CLINICAL AT

Crohn's Disease Exclusion Diet Plus Partial Enteral Nutrition Induces Sustained Remission in a Randomized Controlled Trial

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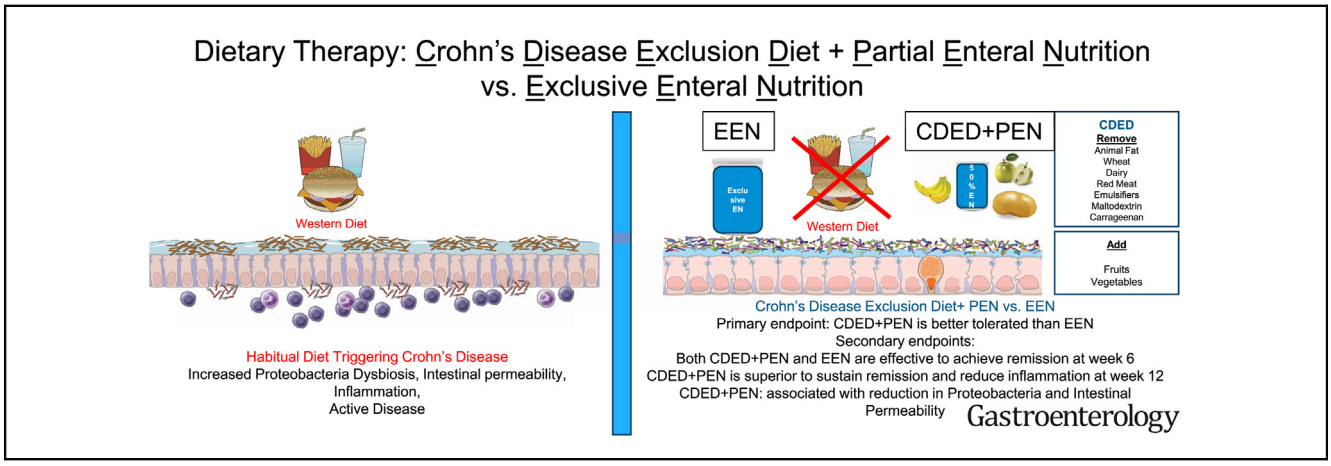

See Covering the Cover synopsis on 269. See editorial on page 295.

BACKGROUND & AIMS: Exclusive enteral nutrition (EEN) is recommended for children with mild to moderate Crohn's disease (CD), but implementation is challenging. We compared EEN with the CD exclusion diet (CDED), a whole-food diet coupled with partial enteral nutrition (PEN), designed to reduce exposure to dietary components that have adverse effects on the microbiome and intestinal barrier. **METHODS:** We performed a 12-week prospective trial of children with mild to moderate CD. The children were randomly assigned to a group that received CDED plus 50% of calories from formula (Modulen, Nestlé) for 6 weeks (stage 1) followed by CDED with 25% PEN from weeks 7 to 12 (stage 2) (n = 40, group 1) or a group that received EEN for 6 weeks followed by a free diet with 25% PEN from weeks 7 to 12 (n = 38, group 2). Patients were evaluated at baseline and weeks 3, 6, and 12 and laboratory tests were performed; 16S ribosomal RNA gene (V4V5) sequencing was performed on stool samples. The primary endpoint was dietary tolerance. Secondary endpoints were intention to treat (ITT) remission at week 6 (pediatric CD activity index score below 10) and corticosteroid-free ITT sustained remission at week 12. **RESULTS:** Four patients withdrew from the study because of intolerance by 48 hours, 74 patients (mean age 14.2 ± 2.7 years) were included for remission analysis. The combination of CDED and PEN was tolerated in 39 children (97.5%), whereas EEN was tolerated by 28 children (73.6%) ($P = .002$; odds ratio for tolerance of CDED and PEN, 13.92; 95% confidence interval [CI] 1.68–115.14). At week 6, 30 (75%) of 40 children given CDED plus PEN were in corticosteroid-free remission vs 20 (59%) of 34 children given EEN ($P = .38$). At week 12, 28 (75.6%) of 37 children given CDED plus PEN were in corticosteroid-free remission compared with 14 (45.1%) of 31 children given EEN and then PEN ($P = .01$; odds ratio for remission in children given CDED and PEN, 3.77; CI 1.34–10.59). In children given CDED plus PEN, corticosteroid-free remission was associated with sustained reductions in inflammation (based on serum level of C-reactive protein and fecal level of calprotectin) and fecal Proteobacteria. **CONCLUSION:** CDED plus PEN was better tolerated than EEN in

children with mild to moderate CD. Both diets were effective in inducing remission by week 6. The combination CDED plus PEN induced sustained remission in a significantly higher proportion of patients than EEN, and produced changes in the fecal microbiome associated with remission. These data support use of CDED plus PEN to induce remission in children with CD. Clinicaltrials.gov no: NCT01728870.

Keywords: Crohn's Disease; Microbiome; Treatment; Inflammatory Bowel Disease.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Diet and dysbiosis are key environmental factors in Crohn's disease pathogenesis. Exclusive enteral nutrition induces remission and mucosal healing: the main mechanism appears to be exclusion of free diet.

NEW FINDINGS

A novel Crohn's Disease Exclusion Diet, coupled with partial enteral nutrition, was better tolerated than exclusive enteral nutrition and demonstrated superior sustained remission and reduction in inflammation by week 12.

LIMITATIONS

The authors did not directly assess mucosal healing by endoscopy within 3 months, as this is not a standard of care in most pediatric centers.

IMPACT

The study identifies a dietary option, which combines food and enteral nutrition, which can help with reducing inflammation in Crohn's disease.

Crohn's disease (CD), one of the inflammatory bowel diseases (IBD), is increasing in incidence worldwide. In spite of advances in medical treatment, CD remains associated with considerable morbidity related to the progressive nature of the disease and the use of drugs that involve immune suppression with an associated risk of serious infections, malignant and autoimmune sequelae.[1–3]

In contrast, dietary therapy by means of exclusive enteral nutrition (EEN), consisting of a liquid formula diet (while avoiding all other oral intake), has been shown to be superior to oral corticosteroids in induction of remission, with no medical side effects, and is recommended as a first-line treatment in pediatric CD.[4–6] However, EEN requires a firm commitment from the child and family to avoid all other food intake for 6 to 8 weeks, commonly requiring the use of nasogastric tube feeding, and has remained notably underused in North America.[7,8]

The pathogenesis of CD appears to involve alteration of the microbiome as well as a breakdown in barrier function with defective bacterial clearance.[9] A different approach to therapy, targeting the microbiome instead of the immune system, is an attractive alternative that needs to be explored further. Diet may play a role in the generation of inflammation by modulating the microbiome, tight junctions, and mucous layer.[9]

An alternative environmental hypothesis for the increasing incidence of IBD and CD especially, is that changes in dietary intake and industrialization of food may induce alteration in the microbiome and impair the barrier function of the mucous layer and intestinal epithelium, which then allows adherence and immune triggering by the altered mucosal microbiome.[9,10] Isocaloric partial enteral nutrition (PEN) with exposure to food was not effective in reducing inflammation or inducing remission, suggesting that complete exclusion of food plays an important role in the success of EEN.[11] EEN may therefore, lead to remission in part by the removal of specific dietary ingredients that trigger inflammation or promote a more proinflammatory microbiome.[12] However, the absence of a more palatable and sustained dietary strategy that achieves the same results remains a barrier to the use of dietary therapy in the wider population.

The CD exclusion diet (CDED), is a whole-food diet coupled with PEN, designed to reduce exposure to dietary components, hypothesized to negatively affect the microbiome (dysbiosis), intestinal barrier, and intestinal immunity.[9,13] It has shown promising ability to induce remission and decrease inflammation in case series in both children and adults with CD, including in patients with secondary loss of response to anti–tumor necrosis factor therapy.[9,14,15] In this multinational randomized clinical trial, we aimed to compare the tolerability and efficacy of CDED coupled with PEN with the current gold standard for induction of remission, EEN, in inducing and sustaining corticosteroid-free remission.

Methods

Trial Design

This was an investigator-initiated prospective randomized controlled trial with 2 interventional arms comparing CDED with 50% PEN (group 1) with EEN (group 2) administered orally over 12 weeks in a pediatric population with mild to moderate active luminal disease (Appendix Figure). Our objectives for this study were to assess the efficacy and tolerability of a novel dietary intervention for CD, based on specific whole foods and PEN, and to compare it with the "gold standard" but difficult to implement dietary intervention of EEN.

§ Authors share co-senior authorship.

Abbreviations used in this paper: **ATE, additive treatment effect; CD, Crohn's disease; CDED, CD exclusion diet; CI, confidence interval; CRP, C-reactive protein; EEN, exclusive enteral nutrition; ITT, intention to treat; L/M, lactulose/mannitol; PCDAI, pediatric CD activity index; OR, odds ratio; PEN, partial enteral nutrition; TMLE, Targeted Maximum Likelihood Estimation.**

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2019.04.021

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We hypothesized that by identifying and withdrawing the most plausible offending dietary components with CDED, we can achieve comparable remission rates by week 6 and decrease in inflammation with improved tolerability, which would also be sustained through 12 weeks with a stepdown diet if the correct agents were removed from the diet.

Participants

Children (aged 4–18 years) with mild to moderate luminal CD, defined by a pediatric CD activity index (PCDAI) $\geq$10 and $\leq$40 and evidence for active inflammation at enrollment, such as elevated C-reactive protein (CRP) >5 g/L, erythrocyte sedimentation rate >20 mm/h, or calprotectin >200 μg/g, within 36 months from diagnosis, were eligible for enrollment. Mild to moderate luminal disease was chosen for the study inclusion because this was the primary indication for EEN, which at the time the protocol was planned was used primarily for ileal or ileocolonic disease in children with a recent diagnosis of nonsevere CD.[6]

Exclusion criteria (Supplementary Table 1) consisted of recent use of steroids or recent initiation or dose adjustment for immunomodulators, past or current biologics use, primary colonic disease with significant rectal involvement, or active perianal disease. Patients were allowed to receive a stable dose of immunomodulator or start thiopurines at or after week 3 or methotrexate at week 6, because the effect of thiopurine is not thought to start until after week 8, which would not affect the week 6 (or even week 12) endpoints. Patients could receive antibiotics for intercurrent infections for up to 10 days, with the exception of quinolones and metronidazole. Use of antibiotics for the treatment of CD after enrollment would lead to deeming the patient a failure on the intention to treat (ITT) principle. Patients were allowed use of a proton pump inhibitor if ulcers or erosions were documented in the stomach or duodenum. Signed informed consent was obtained from all participating families before enrollment. The study was approved by the local ethics board at each of the participating sites.

Interventions

Group 1 received the CDED stage 1 with 50% PEN for calculated energy requirement (Modulen; Nestlé Health Science, Vevey, Switzerland) for the first 6 weeks, and then the stage 2 diet with 25% PEN for the next 6 weeks. Group 2 received standard of care EEN (Modulen) for 6 weeks followed by 25% PEN during weeks 6 to 12, with gradual reintroduction of table foods between week 6 and 9 as per local preference, such that all patients were exposed to PEN+ free diet by week 12. All formulas could be given only orally.

