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Exclusive Enteral Nutrition and Corticosteroids: Two Effective Methods of Induction Treatment in Crohn's Disease

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Abstract

Objective: To compare the effectiveness of corticosteroids (CS) versus exclusive enteral nutrition (EEN), as induction therapy of Crohn's disease to induce remission. **Design:** Systematic literature review. **Methods:** Searches were done in PubMed utilizing the terms: enteral nutrition therapy, exclusive enteral nutrition, inflammatory bowel disease, Crohn's disease, corticosteroids, pediatric, nutrition, and steroids. Articles were excluded with patients > 18 years of age, confounding variables, inclusion of other treatment options, or physician discretion bias in selecting a treatment option. **Results:** Ultimately, three articles were included in our review. Two of three studies examined showed a statistically significant improvement in remission rates in patients receiving EEN with one study showing similar rates. Patients receiving EEN were also noted to have improved intestinal healing, improved growth, and decreased need for biologic agents compared to patients receiving CS treatment. **Conclusion:** EEN appears to be an effective and possibly more beneficial treatment option as it is associated with fewer adverse reactions, promotes intestinal healing, and has similar remission and relapse rates as CS. It cannot be confirmed that EEN will be the preferred induction therapy as the treatment choice must be individualized. Further studies must be done to expand knowledge on the topic. Cost effectiveness and patient compliance are drawbacks to EEN therapy.

Introduction

Crohn's disease (CD), a form of inflammatory bowel disease, causes transmural inflammatory disease affecting all parts of the gastrointestinal tract in children and adults. Patients typically experience gastrointestinal symptoms including bloody diarrhea, abdominal tenderness, and tenesmus. As well, they suffer from constitutional symptoms of fever and fatigue and extra-intestinal symptoms including arthritis, aphthous ulcers, and liver disease.[1] The etiology of CD is not completely understood but is thought to be an immunological response in susceptible individuals, the result of a number of genetic and environmental influences.[2] Incidence of CD peaks between the ages of 15 and 30 years with pediatric patients often experiencing more extensive and severe disease.[1,3] CD can be particularly devastating in the pediatric population as it can lead to low body weight and growth failure based on the degree of inflammation, presence of malnutrition, and medical therapy used.[3]

The two mainstays of induction treatment options for Crohn's disease are corticosteroids (CS) and exclusive enteral nutrition (EEN). CS are either given intravenously (IV) or orally while EEN consists of patients receiving their daily nutrition via liquid formulations either orally or through a nasogastric or gastrostomy tube. There are a variety of formulas that can be utilized in EEN, but no optimal formulation has been identified.[4] Corticosteroids are more commonly used in the U.S., but they are associated with more adverse effects. These include low bone mineral density, adrenal suppression, and growth retardation. EEN has far less adverse effects which consists of gastrointestinal irritation causing nausea, vomiting, and diarrhea.[5] Despite the improved safety profile, EEN has been shown to have poor compliance with a high dropout rate due to the unpleasant taste of the formulations or resistance to placement of a nasogastric or gastrostomy tube.[6]

Although there are many adverse side effects, CS remains the mainstay for short term induction treatment for moderate to severe CD in pediatric patients.[7] It is suggested that there can be significant benefit to the long-term outcomes of patients who are treated with EEN during their induction therapy with significantly fewer side effects compared to the use of CS. The goal of this review will be to compare the efficacy of CS to EEN specifically evaluating time to achieve clinical remission in pediatric patients with CD receiving these two therapies.

Methods

Articles for review were identified through a search of PubMed in September 2018 using the search terms "enteral nutrition therapy, exclusive enteral nutrition, inflammatory bowel disease, Crohn's disease, corticosteroids, pediatric, nutrition, and steroids." Articles that were excluded consisted of case reports or meta-analyses, studies noted to have confounding variables, inclusion

of patients >18 years of age, studies that did not compare the two desired variables or had small sample size, or were published before 2005. This search resulted in ten articles. Five articles were screened and two were excluded due to confounding variables, inclusion of other treatment options, or physician discretion bias in selecting a treatment option. Three articles directly comparing the use of exclusive enteral nutrition therapy and corticosteroids to induce remission in pediatric patients with CD were identified and included in this literature review due to their sample sizes, strength of study design, recent completion dates, and inclusion of the desired variables with minimal confounding factors. This process is outlined in Figure 1.

