

Systematic review with meta-analysis: enteral nutrition therapy for the induction of remission in paediatric Crohn's disease

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None.

Abstract

Background: Despite potential adverse-events in a paediatric population, corticosteroids are used to induce remission in paediatric Crohn's disease. Exclusive enteral nutrition also induces remission, but is infrequently used in the USA because corticosteroids are considered the superior therapy. New data have become available since the publication of the most recent meta-analysis in 2007.

Aim: To see if current literature supports the use of EEN versus CS in paediatric populations.

Methods: All studies with comparator arms of exclusive enteral nutrition and an exclusive corticosteroids, with remission clearly defined were identified by searching eight online databases.

Results: Of 2795 identified sources, nine studies met our inclusion criteria. Eight of these ($n = 451$), had data that could be abstracted into our meta-analysis. Exclusive enteral nutrition was as effective as corticosteroids in inducing remission ($OR = 1.26$ [95% CI 0.77, 2.05]) in paediatric Crohn's disease. There was no difference between Exclusive enteral nutrition and corticosteroids efficacy when comparing newly diagnosed Crohn's ($OR = 1.61$ [95% CI .87, 2.98]) or relapsed ($OR = 0.76$ [95% CI .29-1.98]). Intestinal healing was significantly more likely among patients receiving Exclusive enteral nutrition compared to corticosteroids ($OR = 4.5$ [95% CI 1.64, 12.32]). There was no difference in the frequency of biomarker normalisation including CRP ($OR = 0.85$ [95% CI .44, 1.67]) and faecal calprotectin ($OR 2.79$ [95% CI .79-10.90]).

Conclusions: There is no difference in efficacy between exclusive enteral nutrition and corticosteroids in induction of remission in Crohn's disease in a paediatric population. Exploratory analyses suggest that a greater proportion of patients treated with exclusive enteral nutrition achieved mucosal healing.

1 | INTRODUCTION

Crohn's disease (CD) is a chronic illness characterised by destructive transmural inflammation of the gastrointestinal tract with periods of flares and remission.¹ While CD is most commonly diagnosed among 15-35 year olds, a quarter of patients are diagnosed as children under the age of 18.^{2,3}

Corticosteroids are the most commonly used medication to induce remission in the USA,⁴ but can pose particular risks in a paediatric population including: growth retardation, low bone mineral density, adrenal suppression and body image dissatisfaction.⁵ As an alternative, gastroenterologists sometimes elect to use exclusive enteral nutrition (EEN) as induction therapy in these patients⁶ because adverse effects of enteral nutrition are generally limited to gastrointestinal tolerability (eg, nausea, vomiting, diarrhoea) though rare reports of refeeding syndrome exist.⁷ This therapy is frequently used in Europe, but fewer than 4% of paediatric gastroenterologists use it in North America, though emerging data shows it is gaining more prominence in Canada.^{6,8}

The benefits of enteral nutrition in patients with Crohn's disease were auspiciously identified in the surgical literature when patients administered enteral nutrition to optimise their nutritional status pre-operatively, improved unexpectedly, with some even avoiding the intended surgery.⁹ The mechanism of the beneficial effects of enteral nutrition was hypothesised to be the avoidance of enteral antigens resulting in improvements in intestinal permeability, though recent studies have elucidated other possibilities,¹⁰ including down regulation of pro-inflammatory cytokines.¹¹ Others have found beneficial changes to the gut microbiome among Crohn's patients treated with enteral nutrition.^{12,13}

There are three major categories of enteral nutrition formulas, and they are differentiated by the structure of their protein content. Elemental diets contain no intact protein, only amino acids. Unfortunately, elemental diets are distinctly distasteful and often require a feeding tube to administer. Even semi-elemental diets (ie, peptides of varying length) were found to be intolerable with 57% of patients withdrawing from a major study mostly due to poor palatability.¹⁴ Polymeric diets (ie, intact protein), which are more palatable and do not always require feeding tube placement for administration, have been shown to perform as well as elemental and semi-elemental diets in the induction of remission of CD.¹⁵

Previous comparisons regarding the effectiveness of EEN vs CS in remission induction have yielded mixed results. Five of seven meta-analyses published over the last 20 years have found CS to be superior to EEN at inducing remission.¹⁵⁻¹⁹ Of the seven meta-analyses, two have mixed populations of adults and children, three included only adult studies and two focused only on children. EEN is hypothesised to work more effectively in children than adults, though the reasons for this are unclear.⁶ The two paediatric meta-analyses focused only on induction of remission,^{20,21} found no difference in remission induction comparing CS to EEN.

In the 10 years that have elapsed since the most recent meta-analysis on this subject, several more studies,²²⁻²⁶ have been published, which have included new data on biomarkers and mucosal healing, two previously unexplored end points. Therefore, we performed an updated systematic review and meta-analysis on the efficacy of CS vs EEN in the paediatric population. Our primary outcome was the induction of remission. We distinguished the treatment effects between newly diagnosed and relapsed patients. Because the field has moved towards recognising the importance of more objective criteria to identify improvement and monitor disease status,²⁷ we conducted three hypothesis-generating analyses to examine the effect of EEN vs CS on durability of remission, mucosal healing and biomarkers.

2 | METHODS

2.1 | Inclusion criteria for studies

2.1.1 | Types of studies

All randomised and observational studies with at least two comparator arms including at least one dietary intervention administered by any route and one nondietary intervention in English were considered for inclusion. Abstracts and conference proceedings were excluded, as data suggest that abstracts may be inconsistent with the final published article²⁸ and they have not had the benefit of peer-review.

2.1.2 | Types of participants

Patients under the age of 18 with newly diagnosed or relapsed active Crohn's disease.

2.1.3 | Types of interventions

Administration of EEN in the following formulations: polymeric formula, semi-elemental formula, or elemental formula to one group of patients and CS to the comparator arm were reviewed for the specific outcomes described in this systematic review and meta-analysis. Patients in the EEN arm must not be receiving any other medication, and those receiving CS must only be treated with CS. Although there has been no convincing evidence that there is any difference in benefit between the types of formulas used, and the Zachos et al.¹⁵ Cochrane analysis combined all exclusive enteral nutrition analyses, we conducted both combined and stratified analyses.