Assessment Visits

Patients were seen at baseline and weeks 3, 6, and 12. A telephone conversation by a dietitian was performed at weeks 1 and 9 to support patients and assess adherence. PCDAI was calculated at each visit. Laboratory tests such as a complete blood count, erythrocyte sedimentation rate, CRP, and albumin were assessed at each participating institution; fecal calprotectin was assessed at 1 of 2 central laboratories, Halifax, (EliA on Phadia 250, ThermoScientific, Waltham, MA) and Jerusalem (IDK, Immunodiagnostik AG, Bensheim, Germany) with a cutoff <100 μg/g being reported as normal.

A lactulose/mannitol (L/M) test for intestinal permeability was performed at weeks 0 and 3 by administering a sugar solution containing lactulose (5 g) and mannitol (1 g) and then collecting urine for liquid chromatography tandem mass spectrometry analysis. A cutoff L/M ratio of 0.015 was chosen, based on published literature.[16] L/M testing was analyzed at a central laboratory at the Shaare Zedek Hospital using liquid chromatography tandem mass spectrometry analysis.

Outcomes

Primary outcome. The primary endpoint of this study was the patient's tolerance to the diet by week 6 defined by withdrawal from the study because of patient's refusal to continue the diet. Tolerance was chosen as the endpoint because the effectiveness of EEN in inducing remission in CD is now well established, but it has problematic tolerability over a prolonged period as the sole source of nutrition, often requiring tube feeding in up to 50% to 60% of patients and accompanied by parental or physician refusal to consider this therapy. Our pilot experience with oral CDED+PEN had demonstrated very high rates of remission of approximately 70%[14]; however, a noninferiority design would have been impossible with >70% remission with both diets and even higher response in both arms, necessitating over 10^5 patients. For those reasons, efficacy was chosen as a secondary outcome. Thus, the standard of care for nutritional therapy (ie, EEN) would change only if the CDED+PEN proved to have better tolerance with equivalent efficacy.

Secondary outcomes. Secondary endpoints included response, defined as a drop in PCDAI of 12.5 points or remission, on an ITT analysis at week 6; remission at week 6 (defined as PCDAI $\leq$10 as well as by the more stringent <10, or less than 7.5 without height component).[17] We elected to present both definitions, as many recent studies using drugs or EEN have used PCDAI $\leq$10 as an outcome, and therefore comparison would be possible to previous studies using drugs and EEN.

Other secondary endpoints included decrease or normalization of inflammatory markers at week 6 (CRP, ESR, calprotectin), remission and normalization of CRP at week 12, and poor adherence. Poor adherence was defined by having at least 1 of any of the following 3 items: (1) intolerance: cessation of dietary therapy because of patient's refusal to continue diet; (2) poor adherence by questionnaire to both the child and the parents using the modified Medication Adherence Report Scale questionnaire for assessing patients' adherence (Supplementary Table 2); and (3) physician's assessment of compliance based on direct questioning by the dietitian using 72-hour food diaries and by the physician: any answer other than "adheres to diet very often/always" was considered poorly compliant (Supplementary Table 2).

Microbiome

Sequencing with 16S ribosomal RNA gene (V4V5) was performed on stool samples for which DNA was extracted using the MO BIO PowerFecal DNA Kit (Qiagen, Hilden, Germany) at the Integrated Microbiome Resource of Dalhousie University (cgeb-imr.ca). Sequences were processed following Comeau et al.[18] Diversity and changes in the microbiome at baseline, week 6, and week 12 for EEN and CDED+PEN were analyzed using QIIME2 (https://qiime2.org),[19] Kruskal-Wallis, and linear

discriminant analysis of effect size[20] methods in patients reaching remission.[19]

Power Calculation and Statistics

For independent cases and controls with a 1:1 allocation ratio, based on pilot data and published experience showing the failure rate (failure to tolerate diet) among EEN (taken orally) to be approximately 60% (50% require tube feeding and others refuse/discontinue), we assumed the failure rate for those taking CDED+PEN would be 25%.[21,22] We needed to study 36 children in each group to be able to reject the null hypothesis that the failure rates between the groups were equal, with probability (power) of 80% and a type I error probability of .05.

We used an uncorrected χ^2 statistic (Fischer's exact, as appropriate) to evaluate this null hypothesis using IBM SPSS Statistics (Armonk, NY). Mann-Whitney *U* tests and paired *t*-tests/Wilcoxon Signed Rank tests were used to analyze continuous variables, as appropriate. Logistic regression was used to assess how age, sex, phenotypic factors (disease location), compliance, and diet grouping (Group 1 vs Group 2) were contributing to remission at week 6. Additional analysis of the additive treatment effect (ATE) of CDED+PEN vs EEN accounting for effects of covariates were performed using the Targeted Maximum Likelihood Estimation of point treatment effects (TMLE) in R.[23,24] In brief, to reduce bias due to the effect of covariate difference between treatments we used TMLE with several algorithms (logistic regression, stepwise and generalized linear model, stepwise model with 2-way interaction, and recursive partitioning). Unlike logistic regression, TMLE allows for missing outcomes, thereby allowing us to include all patients in the analysis. For each patient, we also estimated the conditional mean outcome (remission) for each treatment (CDED+PEN and EEN) given the patient's covariates, and investigated if any difference between treatments were associated with a particular covariate.

All analyses were on an ITT basis for response/remission for patients who have used the dietary therapy for at least 48 hours. Patients withdrawing from the study or requiring additional therapy were considered failures and had nonresponse imputed. For patients with a change in medical therapy due to failure (ie, addition of drugs for remission due to withdrawal from diet or nonresponse), continuous variable data were carried forward from the observation before drugs were added (last observation carried forward). All authors had full access to all the analyzed data in the study after study completion, and had final responsibility for the decision to submit for publication and reviewed and approved the final manuscript.

Randomization

Patients were randomized 1:1 in previously generated random blocks of 6 in an Excel (Microsoft, Redmond, WA) platform by sealed, numbered, and opaque envelopes. Envelopes had to be used consecutively and opened only after informed consent was obtained and patients' agreement to the randomization process. Randomization codes were not available to any of the enrolling physicians.

Diet

The principles underlying the diet, developed by one of the senior authors, as well as food allowed in the diet, have been published elsewhere,[9,14] and the foods allowed and disallowed in both stages appear in Supplementary Table 3. Dysbiosis at a phylum level in CD is characterized by increased Proteobacteria and decreased Firmicutes.[9,13] The diet included 5 mandatory foods consumed daily to provide specific fibers and starches as substrates for short chain fatty acids–producing taxa from Firmicutes, as well as sources of lean protein that were low in animal fat to decrease Proteobacteria and improve intestinal permeability, while maintaining a balanced diet. The diet included avoidance or reduction of exposure to foods containing animal/dairy fat, high fat from other sources, wheat, red or processed meat and protein sources rich in taurine, emulsifiers, artificial sweeteners, carrageenans and sulfites. The second phase stepdown diet involves higher exposure to fruits, vegetables, and legumes along with some foods that are reintroduced with restrictions to increase food flexibility and relieve monotony.

To achieve standardized nutritional care, the participants in group 1 received patient education material with the CDED, recipes and dietary instructions, by a CDED-trained registered clinical dietitian. A telephone call by a dietitian or research assistant was performed at weeks 1 and 9 to assess compliance and total Modulen volume and to confirm appointments. Compliance was also assessed by a modified Medication Adherence Report Scale questionnaire at each visit and by compliance phone calls and food diaries. In addition, a hot line managed by a research dietitian was available for patients and dietitians in Israel, and patients were advised to contact the hot line at least once for any questions regarding the diet. In Canada, diet implementation was supported further with a dedicated study Web site, to ensure access to dietary information optimized for a North American audience, in addition to phone support by a dietitian in between scheduled study visits at each participating site. The study Web site was used to assess and improve patient engagement and ensure 2-way knowledge translation for CDED patients, with access to recipes compatible with the diet, depending on the stage each participant was in at a given time. Patients in group 1 received a recommendation to consume 50% of the daily calories in Modulen, but not to exceed 1250 mL/d to guarantee that outcomes were because of CDED and not higher utilization of formula (Supplementary Table 4).

Patients in group 2 received EEN only (1 kcal/mL) at a calculated total volume to meet their caloric needs. Patients in this group did not receive the CDED or any dietary instruction except for preparation of Modulen and the daily volume required. The centers supplied the required amount of Modulen but no other food was provided to any patient in either group.

Results

Seventy-eight patients were randomized (40 to CDED+PEN and 38 to EEN) and included in the analysis from 10 pediatric IBD clinics in Israel (from September 2013) and 2 in Canada (from December 2016) until May 2018, for the primary endpoint of tolerance. Four patients randomized to EEN withdrew within 48 hours for refusal to continue to take Modulen orally between 24 and 48 hours and were included only in the primary endpoint analysis (Supplementary Figure 1). The remaining patients were included in the secondary endpoint analyses. There were no

statistically significant differences in baseline characteristics with regard to age, gender, disease location,[25] duration, activity, CRP, and immunomodulator use (Table 1). One child with a PCDAI of only 10, but elevated CRP and a calprotectin of 2700 was enrolled in the study. This patient was randomized to EEN and went in to remission with a follow up PCDAI of 0 and was therefore not excluded.

The primary endpoint of tolerance was significantly different, favouring CDED+PEN over EEN: 39 of 40 (97.5%) vs. 28 of 38 (73.7%), $P = .002$ (Delta 23.8%; 95% Confidence Interval [CI] 9.0%–38.6%); odds ratio (OR) 13.92 (95% CI 1.68–115.14; Figure 1).

Secondary clinical endpoints on an ITT analysis at week 6 are shown in Figure 1, indicating no statistically significant difference in response (34/40 [85%] CDED+PEN vs 29/34 [85.3%] EEN, $P = .97$; Delta 0.3%; 95% CI ±16%; OR 0.97; 95% CI 0.27–3.53) and corticosteroid-free remission (defined as PCDAI ≤10, 32/40 [80%] CDED+PEN vs 25/34 [73.5%] EEN, $P = .51$; Delta 6.5%; 95% CI ±19.3%; OR 1.44; 95% CI 0.49–4.27), as well as remission by the more stringent PCDAI <10 (achieved by 30/40 [75%] CDED+PEN vs 20/34 [58.8%] EEN, $P = .14$ [Delta 16.2%; 95% CI ±20.7%; OR 2.10; 95% CI 0.78–5.65). Beyond 48 hours of therapy, good compliance was similar between groups (33/40 [82.5%] vs 26/34 [76.5%], $P = .52$ [Delta 6%; 95% CI ±17.8%; OR 1.45; 95% CI 0.46–4.52). Good compliance was strongly associated with achieving remission for both CDED+PEN (OR 9.66; 95% CI 1.55–60.01; $P = .02$) and EEN (OR 23.00; 95% CI 3.10–170.31; $P = .001$).