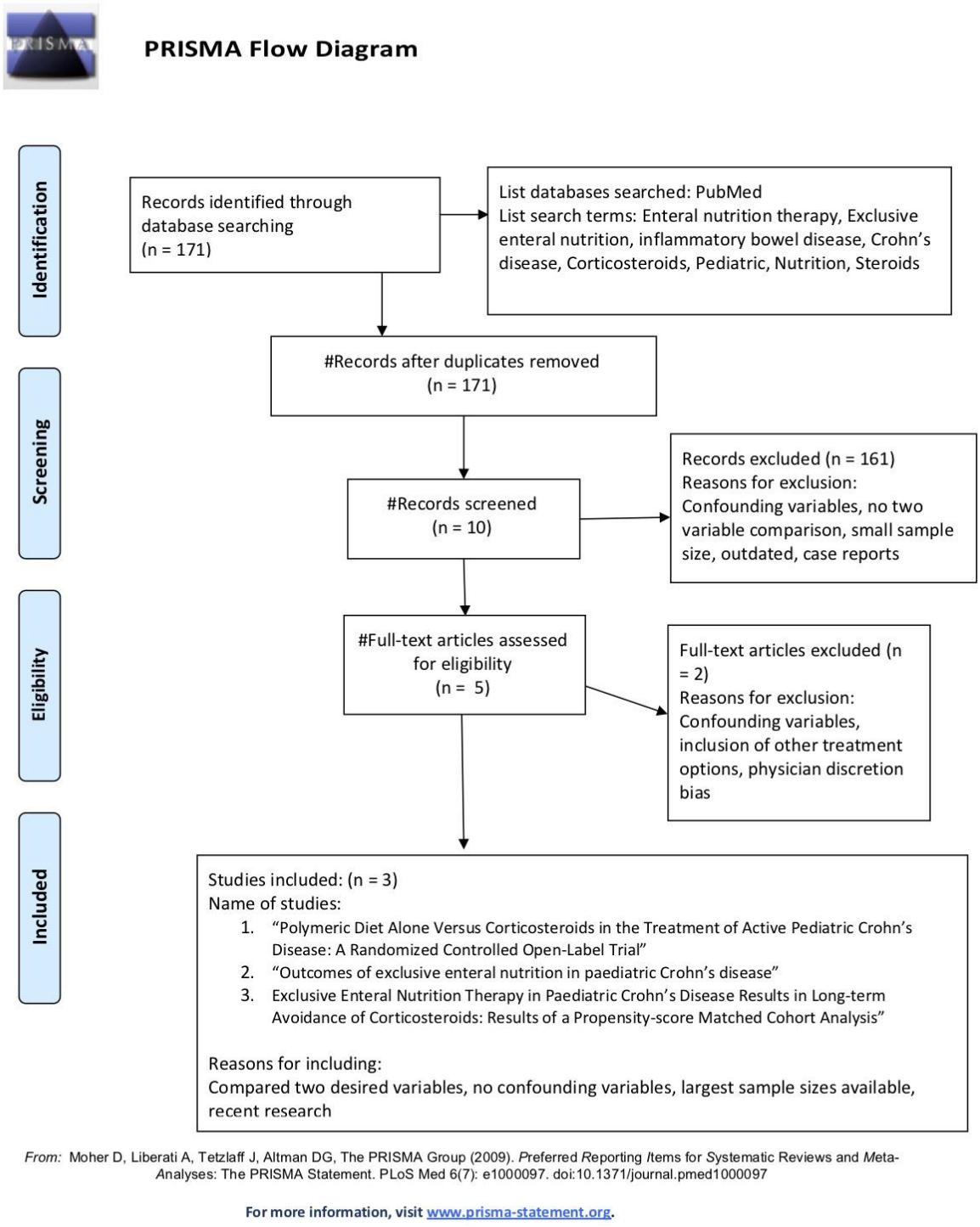

Figure 1. PRISMA flow diagram demonstrating the process of article selection.

Results

Study #1: Exclusive Enteral Nutrition Therapy in Pediatric Crohn's Disease Results in Long-term Avoidance of Corticosteroids: Results of a Propensity-score Matched Cohort Analysis. Connors et al.[8]

Objective: To examine the differences in remission rate (assessed by Pediatric Crohn's Disease Activity Index (PCDAI)) (Appendix A), steroid avoidance, need for immunomodulator or biologic pharmacotherapy, linear growth, and need for surgical resection 2, 4, and 6 years post induction treatment for CD with CS or EEN.

