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BRIEF REPORT



## Crohn's disease exclusion diet in children with Crohn's disease: a case series

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### ABSTRACT

Exclusive enteral nutrition (EEN) represents an established, evidence-based dietary therapy used in Crohn's disease (CD); although successful, EEN is extremely restrictive with limited acceptability and prolonged use. The Crohn's disease exclusion diet (CDED) is a new, sustainable and patient-friendly dietary therapy used for the management of pediatric CD. CDED is designed to reduce exposure to dietary components hypothesized to negatively affect the microbiome, intestinal barrier and immunity. By focusing on five clinical cases, this article illustrates the benefits of using CDED as mono- or co-therapy with partial enteral nutrition in children with mild to moderate CD. CDED combined with partial enteral nutrition is a safe and effective therapeutic option for both induction and maintenance therapy in children with mild to moderate CD. It ensures sustained remission and can induce mucosal healing in children with mild to moderate Crohn's disease.

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Adherence; Crohn's disease (CD); Crohn's disease exclusion diet (CDED); partial enteral nutrition (PEN); remission; tolerance

## 1. Introduction

Crohn's disease (CD) is an idiopathic chronic inflammatory affection involving the gastrointestinal (GI) tract. CD is a life-long, to date incurable affection, whose natural history is characterized by alternating quiescent periods and active flares of inflammation, progressing to bowel damage and subsequent considerable morbidity<sup>1</sup>. 20–30% of patients receive a diagnosis of Crohn's disease (CD) under the age of 17 years, with a progressive acceleration in incidence in the last decades<sup>2–7</sup>.

When arising during childhood or adolescence, these conditions tend to have a more severe and disabling course when compared to adult-onset disease<sup>8</sup>. Despite the exact pathophysiology of CD remains undetermined, it has been widely endorsed that multifactorial etiology including an interaction between genetic and environmental factors can contribute to CD pathogenesis<sup>9</sup>. The dramatic rise in the incidence of IBD in newly industrialized countries shifting to Western dietary habits<sup>10</sup> represents one of the foremost clues of the relevant influence of environmental factors, amongst which diet, in IBD pathogenesis. More specifically, high animal or dairy fat, animal protein, wheat, emulsifiers and thickeners appear to be more strongly associated with intestinal inflammation in animal models<sup>11</sup>. Despite the advent of novel biologic therapies, CD is still associated with progression to complicated disease and consequent morbidity<sup>12</sup>. In addition, immunosuppressant drugs and biologic agents bring with them non-negligible side effects, such as infections and malignancies<sup>13,14</sup>.

Exclusive enteral nutrition (EEN) is a nutritional treatment strategy that provides the total amount of calories requirements of patients through a proprietary liquid formula administered orally *via* an enteral tube for 6–8 weeks<sup>9</sup>. While EEN can effectively induce remission, it is not sustainable for long-term therapeutic courses owing to its extremely restrictive nature<sup>9</sup>. Besides, EEN effects reverse when patients resume their habitual diet and gut inflammation correspondingly increases.

More recently, the Crohn's disease exclusion diet (CDED) combined with PEN, hereafter referred to CDED, a whole-food diet designed to reduce exposure to dietary components hypothesized to negatively affect the microbiome, intestinal barrier and immunity, has been successfully employed to achieve clinical, biochemical and endoscopic healing when coupled with PEN<sup>9</sup>. A randomized controlled trial showed better tolerability of CDED compared to EEN in addition to a sustained remission<sup>15</sup>. In parallel, CDED showed to be as effective as EEN for inducing remission and reducing inflammation<sup>15</sup>. CDED is a high-protein low-fat multistage diet designed with a 12-week induction phase and third-stage maintenance phase wherein access to more foods is allowed every 6 weeks<sup>9</sup>. CDED consists of excluding plausible dietary culprits while access to whole and unprocessed foods, such as fruits, vegetables, chicken, eggs, rice and potatoes, is permitted<sup>9</sup>. CDED is also enriched with beneficial fibers and is combined with liquid formulas to complete energy needs and provide additional sources of protein and calcium<sup>9</sup>.

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Further, this novel dietary approach poses questions to the existing concepts of optimal therapy in CD and at the same time raises queries about how dietary treatment should be used in the management of CD. This article describes five clinical cases aiming to illustrate some of the applications and the benefits of using CDED in children with CD.