2.2 | Exclusion criteria

Trials without an EEN arm and trials without at least one clearly defined CS comparator arm were excluded from this analysis. In

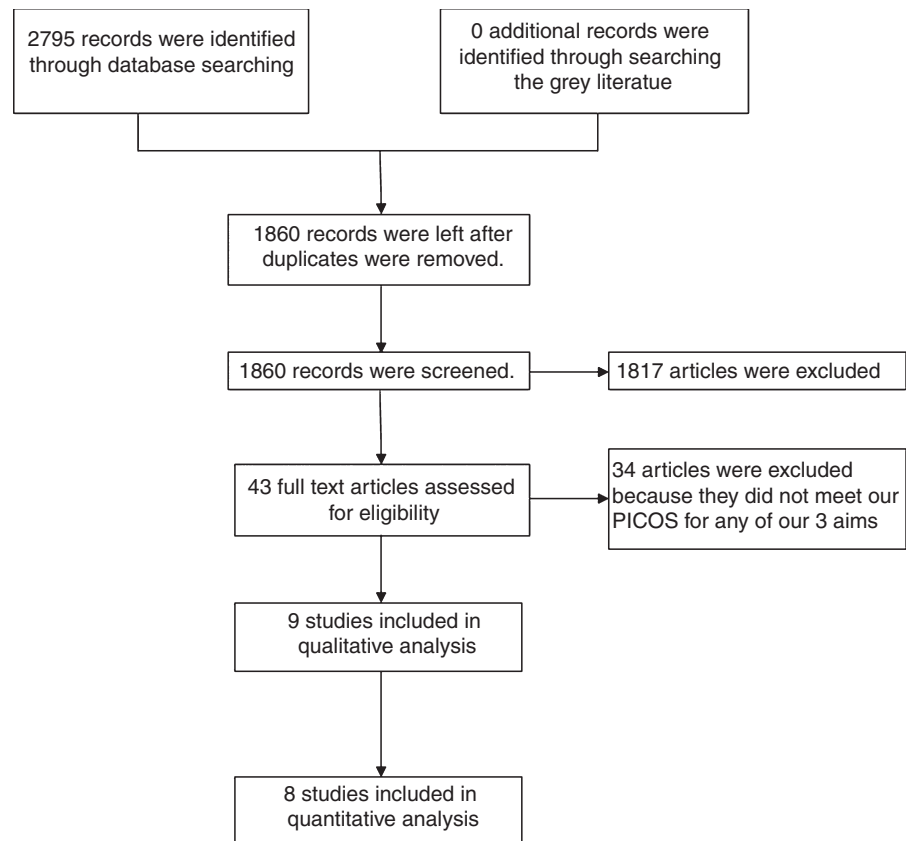


FIGURE 1 PRISMA Flow chart

addition, authors who did not define remission within the text of their manuscript were excluded.

2.2.1 | Types of outcome measures

All of the potential studies that met inclusion criteria (Figure 1) measured disease activity with either the Lloyd-Still index (LSI) or paediatric Crohn's disease activity index (PCDAI). Because the cut-off points for each scale is subjective, we defined our outcome variable as the percentage of patients who remained in remission, as defined by the study authors. In cases where this information was not provided in the published manuscript, the additional information was sought directly from the authors.

2.3 | Search methods for identification of studies

We searched MEDLINE, EMBASE, Web of Science, The Cochrane Library, Open Grey, Grey Literature Report, clinicaltrials.gov and the WHO clinical trials registry platform from inception to September of 2016. All relevant subject headings and free text terms were used to represent Crohn's Disease and enteral nutrition, including exp inflammatory bowel diseases/OR (Crohn\$ adj (disease or enteritis)).tw AND enteral nutrition/OR((enteral or enteric or intragastric or intrainstestinal or intestinal or tube) adj (nutrition or feeding)).tw. These terms were adapted for the other databases.

2.4 | Data collection and analysis

2.4.1 | Study selection

A research librarian (LF) designed and conducted the complete search strategy. Articles were screened independently by three reviewers (SLF, AF and AS). Any disagreement at this stage of screening was remediated by acquiring the full text of the article, and discussion until consensus was achieved. Of the 2795 papers identified through our search strategy, 43 articles potentially meeting inclusion criteria were identified and agreed upon by all three reviewers and the full text was reviewed. Nine articles met inclusion criteria, but three articles (Levine,²⁵ Sanderson,²⁹ and Papadopoulou³⁰) did not provide the necessary data for inclusion in the meta-analysis. These authors were contacted for more complete data. Two authors (Levine²⁵ and Sanderson²⁹) provided additional data, leaving a total of eight papers which were included in the meta-analysis (Table 1, Figure 1). Justifications for excluded articles are included in Table 2.

Levine²⁵ had 4 arms: receipt of only EEN, only CS, only Mesalazine (mesalamine) and last a combined EN and mesalazine arm. In our meta-analysis, we only included the EEN and CS arm. Sanderson et al.²⁹ used corticosteroids and sulfasalazine in one arm, and an elemental diet only in the other arm. Since sulfasalazine has not shown any benefit in inducing remission in small bowel Crohn's disease,³¹ we included this study in the meta-analysis with the assumption that CS + sulfasalazine (in small bowel Crohn's disease) is equivalent to CS only treatment.

