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Article

Exclusive Enteral Nutrition as Induction Therapy for Paediatric Crohn Disease—Efficacy, Outcomes and Predictors of Response Over a Ten-Year Period

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Abstract: Background: Exclusive enteral nutrition (EEN) is the recommended first-line induction therapy for pediatric patients with active luminal Crohn's disease (CD). The primary aim of this retrospective study was to ascertain the efficacy of EEN used as induction therapy for children with newly diagnosed CD resident in the South Island of NZ over a ten-year period (2010 – 2021). Secondary aims were to assess the clinical impact of EEN therapy on anthropometry, biochemistry, the progression to medical therapies over three time periods, and to identify positive predictors of response to EEN therapy. **Methods:** This retrospective clinical case review collected data from children diagnosed with CD at Christchurch Hospital, Christchurch, New Zealand, and prescribed EEN as induction therapy between the years January 1st, 2010 – December 31st, 2021. Descriptive statistics, Spearman's correlation coefficient, multivariate logistic regression test and standard *t*-tests were used for analyses. **Results:** Data were collected for total of 161 children, 128 (80%) children were offered EEN as induction therapy and were included in this analysis. One hundred and twenty-one (94.5%) children successfully completed an eight-week course of EEN, and a decrease in PCDAI scores ≥ 15 points from baseline to the end of week 8 of EEN treatment was seen in 119 (98.3%). L1 and L4 disease location were positive predictors of response ($p < 0.05$). One hundred and two (89.3%) children achieved disease remission defined as PCDAI < 10 at the eight-week time-point. **Conclusions:** These children with newly diagnosed CD from the South Island of NZ achieved high rates of clinical remission using EEN as induction therapy. Moreover, these children also experienced significantly improved growth parameters and biochemical markers of disease consequent to their course of EEN.

Keywords: inflammatory bowel disease; Crohn's disease; exclusive enteral nutrition; paediatrics; nutrition therapy

1. Introduction

Crohn's disease (CD) is a subtype of inflammatory bowel disease (IBD) characterized as a chronic, relapsing, inflammatory condition of the gastrointestinal tract (1). CD often adversely impacts on growth, nutritional status, and quality of life (2, 3). As there is no known cure for CD, treatments focus on resolving symptoms, improving quality of life and establishing mucosal healing.

The primary induction therapy in children with CD is exclusive enteral nutrition (EEN) - defined as a six-to-eight-week, liquid only diet using nutritionally complete formulae (4). Overall, a course of EEN has been shown to induce clinical remission in around 80% of children with high rates of mucosal healing and with associated nutritional benefits (5). For children struggling with adherence, a nasogastric (NG) tube to administer the formula may be considered. The treatment volume of formulae is calculated to also allow for catch-up growth and/or correction of nutritional deficiencies at the time of diagnosis (6). The successful undertaking of EEN requires a motivated child and a supportive family. Furthermore, it is essential that children feel they are supported by their medical team with regular review and encouragement (7).

At the end of a course of EEN, volumes are typically slowly reduced over one to two weeks while habitual foods are progressively reintroduced with monitoring of tolerance (7). Although there is no international consensus on the food reintroduction process, children are typically advised to slowly increase the quantity and range of foods with a focus on wholefoods and limitation of processed or very high fat foods.

The primary aim of this retrospective study was to ascertain the efficacy and to ascertain predictors of response using EEN as induction therapy for children with newly diagnosed CD resident in the South Island of New Zealand (NZ) over a ten-year period (2010 – 2021). Secondary aims were to assess the clinical impact of EEN therapy on anthropometry, biochemistry, the progression to medical therapies over three time periods, and to identify positive predictors of response to EEN therapy.

2. Methods

2.1. Study Population

In this retrospective study all children diagnosed with CD at Christchurch Hospital, Christchurch, NZ, and prescribed EEN as induction therapy between the years January 1st, 2010 – December 31st, 2021, were identified. Diagnosis of CD was made in standard fashion based on radiological, endoscopic and histological findings as per the Porto Criteria (8). These children were eligible for inclusion if they resided within the South Island of New Zealand during this period and were aged less than 18 years of age.

Ineligible participants were children living outside of the South Island of NZ at the time of their diagnosis, or who moved out of the South Island region during EEN therapy. Patients with CD aged older than 18 years or those with other types of IBD (ulcerative colitis or IBD unclassified) were excluded. The presence of perianal disease in conjunction with luminal involvement was not considered to be an exclusion criterion.