In keeping with the comparable rates of clinical remission, using logistic regression, there was no significant effect of the type of dietary therapy (CDED+PEN vs EEN) on achieving ITT-remission at week 6 ($P = .58$; OR 1.5; 95% CI 0.4–5.9) but we did confirm the strong association with good compliance to both diets with achieving ITT-remission at week 6 ($P < .001$; OR 23.28; 95% CI 4.04–133.98). TMLE estimation of additive effect of ITT-remission at week 6 (with gender, age, compliance, disease location, and immunomodulator use at week 6 as covariates) was not significant ($P = .74$). The estimated ATE of CDED+PEN over EEN was just 2.7% at week 6 (95% CI of −13% to 19% and OR of 1.16; 95% CI 0.48–2.8). Adverse events are summarized in Supplementary Table 5.

Effect of Diets on Disease Activity, Weight, and CRP

PCDAI and inflammatory markers decreased significantly between baseline and week 6 in both groups. Median (interquartile range) PCDAI improved from 25 (20–35) at week 0 to 2.5 (0–7.5) at week 6 for CDED+PEN patients and from 27.5 (18.75–32.5) at week 0 to 5 (0–10) at week 6 for EEN (both $P < .001$) (Figure 2).

Median CRP improved from 23.6 mg/L (9.8–54.2) at week 0, to 5 mg/L (2.7–8.0) at week 6 for CDED+PEN patients and from 24 mg/L (10.1–52.9) at week 0, to 4.1 mg/L (1.3–8.4) at week 6 for EEN patients (both $P < .001$; Figure 3).

Mean weight z-score improved significantly in both groups. In the CDED+PEN group, z-score increased from -0.91 ± 1.2 to -0.64 ± 1.05 ($P < .001$) and in the EEN group, z-score increased from -0.92 ± 1.17 to -0.63 ± 1.1 ($P < .001$), after 6 weeks. There was no statistically significant difference between groups ($P = .476$).

Table 1. Baseline Participant Demographics

Variable	CDED n = 40	EEN n = 34	P
Mean age, *yr* ± SD	13.8 ± 2.8	14.5 ± 2.6	.247
Gender (males %)	26 (65)	20 (59)	.58
Disease duration, *mo* ± SD	2.4 ± 6	2 ± 4.8	.88
Median PCDAI (interquartile range)	25 (20–35)	27.5 (18.75–32.5)	.89
Median CRP (g/L) Range 1.1–146 g/L	23.6 (9–55)	24 (9.7–53)	.85
Immunomodulators, n (%)	3 (7.5)	4 (11.5)	.69
Disease location Paris Classification, n (%)			.5
L1	18 (45)	14 (41)	.94
L2	2 (5)	1 (2.9)	
L3	19 (47.5)	15 (34)	
L4a	14 (35)	13 (38.2)	
L4b	2 (5)	3 (8.8)	

There was no statistically significant difference between CDED+PEN and EEN in achieving normal CRP remission at week 6 (20/39 [51.3%] CDED vs 19/34 [55.8%], $P = .69$). Baseline use of immunomodulators was not associated with remission at week 6 ($P = .65$). Patients in the CDED arm consumed slightly more overall calories than in the EEN arm (Supplementary Table 4).

Open-label Crossover

Six participants randomized to EEN refused to continue EEN during treatment between weeks 1 and 3 and were offered open-label CDED before week 6. Five patients opted to participate in the open-label study: all 5 achieved remission by week 6, and 4 of 5 maintained remission until week 12. These patients were not included in the CDED+PEN analysis.

Sustained Remission Week 12

A decline in sustained corticosteroid-free remission following the gradual introduction of free oral diet, by week 12 was more common in EEN (14/31 [45.1%]), whereas more CDED+PEN patients achieved sustained remission (using both the standard cutoff of PCDAI ≤10 and the more stringent PCDAI <10) at week 12 (28/37 [75.6%], $P = .01$; Delta 30.5%; 95% CI 10.4%–52.6%; OR 3.77; 95% CI 1.34–10.59) (Figure 3). Normal CRP, corticosteroid-free remission at week 12 occurred in 22 (75.9%) of 29 CDED+PEN patients compared with only 10 (47.6%) of 21 patients in the EEN group ($P = .04$; Delta 28.3%; 95% CI 1.9%–54.7%; OR 3.45; 95% CI 1.03–11.55).

A subgroup analysis for maintenance of remission including only patients who had achieved corticosteroid-free remission by week 6, showed that patients in the

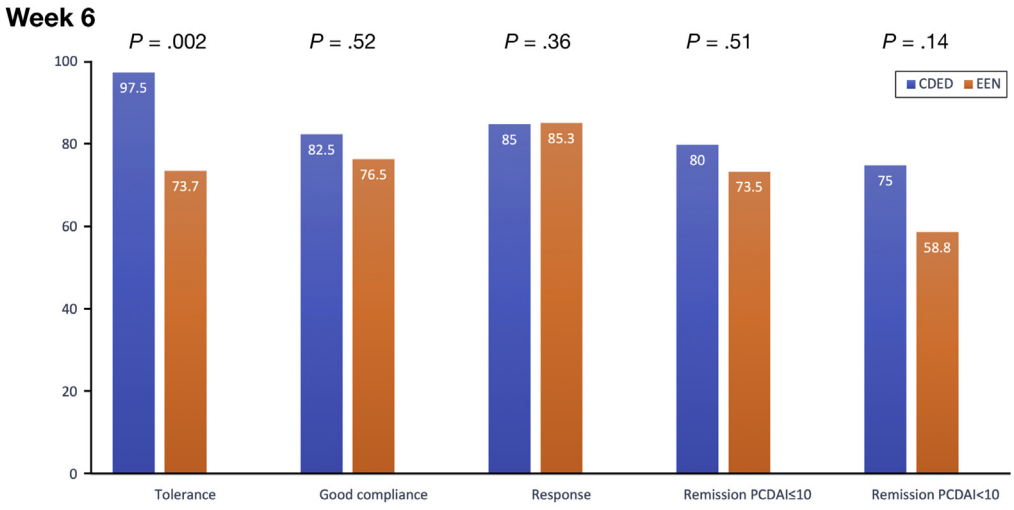

Figure 1. Primary and secondary endpoints CDED vs EEN-tolerance, compliance and ITT-response and ITT-remission.

CDED+PEN group were more likely to maintain corticosteroid-free remission than EEN patients (28/32 [87.5%] vs 14/25 [56%]; $P = .01$; Delta 31.5%; 95% CI 9%–54%; OR 5.5; 95% CI 1.48–20.42) (Figure 3). Use of immunomodulators at week 12 among responders at week 6 did not differ and was present in 12 (37.5%) of 32 in the CDED+PEN arm vs 11 (45%) of 25 in the EEN arm ($P = .61$).

TMLE revealed that the benefit of CDED+PEN to achieving ITT-remission at 12 weeks was significant after correcting for covariate differences between diets ($P = .003$, and an OR of 3.3; 95% CI 1.4–7.6; $P = .005$). The estimated ATE of CDED+PEN over EEN at 12 weeks was 27.5% (95% CI 9%–46%). The difference in the conditional mean treatment outcomes between CDED+PEN vs EEN were plotted according to each patient's status for (1) immunomodulator use at week 6, (2) gender, (3) Paris L1L3, and (4) Paris L4; none of these covariates appear to warrant patient stratification relative to CDED+PEN vs EEN week 12 outcome (Supplementary Figure 2).

Fecal Calprotectin

Fecal calprotectin was markedly elevated in both groups ranging between 50 and 17,000 μg/g at entry. Calprotectin dropped significantly for both groups between week 0 and week 6 (Figure 4; all in μg/g: CDED: median 3126 to 1744, $P = 0.002$; EEN: median 2647 to 1021, $P = .011$). There was no statistically significant difference in median delta calprotectin between CDED+PEN (−1473 μg/g) and EEN (−948 μg/g), $P = .83$, which represents a 47.0% and 35.8% drop in median calprotectin respectively by week 6. There was no statistically significant difference in median calprotectin between groups at week 6 ($P = .43$). Calprotectin continued to decline between week 6 and week 12 in the CDED+PEN group ($P = .22$), whereas there was a nonsignificant increase in the EEN group ($P = 0.36$). Only 10 (5 CDED+PEN/5 EEN, all in ITT-remission at week 6 with PCDAI ≤10) patients had achieved a calprotectin <200 μg/g at week 6, likely due to the very high calprotectin levels at enrollment.

Intestinal Permeability

L/M ratios were available at week 0 and week 3 for 53 patients (26 CDED and 27 EEN).

Mean L/M ratio improved from 0.061 at week 0 to 0.012 at week 3 with CDED ($P = .089$) but showed no statistically significant change with EEN (0.065 to 0.094; $P = .56$)

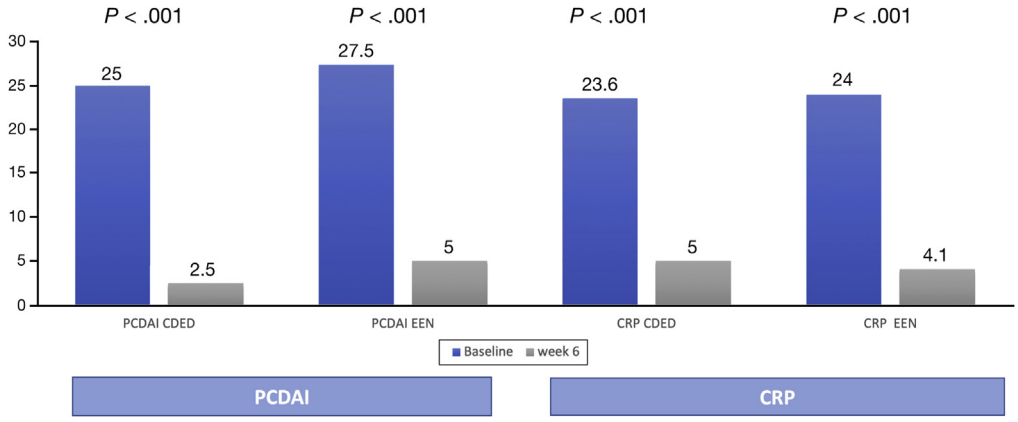

Figure 2. Secondary endpoints: PCDAI and CRP from baseline to week 6.

