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ORIGINAL ARTICLE

Outcomes of exclusive enteral nutrition in paediatric Crohn's disease

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BACKGROUND/OBJECTIVES: Exclusive enteral nutrition (EEN) is a safe and effective treatment modality for inducing remission in paediatric Crohn's disease (CD). The primary aim of this study was to compare the outcomes of EEN to corticosteroid (CS) therapy in newly diagnosed, treatment-naïve patients with CD. A secondary aim was to describe the outcomes of EEN in a national cohort of paediatric CD patients over a 10-year period.

SUBJECTS/METHODS: A retrospective chart review was conducted at the Irish national referral centre for paediatric CD. A case-matched analysis was conducted on two cohorts matched for age, gender, disease location, disease behaviour and disease activity, who received CS or EEN as their initial treatment. Subsequently, cohort analysis was conducted on all patients who undertook a course of EEN therapy between 2004 and 2013.

RESULTS: The case-matched analysis found higher remission rates after treatment with EEN (24/28, 86%) compared with those with CS (15/28, 54%; $P = 0.02$). Dietetic contacts were found to be pivotal to the success of treatment and the attainment of remission. In total, 59 patients completed EEN at some time-point in their disease course and were included in the cohort analysis. Sixty-nine per cent of this cohort entered clinical remission (41/59). EEN was found to be most effective when used as an initial treatment ($P = 0.004$) and less effective in patients aged under 10 years ($P = 0.04$).

CONCLUSIONS: EEN should be strongly considered as a favourable primary treatment over CS, especially in those diagnosed over the age of 10 years.

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory condition characterised by periods of relapse and remission.[1–3] It may present at any age, with ~25% of all cases diagnosed during childhood and adolescence.[4–6] In Ireland, there has been a substantial and sustained increase in the incidence of childhood CD over the past 10 years.[7]

Interactions between the environment, host susceptibility and immune-mediated tissue injury are implicated in CD pathogenesis.[6,8] In addition to the common presenting clinical symptoms of diarrhoea, abdominal pain and weight loss,[1,9] children are at increased risk of impaired linear growth, delayed pubertal development and poor bone health.[2,10] Childhood-onset inflammatory bowel disease (IBD) is characterised by more extensive disease location and more aggressive disease behaviour than adult-onset disease.[11,12]

The choice of induction treatment is influenced by factors including disease phenotype and activity, with exclusive enteral nutrition (EEN) and corticosteroids (CS) predominantly used as first-line induction paediatric therapies. EEN refers to the administration of an enteral formula either orally or via a feeding tube for a 6- to 8-week period, followed by the gradual reintroduction of normal diet.[8,13–15] Recent guidelines advocate the use of EEN as induction treatment for children with inflammatory luminal disease.[16] Comparable paediatric remission rates have been reported following treatment with either EEN or CS.[17–20] The potential benefits of EEN extend beyond nutrition alone, and include improved mucosal healing, linear growth and bone health.[19,21–24] Although CS is clinically efficacious and associated with improvements on endoscopic assessment, mucosal healing is not superior to that seen with EEN.[22,23] Their use is also associated with undesirable side effects including weight gain, striae, linear growth impairment, acne and low mood.[25,26]

In this study we sought to compare the outcomes of patients treated with EEN at diagnosis to a cohort treated with CS at diagnosis, matched for age, gender, disease location, disease behaviour and disease activity. We subsequently evaluated the outcomes of all patients completing a course of EEN as an induction therapy to determine the factors influencing its efficacy.

SUBJECTS AND METHODS

Study design

In Ireland, the National Centre for Paediatric Gastroenterology at Our Lady's Children Hospital Crumlin (OLCHC) is the sole provider of specialty paediatric gastroenterology services. For the first part of this study (case-matched analysis), we compared the outcomes of EEN to CS therapy when used as the first induction treatment in a cohort matched for age, gender, disease location, disease behaviour and disease activity. The second part of the study (cohort analysis) involved a retrospective case review to examine the clinical outcomes of all patients who completed EEN at any stage of

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their disease course in this nationally representative cohort from 2004 to 2013. This study was conducted with the approval of the research ethics committee of OLCHC.