2.2. Primary Outcomes

2.2.1. Establishing Clinical Remission

Clinical remission was defined as a reduction in the Pediatric Crohn's disease activity index (PCDAI) score to 10 or less at the end of the eight-week course of EEN (9). A significant response to EEN was defined as a reduction of the PCDAI score by ≥ 15 by the end of week eight of EEN. Furthermore, treatment failure was defined as the cessation of EEN treatment before the end of the third week of EEN therapy.

Predictors of Response

A multivariate logistic regression test was performed to determine potential positive and negative predictors of response to EEN as defined in section 2.2.1 assessed at baseline, week two of EEN and at the completion of EEN (week eight). The variables included for analyses were anthropometry (weight, height, BMI), demographics, disease characteristics including location (Paris Classification) (10), PCDAI scores (9), adjunctive medical therapies, biochemical inflammatory and nutritional markers (Vitamin D, Albumin, erythrocyte sedimentation rate (ESR), C-Reactive protein (CRP), FC, iron studies and haematocrit (Hct).

2.2.2. EEN Protocol

Formulae

This study defined EEN as a liquid only diet using polymeric formulae (Ensure plus, Abbott Nutrition, Auckland, NZ and/or Fortisip, Nutricia, Auckland, NZ) for a period of eight weeks. Participants were allowed still water and up to three sticks daily of sugar-free chewing gum during this time. The formulae used are 300kcal/200ml serving size, and nutritional requirements were calculated using the Schofield equation with a physical activity index of 1.5 for active disease (11). Daily formula volumes were determined from these calculations.

Monitoring

Children commencing EEN were routinely monitored at baseline and then fortnightly during EEN. The clinicians present at each review typically included the paediatric gastroenterologist, the registrar, the dietitian, and the paediatric nurse. At these times, children completed their height and weight measurements, and their inflammatory and nutritional blood samples are completed by the paediatric nurse. Faecal calprotectin (FC) is completed prior to the child’s clinic review appointments, so that levels are available on the day of their clinic review.

Maintenance Enteral Nutrition

Maintenance enteral nutrition (MEN) was defined as children continuing to have at least 35% of their estimated energy requirements of formulae in addition to their normal diet after completing EEN (12).

2.3. Secondary Outcomes

2.3.1. Data Collection

The electronic medical records of eligible children were reviewed for clinical, biochemical and anthropometric variables prior to starting EEN (week 0), after two-weeks of EEN treatment, after induction therapy (week 8) and 24 weeks after starting EEN.

Biochemistry, Disease Activity and Adjunctive Medical Therapies

The variables listed in section 2.2.1.2. were collected from the medical record retrospectively.

Growth

Anthropometric data including weight (kg), height (cm) and body mass index BMI (kg/m²) were recorded and converted into z-scores using the World Health Organisation (WHO) BMI z-scores for ages 5-19-year-olds (13) to allow for statistical comparisons to be completed.

2.4. Data Analyses

Data were imported from Microsoft Excel (Microsoft 365 MSO (Version 2406) to SPSS software version 27 (IBM Corp, Armonk, NY). Descriptive statistics were reported as mean ($\pm$ standard deviation); N (percent) and/or range (minimum – maximum). Comparative data were calculated in SPSS using a standard *t*-test. A Spearman’s correlation co-efficient test and a multivariate logistics regression test were completed to identify positive predictors of response. Significance at the *P*<0.05 was reported.

Ethical approval was granted by the University of Otago Health Ethics Committee reference number **HD21/004** (January 28 2021).

3. Results

3.1. Study Population

A total of 161 children living in the South Island of NZ were diagnosed with CD during the period of observation. Of these 161 children, 128 (80%) children were offered EEN as induction therapy and were included in this analysis. In the remaining 33 (20.6%) children EEN was not clinically indicated or alternative medical therapies were commenced.

Within the study cohort of 128 children, 77 (64%) were male and the mean age was 11.1 ($\pm$ 2.98) years (**Table 1**). The most common disease location was ileocolonic (L3). Two-thirds of the children had upper gut involvement (L4a or L4b) and 28 (23%) had perianal disease at diagnosis.

Table 1. Demographics of 128 children with Crohn’s disease treated with EEN from 2010-2021.

	Total = 128
	N (%); Mean ($\pm$SD); range
Sex, males	77 (63.6)

Age at diagnosis, years	11.1 (2.98), 2 – 16
Surgical interventions by 6 months	18 (14.9)
Disease location at diagnosis (Paris Classification)	27 (22.3)
L1 (Terminal ileum)	13 (10.7)
L2 (Colon)	69 (57.0)
L3 (Ileocolonic)	68 (67.5)
L4 (a or b) (Upper GI)	28 (23.1)
p (perianal involvement)	

EEN, exclusive enteral nutrition; SD, standard deviation.

