Partial Enteral Nutrition with a Crohn's Disease Exclusion Diet Is Effective for Induction of Remission in Children and Young Adults with Crohn's Disease

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Background: Exclusive enteral nutrition is effective for inducing remission in active pediatric Crohn's disease. Partial enteral nutrition (PEN) with free diet is ineffective for inducing remission, suggesting that the mechanism depends on exclusion of free diet. We developed an alternative diet based on PEN with exclusion of dietary components hypothesized to affect the microbiome or intestinal permeability.

Methods: Children and young adults with active disease defined as a pediatric Crohn's disease activity index >7.5 or Harvey–Bradshaw index ≥4 received a 6-week structured Crohn's disease exclusion diet that allowed access to specific foods and restricted exposure to all other foods, and up to 50% of dietary calories from a polymeric formula. Remission, C-reactive protein, and erythrocyte sedimentation rate were reevaluated at 6 weeks. The primary endpoint was remission at 6 weeks defined as Harvey–Bradshaw index ≤3 for all patients and pediatric Crohn’s disease activity index <7.5 in children.

Results: We treated 47 patients (mean age, 16.1 ± 5.6 yr; 34 children). Response and remission were obtained in 37 (78.7%) and 33 (70.2%) patients, respectively. Mean pediatric Crohn’s disease activity index decreased from 27.7 ± 9.4 to 5.4 ± 8 (P < 0.001), Harvey–Bradshaw index from 6.4 ± 2.7 to 1.8 ± 2.9 (P < 0.001). Remission was obtained in 70% of children and 69% of adults. Normalization of previously elevated CRP occurred in 21 of 30 (70%) patients in remission. Seven patients used the diet without PEN; 6 of 7 obtained remission.

Conclusions: Dietary therapy involving PEN with an exclusion diet seems to lead to high remission rates in early mild-to-moderate luminal Crohn’s disease in children and young adults.

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Key Words: Crohn's disease, child, diet, exclusive enteral nutrition, remission, environment, bacterial penetration cycle, Crohn's disease exclusion diet

Crohn's disease (CD) is caused by a combination of environmental and genetic factors, and a major role of the microbiota has been postulated in the pathogenesis of the disease.1

Although progress has been achieved in determining the genetic and immune basis for susceptibility to the disease, understanding the contribution of potential environmental risk factors has been difficult.2–5 All current therapies are aimed at the downstream events, namely intervention directed towards the host inflammatory response.

An alternative environmental factor, which has not been adequately explored in human subjects, is the effect of diet on CD. Diet has an effect on the composition of the intestinal microbiome and gut immune status.6–7 We have previously proposed that CD may arise from a sequence of events involving changes in the microbiome, intestinal permeability leading to bacterial adherence or penetration of the epithelium, and subsequent stimulation of the adaptive immune response leading to tissue damage.8–11 We have termed this sequence the Bacterial Penetration Cycle Hypothesis.12

The most important evidence-linking diet to CD comes from dietary interventions in children with active CD.12–16 Exclusive enteral nutrition (EEN) is a well-documented method of treatment. It involves placing children on a strict diet composed only of a single polymeric formula, as the sole source of nutrition over 6 to 8 weeks. Use of this treatment method, early in the disease, results in clinical remission in 50% to 80% of children by week 8 with no additional pharmacological treatment.12–16 Previous studies and clinical experience have shown that partial enteral nutrition (PEN) with 50% of calories from a formula with free diet is ineffective in inducing complete remission or reducing acute phase reactants, suggesting that the effect of EEN appears to depend, at least in part, on exclusion of free diet.17 In addition, since the mechanism of response or the triggering foods are unknown, there is no evidence based follow on strategy, to prevent recurrence upon re-exposure to normal diet. Therefore it is...
crucial to try to evaluate which of the excluded dietary components in EEN are responsible for the effect, to allow transition to a safe whole food diet.