Treatment protocols

A course of EEN was defined as per our hospital protocol. The hospital EEN protocol involves taking a liquid enteral formula (polymeric or elemental, depending on patient taste preference), either orally or via a feeding tube, as the sole nutritional source for 6–8 weeks' duration. Patients who have not been fully established on EEN by day 7 are given an alternative induction treatment, but can stay on partial/supplemental EN. The protocol permits negligible amounts of non-nutritive treat foods (jelly, boiled sweets and chewing gum) that have an insignificant caloric value. This is then followed by the gradual reintroduction of normal diet over a 2-week period. A breech of EEN protocol was defined as a requirement for extension of EEN therapy to induce remission, or the need to use CS or biologics as concomitants or alternatives to an already established EEN course. The hospital protocol for oral CS therapy involves prednisolone 1 mg/kg (maximum 40 mg) daily for 4 weeks, followed by a weekly 5 mg wean over the subsequent 7 weeks. A breech of CS protocol was defined as the requirement to either prolong CS course, to reduce the rate of CS taper or to use adjunctive EEN or biologics to induce remission.

Patient selection

For the purpose of the case-matched analysis, patients were eligible for inclusion if they took EEN as their initial primary treatment upon diagnosis ($\geqslant$7 days, up to 6–8 weeks total duration). Each EEN patient was individually best matched in terms of age (±1 year), gender, disease location, disease behaviour and disease activity with a CS candidate. Patients were excluded from the case-matched analysis if they had received previous treatment for CD, if EEN was not fully established within 7 days of starting, if concomitant CS or biologics were commenced simultaneously with EEN treatment (EEN group) or if EEN or biologics were used during CS treatment (CS group). Other concomitant medications did not exclude patients from either cohort but were documented.

A subsequent cohort review included all paediatric patients who undertook a course of EEN therapy during the study period, as per hospital protocol, irrespective of disease stage or duration. Patients with a diagnosis of ulcerative colitis or IBD-unclassified or patients for whom EEN was not the sole source of nutrition were excluded. Concomitant medications were documented but did not exclude patients from the cohort. Treatments with EEN were classified as 'initial' (primary induction agent at first diagnosis), 'subsequent' (second-line induction agent within 3 months of diagnosis) or 'relapse' (commenced to treat a disease relapse in a patient previously in remission).

Study definitions and data collection

Children were diagnosed according to established international clinical, radiological, endoscopic and histological criteria.[27] Clinical assessments and decisions were made by an attending consultant gastroenterologist. Disease phenotype (location and behaviour) and age of diagnosis were defined using the Paris classification criteria.[28] Disease activity was defined using the Paediatric Crohn's Disease Activity Index (PCDAI).[29] A Physician Global Assessment score of the attending consultant gastroenterologist was also recorded in parallel, to ascribe disease activity before and after treatment (0 = inactive, remission; 1 = mild activity; 2 = moderate activity; 3 = severe activity).[30]

Data were collected by two independent investigators (MT, LL) from existing hospital databases, medical and dietetic records and recorded on study-specific case report forms. Data were verified by a senior investigator (AC) and any errors or inconsistencies were resolved with the senior author (SH). The hospital records include a *pro forma* IBD clinic sheet, which includes listing all elements of PCDAI for each clinical assessment. PCDAI scores were calculated retrospectively from these clinic sheets by two investigators before and after treatment. Remission was defined as a PCDAI of $\leqslant$10. Mild disease was classified as a PCDAI of 11–30, moderate disease 31–44 and severe disease $\geqslant$45.[28] Albumin, haematocrit, erythrocyte sedimentation rate, haemoglobin, platelets and C-reactive protein were recorded before and after treatment. These laboratory values form part of the PCDAI score and are ordinarily assessed at patient visits. Our IBD service had a single senior dietitian across the duration of the study period. The dietetic records contained details including the type, duration and mode of administration of enteral formula, and details of any extraneous foods consumed during treatment, as reported by patients and/or families. Dietetic contacts were defined as indirect (telephone or email, sourced from the hospital's health information system) or direct (outpatient appointment or in-patient visit) to allow for a detailed analysis of dietetic resources in EEN service provision. Additionally, all medical and clinical nurse specialist contacts were documented. Nutritional requirements were calculated based on 120% of the Reference Nutrient Intake as recommended in the current literature.[31] Patients' intakes were then compared against requirements to assess nutritional adequacy.