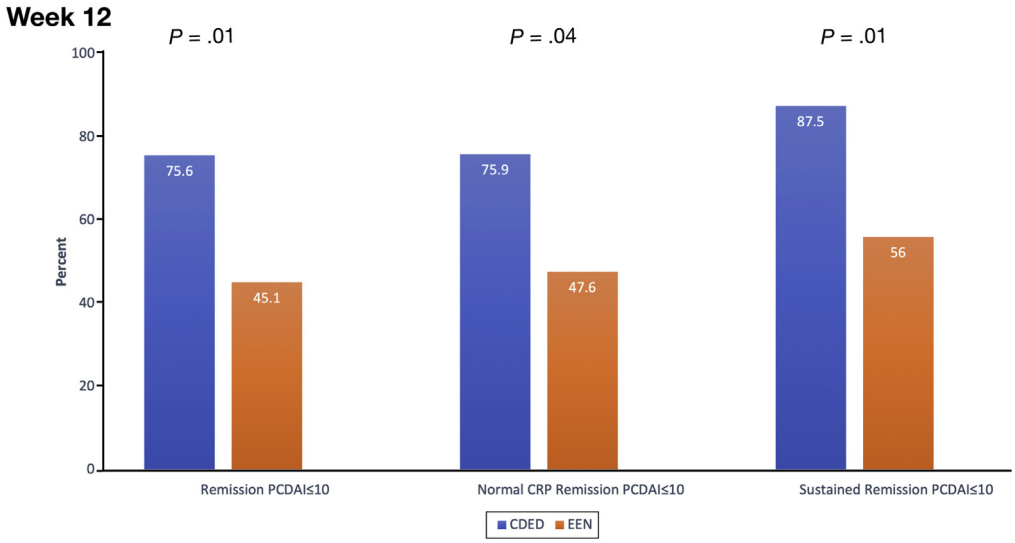

Figure 3. Week 12 remission, normal CRP remission, and sustained remission.

(Supplementary Figure 3). At baseline, 12 (46%) of 26 CDED and 15 (56%) of 27 EEN patients had a normal L/M ratio. At 3 weeks of treatment, the proportion of patients with normal intestinal permeability increased to 18 (69%) of 26 with CDED+PEN but remained unchanged for EEN with 15 (56%) of 27.

Microbiome

DNA sequences from stool samples were collected for 70 patients, 38 CDED+PEN patients (25 at all 3 timepoints) and 32 EEN patients (21 at all 3 timepoints). Here, we focused our analysis on samples of patients achieving remission by ITT at week 6 (21/25 CDED+PEN and 14/21 EEN). Microbiome comparison of baseline, week 6 and week 12, showed significant ($P < .05$) decreases in *Haemophilus*, *Veillonella*, *Bifidobacterium*, *Prevotella*, and *Anaerostipes*, and increases in *Oscillibacter* and *Roseburia*. A comparison across timepoints in EEN identified significant ($P < .05$) differences in many of the same taxa identified in CDED+PEN. In addition, *Lachnospira* decreased and *Subdoligranulum*, *Blautia*, *Ruminococcus,* and Erysipelotrichaceae increased. Although similar taxa were identified, the pattern between the 2 groups differed. CDED+PEN continued to change between week 6 and week 12, whereas

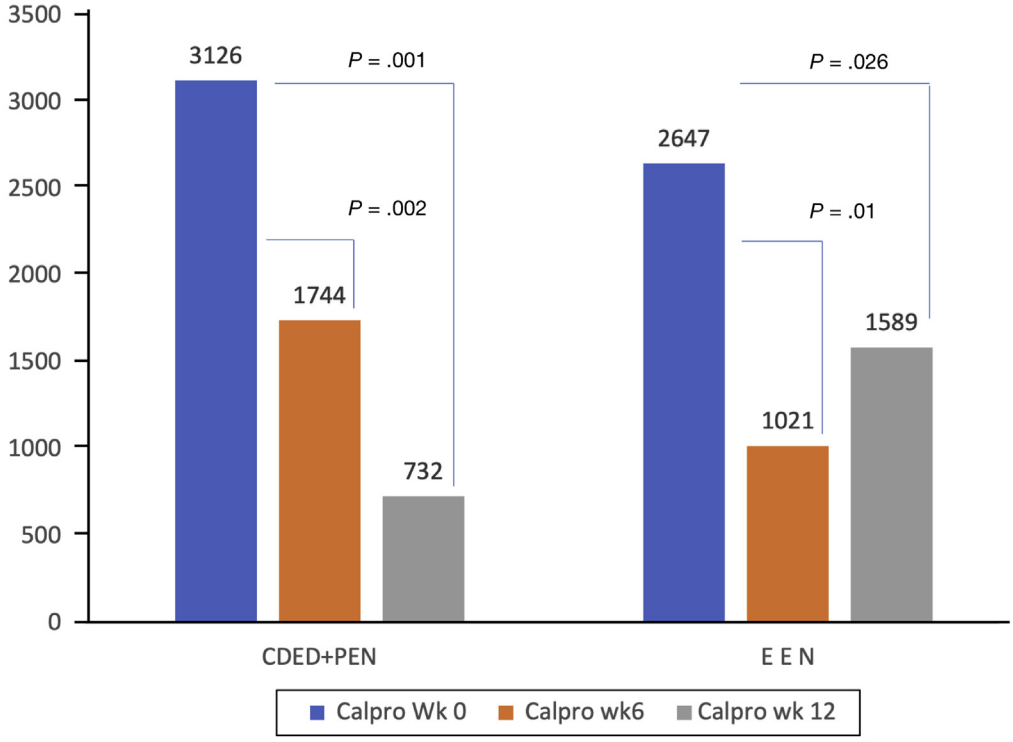

Figure 4. Change in median calprotectin during CDED study.

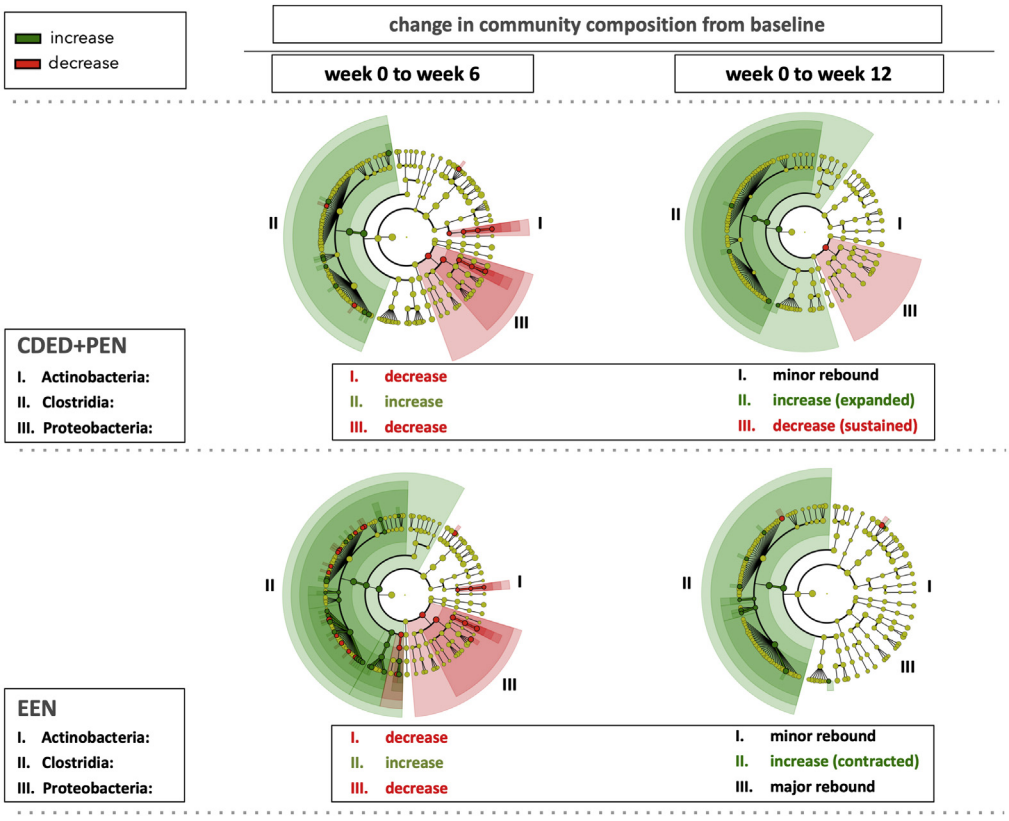

Figure 5. Linear discriminant analysis comparing taxa in week 0 to week 6 and week 12 in remission samples, based on week 6 ITT, in CDED and EEN patients. Each *dot* represents taxa identified in these data. *Red* were found to be significantly more abundant in the week 0 samples and *green* significantly more abundant in the week 6 samples. A decrease in Proteobacteria for both diets is only significant between baseline and week 12 for CDED, due to a rebound toward baseline community structure in EEN samples. Cladograms showing taxonomic labels for each lineage with a significant change between timepoints are provided in Supplementary Figures 4 to 10.

EEN generally rebounded to pretreatment levels at week 12 (Figure 5). Although there is a decrease in Proteobacteria for both diets, the absence of a significant change seen for Proteobacteria in the EEN group at week 12 is due to this rebound toward baseline community structure. Cladograms showing taxonomic labels for each lineage with a significant change between timepoints are provided in Supplementary Figures 4 to 10.

Patients who did not achieve ITT-remission at week 6 (nonresponders) exhibited less change in community composition (Supplementary Figures 8–10) than those who did achieve remission at week 6 (Figure 5 and Supplementary Figure 10). The difference was, in part, due to narrower taxonomic change among the Proteobacteria in the nonresponders (Supplementary Figures 8–10). However, unlike the responders, compositional changes differed between diets among the nonresponders, with EEN exhibiting an increase in total Proteobacteria at week 6. Despite the complexity of this community change, by week 6 the principal features of change among the nonresponders (irrespective of diet) were (1) lower overall change in composition, but (2) more Gammaproteobacteria (Supplementary Figures 8–10). Beyond week 6, patients not achieving ITT-remission were given additional medical therapy to induce remission, confounding interpretation of their microbiomes.

Beta diversity (Bray-Curtis) was computed to summarize community differentiation over treatment. The direction of change within patients was measured by the difference between week 0 and week 12 diversity and week 0 and week 6 diversity; positive differences indicated when patient communities became more differentiated over treatment, and negative differences indicated when they "rebounded" toward baseline. We detected a marginally significant difference in the direction of change in beta diversity associated with CDED+PEN and EEN patients ($P = 0.045$; 2-tailed Welch's t test). Changes within CDED+PEN patients tended to be positive, whereas changes within EEN patients tended to be negative. Average Shannon diversity was measured at weeks 0, 6, and 12 in each diet (Supplementary Figure 11). Although changes for either diet over those timepoints was not significant, the weak pattern observed for EEN is consistent with the observed pattern of change in beta diversity.

Discussion

We present the first multinational randomized, head-to-head, controlled trial of a whole-food oral diet with PEN (CDED+PEN) compared with standard of care EEN in mild to moderate pediatric CD. We have shown that both diets were associated with high and comparable rates of clinical remission and a significant and similar decrease in inflammation by week 6. Both had similar changes in the microbiome induced by diet by week 6. The 2 groups diverged from week 6 (as EEN transitioned to PEN with gradual return to free diet) as sustained remission, maintenance of remission, and normal CRP remission at week 12 were

significantly better in the CDED+PEN-treated group. Calprotectin continued to decrease between week 6 and week 12 in the CDED+PEN group, in contrast to an increase in the EEN group from week 6. These data support our hypothesis that the exclusion of components found in the habitual diet is required to maintain remission,[15] whereas reexposure to food induced rebound in inflammation and decreased sustained remission . This is also supported by the compelling microbiological data. Mirroring the rebound in calprotectin and CRP levels and loss of sustained remission in the EEN group between week 6 and week 12, the microbiome data demonstrated a rebound effect in which the composition of the microbiome (particularly Proteobacteria) tended to revert to the baseline state on returning to regular diet. Use of PEN after a course of EEN did not help to maintain the microbiological changes induced by EEN. These data also suggest that the foods excluded from habitual diet in the CDED are likely to be the candidates for dysbiosis-led inflammation, as this effect did not occur in the CDED+PEN arm despite adding additional foods.