TABLE 1 Characteristics of included studies

Authors	Biases	Comparator arms	Number of participants	New and/or relapsed disease	Disease location	Outcome measurement
Randomised controlled trials						
Sanderson et al.	Randomised, not blinded, fully reported outcomes	Sulfasalazine + EEN vs elemental diet vs CS + sulfasalazine	15	Relapsed	ileal or ileo-colonic disease	LSI
Borrelli et al.	Randomised, blinded, ITT analysis, fully reported outcomes	Oral polymeric formula vs CS	37	New	All	Absence of symptoms related to Crohn's disease and a PCDAI of 10 or less; colonoscopy with CDEIS
Retrospective cohort studies						
Papadopoulou et al.	^a	EEN vs CS	36	Relapsed	All	Biomarkers & LSI
Berni Canani et al.	^a	EEN vs CS	47	New and relapsed	All	Endoscopic & histological remission; PCDAI < 10
Lambert et al.	^a	EEN vs CS	57	New	All	PCDAI < 15
Luo et al.	^a	EEN vs CS	28	New	All	PCDAI < 10
Hojsak et al.	^a	EEN vs CS	74	Relapsed	All	PCDAI < 10
Prospective cohort studies						
Kierkus et al.	^a	EEN vs CS	44	Relapsed	All	PCDAI < 10
Levine et al. ^a	^a	EEN vs CS vs Mesalazine vs EEN + Mesalazine	201	New	All	CRP & PCDAI < 10

RCT, randomised controlled trial; ITT, intent to treat analysis; PCDAI, paediatric crohn's disease; Activity index; LSI, lloyd-still index.

^aSee Table 3 for bias analysis of observational studies according to the New Castle-Ottawa scale.

2.4.2 | Quality assessment

Three authors (SLF, AF, AS) independently reviewed the quality of the studies. We evaluated the bias in observational studies using the New Castle-Ottawa scale³² and randomised controlled trials using the Cochrane RoB tool.³³ Observational studies, less rigorous than randomised controlled trials (RCT), inherently introduced uncertainty and heterogeneity into our meta-analysis. As such, we conducted two sensitivity analyses. First, we removed the study where the author admitted that the study team preferentially assigned patients to the enteral nutrition arm of the trial (Lambert et al.²⁴). Second, we analysed the results for the RCTs, prospective cohort studies, and retrospective cohort studies separately to determine if the results from the non-RCTs affected our heterogeneity calculation or produced a different result from the more robust RCTs. Because there was not a heterogenous effect across strata when we examined each study type separately for our main outcome, we felt it was appropriate to combine study types as hypothesis generating rather than confirmatory analyses.

2.4.3 | Data extraction

Data extraction forms were developed by two of the authors (AF, AS) and confirmed by a third (SLF). Data were extracted jointly by two authors (AF, AS) and then a third author (SLF) independently extracted the data. Disagreements were reconciled by discussion.

Extracted data included: participant age and disease characteristics, number of patients in each treatment arm, outcome measurement (PCDAI vs LSI vs "biochemical remission"), study design, study inclusion criteria, details of enteral nutrition formulation and intervention, details of medical intervention, length of follow-up and remission rates at the follow-up visit.

2.4.4 | Statistical analyses

The percentages of patients in remission at the end of the first follow-up period from each study were pooled. Cross-study variation due either to heterogeneity or chance was quantified using both I^2 and χ^2 where $P < .10$ or $I^2 > 50\%$ indicates substantial heterogeneity. Fixed-effect models were used. If heterogeneity was present, a random effects model was used to calculate the most conservative confidence intervals. Each study's weight was determined using Mantel-Haenszel methods. All analyses were conducted using RevMan5 (version 5.3.5, Copenhagen, Denmark).

3 | RESULTS

3.1 | Risk of bias in included studies

We evaluated bias in randomised controlled trials according to the methods described in the Cochrane Handbook,³³ which includes consideration of the following: blinding, randomisation, completeness

of outcome data and method of reporting data (Table 1). Observational studies were evaluated for bias using the New Castle-Ottawa tool³² (Table 3). Data have been reported according to MOOSE guidelines (see Appendix 1).³⁴

3.2 | Characteristics of included studies

Of the nine trials that met our inclusion criteria (Table 1, Figure 1), eight study authors either included or provided the proportion of patients who entered remission in each arm which could be pooled in the meta-analyses.

Of the eight trials included in the quantitative meta-analysis, seven compared EEN to CS (Borrelli et al.,²⁶ Berni Canani et al.,³⁵ Hojsak et al.,²² Kierkus et al.,²³ Lambert et al.,²⁴ Levine et al.,²⁵ Luo et al.³⁶). Sanderson et al.²⁹ compared EEN to sulfasalazine + CS.

Five studies used a polymeric diet. Sanderson et al.²⁹ used an elemental diet, and Berni Canani et al.³⁵ had separate arms for elemental, semi elemental and polymeric diets that were pooled together for our meta-analysis. Luo et al.³⁶ did not specify the type of enteral nutrition that they used.

Three studies provided specific details about the steroid dosing arms. Berni Canani et al.³⁵ used methylprednisolone (1–2 mg/kg) up to max of 40 mg/d for 4 weeks, and then tapered over the following 4 weeks. Levine et al.²⁵ used prednisone 1–2 mg/kg up to max of 60 mg/d for 8 weeks. Sanderson et al.²⁹ used adrenocorticotrophic hormone (ACTH) 2 IU/kg administered intramuscularly for 5 days followed by oral prednisone 2 mg/kg/d up to maximum of 30 mg/d with a taper starting after 3 weeks.

The study participants in all trials included in the meta-analysis were children, and the diets were administered via nasogastric tube (elemental diets) or orally. Of the eight studies, four studies (Lambert,²⁴ Levine,²⁵ Borrelli,²⁶ Luo³⁶) included only newly diagnosed patients, whereas the others included both newly diagnosed and relapsed patients, or relapsed only. Disease activity and remission were based on PCDAI scores, though the cutoff for remission varied and some studies did include supplemental information from biomarkers or endoscopic scores (CDEIS). Sanderson et al.²⁹ used the LSI along with biomarkers (CRP, ESR, albumin concentration) to determine remission. Correspondence with the author was required to obtain patient level Lloyd Still scores levels at multiple time points. Outcomes were assessed at 6–8 weeks except Borrelli et al.²⁶ assessed outcomes after 10 weeks of treatment.

One other paper met inclusion criteria, but was not included in the meta-analysis because data could not be abstracted from the paper and could not be obtained from the corresponding author. Papadopoulos et al.³⁰ used an elemental diet arm ($n = 19$) and oral prednisone (2 mg/kg/d, max 60 mg/d; $n = 17$) with taper over 8 weeks, but did not provide individual patient status at end of induction. Instead they describe successful treatment of flare episodes (each patient could have more than one episode of flare). They found remission in 83% of episodes treated with EEN and 64% treated with prednisone.