The duration from remission to subsequent relapse, along with the number of relapses from the point of remission to 1 year after treatment were documented. A relapse was defined as an increase in disease activity necessitating a repeat course of EEN or CS, an escalation of medical treatment or surgery. Disease progression was defined as a progression in disease behaviour or extension of disease location from baseline diagnostic phenotype, as defined by the Paris classification.[28] Subsequent medication use after treatment was documented.

Weight and height *z*-scores were calculated using the LMS Growth Excel package (Harlow Printing Limited, Newcastle, UK). Growth delay was classified as a height *z*-score of < -2 at diagnosis, or a reduction in height *z*-score of $\geqslant 0.75$ from diagnosis to 1 year after treatment.[26] Geographic residency of patients was classified as 'rural' or 'urban' using Ireland's Central Statistics Office Small Area Population Statistics interactive mapping tool. A location with $<$1500 inhabitants was defined as 'rural'.[32] Anthropometric measurements were examined at four time-points: pre-treatment, post-treatment, at 1 year and at maximum follow-up. Maximum follow-up was defined as the last documented outpatient appointment or in-patient stay at the time of data collection or before discharge to adult services.

For the case-matched analysis, additional data recorded included type, dosage, route of administration and duration of treatment (including tapering period) of CS therapy.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (Version 22; SPSS, Chicago, IL, USA). Categorical data, such as baseline subject characteristics, were analysed using descriptive statistics. To investigate associations between categorical variables, χ^2 tests for independence were conducted. Statistical significance was defined as a *P*-value of <0.05.

Continuous variables were assessed for normality using the Kolmogorov–Smirnov statistic. Nonparametric continuous variables were presented as medians and interquartile ranges (IQRs), whereas parametric continuous variables were presented as means and s.d. Nonparametric continuous variables were assessed using the Mann–Whitney *U*-test, whereas parametric variables were assessed using independent-samples *t*-tests or paired-samples *t*-tests as appropriate.

RESULTS

Case-matched analysis

The outcomes of newly diagnosed patients receiving EEN as their first treatment were compared with newly diagnosed patients who received CS as their first treatment. Twenty-eight patients underwent EEN therapy at diagnosis. These patients were matched for age, gender, disease location, disease behaviour and disease activity (Table 1). There was no significant difference in age of diagnosis or gender between the two groups.

Remission details. Remission was achieved in a greater proportion of patients after treatment with EEN (24/28, 86%) compared with CS (15/28, 54%; $P=0.02$). No patients taking EEN required extensions of therapy beyond the standard protocol. Ten patients treated with CS required dose adjustments beyond the standard protocol because of interval symptoms; six of these achieved remission. By intention-to-treat analysis, 9/28 patients attained remission on CS compared with 24/28 on EEN ($P<0.001$). Adjunctive medications received during treatment were similar between the cohorts, as documented in Table 1. Responses to treatment as defined by PCDAI are illustrated in Table 2. Interestingly, although a significant difference in remission rates

Table 1. Age, gender, disease location, disease behaviour and disease activity-matched EEN and CS cohorts for case-matched analysis

	EEN (n = *28*) n *(%)*	*CS* (n = *28*) n *(%)*
Age of diagnosis		
A1a	4 (14)	1 (4)
A1b	24 (86)	27 (96)
Gender		
Male	20 (71)	17 (61)
Female	8 (29)	11 (39)
Location		
L1	1 (4)	1 (4)
L1+L4[a]	5 (18)	3 (11)
L2	0	0
L2+L4	4 (14)	4 (14)
L3	4 (14)	1 (4)
L3+L4	12 (43)	16 (57)
L4	2 (7)	3 (11)
Behaviour		
B1	20 (71)	21 (75)
B2	6 (21)	6 (21)
B3	2 (7)	1 (4)
B2B3	0	0
Perianal disease	11 (39)	7 (25)
Route of administration		
Oral	25 (89)	24 (86)
Nasogastric	3 (11)	N/A
Intravenous	N/A	4 (14)
Type of feed		
Polymeric	28 (100)	N/A
Elemental	0 (0)	N/A
Concomitant medication		
Five ASAs	9 (32)	16 (57)
Immunomodulators	3 (11)	6 (21)
Antibiotics	7 (25)	6 (21)

Abbreviations: A1a, age 0– < 10 years; Alb, age 10–17 years; 5ASA, 5-aminosalicylic acid; B1, inflammatory; B2, stricturing; B3, penetrating; CS, corticosteroids; EEN, exclusive enteral nutrition; L1, ileocaecal; L2, colonic; L3, ileocolonic; L4a, oesophagus to ligament of Treitz; L4b, ligament of Treitz to proximal ileum; N/A, not applicable. [a]L4 refers to any of L4a, L4b and L4ab, per Paris classification.

was observed between the cohorts, clinical response rates were equivalent, with only one patient in each cohort not responding to treatment. Disease activity designation was consistent between Physician Global Assessment and PCDAI scores. The impact of treatment on laboratory values is detailed in Table 3.