Many of the microbiome features associated with active CD (eg, in the study by Gevers et al[13]) are addressed by dietary therapy in samples achieving remission. We demonstrated decreases in *Haemophilus, Veillonella, Anaerostipes,* and *Prevotella*, whereas *Roseburia* (an important butyrate producer) and *Oscillibacter* increase.[13] Although similar changes in taxa were identified during the first 6 weeks, the pattern between the 2 groups differed: CDED+PEN continued to change between week 6 and week 12, whereas EEN generally rebounded to pretreatment levels at week 12 (Figure 5 and Supplementary Figures 4–7). These data for the first time pose a plausible cause and effect scenario for this cohort, in which exclusion of dietary components by EEN or CDED reduce Proteobacteria and especially genera previously described as associated with pediatric CD by Gevers et al,[13] while increasing Firmicutes. Upon reexposure, these genera rebound to their previous state and inflammation ensues leading to clinical activity, although an increase in inflammation may also drive these alterations. Taken together, the described microbiome changes are associated with improvement in inflammation and symptoms, but reduction in inflammation alone or in combination with the dietary changes may also be associated with changes in the microbiome.

Importantly, <10% of patients in either arm received an immunomodulator at entry, demonstrating that the effect was induced by the diets and not accompanying drugs. Dietary interventions may sometimes be preferentially used in less inflamed or milder patients. Our study was characterized by significant inflammation at baseline (CRP ranged up to 30 times upper limit of normal, calprotectin up to 17,000 μg/g), thus demonstrating that these results are not due to selection bias. We found an early improvement in intestinal permeability, which was more evident in the CDED+PEN group.

Short-term remission rates >70% (by week 6) and improvement in inflammatory markers are comparable for children who are able to adhere to either diet. Given that compliance is strongly associated with treatment success, improving compliance with CDED+PEN is likely the reason for the numerically superior ITT-response to CDED+PEN at week 6, as our univariate and logistic regression results show.

EEN has been shown more effective in inducing normal CRP remission than corticosteroids, and the use of EEN promotes long-term steroid avoidance and improved growth during critical years of pubertal development.[26–28] Previous studies, which did not restrict the quality of the oral diet component, have shown markedly reduced remission rates.[11,29,30] Coupled with significantly better tolerance, we show here, for the first time, that the CDED+PEN achieves corticosteroid-free remission at week 6 in 75%, using the most stringent definition of remission, through the provision of a controlled diet, and a balanced nutritional plan with PEN (see Supplementary Table 3) with a better sustained inflammatory and clinical response through to week 12. Furthermore, the effect was not confined to a single geographical region, as it was effective in both countries (ITT-Remission PCDAI <10 for Canadian vs Israeli children: CDED+PEN 85.7% [6/7] vs 78.8% [26/33], $P > .99$, and EEN 85.7% [6/7] vs 70.4% [19/27], $P = .644$), that have very different food cultures and sources. The compliance rates were high, as more than 75% of patients were compliant with the induction phase despite restriction to food.

Following EEN, an early clinical flare occurs in up to half of patients on resuming an unrestricted oral diet.[31,32] Through offering a structured, multiphase dietary intervention, the CDED+PEN is able to achieve a significantly higher remission rate by week 12, as compared with EEN (significant additive treatment benefit of use of CDED+PEN over PEN+free diet of 27.5% using TMLE).

Based on the results of clinical trials and inception cohorts (compared with oral corticosteroids), EEN has been recommended as first-line therapy by the European Crohn's & Colitis Organisation–European Society of Paediatric Gastroenterology, Hepatology and Nutrition guidelines for mild to moderate disease at diagnosis. An important feature and strength of this trial is that the CDED was directly compared with this highly effective gold standard rather than to placebo. This study design is in keeping with a recent paradigm shift among pediatric gastroenterologists, toward avoidance of placebo arms for sick children in clinical trials while using an existing treatment as a control arm.[33]

Limitations of the study include the fact that calprotectin was assessed at 2 central laboratories and the fact that we did not directly assess mucosal healing by endoscopy. Repeat endoscopy with general anaesthesia within 3 months is difficult to perform and not a standard of care in most pediatric centers.

In conclusion, we have shown that both CDED+PEN and EEN result in high rates of corticosteroid-free remission with a significant decrease in inflammation; however, CDED+PEN has superior tolerance, sustained remission, and reduction of inflammation by week 12. These data support the use of CDED+PEN as a first-line therapy for children with luminal mild to moderate

active CD, and warrant further study to explore the role of diet in conjunction with drugs to optimize therapy in CD patients.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2019.04.021.

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Received February 4, 2019. Accepted April 21, 2019.

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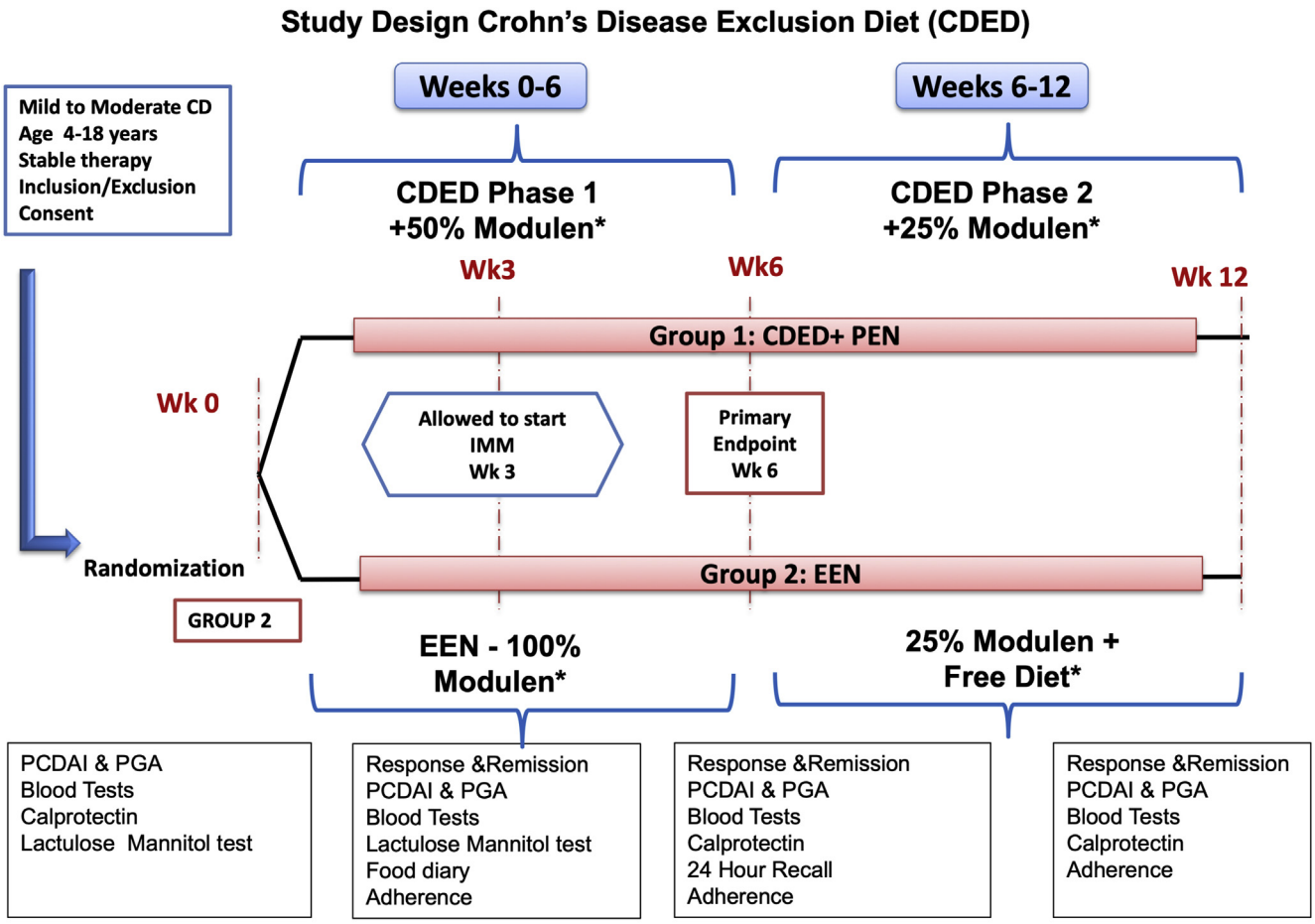
Acknowledgments
The authors thank all participating children and their families, as well as the many colleagues in pediatric gastroenterology and pediatric nutrition at all participating sites who made this study possible: in Tel Aviv (Tamar Pfeffer-Gik who initially coordinated the study), Halifax (Anthony Otley, Mohsin Rashid, Angela Noble, Jessica Connors, Jennifer Haskett, Lisa Parkinson-McGraw, Brad MacIntyre), Edmonton (Hien Huynh, Matthew Carroll, Alexandra Petrova, Min Chen, Jessica Wu).

Antonia Harvey, Registered Dietitian, and Marin Whebby, Research Assistant, modified the CDED-recipes for use in Canada and maintained the Canadian CDED-study Web site, supervised by S. Grant, Department of Applied Human Nutrition, Mount Saint Vincent University, and partially funded by the Mount Saint Vincent University New Scholar's Research Grant. AL was supported by grants from the Azrieli Foundation and Nestlé Health Science. JVL was supported by a Canadian Institutes of Health Research (CIHR)-Canadian Association of Gastroenterology-Crohn's Colitis Canada New Investigator Award (2015–2019), a Canada Research Chair Tier 2 in Translational Microbiomics (2018–2019), and a Canadian Foundation of Innovation John R. Evans Leadership Fund (awards #35235 and #36764), a Nova Scotia Health Research Foundation (NSHRF) establishment award (2015–2017), an IWK Health Centre Research Associateship, a Future Leaders in IBD project grant, a donation from the MacLeod family, and by a CIHR-SPOR-Chronic Diseases grant (Inflammation, Microbiome, and Alimentation: Gastro-Intestinal and Neuropsychiatric Effects: the IMAGINE-SPOR chronic disease network). EW was supported by grants from the Crohn's and Colitis Foundation and Crohn's Colitis Canada as well as a WCHRI Research Capacity Award.