TABLE 2 Characteristics of excluded studies

Study	Year	Reasons for exclusion
Seidman et al.	1991	Abstract only
Seidman et al.	1993	Abstract only
Thomas et al.	1992	Outcome did not match PICOS Criteria
Thomas et al.	1993	Outcome was "improvement," not remission
Breese et al.	1995	Poor classification of steroid exposure, outcome did not match PICOS criteria
Terrin et al.	2002	Non-English publication
Ruuska et al.	1994	No exclusive enteral nutrition arm
Soo et al.	2013	80% of EEN group on AZA and 64% on 5-ASA, not a clean comparison of EEN vs CS
Saadah et al.	2012	Combines data from EEN and CS arm, not a true comparator two armed study
Gorard et al.	2003	Adult population
Mesker et al.	2009	No EN only comparator arm
Zhu et al.	2013	Adult population
Hartmann et al.	2008	No EN only comparator arm
Sigall-Boneh et al.	2014	No nondiet treatment arm
Workman et al.	1984	No nondiet treatment arm
Harries et al.	1983	Adult population
Riordan et al.	1993	Adult population
Matsumoto et al.	2005	No EN only comparator arm, adult population
Grover et al.	2015	No induction data
Hradsky et al.	2016	No induction data
Hradsky et al.	2014	Abstract only
Lee et al.	2014	Abstract only
Lee et al.	2015	Four patients in EEN arm were on concomitant medication, no additional data provided
Matuszczyk et al.	2016	No comparator arm
Morris et al.	2014	No comparator arm
Nobrega et al.	2016	Outcome did not match PICOS Criteria
Otley et al.	2015	Abstract only
Otley et al.	2014	Outcome did not match PICOS criteria
Roch et al.	2016	Abstract only
Rousseff et al.	2015	No comparator arm
Saadah et al.	2012	No true comparator arms, cross-over design
Scarpato et al.	2016	Abstract only
Schulman et al.	2015	Abstract only
Shaoul et al.	2014	Outcome did not match PICOS criteria
Sigall-Boneh et al.	2014	No EEN arm

AZA, azathioprine; 5-ASA, mesalazine; EEN, exclusive enteral nutrition; EN, enteral nutrition; CS, corticosteroids

TABLE 3 New Castle-Ottawa scale for assessing quality of cohort studies

Quality assessment scale	Accepted criteria	Papadopoulos et al.	Berni canani et al.	Lambert et al.	Hojsak et al.	Lou et al.	Kierkus et al.	Levine et al.
Representativeness of the exposed cohort	Representative of average paediatric IBD patient	a	a	a	a	a	a	a
Ascertainment of exposure	Secure records, structured interview	a	a	a	a	a	a	a
Demonstration that outcome of interest was not present at start of study	No prior exposure to EEN/Steroids	a	-	a	a	a	-	a
Comparability of cohorts on the basis of design or analysis	Comparability of medical treatment arm	-	a	a	a	a	a	-
Assessment of outcome	Utilisation of predefined activity score or clinical evaluation	a	a	a	a	a	a	a
Enough follow-up for outcome to occur	At least 4 wk	a	a	a	a	a	a	a
Adequacy of follow-up of cohorts	Follow-up of complete cohort or less than 15% loss to follow-up	a	a	a	-	-	-	a
Total (max = 7)		6	6	7	6	6	5	6

3.3 | Effects of interventions

3.3.1 | Enteral nutrition therapy for induction of remission

This meta-analysis of eight trials included 226 paediatric Crohn's patients treated with an exclusive elemental diet and 225 paediatric Crohn's patients treated with corticosteroids for newly diagnosed or relapsed disease demonstrated no statistically significant difference between the treatment arms (OR 1.26 [95% CI .77-2.05]; Figure 2). Heterogeneity was not demonstrated ($I^2 = 0$).

Given the interest in possible treatment differences between newly diagnosed CD patients and those with relapsed disease, the studies were separately analysed by type of patient. Borrelli et al.,²⁶ Lambert et al.,²⁴ Levine et al.,²⁵ and Lou et al.³⁶ included only newly diagnosed patients. Although these studies were an RCT, two retrospective cohort studies and a prospective cohort study, respectively, we combined them to do an exploratory analysis. The subanalysis of these four trials included 100 patients treated with enteral nutrition and 171 patients treated with corticosteroids. No statistically significant difference was demonstrated (OR 1.61 [95% CI .87–2.98]; Figure 3A). A subanalysis of the three studies including only relapsed patients (Hojsak et al.,²² Kierkus et al.,²³ Sanderson et al.²⁹) included 89 patients treated with enteral nutrition and 44 treated with steroids found no statistically identifiable differences between induction of remission between the groups (OR .76 [95% CI .29–1.98]; Figure 3B). There was no statistically significant difference in remission odds distinguishing newly diagnosed patients and relapsed patients, though the trend was towards EEN being more effective in those who were newly diagnosed as opposed to relapsed patients. Heterogeneity was not demonstrated ($I^2 = 1\%$).

3.3.2 | Benefit of enteral nutrition therapy beyond end of induction

An exploratory subanalysis of two studies (Sanderson et al.,²⁹ Berni Canani et al.³⁵) was performed to ascertain if being induced into remission with EEN vs CS had led to a more durable remission. Although Sanderson et al.²⁹ was an RCT and Berni Canani et al.³⁵ was a retrospective cohort study, we combined their results in an effort to generate a hypothesis regarding the potential durability of remission under the two treatment regimes. Sanderson et al.²⁹ provided data at 12 weeks (6 weeks after end of induction). Patients who had achieved remission in the steroid group were maintained on prednisone 10mg daily. Those who had achieved remission in the EN group were in a prespecified food reintroduction program with tapering doses of EN. At 12 weeks, six of seven patients in the steroid induction group remained in remission whereas, seven of eight patients in the EN induction group remained in remission.