Relapse details. The median time to relapse in this EEN cohort was 3 months (IQR: 4) and 2 months in the CS cohort (IQR: 3). Thirteen patients (46%) who received EEN and 12 (43%) who were treated with CS experienced a clinical relapse in the first year after treatment. Overall, there was no significant difference in the number of relapses observed in either cohort. The subsequent use of immunomodulators also did not differ significantly between the groups (EEN, $n = 23$, 82%; CS, $n = 22$, 79%).

Medical and clinical nurse specialist contacts did not differ between urban and rural dwellers and did not influence remission rates. However, increased dietetic contacts during treatment were independently associated with higher remission rates. Urban-dwelling patients had a significantly greater number of dietetic contacts during EEN therapy and also had higher remission rates than rural dwellers (5 vs 2.5; $P = 0.03$).

Growth parameters. An equal proportion of patients (5 vs 4) in each cohort were classified as underweight on commencement of treatment. Within each cohort, significant changes in weight *z*-scores were observed at the end of induction treatment, 1 year after treatment and at maximum follow-up (Table 4). Height *z*-scores declined in the CS but not in the EEN cohort during the follow-up period (Table 4).

Upon subanalysis, five patients had significant growth delay pre-treatment (height *z*-score < -2). The mean height *z*-score after treatment with EEN (-0.65 ± 2.34, 2/28) was clinically superior to that with the CS cohort (-2.43 ± 0.23, 3/28). At 1-year follow-up, despite not reaching statistical significance, the mean height *z*-score of those treated with EEN remained clinically superior (-0.53 ± 2.30, 2/28 vs -2.35 ± 0.31, 3/28).

Cohort analysis

Two hundred and seventy-eight patients were diagnosed with CD at OLCHC between 2004 and 2013. The characteristics of all patients meeting the inclusion criteria ($n = 59$) are presented in Table 5. Of the 59 patients who completed the 6- to 8-week course of EEN, 57 patients (97%) took polymeric feeds and 2 patients (3%) received elemental feeds. Overall, 51 patients (86%) consumed feeds orally, with eight patients (14%) requiring tube feeding. Thirty-five patients (59%) achieved $>90\%$ of their energy requirements during the EEN treatment period, with 58 patients (98%) meeting $>90\%$ of their protein requirements.

Remission details. Forty-one patients (69%) entered clinical remission (PCDAI $\leqslant 10$) following EEN treatment. Greater remission rates were observed in patients receiving EEN as an initial (25/29) or subsequent (3/3) treatment rather than as a relapse treatment (13/27; $P = 0.004$; Table 6). The use of EEN was not limited to certain diagnostic phenotypes. There was no association between diagnostic phenotype and attainment of remission. Clinical remission rates were significantly higher in older-onset paediatric IBD (A1b) compared with those in early-onset IBD (A1a), as defined by the Paris classification ($P = 0.04$). Patients who occasionally consumed concomitant foods during EEN treatment had higher remission rates (21/24, 88% vs 20/35, 57%; $P = 0.03$). Following treatment, 49 patients (83%) continued on supplementary polymeric enteral nutrition drinks. The study end point of achieving remission was neither dependent on consuming $\geqslant 90\%$ of recommended daily protein or caloric intakes, nor influenced by taking concomitant medications.

Changes in disease activity upon completion of treatment are detailed in Table 2 for both study populations. Changes in laboratory values following treatment are outlined in Table 3.

In total, 56 patients (95%) experienced a clinical relapse according to the study definition in the first year after treatment. For patients who achieved remission, the median duration to relapse was 2 months (IQR: 4.5 months), irrespective of the time of EEN administration (initial, subsequent and relapse). Two patients (3%) had a change in disease behaviour at 1-year follow-up.