We report a dietary intervention that involves whole foods but reduces exposure to dietary components have been shown to induce inflammation, change the microbiome, affect the mucous layer, increase IP or adherence and translocation of bacteria in rodent or cell line models.\(^{18-24}\)

Our experience started with 2 adolescents who had difficulty in continuing EEN despite an initial clinical response, they were placed on this structured diet with only 50% of calories from Modulen (Nestle, Switzerland), and went into complete remission with normalization of acute phase reactants. The diet subsequently became the standard of practice for patients with luminal uncomplicated mild-to-moderate disease who were not willing to use EEN. We report our experience with use of 50% PEN with CDED or CDED alone as the primary method for induction of remission in children and young adults with mild-to-moderate active CD.

**MATERIALS AND METHODS**

This is a report of our experience with a combination of PEN with CDED or CDED alone, developed by the senior author (A.L.) for active CD in outpatient children (≤18) and young adults. Patients received the diet between May 2011 and December 2013 at a pediatric IBD center and a gastroenterology outpatient center. The current report involves all patients treated by the time of submission and was not based on a calculated sample size. CD was confirmed by established criteria based on clinical, radiological, endoscopic, and histopathological findings.\(^{25,26}\)

Location of disease and disease behavior were defined by macroscopic involvement using the Paris classification.\(^{18}\) At baseline, patients were asked to perform a complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and albumin. All patients could schedule same week appointments if their situation deteriorated.

Inclusion criteria included children and young adults with active CD, defined as a Pediatric Crohn’s Disease Activity Index (PCDAI) \(\geq 10\)\(^{27}\) in children or Harvey–Bradshaw Index (HBI) \(>3\), evidence for active disease such as elevated CRP, ESR, or active disease by colonoscopy or capsule endoscopy, and available data for disease activity at baseline and at the 6-week follow-up visit. From January 2012, a PCDAI and HBI were routinely calculated at baseline and at weeks 6 and 12. The retrospective study was approved by the hospital’s ethical committee.

Patients were excluded (Fig. 1) (n = 4, 3 remission and 1 failure), if the patient’s charts were not available, if they had penetrating disease, active perianal disease or active extra-intestinal disease, high fever, or if they had received any other medication for inducing remission in addition to diet such as antibiotics, steroids, or 5-ASA.

Patients with strictures and evidence for active inflammation were not excluded. All patients receiving the diet were offered an immunomodulator because this is the standard clinical practice when using EEN in our institution. Concurrent stable dose maintenance therapy with immunomodulators such as thiopurines and methotrexate was allowed, as was initiation of thiopurines at onset or at the 3-week visit of nutritional therapy because this is the standard clinical practice for use of EEN in children, and thiopurines do not induce remission in active disease before the time of our endpoint at 6 weeks. Patients who received

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**FIGURE 1.** Flow chart of patients treated with diet.
concurrent induction of remission medications such as steroids, 5-ASA, methotrexate, or antibiotics were excluded, as were patients who were receiving induction doses of a biologic. Patients who were on stable biologic therapy who had failed therapy after the first 3 doses or lost response were included as long as no change in the biologic dose or schedule occurred.

All adult patients included in this study were adults who had failed a previous medical therapy and had approached the senior author for dietary treatment. All patients who tried the diet, met inclusion exclusion criteria and had available data, were included in this study.