Berni Canani et al.³⁵ provided data at 12 months of follow-up (10 months after the end of induction). All patients in both EN and CS groups who achieved remission were treated with mesalazine 50–75 mg/kg daily. At 12 months, 22 of 37 patients in the EEN induction group remained in remission while only three of 10 patients in the steroid induction group remained in remission.

Although there was no statistically significant difference between the groups (OR 2.75 [95% CI .72-10.53]; Figure 4) the trend was towards benefit with EEN. Heterogeneity was not demonstrated ($I^2 = 0\%$).

3.3.3 | Polymeric formula and elemental formula for remission induction

The majority of the included studies (Hojsak et al.,²² Kierkus et al.,²³ Lambert et al.,²⁴ Levine et al.,²⁵ and Borrelli et al.²⁶), used a polymeric formula in their enteral nutrition arm. When we compared

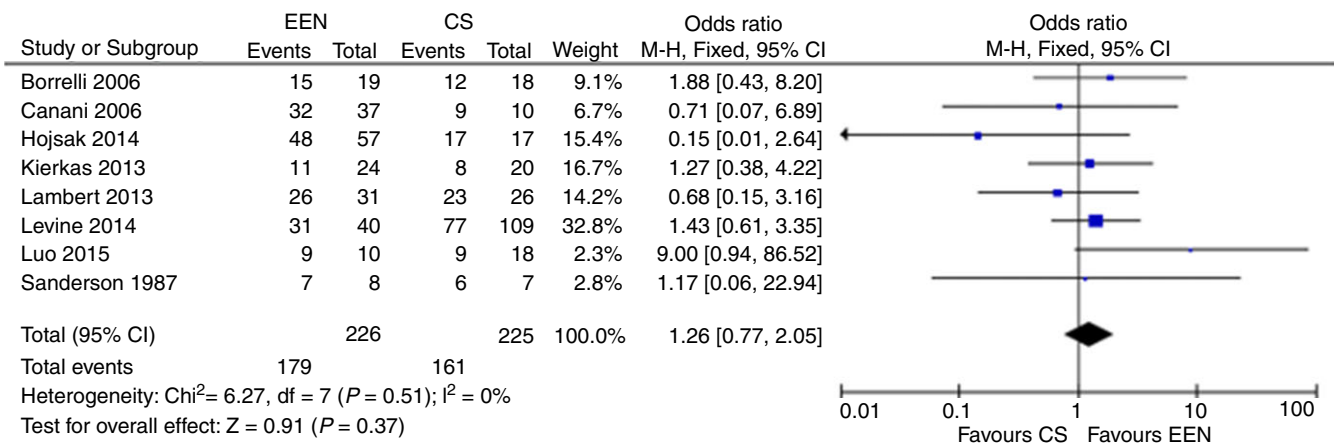


FIGURE 2 Comparison of remission induction for EEN vs CS

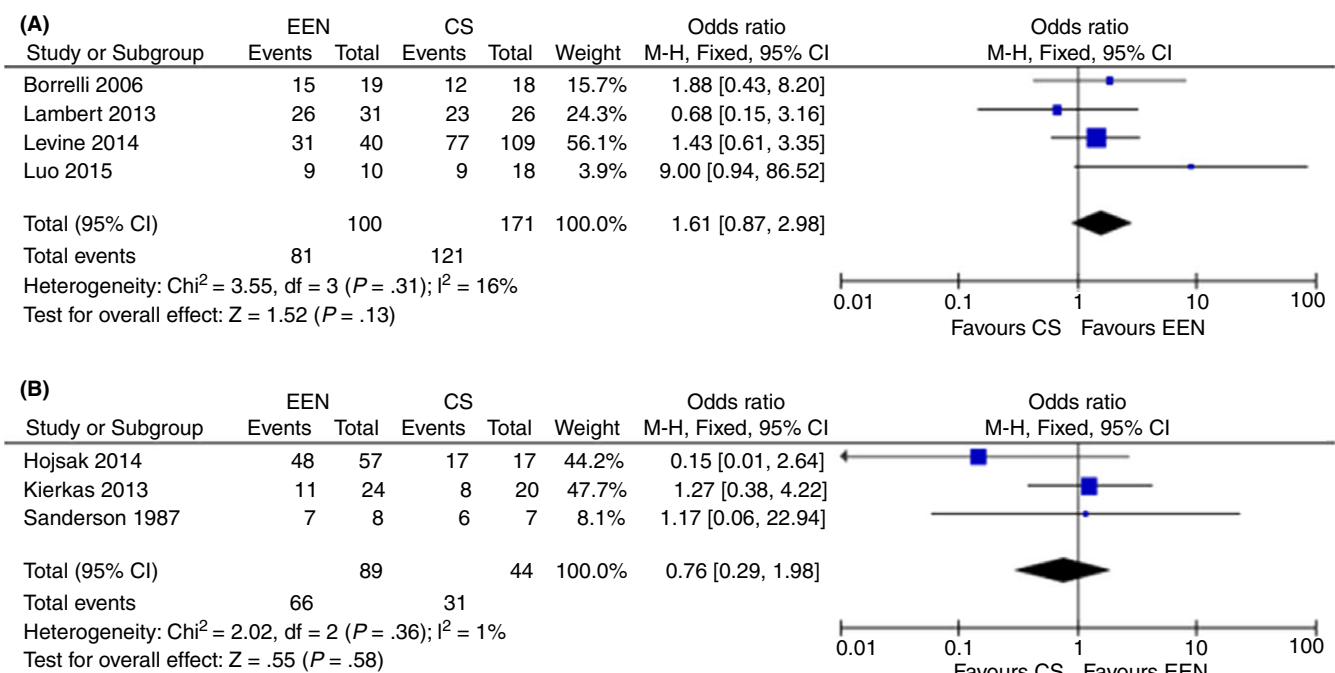


FIGURE 3 (A) Comparison of EEN vs CS in newly diagnosed patients only (B) Comparison of EEN vs CS in relapsed patients only

only these five studies for remission induction, there was no difference between CS and the polymeric formula of enteral nutrition (OR 1.10 [95% CI .64-1.89]; Figure 5). Sanderson et al.²⁹ was the only study which used an elemental diet only arm and Lou et al.³⁶ did not specify the type of formula used in their study.

