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ORIGINAL ARTICLE

Gastroenterology: Inflammatory Bowel Disease

A real-life pediatric experience of Crohn's disease exclusion diet at disease onset and in refractory patients

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Abstract

Objectives: We aimed to appraise the real-life efficacy of Crohn's disease exclusion diet (CDED) coupled with partial enteral nutrition (PEN) in inducing clinical and biochemical remission at disease onset and in patients with loss of response to biologics and immunomodulators.

Methods: We retrospectively gathered data of patients aged less than 18 years of age with a diagnosis of Crohn's disease (CD), who received CDED coupled with PEN at a tertiary level pediatric inflammatory bowel disease center.

Results: Sixty-six patients were identified. Forty (60.6%) started CDED plus PEN at disease onset and 26 (39.4%) received CDED with PEN as add-on therapy. Forty-six (69.7%) patients achieved clinical remission (weighted Pediatric Crohn's Disease Activity Index < 12.5) at the end of Phase 1, 44 (66.7%) normalized c-reactive protein levels (<0.5 mg/dL) and 18 (27.2%) patients normalized calprotectin levels (<150 microg/g). Nine of 19 (47.3%) of patients with clinically severe disease (defined by Physician Global Assessment) achieved clinical remission at the end of Phase I. Patients with extraintestinal manifestations had statistically lower clinical response rates to the dietary regimen ($p = 0.018$). Among patients who received CDED + PEN as add-on treatment, a previous successful course of Exclusive Enteral Nutrition was associated with statistically higher clinical remission rates at Week 8 ($p = 0.026$). Clinical response at Week 4 was an independent predictor of clinical remission and fecal calprotectin normalization at Week 8 ($p = 0.002$).

Conclusion: CDED with PEN confirmed its efficacy in a real-life setting, proving to be effective also in refractory patients and those with severe disease. Early clinical response predicts clinical remission at the end of Phase 1.

KEYWORDS
CD, CDED, nutritional therapies, PEN

1 | INTRODUCTION

The incidence of pediatric Crohn's Disease (CD) is increasing worldwide, particularly in countries with previously reported low rates of inflammatory bowel diseases (IBD).[1,2] The dramatic rise in incidence of IBD in newly industrialized countries shifting to Western dietary habits, represents one of the foremost clues of the relevant influence of environmental factors, among which diet, in the

pathogenesis of CD.[3,4] Despite the increasing body of evidence indicating the likely role of diet in IBD pathogenesis, very few dietary regimens have demonstrated clear clinical benefits in patients with IBD. To date, most evidence-supported nutritional therapy for patients with IBD is exclusive enteral nutrition (EEN), which is recommended as the first line treatment for the induction of remission in pediatric CD.[5] EEN is highly effective and free of side effects. Unfortunately, patients receiving EEN often experience monotony of food and taste fatigue.[4,6] CD exclusion diet (CDED) plus partial enteral nutrition (PEN) has emerged as an alternative to EEN with the potential to overcome its barriers.[7] Since the publication of the pathfinder CDED randomized controlled trial (RCT),[8] CDED has entered clinical practice in pediatrics and its efficacy has been demonstrated by a further RCT conducted in adult patients affected by CD.[9] Despite the accumulating body of evidence of the efficacy and tolerability of CDED plus PEN, there is still a paucity of real-life studies regarding its use in everyday clinical practice.[10–12] Moreover, the two RCTs[8,9] were limited to patients with mild-to-moderate CD phenotype. Severe, stricturing, penetrating, isolated colonic, or perianal disease were excluded from these trials. Similarly, data on the combination of CDED + PEN with other medical treatments are limited to small case series.[13,14]

This study aims to appraise efficacy and tolerability of CDED coupled with PEN in a large cohort of pediatric patients affected by CD in a real life setting, exploring its use in new-onset disease and in patients experiencing a disease flare while on immunomodulator or biologic treatment.

2 | METHODS

2.1 | Population

This was a single-center, retrospective, observational study conducted at a single Italian national referral pediatric IBD center (Meyer Children's Hospital IRCCS). Starting from its early reporting, at our center, we started to adopt CDED + PEN as the first-line induction treatment for children with newly diagnosed CD and for patients experiencing a disease flare while on other maintenance regimens. Incident patients who received CDED coupled with PEN from January 1, 2020, to October 31, 2023, as treatment strategy for the induction of remission or in the setting of loss of response to other therapies were included in our cohort. All patients were younger than 18 years of age at the moment of CDED + PEN initiation and had a diagnosis of CD in accordance with established clinical, endoscopic,

> **What is Known**
>
> - Crohn's disease exclusion diet (CDED) plus partial enteral nutrition (PEN) has emerged as an alternative to exclusive enteral nutrition.
> - CDED + PEN is effective in inducing remission in patients with mild-to-moderate Crohn's Disease (CD).
>
> **What is New**
>
> - In a real-life setting, CDED + PEN has proven to be effective in inducing remission also in patients with clinically severe disease and in those with colonic phenotype.
> - A higher inflammatory burden and the presence of extraintestinal manifestations are associated with lower remission rates at the end of Phase I.

and histological criteria.[15] All the patients included in our cohort had active disease, documented by an increase of fecal calprotectin (fCal) of more than 250 microg/g, at CDED + PEN initiation. Disease classification and behavior were defined according to the Paris classification for pediatric IBD.[16] Clinical, demographic, anthropometric, laboratory, and treatment data were extracted from each patient's medical record at diagnosis, at the time of CDED + PEN initiation at the half of Phase I (Week 4) and at the end of Phase I (Week 8).