## 2. Case reports

### 2.1. Patient 1 – 12-year old boy suffering from mild CD treated with CDED monotherapy

#### 2.1.1. Case description

A 12-year-old boy with unremarkable past medical history presented to our outpatient clinic with a 3-month history of epigastric pain, reduced appetite and weight loss. Prior to our center's referral, the patient was evaluated at a secondary-level pediatric center and a 2-week empirical trial with a proton pump inhibitor was attempted, without symptoms alleviation. Physical examination was unremarkable except for the presence of 2 perianal skin tags. His blood tests revealed a slight increase of C-reactive protein (CRP, 1.15 mg/dL), with normal erythrocyte sedimentation rate (ESR); and fecal calprotectin was elevated at 500 microg/g. Hemoglobin was 12.9 g/dL, albumin and transaminases were in the normal range with a pediatric Crohn's disease activity index (PCDAI) of 20. Bowel ultrasound scan showed no abnormal bowel thickenings. Esophagogastroduodenoscopy (EGD) showed aphthous ulcers in the duodenal bulb but was otherwise normal. Ileocolonoscopy revealed aphthous ulcers in the terminal ileum, cecum, ascending and descending colon. Biopsies collected during endoscopies confirmed chronic inflammation with mucosal architecture disruption, confirming diagnosis of CD. A magnetic resonance enterography (MRE) revealed multiple enhancement with only limited thickening in the terminal ileum and in the upper digestive tract distally to Treitz' ligament. No strictures or fistulas were observed (Paris Classification: A1b, L3-L4a, B1, G1, P1)<sup>16</sup>.

#### 2.1.2. Nutritional status

The first physical evaluation revealed a good nutritional status. Height (159 cm; 75° centile) and weight (52 kg; 50° centile) were within normal range for age and sex. The body mass index (BMI) was 20.6 kg/m<sup>2</sup> (z-score: 0.8). Despite a good nutritional status, the patient reported a weight loss of 10 kg during 3 months prior to referral to our center.

#### 2.1.3. Clinical course, treatment and outcomes

As the patient was not affected by stricturing or fistulizing disease, a 6-week diet regimen was prescribed. The patient started CDED with partial enteral nutrition (PEN; Modulen IBD<sup>®</sup>); the CDED was well tolerated and adherence to diet regimen was good. After 6 weeks of treatment, the patient's appetite was markedly increased with a 4-kg weight gain; the symptoms resolved completely (PCDAI: 0). Blood tests were all in normal range, fecal calprotectin was negative (below 100 microg/g). Unfortunately, the patient developed

perianal disease. Therefore, fistulectomy with seton placement was performed and treatment with anti-TNF alpha agent (infliximab) was initiated. Post-operative course was uneventful. The patient transitioned to phase 2 and 3 of CDED diet and continued phase 3 of CDED with a good reported adherence since the last follow up, on February 2021. He concurrently continued infliximab with infusions every 8 weeks. The patient did not experience disease flares, hospitalization or further surgical interventions.

### 2.2. Patient 2 – 13-year old boy suffering from mild CD treated successfully with CDED induction monotherapy

#### 2.2.1. Case description

A 13-year-old boy referred to our outpatient clinic with a 2-month history of recurrent abdominal pain. Past and family medical history was unremarkable and his physical examination was normal. Blood tests revealed an increased CRP (1.87 mg/dL) and ESR (87 mm/h) along with a microcytic anemia (hemoglobin: 11.2 g/dL, mean corpuscular volume: 65 fL). The PCDAI was slightly elevated (22.5). Fecal calprotectin was markedly increased at 1980 microg/g. Esophagogastroduodenoscopy was normal. Ileocolonoscopy revealed aphthous ulcers in the terminal ileum in a context of erythematous mucosa along with erosions in descending and sigmoid colon. Biopsies collected during endoscopies confirmed chronic inflammation with mucosal architecture disruption and epithelioid granulomas, confirming diagnosis of CD (Paris Classification: A1b, L3, B1, G0, P0)<sup>16</sup>.

#### 2.2.2. Nutritional status

The first physical evaluation revealed a good nutritional status. Height (155.3 cm; 50–75° percentile) and weight (49.3 kg; 50–75° percentile) were within normal range for age and sex, and the BMI was 20.5 4 kg/m<sup>2</sup> (z-score: 0.8).