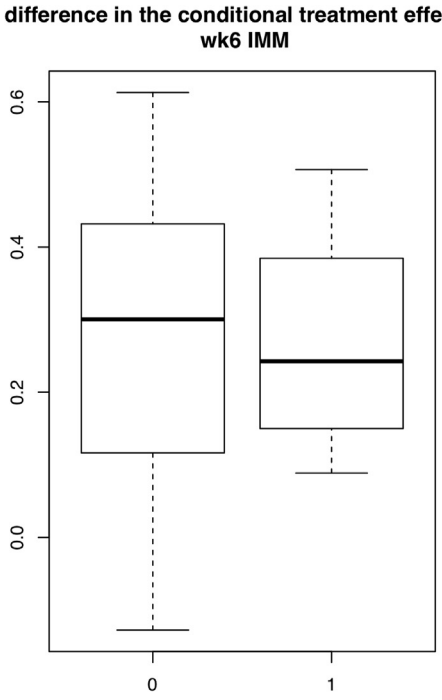
Author Contributions: AL: design of CDED diet, funding for clinical study, patient enrollment, and review of manuscript. EW: patient enrollment, data analysis, writing of manuscript. RSB: design of support system, design of case report form, coordination of study, data management and analysis, article figures and tables. AA, RS, MK, SC, SP, AO, HS, PM: patient enrollment. TBZ, GA: data analysis. LA: dietary data management. SG: design of dietary support system. JVL was Principal Investigator for the Canadian arm, design of patient support system, funding of study, patient enrollment, data analysis and writing of manuscript, and performed the microbiome translational aspects of the study along with KAD and JPB.

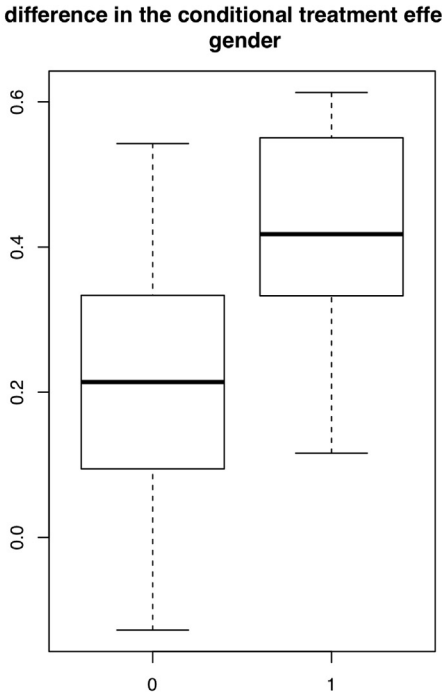
Conflicts of interest
These authors disclose the following: AL reports grants, from Nestlé Health Science, and grants from Janssen unrelated to this field; advisory boards, travel, speaker fees or DSMBs from Celgene, Takeda and AbbVie, and a licensing and consulting agreement with IP with Nestlé health to develop new products based on diet. EW reports personal fees from Janssen, personal fees from AbbVie, outside the submitted work. RSB reports personal fees from Consulting to Nestlé Health Science, during the conduct of the study; personal fees from Invited speaker by Nestlé Health Science, personal fees from Invited speaker by Takeda, outside the submitted work. RS reports personal fees from Janssen, AbbVie, Mead Johnson, Lapidot and Abbott, outside the submitted work. JVL reports consulting, travel and/or speaker fees and research support from AbbVie, Janssen, Nestlé Health Science, Merck, P&G, GSK, Illumina, Otsuka. The remaining authors disclose no conflicts.

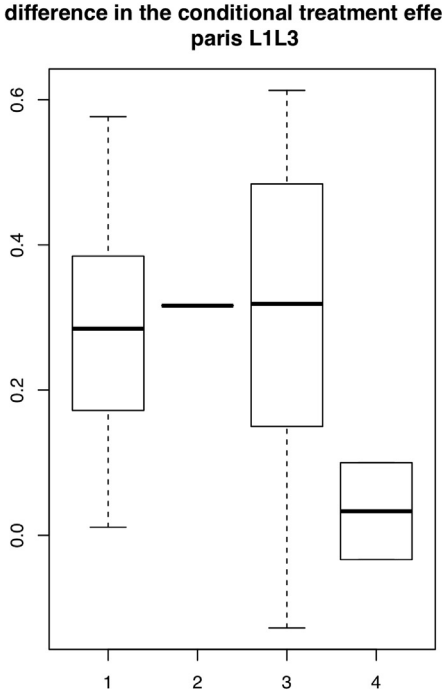
Funding
Initial funding for the study in Israel was provided by unrestricted grants from the Azrieli Foundation and Nestlé Health Science to AL. Nestlé Health Science also kindly provided Modulen to all participating sites to ensure uniformity of the formula used among participants and provide the formula to enrolled patients for the duration of the study. The conduct of the study in Canada (Halifax, Edmonton) was supported by local divisional funds, a Women and Children's Health Research Institute (WCHRI) Research Capacity Building Award (EW) and a Canadian Institutes of Health Research (CIHR) New Investigator award (JVL). The funders of the study had no role in the design of the study, data collection or analysis, interpretation of data, writing of the report, or in the decision to submit the paper for publication. None of the funders or participating physicians had access to the data. All data were held confidentially by a single research coordinator and data manager who validated the data and performed an extensive query process (RSB).

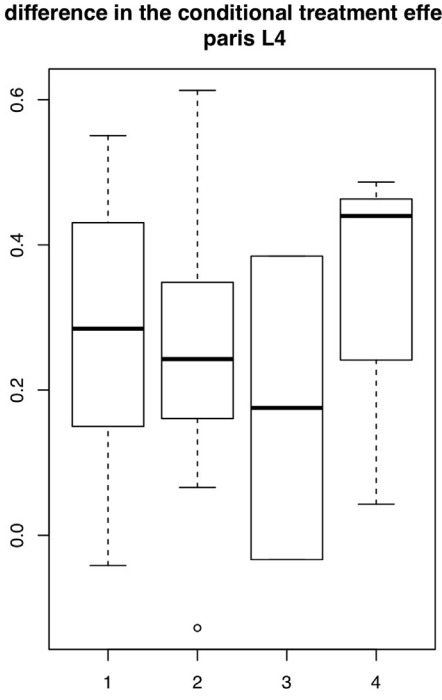


Supplementary Figure 1. CONSORT Crohn's Disease Exclusion Diet Flow Diagram.

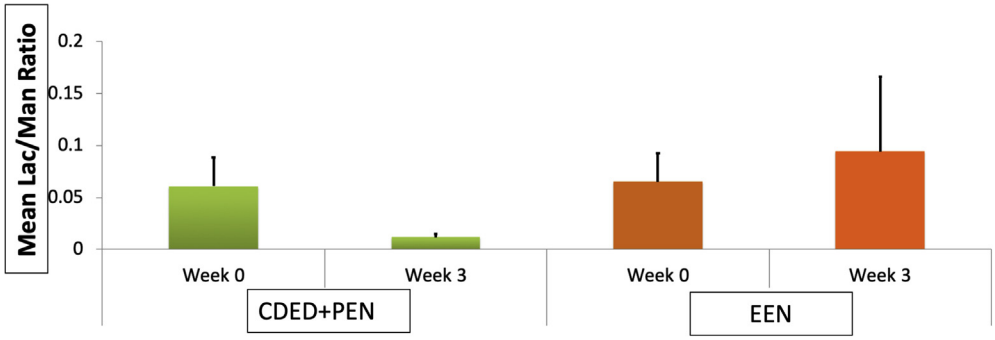




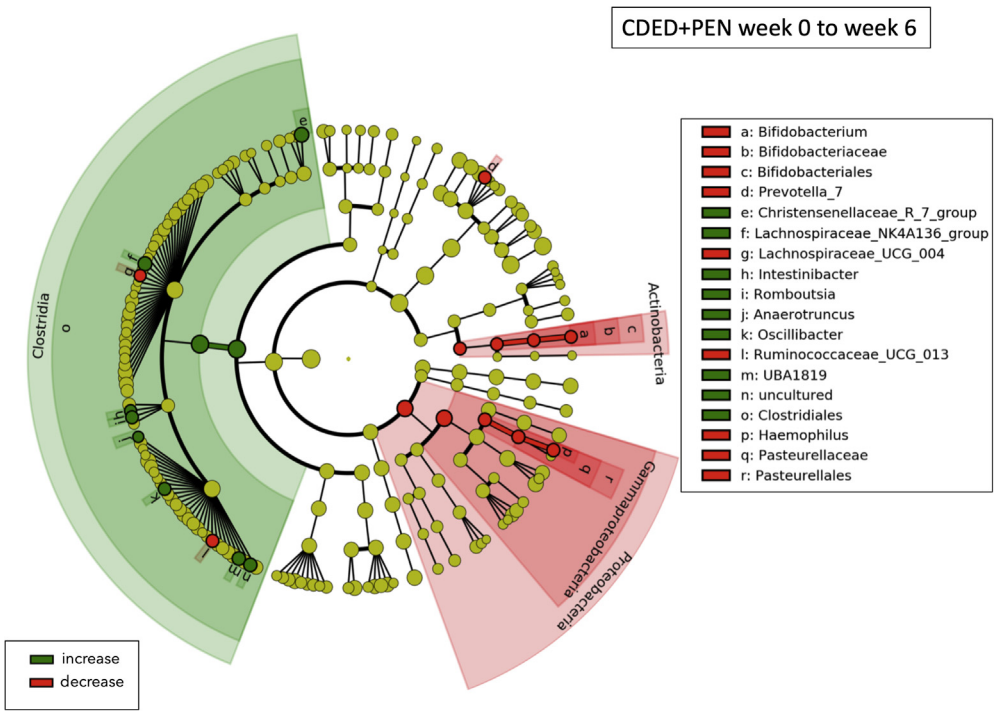




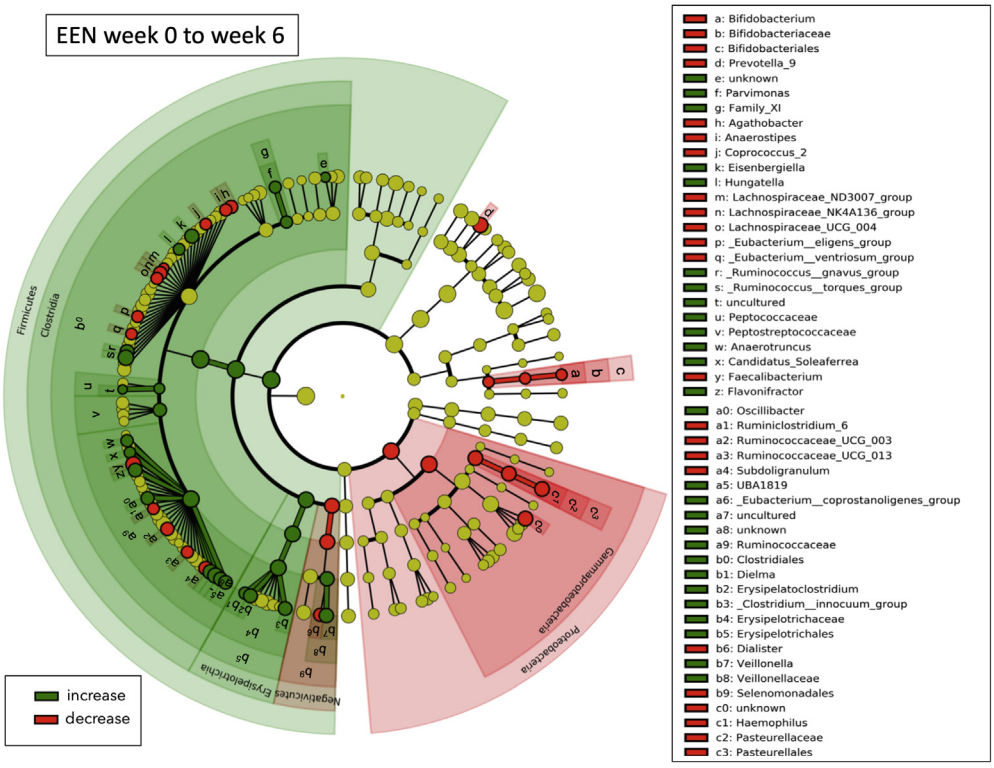
Supplementary Figure 2. The difference in the conditional mean treatment outcomes between CDED+PEN vs EEN were plotted according to each patient's status for (1) immunomodulator use at week 6, (2) gender, (3) Paris L1L3, and (4) Paris L4; none of these covariates appear to warrant patient stratification relative to CDED+PEN vs EEN week 12 outcome.