3.3.4 | Mucosal healing

Borrelli et al.²⁶ and Berni Canani et al.³⁵ provided mucosal healing data at the end of induction. Although these were two different types of studies—an RCT and a retrospective cohort study, we conducted a hypothesis generating analysis to determine whether mucosal healing rates were higher among patients who received EEN compared to those who received CS.

Borrelli et al.²⁶ found 26 of 37 patients in the EEN group achieved mucosal healing, where only four of 10 in the steroid group achieved the same end point. Berni Canani et al.³⁵ found 14 of 19 patients induced with EEN achieved mucosal healing whereas only six of 18 patients treated with CS achieved the same endpoint. Overall, patients who received EEN were 4.5 times more likely to demonstrate mucosal healing (OR 4.50, [95% CI 1.64, 12.32]; Figure 6) compared to those who received CS. This result was statistically significant. Heterogeneity was not demonstrated ($I^2 = 0\%$).

3.3.5 | Effect of EEN vs CS on CRP normalisation

Hojdak et al.,²² Levine et al.,²⁵ and Sanderson et al.²⁹ measured CRP at baseline and at the end of induction in patients receiving EEN

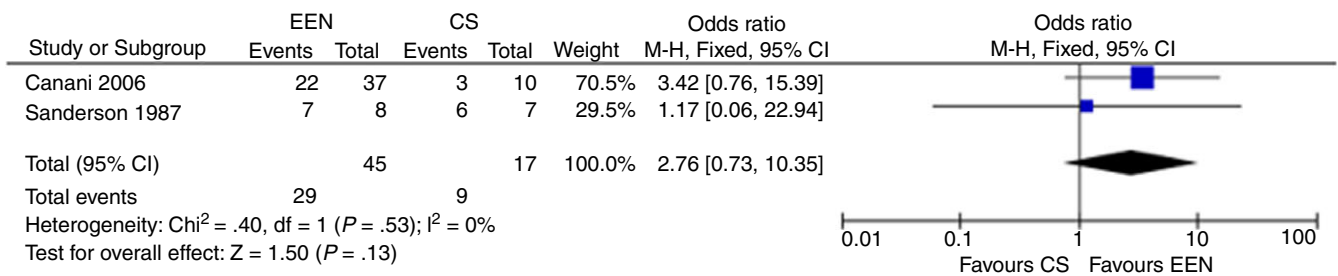


FIGURE 4 Durability of remission, EEN vs CS

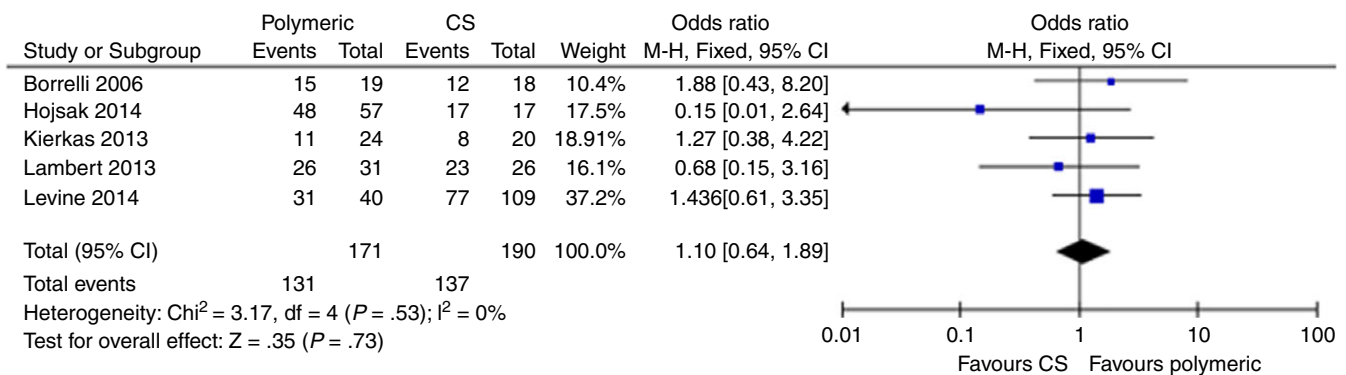


FIGURE 5 Polymeric formula only for remission induction, EEN vs CS

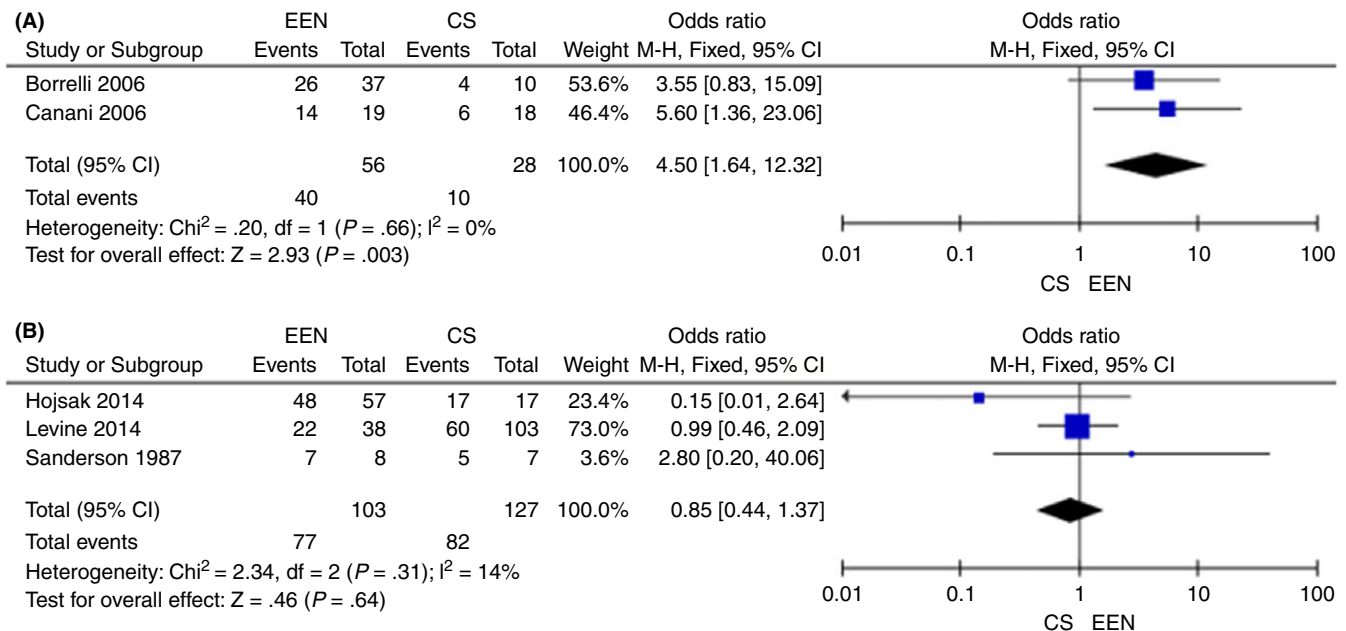


FIGURE 6 (A) Comparison of mucosal healing in EEN vs CS (B) Comparison of CRP normalisation in EEN vs CS

and CS. Again, although these were three different types of studies—a retrospective cohort study, a prospective study, and an RCT—we conducted a hypothesis generating analysis to ascertain whether patients who received EEN vs CS had differed in rates of CRP normalisation. Correspondence with Hojsak and Sanderson provided data that were not included in their original published papers.

Hojsak et al.,²² found CRP normalised in 48 of 57 patients treated with EEN and all 17 patients treated with CS. Levine et al.,²² found 22 of 38 patients treated with EEN had normalisation of CRP compared to 60 of 103 patients treated with CS. Sanderson et al.,²⁹ found seven of eight patients treated with EEN and five of seven patients treated with CS had normalisation of CRP. Overall, no

difference was detected in CRP normalisation between patients who received CRP or EEN (OR .85 [CI 95% .44, 1.67]; Figure 6B). Again, heterogeneity was not demonstrated ($I^2 = 0\%$).

4 | DISCUSSION

Our systematic review and meta-analysis of induction regimens in children with Crohn's disease, did not find a treatment benefit of corticosteroids over exclusive enteral nutrition. This finding held true in the subanalysis of newly diagnosed patients. In our hypothesis generating analysis, EEN also had superior mucosal healing odds ($P < .05$), suggesting that this is an end point to be explored in future trials. There is also a possibility that the benefits of induction with enteral nutrition are more durable than induction with corticosteroids, but this finding is driven by one study, Berni Canani et al.³⁵ In fact, the two studies combined to study this question may not reflect current practice, namely using steroids or mesalamines as post-induction maintenance regimen in Crohn's disease.^{29,35}