#### 2.2.3. Clinical course, treatment and outcomes

As no strictures or fistulas were present, a 6-week diet regimen was prescribed. The patient started CDED with PEN (Modulen IBD<sup>®</sup>); with good tolerance and optimal adherence to diet regimen. Due to the endoscopic burden of the disease, azathioprine was added as maintenance therapy. After 6 weeks of treatment, symptoms resolved completely (PCDAI: 0). Blood tests were all in the normal range, and fecal calprotectin was negative (below 100 microg/g). The patient transitioned to phase 2 and 3 of the diet and maintained sustained clinical remission until last follow-up (December 2020). In December 2020, we performed a capsule endoscopy evaluation in order to assess mucosal healing. The exam showed a global improvement of the inflammation throughout the intestine. However, few millimetric erosions in the terminal ileum were still present.

### **2.3. Patient 3 – 17-year old boy suffering from CD treated with PEN and CDED to promote mucosal healing**

#### **2.3.1. Case description**

A 17-year-old boy was referred to our center from an Italian adult gastroenterology center following a diagnosis of ileo-cecal CD. Mesalazine was started then interrupted after 3 weeks and replaced with budesonide because of the occurrence of cutaneous adverse reaction. The physical examination was unremarkable. Blood tests revealed only an increase CRP level (2.26 mg/dL), whereas the other parameters were in the normal range. Endoscopic re-assessment (EGD, ileo-colonoscopy and capsule endoscopy) was performed, revealing multiple erosions and aphthous ulcers in the proximal duodenum and terminal ileum. Biopsies confirmed the presence of chronic inflammation along with epithelioid granulomas. No strictures or fistulas were observed on MRE (Paris Classification: A2, L1-L4a, B1, G0, P0)<sup>16</sup>.

#### **2.3.2. Nutritional status**

The first physical evaluation revealed a discrete nutritional status. Height (184 cm; 90° centile) and weight (60.8 kg; 25° centile) were within the normal range for age and sex, and the BMI was 18 kg/m<sup>2</sup> (z-score: –1.58).

#### **2.3.3. Clinical course, treatment and outcomes**

The patient started a CDED with PEN (Modulen IBD). The CDED was well tolerated and adherence to diet regimen was good. After 6 weeks of treatment, symptoms resolved completely (PCDAI: 0). Blood tests showed a marked decrease of CRP (1 mg/dL) and a significant reduction of fecal calprotectin (from 1240 microg/g to 234 microg/g). The patient transitioned successfully to phase 2 and 3 of the diet and azathioprine was introduced as maintenance therapy. At week 12, the patient maintained clinical remission and fecal calprotectin and inflammatory markers returned all in normal range (fecal calprotectin < 100 microg/g, CRP < 0.5 mg/dL and ESR < 15 mm/h). A capsule endoscopy re-assessment was performed 9 months after diagnosis showing a clear improvement of duodenal and ileal mucosal inflammation, with only few erosions persisting in terminal ileum. The patient was therefore transitioned to an adult center since he reached 18 years old.

### **2.4. Patient 4 – 8-year old boy suffering from refractory CD treated with CDED rescue therapy**

#### **2.4.1. Case description**

An 8-year-old boy was referred to our outpatient clinic from another referral center in Italy, following a diagnosis of ileo-colic CD complicated by perianal involvement (Paris Classification: L3, B1, G1, P)<sup>16</sup>. An anti-TNF alpha treatment with adalimumab was promptly initiated, along with PEN (Modulen IBD). Despite interrupting PEN after only few weeks due to scarce tolerance, the patient showed a marked improvement of both abdominal and perianal disease

symptoms and normalization of laboratory parameters. Twelve months later, a recrudescence of complex perianal disease was observed; pelvic magnetic resonance imaging (MRI) showed 2 trans-sphincteric fistulae tracts. Therefore, fistulectomy with seton placement was performed. Post-operative course was regular and seton was removed 6 months after surgery with complete healing of the tract. Despite complete resolution of perianal inflammation, the patient experienced luminal disease relapse symptoms recurrence and iron-refractory anemia. Ileo-colonoscopy revealed aphthous ulcers involving the terminal ileum, whereas capsule endoscopy showed also jejunal involvement. Despite the intensification of adalimumab regimen, laboratory tests showed persistently elevated inflammatory markers (CRP 11.2 mg/dL, ESR 86 mm/h) and fecal calprotectin (686 mg/kg). Moreover, MRE revealed multiple enhancement with only moderate thickening in the terminal ileum (transmural thickening: 8 mm).