**Dietary Intervention**

All patients were treated in an identical fashion with the same diet, and all were seen at baseline, again at week 6, and those who responded again at week 12. Children with moderate or severe disease also had a follow-up visit already at week 3. All patients received an identical dietary format, which was used for a period of 6 weeks, and then a step-down diet for an additional 6-week period (total 12 wk). The first period involved a more restricted diet (abbreviated diet in Appendix). All patients received a 3-page handout with instructions regarding the diet, and preparation of food, including a list of allowed and disallowed foods and products, as well as cooking tips. An explanation regarding the principles was given to all patients by a dietician or one of the physicians. All patients were offered 1 of 2 palatable polymeric formulas containing 1 Kcal/mL, either Modulen (Nestle, Vevey, Switzerland) or Pediasure (Abbott B.V., Hoofddorp, Netherlands) irrespective of age, after tasting the formula, according to preference, with a volume calculated to provide 50% of calories from the formula based on current weight, not to exceed 1250 kcal/d. Specific spices and herbs were also allowed, whereas all other condiments and sauces were not allowed. Specifically, gluten, dairy products, gluten-free baked goods and breads, animal fat, processed meats, products containing emulsifiers, canned goods, and all packaged products with a due date were not allowed. The diet allows up to 18 to 20 g of fiber per day. In the second 6-week period formula to supply only 25% of calories was continued, a fixed portion of whole grain bread was allowed as were small amounts of nuts fruits legumes and vegetables. Patients with strictures continued quantitative restriction of fruits and vegetables on an individual basis. Individuals who refused to drink the formula could take the diet without supplementation; however, this was discouraged by the team because the formula was the primary source of calcium. Children were asked to return after 3 weeks to determine response and compliance, and all patients were asked to return after 6 weeks. From January 2012, a specific dietary team answered all questions regarding the diet. Two research dieticians (R.S-B. and T. P-G.) were available for questions and cooking tips 5 days a week, and from 2013, a hot line was instituted to take calls in addition to office visits. Patients responsive to dietary therapy and entering remission were then educated about suspected dietary factors and asked to practice self-restriction by reducing dietary exposure to these products after week 12, but no structured specific diet was supplied after week 12.

**Endpoints**

Our primary endpoint was remission on an intention to treat principle after 6 weeks of therapy defined by a HBI for all patients. Remission defined by PCDAI was calculated separately for pediatric patients only (defined as a PCDAI <7.5 without the height item29 or a HBI ≤3).28

Secondary endpoints were normalization of CRP (defined as ≤0.5 mg/dL), response defined as a drop in PCDAI of at least 12.5 points for children or a drop in HBI of at least 2 points, change in specific blood tests from baseline such as hemoglobin, albumin, ESR, and CRP.

**Data Analysis**

Data were stored on spreadsheet and analyzed on SPSS (version 21; IBM Inc). Distributions of continuous variables were assessed for normality using the Kolmogorov–Smirnov test (cutoff at P < 0.01). Continuous variables with distributions significantly deviating from normal are described as median (minimum–maximum), whereas those with approximately normal distributions are presented as mean ± SD. Continuous variables were compared over time using the t-test for paired samples or the Wilcoxon signed ranks test as appropriate. Dichotomous variables were compared over time using the McNemar test. Additionally, responders were compared with others using the t-test for independent samples or the Mann–Whitney U test (as appropriate). Nominal variables were compared by response type using the chi-square test, exact as appropriate. All tests are two-sided and considered significant at P < 0.05.

**RESULTS**

**Patient Data**

Forty-seven patients meeting all inclusion and exclusion criteria (34 children, 13 adults; mean age was 16.1 ± 5.6 yr; mean disease duration, 2.1 ± 3.4 yr; range, 6–32 yr) were available for analysis. Four patients who were excluded (Fig. 1) because the patient’s data from either the baseline or week 6 visit were not available (n = 4, 3 remission and 1 failure), and 2 were excluded because they had received concurrent antibiotics. Baseline data, stratified by age of onset are presented in Table 1. Adults did not differ from children regarding HBI, disease location, baseline acute phase reactants, or albumin. Although disease was longer in adults (mean, 3.9 ± 4.9 versus 1.45 ± 2.1 yr) it was not significant, and there was a nonsignificant trend for more females in the adult group (P = 0.09).

