission rates were higher in malnourished children. Further studies are required to determine the relative importance of the other hypotheses. Hopefully, this knowledge will enable us to optimise EEN treatment regimens.

Another unresolved question regarding EEN treatment is the effect of disease location on treatment outcome. The prevailing opinion of paediatric gastroenterologists is often that EEN is not as effective for isolated colonic disease as it is for ileal or ileocolonic disease. Previous paediatric studies however have yielded conflicting results. and used a clear definition to classify disease location, thereby finding the highest response rates (88%) in children with isolated ileal/ileocaecal disease versus response rates of approximately 50% in children with colonic involvement.

Despite the frequent use of azathioprine maintenance therapy, the likelihood of relapsing disease within the first year after EEN treatment was 59%, which is markedly higher when compared with the results of the pivotal placebo-controlled randomised trial of Markowitz et al. In this study, 55 newly diagnosed children with CD were randomised to treatment with corticosteroids and either 6-mercaptopurine (6-MP) or placebo. After discontinuation of corticosteroids, only 9% of patients on 6-MP relapsed compared with 47% of controls during a follow-up period of 18 months. However, subsequent observational paediatric studies have not been able to reproduce these low relapse rates, as rates of 40 to 60% were found, comparable with the relapse rate in our study. These differences might be caused by different clinical settings: an ideal clinical setting with monthly outpatient clinic visits, weekly telephone contacts, and verification of treatment adherence by pill count versus standard clinical practice with less frequent contacts and limited possibilities to verify treatment adherence. Another explanation could be

Figure 2 Kaplan–Meier analysis of duration of remission in newly diagnosed paediatric Crohn’s disease patients who achieved complete remission after a six-weeks induction course of exclusive enteral nutrition and had at least 3 months of follow-up after cessation of exclusive enteral nutrition (n = 37). In most of these patients (n = 34), azathioprine maintenance treatment was initiated during or shortly after the course of exclusive enteral nutrition.
differences in study population, with a more heterogeneous population of paediatric CD patients in the observational studies.

In our study, relapses were treated with corticosteroids in more than half of the cases (55%), which illustrates that the long-term avoidance of corticosteroid therapy in this patient group is still difficult. Supplementary enteral nutrition as additional maintenance treatment after the initial induction course has been demonstrated to have a positive effect on duration of remission.35,40 Our patients were advised to continue supplemental nutrition after a successful course of EEN (1 to 2 HSF daily). The volume of supplemental nutrition taken and adherence were however not carefully recorded, as this was not a prospective study. Consequently, we could not assess the effect of supplemental nutrition on our relapse rates.

We acknowledge that our study also has other limitations due to its retrospective design. Retrospective studies are sensitive to bias, such as selection bias, as treatment was not allocated by randomisation. Secondly, it was impossible to use the PCDAI (Paediatric Crohn’s Disease Activity Index) for determination of treatment outcome, due to missing data in the medical records. Instead, we used a previously published pattern recognition model to evaluate EEN treatment response.14 This model has also been demonstrated to be useful for the evaluation of treatment outcome of corticosteroids and infliximab in IBD patients.15–17 Additionally, the results on non-adherence are based on self-report assessments documented in the medical record. It is likely that the occurrence of suboptimal adherence is even higher, as patients are often reluctant to tell their doctor about the difficulties they experience with their treatment.41 The results on the factors that may have influenced adherence should therefore be interpreted with some caution.

In conclusion, this study has demonstrated the effectiveness of a six-week course of EEN, but also the problems that occur with EEN in everyday practice and that limit the success of this treatment. Type of formula does not seem to influence treatment outcome, but there is a trend towards more adherence issues when HSF are prescribed. Non-adherence also occurred more often in older children, females, and children from non-Dutch parents. Adherence issues should be actively addressed during a course of EEN, for example by a weekly (telephone) contact with the dietician and/or IBD nurse during a course of EEN. After cessation of EEN, relapse rates are high, despite frequent use of azathioprine maintenance treatment. Further research is urgently needed to determine the mechanism of action of this treatment, which will enable optimisation of EEN treatment regimens.

Conflict of interest

None.

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References