Study Design: This retrospective cohort study examined 111 patients aged 3-16 years with newly diagnosed CD by clinical, endoscopic, radiologic, and/or histological criteria receiving induction therapy in Nova Scotia from 2001-2005 from a prospectively maintained departmental database. Children received induction therapy for CD with EEN for 8-16 weeks, provided by mouth or via nasogastric tube (NGT) (n=76) or CS therapy with prednisone or budesonide (n=35). PCDAI was calculated at diagnosis and reassessed at a 4-12 week follow-up visit to assess remission (defined as PCADI <7.5). Results were analyzed using multinomial logistic regression analysis while controlling for factors including gender, age, weight, height, PCADI score at diagnosis, disease location, and presence of perianal disease.

Study Results: All patients in the study had a documented PCDAI score <10 at the time of diagnosis. After 4-12 weeks of induction therapy, there was a statistically significant higher number of patients who achieved clinical remission (PCADI <7.5) in the EEN group (86.6%), compared to the CS group (58.1%) ($p<0.01$) (Table 1).

Table 1. Comparison of PCDAI Score and Incidence of Clinical Remission Achieved in CS and EEN Groups

	Corticosteroids	EEN	p-Value
PCADI Score at Baseline (median)	30 ± 9.1	30 ± 11.6	0.43
PCADI Score at follow-up (4-12 weeks) (median)	7.5 ± 10.2	2.5 ± 4.3	<0.01
Remission by 12 weeks (%)	58.1	86.6	<0.01

The EEN group did show a statistically significant improvement in linear height one year following diagnosis compared to the CS group ($p<0.01$). Patients on EEN also were noted to have less frequent use of biologic therapy within 2 years of diagnosis and were less likely to be exposed to steroids during the 6-year follow-up period, although this was not statistically significant. Immunomodulator use was almost equal between the two groups at 4 weeks after initiating induction and did not have a significant impact on achieving remission in either group. Additionally, there was no difference in hospitalization rate over the subsequent two years or need for CD-related surgery between the two groups. Overall, the authors concluded that EEN was an effective induction method for pediatric patients with CD that can lead to high rates of remission, improvement in linear growth, and avoidance of steroids and other drugs to control disease.

Study Critique: Although this study was a retrospective cohort study, it was one of the stronger study designs found, one of the largest subject sizes, and directly compared the two desired variables with minimal contribution from confounding variables. The duration of follow-up for up to 6 years was also a strength of this study. The biggest weakness of the study was the lack of randomized selection, which could introduce bias between the groups. While disease severity and location were controlled for, health care providers may have been more likely to recommend EEN for patients seeming more compliant or by patient choice.

Study #2: Polymeric Diet Alone Versus Corticosteroids in the Treatment of Active Pediatric Crohn's Disease: A Randomized Controlled Open-Label Trial. Borrelli et al.[9]

Objective: To compare the efficacy of nutritional therapy alone versus corticosteroids in patients newly diagnosed with Crohn's disease in terms of remission rates and intestinal healing as documented by endoscopy and histology.

Study Design: This was an open-label randomized controlled trial involving 37 patients. The patients were required to be 18 years of age or younger, had a recent diagnosis of Crohn's disease within the last 12 weeks, have a moderate-to-severe disease state determined by the PCADI, and the ability to start treatment right away. Exclusion criteria are listed in Table 2. The patients were randomly placed into a treatment group via a computer-generated randomization schedule to receive a 10-week course of their designated treatment. 19 were assigned polymeric diet (intact protein formula), and 18 were assigned corticosteroid treatment. The patients could not be receiving any other treatment for their Crohn's disease; however, treatment with proton pump inhibitors and H2-receptor antagonists was allowed.

Table 2. Patient Exclusion Criteria

Exclusion criteria for Borelli et al. Study
Fistulizing and/or anorectal CD
Stenosing CD
Pre-existing systemic disease
Hepatic or renal dysfunction
Lung disease
Suspected pregnancy
Contraindication to corticosteroid therapy
Received corticosteroid therapy within 4 weeks of randomization
Previous treatment with immunosuppressive agents at any time

Those chosen to receive the oral polymeric diet were also allowed to consume clear liquids. A pediatric dietitian calculated the amount of polymeric feed needed to meet 120-130% of the patient's recommended daily requirements. A NGT was utilized if the patient was unable to

consume it orally. Those chosen to receive CS followed a dosing regimen with methylprednisolone. The dose was determined using the patient's body weight and was determined to be 1.6 mg/kg/day for 4 weeks then a 6-week tapering course until 5-10 mg/day dose was met.