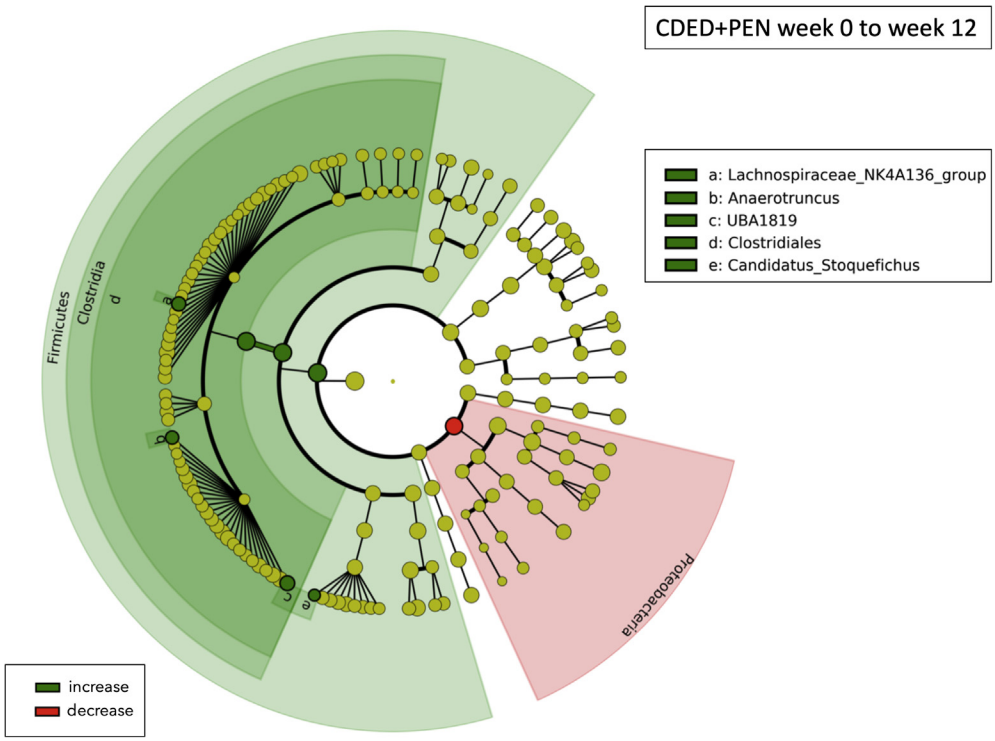
Supplemental Figure 3. Mean (± SEM) Lactulose/Mannitol Ratio Changes with CDED+PEN vs EEN. L/M ratio appears to improve with CDED but not with EEN (*t* test: $P = .089$ and .56, respectively).



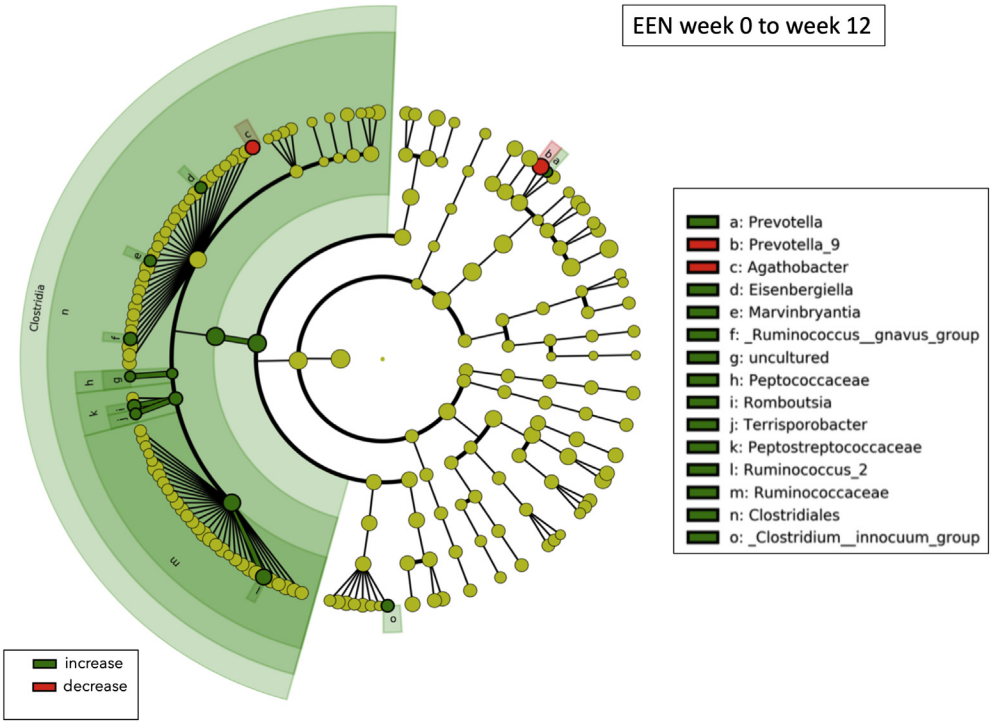
Supplementary Figure 4. Detailed LDA listing taxa changing significantly between week 0, and week 6 for CDED+PEN.



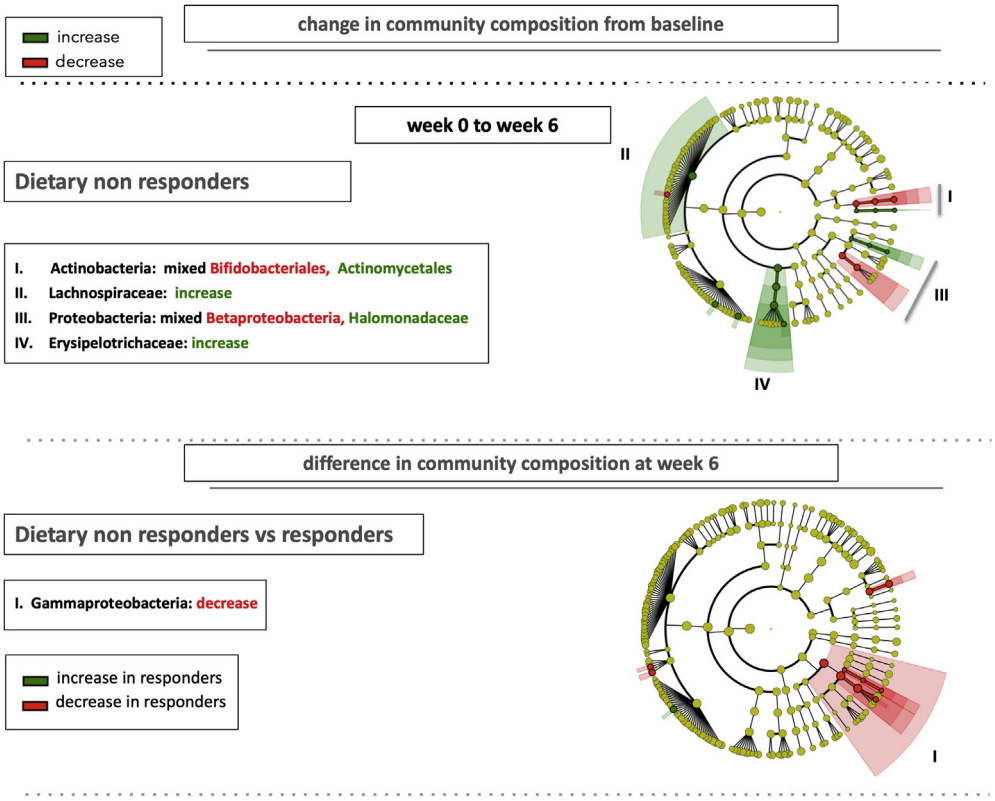
Supplemental Figure 5. Detailed LDA listing taxa changing significantly between week 0 and week 6 for EEN patients.



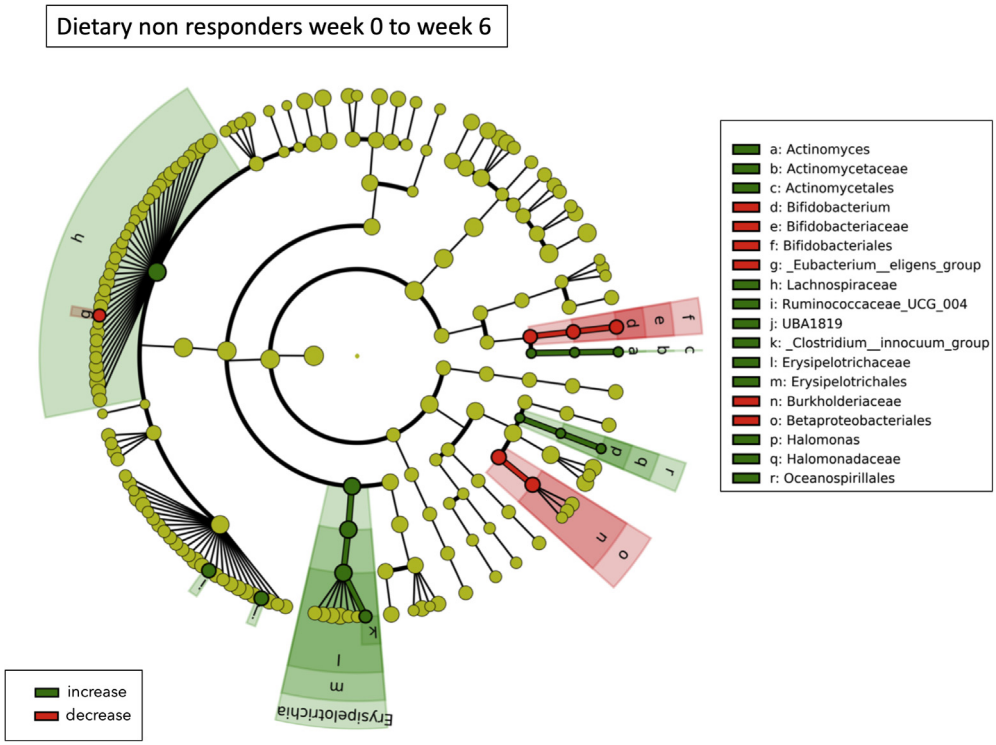
Supplemental Figure 6. Detailed LDA listing taxa changing significantly between week 0, and week 12 for CDED+PEN.