3.2. Study Outcomes

3.2.1. Primary Outcome Variables

Completion of EEN Course

One hundred and twenty-one (94.5%) children successfully completed an eight-week course of EEN. Treatment failure was seen in seven (5.5%) children: each of these children chose to stop their treatment before the end of the third week of EEN (**Table 2**). Of these seven children, five (71%) were non-responsive to EEN and the remaining two (29%) were non-adherent to EEN.

Table 2. Summary of the completion rates, feed modality, subsequent courses of EEN and prevalence of maintenance enteral nutrition in a cohort of 128 children treated with EEN.

Population overview January 1 st , 2010 – December 31 st , 2021.	
Completed 8 weeks of EEN.	121 (94.5)
Incomplete treatment with EEN	7 (5.8)
Total number of days EEN, mean (range)	57.7 (54 – 84)
Route of EEN	
Oral	105 (82.0)
Nasogastric tube (NG)	16 (12.5)
Maintenance enteral nutrition (MEN) n**	106 (87.6)
Subsequent further EEN course **	17 (14.0)

Values are n (%). Abbreviations: CD, Crohn’s disease; EEN, exclusive enteral nutrition; NG, nasogastric; MEN, maintenance enteral nutrition. ** values only in the group of 121 children who completed EEN.

Predictors of Response to EEN

L1 (Ileal) and L4 (upper gastrointestinal) disease location were both positive predictors of response to EEN treatment (both $p < 0.05$). Sex, age, baseline and week-two PCDAI scores or FC at baseline and week-two did not predict response to EEN ($p>0.05$ for all).

Change in PCDAI

Of the 121 children who successfully completed eight weeks of EEN, a decrease in PCDAI scores ≥ 15 points from baseline to the end of week eight of EEN treatment was seen in 119 (98.3%). One hundred and two (89.3%) children achieved disease remission defined as PCDAI <10 at the eight-week time-point (**Table 3**). The presence of perianal involvement did not affect the response to EEN (data not shown).

Table 3. Study outcomes at baseline, 8-weeks (completion of EEN) and 6 months in 128 children managed with EEN after diagnosis of CD.

	Baseline N = 121 N (%); Mean (±SD); min-max	Post-EEN (at week 8) N = 121 N (%); Mean (±SD); min-max	6 Months post-EEN N = 121 N (%); Mean (±SD); min-max
Weight z-score	-0.02 (1.18) -3.86 – 2.4	0.39 (1.03) * -2.46 – 3.30	0.75 (1.14) * -2.30 – 3.62
Height z-score	0.24 (1.36) -2.58 – 3.96	0.39 (1.33) -2.58 – 4.17	0.87 (2.30) * -2.76 – 2.50
BMI, kg/m² z-score	-0.35 (1.24) -4.7 – 2.37	0.09 (0.94) * -2.6 – 2.90	1.41 (2.74) -2.90 – 2.17
Total weight gain (percent) post-EEN		8.94 (9.30) 0.0 – 48.2	
Total weight gain (kg) post EEN		2.85 (3.10) -3.80 – 15.0	
Biochemistry			
ESR (mm/hr)	21.93 (14.97)	14.5 (10.60) *	16.38 (12.42)
Albumin (g/dL)	34.46 (6.38)	38.10 (4.13) *	38.31 (4.78)
Haematocrit (g/L)	0.37 (0.04)	0.38 (0.03)	0.39 (0.03)
CRP (mg/L)	27.4 (33.39)	8.68 (14.73) *	12.95 (26.79)
Vitamin D (nmol)	71.31 (26.07)	86.31 (36.47) *	76.49 (36.77)
Iron deficiency N (%) #	74 (61.2)	49 (40.5)	28 (25)
Vitamin D deficiency ##	19 (16.0)	1 (0.83)	12 (11.7)

BMI, body mass index using the WHO standard indices; CRP, C-reactive protein; EEN, exclusive enteral nutrition; ESR, erythrocyte sedimentation rate; SD, standard deviation; # iron deficiency, iron <6 (mg/dL and/or ferritin <15 µg/L); ## Vitamin D deficiency (<50 nmol) *P < 0.05.

Table 3. Study outcomes at baseline, 8-weeks (completion of EEN) and 6 months post-EEN continued.