Duration of disease ranged from disease onset to 13 years of disease. In 14 patients, this was the first treatment offered after diagnosis. In all others, the treatment was offered because of a relapse or lack of response to a previous therapy. Seven patients relapsed while on PEN as supportive therapy and

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TABLE 1. Characteristics of Patients at Baseline

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Total Cohort (n = 47)</th>
<th>Children (n = 34)</th>
<th>Adults (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>30 (63.4%)</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td>Age at onset, yr</td>
<td>13.86 ± 4.71</td>
<td>11.8 ± 3.1</td>
<td>19.3 ± 3.9*</td>
</tr>
<tr>
<td>Age range at onset, yr</td>
<td>6–28</td>
<td>6–18</td>
<td>12–28</td>
</tr>
<tr>
<td>Age at baseline diet, yr</td>
<td>16 ± 5.6</td>
<td>13.2 ± 2.6</td>
<td>23.4 ± 4.1*</td>
</tr>
<tr>
<td>Age range at diet, yr</td>
<td>9–31</td>
<td>7.5–18</td>
<td>18.3–32</td>
</tr>
<tr>
<td>Disease duration, yr</td>
<td>2.17 ± 3.53</td>
<td>1.45 ± 2.1</td>
<td>3.9 ± 4.9</td>
</tr>
<tr>
<td>New onset disease</td>
<td>12 (26%)</td>
<td>10 (29.5%)</td>
<td>2 (15.4%)*</td>
</tr>
<tr>
<td>Location (Paris)</td>
<td>L1-ileal/ileoceleal</td>
<td>21 (44.6%)</td>
<td>16 (47%)</td>
</tr>
<tr>
<td>L2-colon</td>
<td>3 (6.4%)</td>
<td>3 (8.8%)</td>
<td>—</td>
</tr>
<tr>
<td>L3-ileoceleonic</td>
<td>7 (14.9%)</td>
<td>5 (14.7%)</td>
<td>2 (15.4%)</td>
</tr>
<tr>
<td>L4a-gastric</td>
<td>1 (2.1%)</td>
<td>1 (2.9%)</td>
<td>—</td>
</tr>
<tr>
<td>L4b-proximal ileum or jejunum</td>
<td>2 (4.2%)</td>
<td>1 (2.9%)</td>
<td>1 (7.2%)</td>
</tr>
<tr>
<td>L4a + L1</td>
<td>2 (4.2%)</td>
<td>1 (2.9%)</td>
<td>1 (7.2%)</td>
</tr>
<tr>
<td>L4b + L3</td>
<td>1 (2.1%)</td>
<td>1 (2.9%)</td>
<td>—</td>
</tr>
<tr>
<td>L4b + L1</td>
<td>3 (6.3%)</td>
<td>1 (2.9%)</td>
<td>2 (15.4%)</td>
</tr>
<tr>
<td>L4a + L3</td>
<td>4 (8.5%)</td>
<td>4 (11.8%)</td>
<td>—</td>
</tr>
<tr>
<td>L1 + L4b</td>
<td>1 (2.1%)</td>
<td>—</td>
<td>1 (7.2%)</td>
</tr>
<tr>
<td>Severity</td>
<td>Baseline IMM (%)</td>
<td>26 (55.3%)</td>
<td>21 (61.8%)</td>
</tr>
<tr>
<td>Baseline PCDAI (n = 34)</td>
<td>—</td>
<td>27.7 ± 9.4</td>
<td>—</td>
</tr>
<tr>
<td>Mild (7.5–27.5)</td>
<td>—</td>
<td>19 (55.8%)</td>
<td>—</td>
</tr>
<tr>
<td>Moderate (30–37.5)</td>
<td>—</td>
<td>9 (27.2%)</td>
<td>—</td>
</tr>
<tr>
<td>Severe (&gt;40)</td>
<td>—</td>
<td>5 (15.2%)</td>
<td>—</td>
</tr>
<tr>
<td>HBI baseline</td>
<td>6.37 ± 2.74</td>
<td>6.12 ± 2.89</td>
<td>6.9 ± 2.17</td>
</tr>
<tr>
<td>Remission &lt;4</td>
<td>4 (10.6%)</td>
<td>4 (11.8%)</td>
<td>1 (7.2%)</td>
</tr>
<tr>
<td>Mild 4–6</td>
<td>21 (44.6%)</td>
<td>15 (44.1%)</td>
<td>5 (35.7%)</td>
</tr>
<tr>
<td>Moderate 7–8</td>
<td>12 (25.5%)</td>
<td>8 (23.6%)</td>
<td>4 (30.8%)</td>
</tr>
<tr>
<td>Severe &gt;9</td>
<td>10 (21.3%)</td>
<td>7 (20.6%)</td>
<td>3 (21.5%)</td>
</tr>
<tr>
<td>B2-stricture present</td>
<td>6 (12.7%)</td>
<td>4 (11.7%)</td>
<td>2 (15.3%)</td>
</tr>
<tr>
<td>Baseline CRP (mg/dL)</td>
<td>3 ± 2.8</td>
<td>2.86 ± 2.62</td>
<td>2.9 ± 3.32</td>
</tr>
<tr>
<td>Baseline ESR</td>
<td>30.5 ± 17.49</td>
<td>31.0 ± 16.6</td>
<td>27.9 ± 19.9</td>
</tr>
<tr>
<td>Baseline Albumin (g/L)</td>
<td>4.16 ± 1.83</td>
<td>4.22 ± 2.03</td>
<td>3.98 ± 0.47</td>
</tr>
</tbody>
</table>