Assessment of each patient was performed at baseline and at 2, 4, 5, 8, and 10 weeks after treatment initiation utilizing the PCDAI. A complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, albumin, urea, iron, creatinine, electrolytes, and pancreatic and liver function tests were obtained at each visit. Additionally, patients were assessed for proteinuria and hyperglycemia at each visit.

Each patient had an ileocolonscopy performed at baseline and after the 10 weeks of treatment was finished. Biopsies were taken from the most inflamed areas and read by the same pathologist. Endoscopy was also performed, and lesions were graded according to the Crohn's Disease Endoscopic Index of Severity. Each endoscopy was performed by the same operator who was unaware of any patient information or the treatment modality.

Study Results: Children were chosen to participate in the trial and were randomized into treatment groups. Five of these children withdrew for various reasons. Using the intention-to-treat analysis, 79% of the polymeric diet group reached clinical remission with a 95% confidence interval while 67% of the corticosteroid group reached clinical remission with a 95% confidence interval but was not found be statically significant (P=0.4). Using the per-protocol basis, there was no statistical significance between the two treatment modalities in terms of clinical remission. The PCDAI scores used to determine clinical remission decreased similarly and with statistical significance in both groups at the end of the 10-week treatment period. Additionally, there was no statistically significant difference in ESR, CRP, or albumin levels at the end of the trial.

For both the intention-to-treat and per-protocol analysis, there was improved healing of intestinal inflammation in the oral polymeric diet treatment group. For intention to treat, 74% of polymeric diet patients showed healing while only 33% of the corticosteroid group did. For per-protocol analysis, 82% of polymeric diet patients showing healing while only 40% of the corticosteroid group did.

The post-trial endoscopic score was only significantly lower in the group receiving oral polymeric diet therapy. Ulcerative lesions in the ileum disappeared in 87% of the polymeric diet patients and in only 42% of the corticosteroid patients. Ulcerative lesions in the colon disappeared in 75% of polymeric diet patients and in only 31% of corticosteroid patients. There was found to be a significant decrease in both histological ileal and colonic scores in only the polymeric diet group.

Throughout the trial, it was noted that side effects occurred significantly less in the PD group than the CS group. Of the PD patients, 23% reported an adverse effect while 67% of the CS patients reported one. The most common side effect of the polymeric nutrition was flatulence followed by vomiting whereas the most common side effect of corticosteroid therapy was a cushingoid appearance.

Study Critique: Strengths of this study included a randomized controlled study design with few to no confounding variables. Using a computer program to assign treatment groups prevented any bias. The study focused on the use of the same operator to perform the endoscopies and the same pathologist to interpret biopsy results, which prevented any interobserver error. Including patients recently diagnosed with CD who have not yet received treatment is beneficial in helping providers determine the initial mainstay of treatment.

There are several limitations to this study. The small population size does not reflect the prevalence of this disease throughout the world. Losing several patients to follow-up worsened this problem further. The study only looked at the initial and short-term impact of these treatment modalities. The patients were only followed for 10 weeks, which fails to address any long-term issues, complications, or disease trends that may arise following this period.

Study #3: Outcomes of exclusive enteral nutrition in paediatric Crohn's disease. Lafferty et al. [10]

Objective: This was a two-part study that compared remission rates of Crohn's disease in pediatric patients using EEN and treatment with CS. The first part was a case-matched analysis that compared outcomes of patients with Crohn's disease who used either EEN or CS as their initial treatment. The second part was a retrospective cohort study that looked at outcomes of patients who received EEN at any point in their treatment. Disease activity was classified using the PCDAI.

Study Design:

Case-matched analysis: The EEN treatment consisted of a liquid enteral formula, either polymeric or elemental (completely hydrolyzed protein formula), and was given either orally or through NGT as the patient's sole nutrition source for 6-8 weeks. This study allowed for these patients to have negligible amounts "non-nutritive treat foods" such as jelly, boiled sweets, and gum, with minimal caloric value. The CS therapy consisted of prednisolone 1mg/kg (with a maximum 40 mg dose) once daily for 4 weeks followed by a weekly 5 mg taper for the next 7 weeks.

Patients were eligible for the study if either the EEN or CS was their primary treatment. Each EEN patient was then matched with a similar CS patient based on age, gender, disease location, and disease activity. Patients were excluded from the study if they had received previous treatment for their CD, if EEN was not fully successful within 7 days of starting, or if other CD medications or

biologics were started. The patients could be on medications for other conditions, which was thoroughly documented in the study.