Our findings are in contrast with the most recent Cochrane review on the subject¹⁵ which found corticosteroids superior to enteral nutrition (OR 0.33). This is potentially explained by the fact that we only used high-quality studies. When the Cochrane authors restricted their analysis to only high-quality studies, they also found no difference between CS and EEN. Another potential explanation for their contrary findings is that they combined data from studies of both adults and children. Of the seven studies ($n = 352$) they pooled, only one study ($n = 37$, Borrelli et al.²⁶) was composed of paediatric patients. Given the heterogeneity of the results when stratifying by population age, it would seem reasonable to avoid combining paediatric and adult data in future analyses as it may result in underestimating the benefit of enteral nutrition in the paediatric population. Some physicians believe that the discordance in efficacy between adults and children is overstated. In clinical situations where tolerability of the EN product is high, enteral nutrition can induce remission in adult populations, suggesting that improved tolerability should be an area of further research.

Two previous meta-analyses and two systematic reviews on the subject of treatments for induction of remission in children with Crohn's disease have been performed, and our results confirmed their findings. Heuschkel et al.²¹ ($n = 194$), concluded that there was no difference in efficacy between enteral nutrition and corticosteroids to treat active Crohn's disease. However, this study was underpowered ($n = 144$) to identify differences less than/equal 20% between the steroid and EEN groups.⁶ Of the seven studies combined in their meta-analysis four did not meet our inclusion criteria. Two studies^{38,39} have only ever been published as abstracts, and have not undergone detailed peer-review. It is not clear whether patients overlapped between the two studies by the same author and the decision to avoid including in their meta-analysis was shared by the Cochrane review group.¹⁵ Thomas et al.,³⁹ was excluded from our analysis because their outcome was "improvement," rather than remission. Another, Breese et al.,⁴⁰ included eight different steroid

dosing strategies (prednisone 5 mg/d - 40 mg/d) among 10 patients treated with corticosteroids. The heterogeneous patient populations and an inability to evaluate details of trial mechanics, made outcomes for more than 50% of the included population impossible to assess.

An earlier meta-analysis, Dziechciarz et al.²⁰ ($n = 204$), also suggested similar efficacy between EN and CS for treating active Crohn's disease in children. Their meta-analysis combined 4 studies. Three of these studies did not meet our inclusion criteria. Like Heuschkel et al.,²¹ Dziechciarz et al.²⁰ also included the same two abstracts from Seidman et al.^{37,38} as previously described. Terrin et al.² was published in an Italian journal with an English abstract and non-English manuscript. As the full manuscript was not in English, we excluded it from our meta-analysis.

Recently, Pegnani et al.⁴¹ conducted a large systematic review of paediatric nutrition and CD with several end points, including the efficacy of enteral nutrition on the induction of remission in a paediatric population. While they did not conduct a meta-analysis themselves, using evidence from Heuschkel et al.²¹ and Dziechciarz et al.,²⁰ they concluded that enteral nutrition in a paediatric population can effectively induce remission. However, they included Thomas et al.³⁹ and Terrin et al.,² which we excluded for the reasons listed in the previous paragraph. They also included Ruuska et al.,⁴² Grover et al.,⁴³ and Soo et al.,⁴⁴ which we excluded because the former two articles did not use remission as their primary end point and the latter one did not have an enteral nutrition only arm.