PCDAI in patients <18.
*P < 0.01.
IMM, immunomodulator; PCDAI, pediatric Crohn’s disease activity index.

Response by Week 6

Response was obtained in 37/47 patients (78.7%), and remission was obtained in 33/47 patients (70.6%). Among children, full remission was obtained in 18/24 (75%) patients with mild disease, 5/7 (71%) with moderate disease, and 1/3 (33.3%) with severe disease. Table 2 presents data regarding disease activity and severity before and after therapy. Five patients were not compliant (2 did not perform the diet at all as instructed, due to lifestyle, and failed to improve), and 3 complied for the most part but allowed occasional products that were not allowed (2/3 full remission). In addition, 7 refused to take any formula but were compliant with the CDED. The rest of the patients used the diet as instructed for the first few weeks unless no improvement was seen, and they were treated with other medications.

Thirty-four patients were 18 years or younger (remission 24/34, 70.1%), 13 adults were aged 19 to 32 years (9/13 remission, 69.2%), thus remission rates were similar in children and adults. Among new onset patients (n = 12), remission was obtained in 6/10 (60%) children and in 2/2 adults. Among patients with relapses, remission was obtained in 18/24 (75%) children and 7/11 (63.6%) of adults.

Normalization of CRP (CRP ≤0.5 mg/dL) was present in 21/30 patients with previously elevated CRP in remission (70%). Among responders, a CRP <1 mg/dL occurred in 31/34 (90%) responders with a previously elevated CRP. A significant decline (P < 0.001) by week 6 was seen for mean PCDAI, HBI, ESR, and CRP, whereas changes in albumin and weight were not statistically significant at this time point, but were significant by week 12. Changes between weeks 0 and 6 CRP and PCDAI for individual patients are portrayed in Figure 2A, B.

Factors Predicting Response at Week 6

The only significant predictor of response was baseline disease severity for children. The mean PCDAI without height component for those entering remission was 26.1 ± 9 versus 32 ± 9 for failures (P = 0.013). Mean HBI for the whole cohort,

| TABLE 2. Pairwise Comparisons of Parameters Between Baseline and Week 6 |
|----------------|$N=47$|Baseline|Week 6|P|
|HBI|6.37 ± 2.74|1.85 ± 2.93|0.000|
|PCDAI (n = 34)|27.7 ± 9.4|5.4 ± 7.98|0.000|
|CRP|2.9 ± 2.7|0.86 ± 1.0|0.000|
|ESR|29.3 ± 16.6|17.0 ± 10.9|0.000|
|Hemoglobin|12.2 ± 1.3|12.3 ± 1.2|0.5|
|Albumin|4.2 ± 2|4.07 ± 0.40|0.67|

Pairwise comparisons only in subjects with parameters at both time points. HBI calculated for all patients. PCDAI calculated only for children and adolescents through age 18 years.
however, was not significantly different (Table 1). There was no difference between patients obtaining remission and those not obtaining full remission regarding inflammatory biomarkers or use of an immunomodulator (61.7% versus 60%; \( P = 0.66 \)). All but 7 patients in response were on a stable dose immunomodulator or biologic or did not receive immunomodulation before week 6.