	Baseline N = 128	Post-EEN (at week 8) N = 121	6 Months post-EEN N = 121
	N (%); Mean (±SD); min-max	N (%); Mean (±SD); min-max	N (%); Mean (±SD); min-max
Faecal calprotectin (< 50µg/g)		N = 77	
	17 (13.3)	18 (24.7)	66 (54.5)
Haematocrit (>0.35g/L)	102 (79.7)	115 (95.0)	119 (98.3)
CRP (<5mg/L)	30 (23.4)	84 (69.4)	52 (43.0)
ESR (<10mm/hr)	26 (20.3)	48 (39.7)	39 (32.2)
Albumin (>35g/L)	98 (76.5)	105 (86.8)	109 (90.1)
PCDAI scores – Mean SD, range	42.47 (9.52) 10 – 92.5	7.15 (11.23) * 0 – 47.5	23.13 (10.10) * < 10 – 45
PCDAI clinical response, N (%)		119 (98.3)	
PCDAI clinical remission, N (%)		102 (89.3)	

BMI, body mass index; Nutritional risk as defined by the WHO BMI z-score aged 5-19 years; PCDAI, Pediatric Crohn’s disease activity index < 10 = remission; PCDAI clinical response = N (%) of children with PCDAI reduction > 15 points during weeks 0-8 of EEN; PCDAI clinical remission = N % with PCDAI scores <10 at week 8 of EEN; SD, standard deviation; WHO, World Health Organisation. *P<0.05, statistically significant.

3.2.2. Secondary Outcomes

Changes in Anthropometry and Biomarkers of Inflammation Over Time

Weight and BMI z-scores improved from baseline to week eight (both p<0.05) (**Table 3**). Furthermore, albumin, ESR, CRP, vitamin D and iron stores all improved from baseline to week eight (p <0.05 for all).

Adjunctive Medical Therapies (Baseline to Week Eight)

During EEN therapy, 18 (14.9%) of children received an antibiotic and 29 (24%) were started on an immunosuppressant (azathioprine) or an aminosalicylate. None of the 121 children within the EEN cohort received corticosteroids during their course of EEN.

Outcomes Beyond 8 Weeks

One hundred and six (87.6%) of the 128 children were prescribed MEN after week eight of EEN treatment. Seventeen (14%) of children completed two or more courses of EEN within the timeframe of this study. Eighteen (14.9%) of children had some form of surgical intervention by six months from their initial EEN treatment. Two children had a percutaneous gastrostomy feeding tube inserted, one child had a right hemicolectomy and the remaining 14 (78%) children had surgical intervention for their perianal disease.

4. Discussion

This retrospective study has illustrated high rates of successful completion of EEN and consequent clinical remission in this group of children with Crohn's disease. Furthermore, these children experienced significantly improved weight and height z-scores, reduced inflammatory markers and improved nutritional biochemistry consequent to and after the completion of EEN therapy.

The primary outcome of the current study was clinical remission defined as a PCDAI score ≤ 10 by the end of the eighth week of EEN. Almost 90% of this group achieved this outcome. Further to this remission rate, 98.3% of the children had a reduction in PCDAI score of ≥ 15 . A number of reports have demonstrated successful outcomes with EEN in children with remission rates typically of around 80-85%, and response rates varying between 60% and 90% (14, 15). Regional studies in Australasia have shown a range of outcomes, however direct comparisons between studies are difficult due to the heterogeneity of study criteria.

In addition to improved disease activity, EEN is also known to have various other benefits including avoidance of corticosteroids, improved inflammatory markers, improved nutrition and high rates of mucosal healing (16-20). The current retrospective study did not include any comparison between EEN and other treatments, nor was an assessment of mucosal healing undertaken.

However, reductions in all the measured inflammatory markers were seen in the current study. These outcomes are comparable to previous reports as determined by a PCDAI < 10 at the end of EEN therapy (16, 21-25). In a prospective cohort of 21 children with CD, Grover et al. (26) compared endoscopic, transmural, clinical, and biochemical remission rates after a 6-week period of EEN. Rates of remission determined using clinical or biochemical measures were higher than endoscopic or transmural measures (84% vs. 42%, respectively). However, it is not feasible to establish remission using endoscopic and transmural measures due to the availability of resources, the invasiveness of the procedures and the prohibitive cost. Further studies are required to develop non-invasive measures of mucosal activity that would lead to more effective monitoring strategies and reduce the need for ongoing colonoscopies.

With regards to assessing predictors of response to EEN, this study demonstrated like other studies that ileal involvement (L4) is a positive predictor of response to treatment (27). This contrasts to the findings from a 2009 study by Buchanan et al (28), which reported no association between disease location and treatment efficacy. There were no other significant predictors of response identified in this particular study which differs from findings in the Spanish PRESENCE study (27). That study showed that children with mild-moderate disease (wPCDAI < 57.5), FC < 500 $\mu\text{g/g}$, ileal involvement, and CRP > 15 mg/L had a better response to EEN.