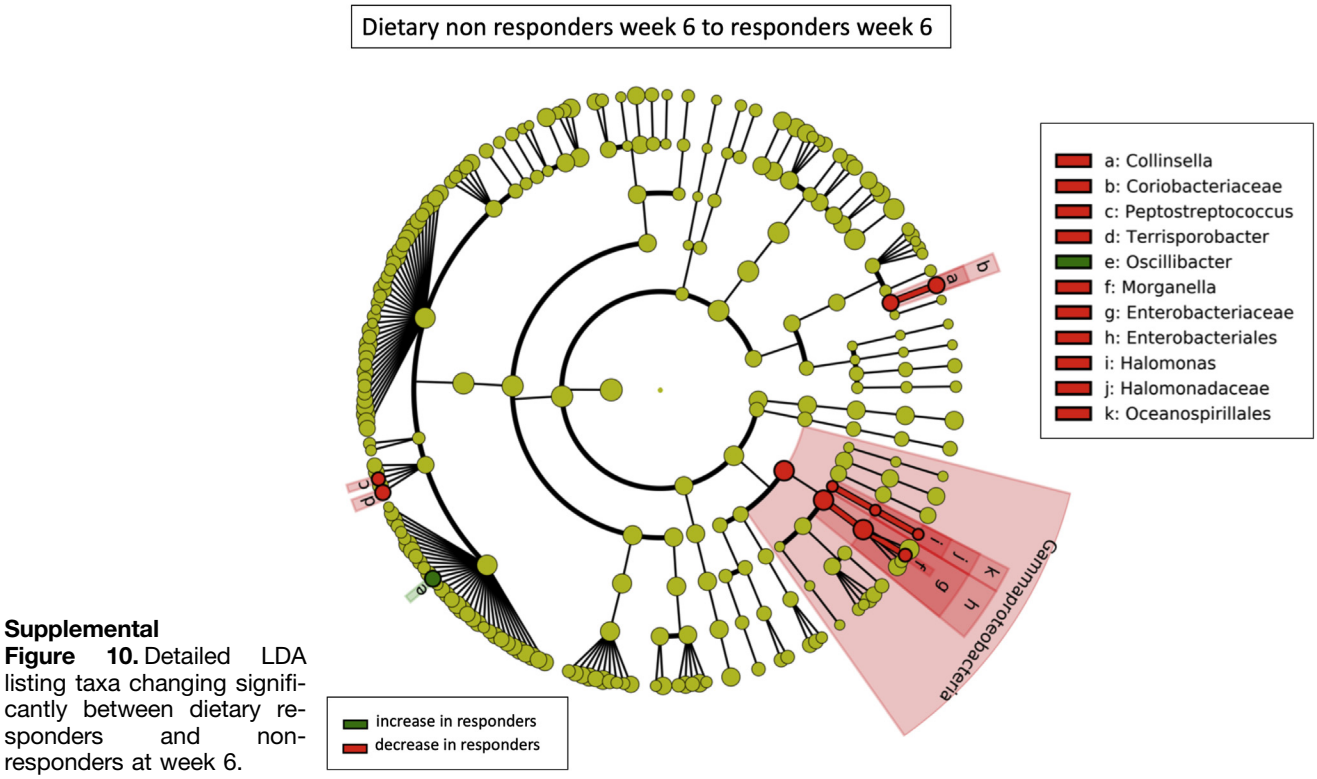
Supplemental Figure 7. Detailed LDA listing taxa changing significantly between week 0, and week 12 for EEN.



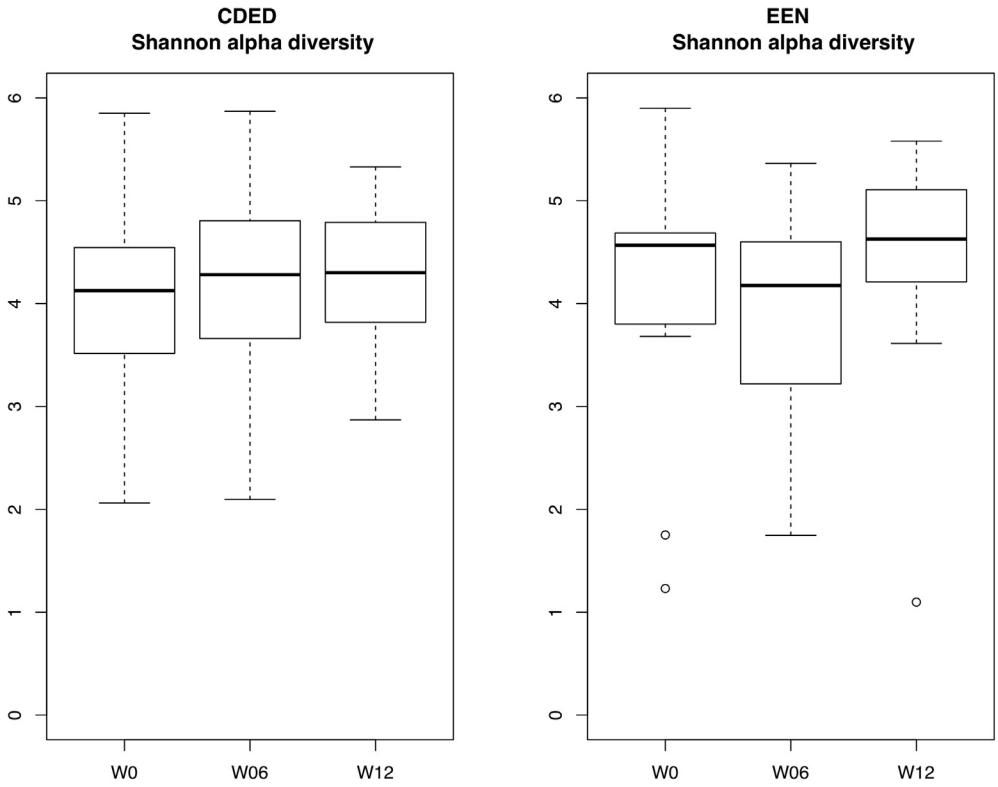
Supplementary Figures 8. Detailed LDA listing taxa changing significantly between dietary responders and nonresponders.



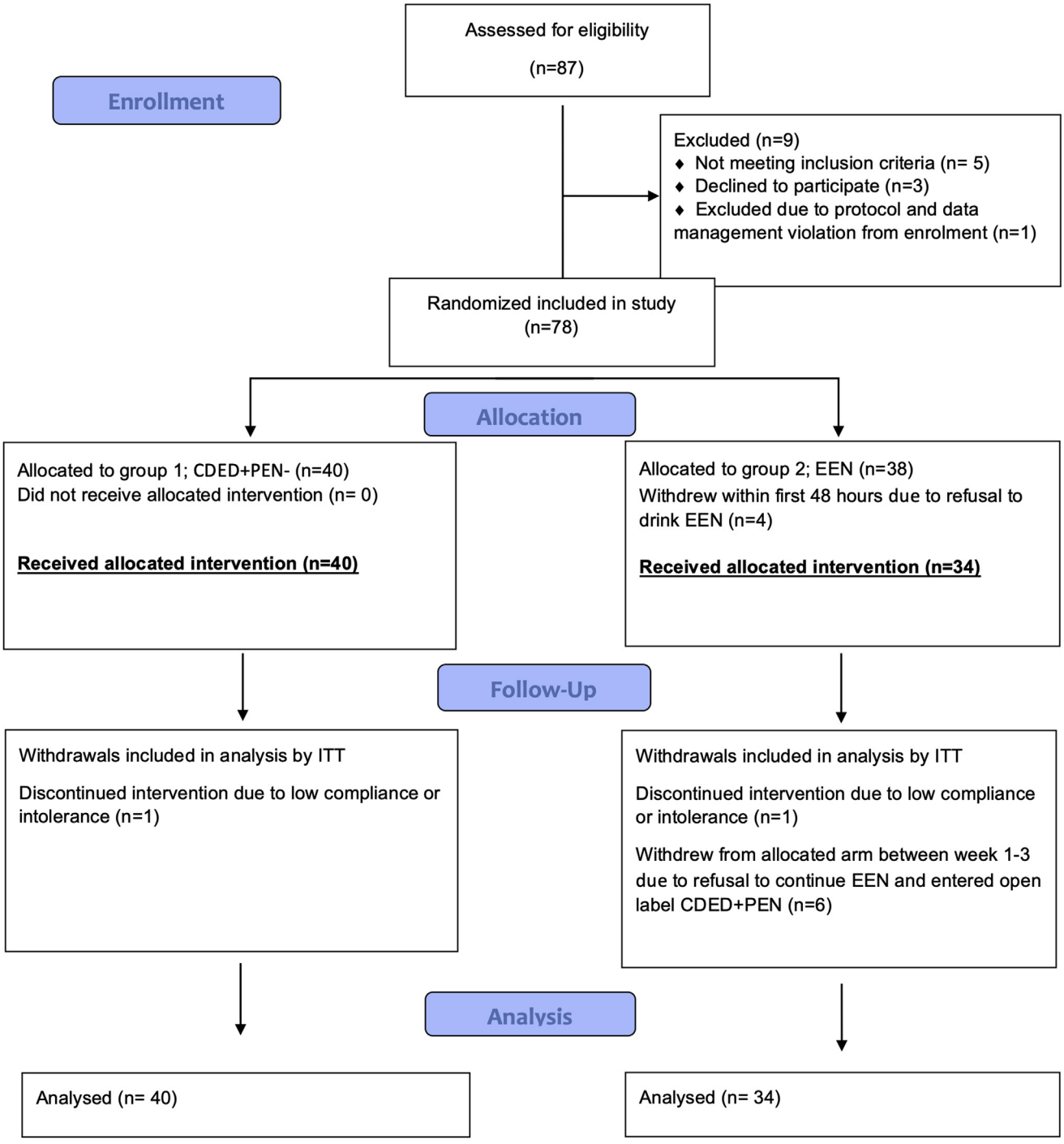
Supplemental Figure 9. Detailed LDA listing taxa changing significantly between week 0, and week 6 for dietary non-responders.



Supplemental Figure 10. Detailed LDA listing taxa changing significantly between dietary responders and non-responders at week 6.



Supplementary Figure 11. Average Shannon diversity at weeks 0, 6, and 12 in CDED+PEN and EEN.



Supplementary Appendix Figure. Study design CDED.