Day et al.⁴⁵ also conducted a broad-view systematic review without meta-analysis on enteral nutrition in the treatment of paediatric Crohn's disease with several end points. While they also found that enteral nutrition can induce remission, they included the Seidman et al. abstracts,^{37,38} the Thomas et al.³⁹ paper and the Terrin et al.² papers that we excluded for previously explained reasons. While both of these systematic reviews contribute substantially to the understanding of paediatric CD and enteral nutrition, they were both broad in scope. Because we took a narrower viewpoint and only looked at enteral nutrition and its ability to affect remission induction, we were able to more completely examine the topic.

The goal of every meta-analysis is to include the best possible data and pool data from comparable patient populations. Our rigorous inclusion criteria disallowed the majority of studies included in two previous meta-analyses. Our meta-analysis included data from randomised controlled trials, prospective cohorts and retrospective cohort studies. Our systematic sensitivity analysis showed that when we stratified our results by study design, there was no difference across strata, meaning that the results from the prospective studies were similar to those from the retrospective studies and the RCTs.

By not including abstracts, we may have introduced publication bias into our study, but by only including full manuscripts, we were able to more fully assess the limitations of each study and understand sources of bias in assignment of EEN vs CS. We have detailed these biases in Table 1. Moreover, we had no heterogeneity in the majority of our analyses, making our findings robust. A limitation to our systematic review is that the primary outcome for most included

studies was clinical remission, which is measured by PCDAI, a scale considered to be a fallible measure for evaluating response to therapy. As such, we included the previously unexplored end point of mucosal healing, a more robust measure of therapy response. Another limitation to any research involving exclusive enteral nutrition is, of course, the different dietary cheats allowed and the difficulty in measuring the amount of nonformula nutrition ingested by participants. However, we believe this error to be random, and therefore would bias our results towards the null. A final potential limitation to our paper is that we chose our statistical models based on heterogeneity, while current Cochrane guidelines warrant choosing a model *a priori* and then using an alternative test as a sensitivity analysis.

Current clinical guidelines, from both the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition and its European counterpart, consider enteral nutrition acceptable to use in all patients with Crohn's disease.^{46,47} In fact, the European Society for Clinical Nutrition and Metabolism guidelines recommend EN as a first line therapy for children and adolescents with CD, with "strong consensus".⁴⁷ However, there are many persistent unanswered questions on this subject. Specifically, the mechanism of action of enteral nutrition remains vague and there is still little guidance on which types of patients would be most likely to benefit, though weak evidence suggests effectiveness is greater with small bowel involvement.⁷ With regard to disease duration, our analysis suggests that outcomes may differ between newly diagnosed and previously diagnosed patients. Future guidelines may need to make that distinction when it comes to benefits of induction with these therapies.⁴⁶ Challenges also remain in considering induction treatment duration and the best strategy to maintain remission as long-term exclusive enteral nutrition is unlikely to be acceptable to most patients.

In summary, our study suggests that exclusive enteral nutrition works equally as well as corticosteroids in inducing remission in paediatric Crohn's disease based on clinical symptom scores, but EEN could potentially be superior when assessing improvement by mucosal healing end points. We believe these results suggest a need for further research in this area. EEN may have the added benefit of minimising growth failure, avoiding undesirable and difficult to reverse changes to body habitus, and can potentially result in a deeper and longer duration of remission. As such, greater advocacy for this therapy among physicians from the USA may be warranted.

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AUTHORSHIP

Guarantor of the article: A. Swaminath, MD

Author contributions: He was responsible for the study concept and design, analysis and interpretation of the data as well as the drafting and supervision of the manuscript. Alexandra Feathers completed the

analysis and interpretation of data and assisted in the drafting of the manuscript. Ashwin Ananthakrishnan was responsible for critical revision of the manuscript for important intellectual content. Louise Falzon wrote the search terms for the review and acquired the data. Sophia Li Ferry assisted in the development of the study concept and design, with analysis and interpretation of data as well as drafting of the manuscript. All authors have contributed to, and have read and approved submission of this manuscript. The manuscript represents an original, unpublished report and is not being considered for publication elsewhere, in whole or part, in any language.

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APPENDIX

MOOSE GUIDELINES FOR META-ANALYSES AND SYSTEMATIC REVIEWS OF OBSERVATIONAL STUDIES³⁴

1. Title identifies the study as a meta-analysis (or systematic review)
2. Abstract uses the journal's structured format

Introduction Presents:

1. The clinical problem
2. The hypothesis
3. A statement of objectives that includes the study population, the condition of interest, the exposure or intervention, and the outcome(s) considered

Sources Describe:

1. Qualifications of searchers (eg, librarians and investigators)
2. Search strategy, including time period included in the synthesis and keywords
3. Effort to include all available studies, including contact with authors
 - a. Databases and registries searched
4. Search software used, name and version, including special features used (eg, explosion)
5. Use of hand searching (eg, reference lists of obtained articles)
6. List of citations located and those excluded, including justification
7. Method of addressing articles published in languages other than English
8. Method of handling abstracts and unpublished studies
9. Description of any contact with authors

Study Selection Describes:

1. Types of study designs considered
2. Relevance or appropriateness of studies gathered for assessing the hypothesis to be tested
3. Rationale for the selection and coding of data (eg, sound clinical principles or convenience)
4. Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)
5. Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)
6. Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results
7. Assessment of heterogeneity
8. Statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated

Results Present:

1. A graph summarising individual study estimates and the overall estimate
2. A table giving descriptive information for each included study
3. Results of sensitivity testing (eg, subgroup analysis)
4. Indication of statistical uncertainty of findings

Discussion Discusses:

1. Strengths and weaknesses
2. Potential biases in the review process (eg, publication bias)
3. Justification for exclusion (eg, exclusion of non-English-language citations)
4. Assessment of quality of included studies
5. Consideration of alternative explanations for observed results
6. Generalisation of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)
7. Guidelines for future research
8. Disclosure of funding source