Growth parameters. Changes in anthropometric parameters from pre-treatment to maximum follow-up for the cohort analysis population are detailed in Table 4. A mean weight gain of 4.4 kg (±3.2) was observed with EEN treatment. Significant improvements in weight *z*-scores were observed at all time-points, whereas an improvement in height *z*-score was only seen at maximum follow-up.

Table 2. Disease activity before and after treatment as determined by PCDAI[a]

	Remission, n *(%)*	*Mild,* n *(%)*	*Moderate,* n *(%)*	*Severe,* n *(%)*
Case-matched analysis				
EEN ($n=28$)				
Pre-treatment	0 (0)	7 (25)	15 (54)	5 (18)
Post-treatment	24 (86)	4 (14)	0 (0)	0 (0)
CS ($n=28$)				
Pre-treatment	0 (0)	6 (21)	14 (50)	7 (25)
Post-treatment	15 (54)	13 (46)	0 (0)	0 (0)
Cohort analysis				
EEN ($n=59$)				
Pre-treatment	0 (0)	22 (37)	28 (47)	9 (15)
Post-treatment	41 (69)	16 (27)	2 (3)	0 (0)

Abbreviations: CS, corticosteroids; EEN, exclusive enteral nutrition; mild, PCDAI 11–30; moderate, PCDAI 31–44; PCDAI, Paediatric Crohn's Disease Activity Index; remission, PCDAI $\leqslant 10$; severe, PCDAI $\geqslant 45$. [a]This table presents results from analysis conducted, initially focusing on EEN vs CS as first-line treatments at diagnosis and subsequently a larger group of patients who were treated with EEN at any stage of their disease course. As illustrated in case-matched analysis, pre-treatment of disease activity scores are rigorously matched, further strengthening comparison of post-treatment outcomes.

Table 3. Mean laboratory parameters before and after treatment[a]

	Case-matched analysis		*Cohort analysis*
	EEN (n = *28*)	*CS* (n = *28*)	*EEN* (n = *59*)
CRP (mg/l)			
Pre-treatment	48	53	37
Post-treatment	8	19	13
Platelets (x10^{3}µl)			
Pre-treatment	557	544	488
Post-treatment	355	422	371
Hb (g/l)			
Pre-treatment	112	109	113
Post-treatment	118	113	117
HCT (%)			
Pre-treatment	34	33	35
Post-treatment	48	35	40
ESR (mm/h)			
Pre-treatment	37	50	34
Post-treatment	18	20	23
Albumin (g/dl)			
Pre-treatment	31	32	34
Post-treatment	40	40	40

Abbreviations: CS, corticosteroids; CRP, C-reactive protein; EEN, exclusive enteral nutrition; ESR, erythrocyte sedimentation rate; Hb, haemoglobin; HCT, haematocrit. [a]Illustration of changes in laboratory parameters for case-matched and cohort analysis groups from pre-treatment to post-treatment.

Table 4. Comparison of weight and height *z*-scores from pre-treatment to maximum follow-up in patients who completed a full treatment course

	Weight z-score		*Height z-score*	
	Mean ± s.d.	P-*value*[a]	*Mean* ± s.d.	P-*value*
Case-matched analysis				
EEN (n = 28)				
Pre-treatment	−1.06 ± 1.12		−0.61 ± 1.07	
Post-treatment	−0.38 ± 0.90	0.000	−0.68 ± 1.05	N/A
One-year follow-up	−0.45 ± 0.96	0.000	−0.66 ± 1.11	0.646
Maximum follow-up[b]	−0.09 ± 0.92	0.006	−0.37 ± 0.76	0.101
CS ($n=28$)				
Pre-treatment	−0.99 ± 1.30		−0.71 ± 1.06	
Post-treatment	−0.26 ± 0.93	0.000	−0.88 ± 1.08	N/A
One-year follow-up	−0.46 ± 1.16	0.001	−0.81 ± 1.09	0.152
Maximum follow-up[b]	−0.43 ± 1.07	0.002	−0.92 ± 0.84	0.884
Cohort analysis				
EEN ($n=59$)				
Pre-treatment	−0.98 ± 1.32		−0.66 ± 1.2	
Post-treatment	−0.40 ± 1.07	0.000	−0.67 ± 1.19	N/A
One-year follow-up	−0.49 ± 1.28	0.000	−0.55 ± 1.19	0.346
Maximum follow-up[c]	−0.31 ± 1.11	0.000	−0.36 ± 0.91	0.035

Abbreviations: CD, Crohn's disease; CS, corticosteroids; EEN, exclusive enteral nutrition; N/A, not applicable. EEN course as induction therapy for CD from 2004 to 2013 ($n=59$). [a]*P*-value <0.05 was considered statistically significant. [b]Maximum follow-up ranges from 0.31 to 7.31 years (median: 2.09 years). [c]Maximum follow-up ranges from 0.31 to 5.99 years (median: 2.04 years).