Retrospective cohort: Any patient that underwent EEN therapy regardless of disease stage or prior treatments was eligible for this study. Patients with ulcerative colitis or unclassified inflammatory bowel disease were excluded. Based on the stage of disease when EEN therapy was provided, the patients were placed into three different categories. They were classified as "initial" if it was their primary treatment, "subsequent" if it was a second-line treatment within 3 months of diagnosis, or "relapse" if it was used to treat a patient previously in remission.

For both studies, the data was obtained from existing hospital databases. PCDAI scores, albumin, hematocrit, hemoglobin, platelets, ESR, and CRP were all recorded before and after treatment. The study looked at the duration from remission to the next relapse and the number of relapses over a 1-year period following treatment.

Study Results: Case-matched analysis: The study compared 28 patients undergoing EEN treatment to 28 patients undergoing CS treatment. Of patients receiving EEN, 86% achieved remission compared to the 54% of patients receiving CS (P=0.02). Additionally, EEN patients took an average of 3 months to relapse compared to CS patients who took about 2 months to relapse. However, there was no statistically significant difference in the number of relapses in the first year among treatment groups.

Retrospective Cohort analysis: Fifty-nine patients were included in this study. Of this group, 69% achieved clinical remission. The highest remission rates were among patients in the "initial" and "subsequent" treatment groups. Within 1 year following treatment, 95% of the patients experienced a relapse.

Study Critique: There were several strengths of this study. This study compared very similar patients receiving different treatment modalities. There were straightforward guidelines on the methods of treating with EEN therapy or CS therapy as defined per hospital protocol. Following the patients for 1 year after the treatment was completed allowed for brief insight into the complications and progression of the disease.

Limitations of this study included confusion in combining two different study-types in one article. The sample size was small given the number of pediatric patients that suffer from Crohn's disease in Ireland and brings into question how representative this is of CD patients throughout the world. A downfall of the inclusion and exclusion criteria was that patients were able to take medications for other conditions, which could have influenced the outcomes and acted as confounding variables. Since CD is a lifelong illness, a study that follows patient for longer than 1 year would certainly be more beneficial to look at disease progression following treatment.

Discussion

This review has provided evidence that EEN is as effective as CS when used as an induction therapy, if not more effective, in inducing remission in pediatric patients with CD. Two of the three studies examined showed a statistically significant improvement in remission rate in patients receiving EEN with one study showing similar rates of remission.[8–10] In addition to showing success as an induction therapy, patients on EEN were noted to have improved intestinal healing, improved growth, and decreased use of biologic agents compared to CS without an increase in episodes of relapse. While larger, more powerful trials are needed to prove these results, the findings are encouraging that EEN can be used as an effective and safer alternative to induce remission in children with CD.

Although these results are scientifically promising, the studies examined are not without flaws. Overall, the study sizes were small with only one study of greater than 100 patients; therefore, it is difficult to say how the results will apply to the population at large. Despite the small sample sizes, the study populations were relatively homogeneous with patients of similar ages who were newly diagnosed with CD. The long-term follow-up time was inconsistent between studies with only one study following patients for six years, although dropout rate was high by this point in this study. Therefore, it is difficult to say exactly how EEN will affect long term outcomes in patients with CD.

The study design likely contributed to potential bias introduced in this review. Lafferty et al. was the only randomized controlled trial; therefore, bias could have been an influence in the other two retrospective cohort studies. Patients were assigned to a treatment group by the treating physician. Patients that were more compliant or motivated could have been chosen for the EEN group, increasing treatment compliance and, therefore, inducing remission at a higher rate. Compliance with EEN therapy could also have been altered depending on if the formula was provided by mouth or by NGT. Neither study that allowed EEN administration through NG tube discussed the potential adverse effects that could occur, such as aspiration or infection. The studies also varied in what additional foods were allowed in addition to enteral formula, which could significantly skew results depending on the nutrition content of the foods allowed. The studies were all analyzed using different statistical methods, and not all results were statistically significant. Lastly, evaluation of side effects of treatment in the studies was subjectively measured. Limitations in this population are difficult to overcome; however, studies were screened to attempt to maximize reliability.