Five patients started the diet after failing to achieve remission with a biologic or after loss of response to biologics (infliximab, \( n = 3 \); infliximab + methotrexate, \( n = 1 \); loss of response to both adalimumab and infliximab, \( n = 1 \)); of these, 3 of 5 obtained remission with the diet and 2 failed. Seven patients took the diet without any formula because of intolerance or taste issues, 6 of 7 obtained remission with the whole food diet alone.

**Changes After Week 6**

Table 3 portrays pairwise comparisons between weeks 0 and 12 for the whole cohort without medication change and with follow-up after reintroduction of limited bread and free exposure to fruits vegetables and nuts (unless a stricture was present). Because of abnormal distribution of HBI results, HBI is also portrayed as median with range in Table 3. Significant improvement compared with baseline was present for PCDAI and HBI, CRP, and ESR as well as weight gain and improvement in albumin.

At week 12, 27/32 (84%) patients in remission with follow-up were still in remission after the step-down phase, 28/32 had repeated acute phase reactants. Three patients who relapsed by week 12 performed the first stage diet again and 2/3 regained remission. Two required other therapies.

At present, we have data for 15 patients who have remained on stable therapy without change in medication and practiced dietary restriction, regarding mucosal healing (14 follow-up colonoscopy, 1 MRE + calprotectin, range 6 mo–2 yr after treatment). Eleven patients were on an immunomodulator and 4 were on diet alone without medication. Eleven of these 15 patients had complete mucosal healing or normal MRE with normal calprotectin, including the 4 on diet alone, 3 had active disease, and 1 patient with previous extensive disease had complete healing in most segments but had residually active disease in a strictured segment of bowel.

**DISCUSSION**

EEN is very effective for induction of remission in mild-to-moderate recent onset pediatric CD. However, reported remission rates in pediatric studies have varied from 40% to 80%\(^{14,16,17,30}\). Bias by type of analysis (per protocol or intention to treat) and patients reported may exist. Thus, in a per protocol analysis including only patients who completed EEN from a Dutch group, the remission rate was 71%, whereas in 2 other studies with intention to treat, analysis rates at disease onset varied from 75% to 80%.\(^{16,30,31}\) Results from

**TABLE 3. Pairwise Comparisons of Parameters Between Weeks 0 and Week 12**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Week 0</th>
<th>Week 12</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBI, mean</td>
<td>5.9 ± 2.7</td>
<td>0.75 ± 1.75</td>
<td>0.000</td>
</tr>
<tr>
<td>HBI, median (range)</td>
<td>6.0 (0–13)</td>
<td>0.0 (0–6)</td>
<td>0.000</td>
</tr>
<tr>
<td>PCDAI (n = 24)</td>
<td>25.7 ± 8.9</td>
<td>6.44 ± 8.07</td>
<td>0.000</td>
</tr>
<tr>
<td>CRP</td>
<td>2.3 ± 2.3</td>
<td>0.81 ± 0.64</td>
<td>0.002</td>
</tr>
<tr>
<td>ESR</td>
<td>25.7 ± 12.7</td>
<td>17 ± 8.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>12.0 ± 1.4</td>
<td>12.6 ± 1.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.8 ± 0.42</td>
<td>4.12 ± 0.39</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Pairwise comparisons only in subjects with parameters at both time points. Abnormally distributed variables are present as median values. HBI (used in all patients). PCDAI calculated only for children and adolescents through age 18 years. PCDAI, pediatric Crohn’s disease activity index.
adult studies have been more variable, but similar remission rates were reported in several small studies.\textsuperscript{32,33} One randomized controlled study in adults demonstrated that 21/30 patients refractory to steroids entered remission with enteral nutrition.\textsuperscript{33}