Another retrospective study reported the outcomes of EEN in 376 children (29). Older children (age > 15 years) and those with more severe disease (PCDAI > 40) were less likely to respond to EEN. These authors also noted that colonic involvement and FC > 600 $\mu\text{g/g}$ at diagnosis were associated with a reduced adherence to EEN.

Given the significance and impact of malnutrition in children with CD (3), an intervention that attends to this is important. The children in the current study had improved weight and BMI z-scores during their course of EEN. These changes are consistent with prior reports (14, 28). Several earlier studies of EEN indicated rapid improvements in nutrition with EEN (30). Weight gain during EEN is typical and expected (31, 32).

Further to short term improvements in weight, the children in the current cohort also had enhanced linear growth in the first six months after diagnosis. Other studies have also demonstrated enhanced linear growth over the subsequent months after EEN (33, 34). One study showed that a group of children managed initially with EEN had better linear growth 24 months after diagnosis than a comparative group of children managed initially with corticosteroids (35).

In New Zealand, during the period of this study the only available biological therapies supported for use in children with severe active CD unresponsive to standard therapy, or with fistulising disease were infliximab and adalimumab (36, 37). Consequently, children were commonly treated using an immunomodulator as monotherapy in the first instance prior to escalation to a biologic therapy if certain regulatory criteria were met. Subsequently, the use of nutritional therapies including EEN and MEN are consistently utilised to prolong the efficacy of monotherapy considering limited access to biological therapies when compared to international access.

Several children in the current study continued to take MEN after completing their course of EEN, either as an adjunct to maintenance medical therapy or as sole therapy. A prior report has illustrated that children having ongoing MEN had significantly improved nutrient intakes compared with their healthy siblings (38). Several reports have demonstrated that MEN administration contributes to maintenance of remission (39, 40) and to enhanced growth over time (12). Other reports have not supported the use of MEN. Indeed, European guidelines suggest the use of MEN only in select children (41). The current report focused on the outcomes of EEN in this cohort and did not evaluate on the impact or potential adverse effects of MEN. Consequently, further assessment of MEN in children is required.

The cost of nutritional treatment can be a barrier to its use in some jurisdictions (42). Throughout NZ, EEN is fully subsidised for up to three months from the time of clinician application (43). The provision of formula without additional cost may enhance both the selection of EEN as an intervention by practitioners and contribute to high adherence completion rates during EEN. The current study was not, however, designed to obtain patient or parent perspectives on this.

While easy access to formula for EEN without out-of-pocket costs may improve EEN outcomes, other disease or patient factors are also important. Disease location was noted to impact response rates in the current group, with ileal and upper gastrointestinal involvement associated with superior outcomes. Ileal disease location has been demonstrated to influence outcome in one study (27), but to be less relevant in other reports (29). Personality factors have been shown to be important in completion of an EEN course in young adults (44). While this was not able to be evaluated in the current study, due to the retrospective study design, the study did show high rates of completion.

EEN is generally considered to be safe without significant side-effects, whilst also enabling the avoidance of alternative agents, such as corticosteroids, which have various common side-effects (45). Side-effects that have been described include refeeding syndrome and elevated transaminases (46, 47). Neither of these occurrences was seen in the children in the current cohort. No other adverse effects were seen or noted in the current cohort.

The major limitation of this study is its retrospective study design. Further, the study was focused solely on the outcomes of EEN and did not include any comparison to the outcomes of other therapies. The strengths of this study included the large population-based sample size seen over a decade with evaluations for the first six months after diagnosis. Furthermore, the children were managed within a single team with clear and distinct treatment protocols. The children in the current cohort were generally comparable to prior NZ paediatric cohorts (48, 49).

5. Conclusions

These children with newly diagnosed CD from the South Island of NZ achieved high rates of clinical remission using EEN as induction therapy. Moreover, these children also experienced significantly improved growth parameters and biochemical markers of disease consequent to their course of EEN. Given the recent emergence of novel diet therapies for the induction of remission of active luminal CD, this study adds to the literature the efficacy and outcomes of EEN in paediatric CD, so that children and their families can make the best informed, evidence-based decision for induction therapy of CD. Further research is required to better understand disease or patient-specific factors that contribute to an optimal response to EEN. In addition, while MEN was commonly used in this cohort, the outcomes of this intervention require further focused evaluations.

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