DISCUSSION

This study, in a nationally representative cohort, confirms that a 6–8-week course of EEN is an effective primary therapy for inducing remission in paediatric CD, especially in patients over 10 years, and is dependent on the support of a trained dietitian. Uniquely, this study is the first to our knowledge to compare EEN with CS by rigorously matching patients in terms of age, gender, disease location, disease behaviour and disease activity, which allowed for in-depth comparison of outcomes. Our results illustrate that EEN is more effective than CS in inducing remission when used as the first induction therapy at diagnosis. The results affirm the many recognised advantages of EEN, and our outcomes compare favourably with published literature in this area, especially with regard to remission rates and anthropometric outcomes.[8,10,14,22,23,33,34]

Our finding that EEN was more effective clinically than CS at inducing remission at diagnosis contrasts with previous reports of their equivalent remission rates in paediatric populations.[9,17,18,22,23,35] Our results give further support to the current recommendations to use EEN as first-line induction therapy in CD.[16] We attempted to mitigate potential bias and confounding factors by comparing only patients who received EEN or CS as their first treatment on diagnosis. This rigorous matching significantly reduced our sample size. A comparison of mucosal healing between EEN and

Table 5. Demographics of patients who completed a full EEN course as induction therapy for CD from 2004 to 2013 ($n = 59$)

	n *(%)*
Gender	
Male	39 (66)
Female	20 (34)
Age of diagnosis years (± IQR)	12.34 ± 3.82
Mean age of commencement of EEN years (range)	13.27 (1.99–17.57)
Disease location	
L1	1 (2)
L1+L4[a]	5 (8)
L2	6 (10)
L2 +L4	11 (19)
L3	9 (15)
L3+L4	20 (34)
L4	7 (12)
Disease behaviour	
B1	48 (81)
B2	8 (14)
B3	2 (3)
B2B3	1 (2)
Perianal disease	21 (36)

Abbreviations: CS, corticosteroids; EEN, exclusive enteral nutrition; CD, Crohn's disease; L1, ileocaecal; L2, colonic; L3, ileocolonic; L4a, oesophagus to ligament of Treitz; L4b, ligament of Treitz to proximal ileum; B1, inflammatory; B2, stricturing; B3, penetrating. [a]'L4' refers to any of L4a, L4b and L4ab, as per Paris classification.

Table 6. Potential influencing factors on remission rates following completion of a full course of EEN ($n = 59$)

	Total, n	*Remission*	
		n *(%)*	P-*value*[a]
Treatment type			
Initial	29	25 (86)	
Subsequent	3	3 (100)	
Relapse	27	13 (48)	0.004
Age at diagnosis			
A1a	17	8 (47)	0.039
A1b	42	33 (79)	
Age at treatment (years)			
0– < 10	12	7 (58)	0.556
⩾10	47	34 (72)	
Gender			
Male	39	28 (72)	0.812
Female	20	13 (65)	
Dietetic contacts[b]			
⩾4		41 (69)	0.025
< 4		18 (31)	

Abbreviations: A1a, age < 10 years; Alb, age 10–17 years; EEN, exclusive enteral nutrition. [a]*P*-value < 0.05 was considered statistically significant. [b]Dietetic contacts were defined as direct (outpatient appointment, face to face) or indirect (telephone or email).

CS groups was not possible retrospectively, as routine post-treatment endoscopy is not appropriate in children, and faecal calprotectin levels were not routinely measured.