#### **2.4.2. Nutritional status**

Physical evaluation revealed a deficient nutritional status. Height was within normal range (50° centile), whereas weight was below lower centiles (<3°). The BMI was 14.6 kg/m<sup>2</sup> (z-score: –1.83).

#### **2.4.3. Clinical course, treatment and outcomes**

As the patient was not satisfactorily responding to adalimumab, prior to switching to another biologic agent, CDED with PEN was prescribed. The CDED was well tolerated and adherence to diet regimen was excellent. After 6 weeks of treatment, the symptoms resolved completely (PCDAI: 0). Inflammatory markers were all in normal range (CRP < 0.5 mg/dL and ESR < 15 mm/h), and fecal calprotectin was markedly decreased (220 mg/kg). The patient transitioned to phase 3 and maintained a sustained clinical remission (PCDAI below 10) until last follow-up in December 2020.

### **2.5. Patient 5 – 13-year old boy suffering from refractory CD treated with CDED rescue therapy**

#### **2.5.1. Case description**

A 13-year-old boy with a 4-year history of a multidrug refractory CD. He was diagnosed at the age of 9 years with a terminal ileum localization. Due to the unresponsiveness of the disease to multiple medical agents (azathioprine, adalimumab, infliximab, methotrexate and thalidomide), the patient underwent ileal and right colon resection with a primary ileo-colic anastomosis. The patient experienced an early disease relapse and surgical revision was required. Immediately after the early disease relapse, adalimumab was re-started. One-year endoscopic re-assessment displayed disease recurrence despite ongoing anti-TNF alpha treatment (Rutgeerts score: i4). For this reason, ustekinumab treatment was initiated with initial good clinical and laboratory response. Nevertheless, our patient experienced a new disease relapse after 6 months despite the novel biologic agent introduction. Serum drug levels of ustekinumab were elevated and

anti-drug antibodies were negative. Despite treatment intensification, our patient showed persistently elevated serum inflammatory markers (CRP 3.8 mg/dL) and calprotectin (1000 mg/kg).

### 2.5.2. Nutritional status

The patient presented a deficient nutritional status. Both height and weight were below the normal ranges, being both <3<sup>o</sup> centile.

### 2.5.3. Clinical course, treatment and outcomes

As the patient was affected by medical treatment-refractory disease, a 6-week diet regimen was prescribed. The patient started a CDED with PEN (Modulen IBD), with initial good tolerance and optimal adherence to diet regimen. After 6 weeks of treatment, the patient's appetite was markedly increased with a weight gain of almost 3 kg; the symptoms resolved completely (PCDAI: 0). Blood tests revealed negative inflammatory markers (CRP < 0.5 mg/dL and ESR < 15 mm/h) and also a decrease in fecal calprotectin (from 1000 mg/kg to 700 mg/kg). The patient continued ustekinumab (45 mg every 5 weeks) and transitioned to phase 2 then to phase 3, displaying good symptoms control (PCDAI below 10) with the combination of CDED and biologic therapy up to the last follow-up in February 2021.

## 3. Discussion

The incidence of pediatric onset CD has significantly risen in the past decades<sup>8</sup>. Despite the increasing knowledge about CD, this disease remains associated with many complications due to its progressive nature<sup>12</sup>. Moreover, one of the great challenges of CD treatment is the safety in terms of infections and malignancies<sup>17</sup>. From this perspective, CDED, a whole-food diet coupled with PEN<sup>11</sup> aims to reduce the exposure to dietary components which have shown positive association with intestinal inflammation and with dysbiosis. This diet has demonstrated to be well tolerated and effective in inducing remission in children affected by CD<sup>15</sup>. In this context, these 5 educational cases focused on the dietary management of pediatric CD using CDED as mono- and co-therapy and its longer-term impact in children who were still on remission for several months.