Although the mechanisms of EEN are not fully substantiated, there are, however, a number of lines of evidence now known.\textsuperscript{6–12} It is unclear at present if the mechanism depends on the supply of specific nutrients or the exclusion of dietary factors. The biggest drawback is the difficulty in implementing an exclusive monotonous liquid diet for 6 to 8 weeks. We have previously proposed that the mechanism may be exclusion of dietary products that may affect intestinal permeability, enhance translocation or adherence of bacteria to epithelium, or promote a proinflammatory microbiome in animal models and cell lines.\textsuperscript{12}

We have shown that a dietary intervention in mild-to-moderate disease, based on 50% PEN and a structured diet that excludes these products can induce clinical remission with a reduction in inflammatory markers. The CDDED, which avoided or reduced exposure to animal fat, dairy products, gluten, and emulsifiers and enabled exposure to fiber from fruits and vegetables led to remission in 70% of patients, primarily in patients with early mild-to-moderate disease. Furthermore, this diet was accompanied by a significant decrease in CRP and ESR and normalization of CRP in approximately 70% of patients entering remission. A previous study has shown that 50% PEN with free diet induced remission only in 15% of patients and did not decrease inflammatory markers,\textsuperscript{17} so it is likely that the higher remission rates and significant decrease in CRP shown in our study are likely due to the inclusion of dietary factors.\textsuperscript{17} This is further supported by the fact that 7 patients were active, despite ongoing PEN and responded to PEN with CDDED instead of PEN with free diet. In addition, the diet seemed to be effective even in patients who did not take any supplemental formula (no PEN), as evidenced by the fact that 6/7 patients who just used the CDDED without any formula entered full remission. This is significant because the CDDED allows access to specific foods to improve palatability and allowed patients who would have otherwise refused to use nutritional therapy, an alternative to steroids and biologics for induction of remission in mild-to-moderate disease. Furthermore, in this small cohort, young adults responded as well as children and adolescents. This may allow broader use of nutritional therapy in adults.

Although we cannot compare head-to-head efficacy, the remission rate in our study (70%) is similar to the 75% remission rate using oral EEN therapy in a large French study.\textsuperscript{16} Although our limited data on mucosal healing in patients who achieved remission with dietary therapy is very encouraging, most of these patients (10/14 with complete mucosal healing) had received an immunomodulator for maintenance therapy, which does not allow us to gain insight in to the effect of the diet for maintenance of remission.

Similar to all previous studies involving dietary therapy,\textsuperscript{13,14,16,17} the population investigated was a selective population involving primarily children and very young adults with a relatively short duration of uncomplicated disease. Our patients were primarily those with small intestinal or ileocolonic disease with mild-to-moderate luminal disease, although 5 patients with severe disease were treated and therefore included in this report. We investigated very few patients with isolated colonic disease, and all of these patients in our cohort were patients who had previously failed steroids or a biologic. Within our selected population, disease severity was the only significant predictor of response, which is probably true for most therapies. However, current severity as based on disease activity scores may be misleading because the diet succeeded in obtaining remission in 3/5 patients who failed to achieve remission or lost response to biologics.