Additional drug therapy allowed also varied between studies. Borrelli et al. allowed patients to take proton pump inhibitors or H2 blockers in addition to the prescribed induction treatment, which could have altered gut function and impacted remission rate. Lafferty et al. also accepted patients into the EEN group who had received previous treatments prior to starting EEN. Lastly Borelli et al. used both prednisone and methylprednisolone as CS options for patients in this group.

Conclusion

EEN therapy has proven to be the more beneficial treatment option as it causes fewer adverse reactions, promotes better intestinal healing, and has very similar remission and relapse rates as compared to CS therapy. However, it is difficult to state that EEN is the preferred induction therapy for every patient as many factors are involved in choosing the best treatment plan and must be individualized. There are certainly issues to address in future studies that could expand the knowledge on the topic and help clinicians make better decisions.

Each of the studies in this review took place in a different country with none of them being in the United States. The patient population is going to vary country to country, and the way medicine is practiced could differ as well. It is then important to consider if these results can be applied to an international population. Future studies involving a wide variety of countries with some taking place in the United States could be more applicable.

While this review has established EEN as an effective treatment method, it does not identify one specific formula type or administration route as being more efficacious. These results could ease clinician decision making and benefit patient outcomes. Future studies comparing polymeric and elemental formulas as well as oral and NG tube administration should be performed. Future

studies could assess other benefits of EEN such as its impact on bone density and relapse rate. Later studies could provide further evidence that EEN is a more beneficial treatment option.

Since Crohn's is a lifelong irreversible disease, it is important to follow these patients long-term to truly understand the effects of treatment, remission, and relapse rates. The lack of follow-up inhibits us from knowing any potential long-term side effects either of the treatment modalities may have caused. These studies mostly looked at using EEN as an initial induction treatment, which means there is a need to know how relapsing patients respond to EEN compared to CS. Future studies with extended patient follow-up could close some of these knowledge gaps.

Lastly, it is important to consider the cost effectiveness of these two treatment modalities. It is important to note that EEN therapy is far more expensive than CS therapy. While EEN may be more beneficial, some patients may be unable or unwilling to pay the high costs associated with it. EEN treatment for 10 weeks can cost an average of $3,500. Information about insurance coverage is unclear and seems specific to the insurance plan. CS treatment for 10 weeks can cost an average of $70 to $130 even without insurance.[11,12] A thorough patient-provider discussion should address the financial burdens of each as well as the pros and cons of each treatment modality to ensure the best choice is made.

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Appendix A. Pediatric Crohn's Disease Activity Index (PCDAI)[13]

Paediatric Crohn's Disease Activity Index

ITEM	POINTS
Abdominal pain	
None	0
Mild (brief episodes, not interfering with activities)	5
Moderate/severe (frequent or persistent, affecting with activities)	10
Stools	
0-1 liquid stools, no blood	0
2-5 liquid or up to 2 semi-formed with small blood	5
Gross bleeding, >6 liquid stools or nocturnal diarrhoea	10
Patient functioning, general well-being (Recall, 1 week)	
No limitation of activities, well	0
Occasional difficulties in maintaining age appropriate activities, below par	5
Frequent limitation of activities, very poor	10
EXAMINATION	
Weight	
Weight gain or voluntary weight loss	0
Involuntary weight loss 1-9%	5
Weight loss >10%	10
Height	
< 1 channel decrease (or height velocity > -SD)	0
> 1<2 channel decrease (or height velocity < -1SD> -2SD)	5
> 2 channel decrease (or height velocity < -2SD)	10
Abdomen	
No tenderness, no mass	0
Tenderness, or mass without tenderness	5
Tenderness, involuntary guarding, definite mass	10
Peri-rectal disease	
None, asymptomatic tags	0
1-2 indolent fistula, scant drainage, tenderness of abscess	5
Active fistula, drainage, tenderness or abscess	10
Extra-intestinal manifestations	
Fever > 38.5 x 3 days in week, arthritis, uveitis, erythema nodosum, or pyoderma gangrenosum	
None	0
One	5
Two	10
LABORATORY	
Hct (%)	
<10yrs / 11-14 (male) / 11-19 (female) / 15-19 (male)	
> 33 / > 35 / > 34 / > 37	0
28-33 / 30-34 / 29-33 / 32-36	2.5
< 28 / < 30 / < 29 / < 32	5
ESR (mm/hr)	
< 20	0
20-50	2.5
> 50	5
Albumin (g/L)	
>35	0
31-34	5
<30	10

Disease activity
<10 – remission
10-27.5 – mild
30-37.5 – moderate
>40 – severe

TOTAL =