EEN was most effective when used as an initial treatment in newly diagnosed patients, especially in older children, irrespective of diagnostic phenotype. An Australian study previously reported better remission rates in newly diagnosed CD patients following EEN treatment, compared with those with long-standing disease.[35] The lower 1-year relapse rate in the case-matched EEN group compared with the overall post-EEN relapse rate also suggests more favourable long-term benefits when EEN is used as a primary induction therapy. The low rates of progression of disease location and behaviour observed in our cohort are in keeping with previous reports from the Irish population.[7] Emerging data have challenged historic opinion that only certain inflammatory phenotypes of IBD respond effectively to EEN.[16,33,36,37] Our findings corroborate these data, reflecting current prescription trends in the use of EEN, although not all phenotypes were well represented (L2) within the limits of our sample size.

Our study has identified novel disease-independent factors that influenced EEN induction success. This is the first study to show that patients who were diagnosed over the age of 10 years were more likely to attain remission on completion of treatment than younger children. Whether higher success rates in older children reflect better acceptability and compliance in this age group, or underlying differences in disease biology, needs to be substantiated by further research. It remains intriguing why urban-dwelling patients had better EEN success rates than rural dwellers. Speculative reasons include more limited transportation, connectivity and dietetic access opportunities for children living in remote locations. Patients with more dietetic contacts during treatment also had higher rates of remission. This was independent of other multidisciplinary team member contacts. This finding requires further validation, but has potentially significant implications for resource planning at paediatric IBD referral centres, especially given the impetus to use EEN as primary induction therapy.[16] Our hospital protocol did not have defined guidelines regarding dietetic contacts upon discharge to community during the study period. Only two previous studies have reported defined protocols for dietitian contacts, but neither study related this to treatment outcomes.[37,38] Our protocol, in line with current practice, recommends the use of polymeric feeds to help improve tolerability.[9,16] Consumption of small amounts of additional foods during EEN treatment was associated with higher remission rates. This may have improved EEN acceptance and compliance, or helped to break the potential monotony of EEN taste and texture. Recent studies have also found that EEN efficacy is not diminished significantly when small volumes of certain additional foods are consumed.[12,33,39,40]

We endeavoured to reduce the potential limitations involved in our retrospective study and acknowledge those that remain. Including only those patients who completed their EEN course and not excluding those on concomitant therapies enabled us to better reflect a 'real-world' experience of EEN. However, we acknowledge that antibiotic therapy could have influenced remission rates, given the potential anti-inflammatory effect of these medications. A larger sample size and longer follow-up time may have allowed detection of significance in a number of observed trends, and strengthened those we identified, especially our anthropometric data. In particular, the illustrated superiority of EEN may have been strengthened if multiple matching of CS controls had been in place. As our study was retrospective, researchers were reliant on chart notes to ascertain compliance, and the brevity of these notes did not facilitate further exploration of compliance challenges. Treatment selection was not randomised and was at physician and/or patient discretion. Our retrospective study design did not enable us to explore physician and patient factors regarding treatment choices and preferences, leading to a potential for selection bias. Although this cannot be absolutely excluded retrospectively, we attempted to compensate for this, in part, by age-matching patients for disease activity as

well as disease phenotype. It remains unclear whether EEN was more likely to be offered to more motivated patients/families or to older rather than younger patients. It is also possible that induction treatments other than EEN were prescribed in severe isolated colonic inflammatory disease, such as L2, B1. This may have skewed patient representation and outcomes in these groups. The effectiveness of all induction therapies used during the study period lay outside the scope of the present study, but would have allowed us to present more contextualised intention-to-treat analysis data of all treatment outcomes in our population. In our group's experience, patients who do not fully establish EEN by day 7 do not persevere with it, and so commence alternative treatments. Our retrospective study design did not enable us to study potential barriers to completion of treatment. We also interpret with caution our lack of EEN protocol breaches, which reflects our relatively limited study size, as it is quite likely that a much larger cohort would include such cases and affect results accordingly. Further analysis of our more novel findings is currently being evaluated in a prospective setting.

CONCLUSION

This study reaffirms the role and effectiveness of EEN in the therapeutic armamentarium for treating paediatric CD, especially as a first-line induction strategy at diagnosis in older children. A number of novel disease-independent factors have been identified that enhance EEN success, including the pivotal role of dietitian contacts, allowing consumption of small amounts of non-nutritive foods during treatment and older age at diagnosis. Future research on defining EEN regimens, the efficacy of EEN in younger children and the influence of dietetic support and protocols on treatment success and longer-term outcomes are keenly awaited.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

Study concept and design: SH, AC, MH and SS. Data collection and analysis: MT, LL and AC. Manuscript drafting: all authors. Study guarantor: SH.

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