Research in animal models and cell lines have supplied us with candidates for environmental factors that may allow stimulation of the adaptive immune response by luminal bacteria.\textsuperscript{12} Bacterial adherence and translocation are inhibited by the mucous layer, the integrity and selective permeability of the epithelium, and bacterial clearance mechanisms. Processed or industrialized foods contain numerous combinations of products that may affect the intestines’ ability to contain bacteria to the lumen. Roberts et al\textsuperscript{23} demonstrated that translocation of adherent invasive \textit{E. coli} (AIEC) across intestinal M cells and Peyer’s patches is increased by exposure to low levels of a commonly used emulsifier (polysorbate 80) commonly used in ice creams, whipping creams, dessert toppings, and condiments. This emulsifier is in dill pickles. Carboxymethylcellulose (E 466), an emulsifier and thickener commonly used in dairy products, processed meats, and breads may allow bacteria to migrate and adhere to the epithelium, possibly by affecting the mucous layer.\textsuperscript{22} The microbiome is clearly altered by diet.\textsuperscript{6} Milk fat and animal fat have been shown to increase IP and alter the microbiome.\textsuperscript{21} Martinez et al\textsuperscript{19} compared CEABAC10 mice with or without \textit{AIEC} with WT mice with or without \textit{AIEC}; both groups were fed a western diet rich in fats and simple sugars or regular chow. The Western diet promoted mucin-degrading bacteria increased AIEC counts and increased intestinal permeability.\textsuperscript{19} Gliadin from Gluten induces zonulin release in the small intestine, increasing IP in a dose-dependent fashion.\textsuperscript{24} Maltodextrin has been found to promote AIEC biofilms and increase adhesion of AIEC strains to epithelial cells and macrophages.\textsuperscript{35} Maltodextrin is a thickening and binding agent found in breakfast cereals and aspartame and sucralose, commonly used as artificial sweeteners.

Although research in animal models has helped identify specific suspects\textsuperscript{3,9,23,35} and allows plausible incorporation of these factors into models for pathogenesis,\textsuperscript{12,26} only human studies can confirm the actual role of these components in triggering inflammation.

We clearly need additional research to develop this theme further; however, it could be incredibly difficult to evaluate individual components in isolation, because food is so complex and many of these products may act synergistically. Thus, we
elected to evaluate the concept of elimination of multiple suspect foods for therapy and believe that our study may help to develop additional therapeutic alternatives to augment our present therapeutic strategies. There clearly is a need for a randomized controlled trial to increase the level of evidence and compare the clinical utility of this method to EEN, although we believe that given the remission rates with both methods, any such trial will encounter difficulties with sample size and difficulty in proving non inferiority. In the interim, we believe that PEN with the CDED may be useful for patients with mild-to-moderate disease as an alternative to EEN.

REFERENCES

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**APPENDIX: Abbreviated CDED Weeks 0-6**

Allowed Foods Daily Meals: Foods may be grilled, fried, baked, boiled, and broiled
Fresh Chicken Breast, Fresh Fish—unlimited
Fresh Unprocessed Beef Steak (lean meat such as sirloin)—once a week
White Rice
Rice Noodles
2 fresh Potatoes (Peeled), frozen potatoes not allowed, not to be consumed at same meal
2 Eggs
2 Tomatoes
2 Cucumbers (peeled)
1 Carrot (shavings)
Fresh Spinach (side portion)
1 Apple (peeled—if no tight stricture)
2 Bananas
1 Avocado
Few Strawberries
Slice Melon

Allowed Condiments for cooking:
Olive oil, Canola oil
Salt, Pepper, Paprika, Cinnamon stick
Fresh Herbs (Mint leaves, oregano, coriander, rosemary, sage, basil, thyme)
Fresh onion or garlic or ginger
Fresh Carrot shavings for salad, rice or soup
True Honey
Table Sugar (2–3 Teaspoons a day for Cooking or Tea)
Beverages
Water, Soda, herbal teas
One glass of freshly squeezed orange juice daily (not from cartons or bottles)
Not allowed
Dairy products of any kind, margarine
Wheat, breakfast cereals, breads and baked goods of any kind, yeast for baking
Gluten-free products not listed above, Soya products, potato or corn flour
Processed or smoked meats and fish (sausages, luncheon meats, salamis, fish sticks)
Sauces, salad dressings, syrups and jams of any kind
Canned products and Dried Fruits
Packaged snacks (potato chips, pretzels, popcorn, nuts, etc)
All soft drinks, fruit juices and sweetened beverages, alcoholic beverages, coffee
Candies, chocolates, cakes, cookies and gum