The first case reported successful induction and maintenance of clinical and laboratory remission in a young patient affected by mild CD with CDED monotherapy. This patient developed complex perianal disease soon after disease onset and therefore underwent surgery. Despite surgery, the patient successfully transitioned to further phases of the diet, maintaining adherence for a relatively long period (9 months). This case illustrates how CDED combined with PEN, can be offered as a first-line option with short- and long-term positive impact on the disease progression. While the study by Levine et al.<sup>15</sup> excluded patients with perianal disease, the present case offered an insight on how CDED might be useful to optimize nutritional status and minimize post-operative complications in patients requiring surgery,

both for perianal and luminal disease. The second and third cases showed how CDED combined with PEN can be offered as a first-line treatment in motivated patients with mild to moderate CD providing clinical, laboratory remission, and mucosal inflammation improvement. The fourth and fifth cases demonstrated how CDED may be used as a rescue therapy for refractory patients, with the advantage of reducing exposure to further drugs, avoiding surgery, while targeting the source of inflammation at deeper levels.

The proven efficacy of selected nutritional interventions such as EEN and CDED coupled with PEN in ameliorating active disease in pediatric CD highlights the importance of diet in the management of children and adolescents affected by IBD. Patients and their families frequently ask their physicians for recommendations about food and diet, seeking ways to improve, or even to cure their IBD. Moreover, patients often attribute the clinical symptoms of IBD to their diet. As patients frequently seek ways to modify their diet to control their disease, the identification of the putative causative dietary components undoubtedly represents one of the foremost priorities in CD management at present. There is convincing evidence that specific dietary triggers of gut inflammation in IBD exist and can be detected. Therefrom, the need to design high-quality dietary studies is urgent, in order to both exploit therapeutic properties of dietary interventions and simultaneously to untangle the mechanisms of action through which these triggers ignite and foster disease pathology. Biologic agents have become a cornerstone of IBD therapy. They induce a rapid response and remission. However, despite optimization strategies, such as combination with immunosuppressant agents and/or therapeutic drug monitoring, loss of response over time is concerning. Also, there is an unmet need with the alternative non-pharmacological strategies to induce remission in patients whose disease is refractory to conventional therapies, especially for children and adolescents where disease is expected to be long lasting. In this context, the results obtained with the CDED are game changing for IBD research. Such an intriguing path would also likely reduce treatment burden and bring new insights to the disease itself.

While case reports are assigned limited level of evidence and are unable to deliver quantitative data, they still provide practical clinical real-world facts and are still indispensable for broadening medical knowledge<sup>18</sup>. They provide an in-depth understanding of each individual case as opposed to large research studies with their "nomothetic approach"<sup>19</sup>. Indeed, a case report is the only way to describe in details any unusual observations regarding symptoms, medical history, clinical findings, course of disease, pharmacological and non-pharmacological interventions and their complications, associations of diseases, side effects of drugs, etc.<sup>18</sup> Consequently, a case report is a major educational tool that can inform readers on new observations, generate hypotheses, and facilitate detection of similar or identical cases. While the present cases confirmed the hypothesis on the effectiveness of CDED in the management of CD in children and adolescents, larger comparative (observational and interventional) studies are needed to confirm the benefits of

CDED and to allow generalizations on a larger population of people affected by CD. Additionally, a better understanding and characterization of intestinal dysbiosis will allow to identify patients who will more importantly benefit from CDED. On a different note, advances in computational tools along with the advent of multiple “omics” techniques will help to grasp the complex entanglement among the diet, the host and the intestinal microbiota. Such ambitious goal will also hopefully allow to identify predictors of response to novel dietary treatments and to provide more personalized dietary options to control the disease activity.

#### 4. Conclusion

To conclude, it is clear that the role of the diet in triggering intestinal inflammation is pivotal; such observation has led to explore new treatment options, which combine targeting one of pathogenic mechanisms of CD with pursuing nutritional optimization and with minimizing potential adverse effects due to prolonged drug exposure. Finally, CDED represents a safe and effective therapeutic option as both induction and maintenance monotherapy for mild to moderate disease and as a “trump card” for severe refractory disease.

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##### *Author contributions*

PL and LS were involved in the writing of the clinical cases, discussion and conclusion. EB and VP were involved in the writing of the clinical cases, collection of patient and diet data. All authors contributed to patient care. All the authors reviewed and approved the final article.

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#### Data availability statement

The data that support the findings of this study are available from the corresponding author [PL], upon reasonable request.

#### Ethical approval and consent to participate

Informed consent was obtained from the parents/legal representative of the five patients for the publication of the present case reports. The institutional review board of our center approved the study design.

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