2.2 | Dietary protocol

Principles of CDED have been already described elsewhere.[8,13,17] CDED is a whole-food diet coupled with PEN and it is specifically designed to avoid exposition to noxious substances hypothesized to have harmful effect on microbiome, intestinal permeability, and immunity. All patients were treated with the same diet. The first phase of the diet lasts 8 weeks. The different duration of CDED + PEN in our protocol stems from the previous experience from our center with EEN, whose course lasted 8 weeks. Similarly, also Phase II lasts 8 weeks in our dietary protocol. During Phase I patients received PEN with polymeric formula with a volume calculated to provide 50% of the calories based on weight (not exceeding 1250 kcal/day).

A registered dietitian (E.B. and A.D.B.) administered the dietary regimen and followed up the patient, jointly with the physician, at every consultation (CDED + PEN initiation, Week 4 and Week 8). On

top, every patient had a direct communication channel with the dietitian (via email or phone call).

2.3 | Outcomes

Clinical remission at the end of each phase was defined by a weighted Pediatric Crohn's Disease Activity Index (wPCDAI) below 12.5. Clinical response was defined as a decrease of wPCDAI of more than 17.5 points. Biochemical remission was defined by a c-reactive protein (CRP) lower than 0.5 mg/dL and an erythrocyte sedimentation rate (ESR) lower than 20 mm/h. A fCal lower than 150 mg/kg was used as a surrogate of mucosal improvement.

2.4 | Statistics

Data were managed and analyzed using SPSS (v. 28th) software. Categorical variables were described as frequency and percentages. Continuous variables were evaluated for normal distribution with histograms and Q–Q plots. Normally distributed continuous variables were presented as mean ± SDs. Non-normally distributed continuous variables were presented as medians (interquartile ranges [IQR]). Categorical variables were compared by the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were compared by the unpaired t test or by Mann–Whitney test, where indicated. Children who discontinued CDED + PEN due to lack of adherence were considered treatment failures and were imputed as nonresponse. For children who did not respond to dietary regimen and/or who interrupted the diet, the last observation carried forward was used for biochemical parameters. Comparison among paired categorical variables was performed by the McNemar test. Differences among paired continuous were explored by the paired t test or by the Wilcoxon test, where appropriate. A univariate binary logistic regression model was sought for exploring crude predictors for the studied outcomes (clinical remission, CRP, and fCal normalization). We, furthermore, performed multivariable binary logistic regression analysis, including clinically relevant variables. All the statistical tests were two-sided, and a $p < 0.05$ was considered as the statistically significant threshold.

2.5 | Ethical considerations

The study design was approved by the ethic committee of Meyer Children's Hospital IRCCS. The study was

conducted according to the criteria set by the Declaration of Helsinki.

3 | RESULTS

3.1 | Study population

Sixty-six patients (54.5% males) met the inclusion criteria and were included in the analysis. Table 1 summarizes population characteristics at baseline and CDED initiation. Median age at diagnosis was 12.3 years (25th–75th centile: 9.5–14.7 years). Five (7.6%) patients had isolated colonic disease. Forty (60.6%) patients received CDED + PEN as the first induction treatment, 26 (39.4%) were treated with CDED + PEN because of a secondary loss of response to a previous maintenance treatment. In the latter group, the median disease duration was 31 months (IQR: 50 months). Thirteen (22.4%) patients had either stricturing or penetrating phenotype at the CDED + PEN initiation, with this phenotype occurring less frequently in patients who were treated at disease onset compared to those who received the dietary treatment as an add-on strategy ($p = 0.025$). Patients in the "disease-onset" group had higher disease activity according both to wPCDAI and Physician Global Assessment (PGA) ($p < 0.01$ and $p = 0.014$, respectively) at CDED initiation compared to those in the "add-on" group. Similarly, patients in the "disease-onset" group had higher levels of ESR and fCal ($p = 0.036$ and $p < 0.01$) and had a trend towards higher level of CRP ($p = 0.056$) (Table 1).

3.2 | Compliance to dietary regimen

A Likert scale ranging from 0 (interruption of diet due to lack of adherence) to 2 (complete adherence to the dietary regimen) was used to investigate the patient's compliance to the dietary regimen at the end of each phase of the diet. Only three (4.5%) patients interrupted the diet reporting complete lack of adherence. Nine (13.6%) reported overall good adherence to the diet, whereas most patients (54, 81.8%) reported complete adherence to the dietary regimen. After Phase I, 40 (60.6%) patients progressed to Phase II. Of them, only one (2.5%) interrupted diet due to lack of adherence, six (15%) reported good adherence, and most of them (33, 82.5%) reported optimal adherence.

3.3 | Clinical and biochemical outcomes with CDED + PEN

We gathered clinical and laboratory data at Week 4 during Phase I of CDED + PEN and at Week 8 at the end of Phase I. Median wPCDAI decreased significantly both at Week 4 and Week 8 ([32.5 vs. 7.5,

TABLE 1 Population characteristics at baseline.

Characteristic	Overall (N = 66)	Disease onset (N = 40)	Add-on (N = 26)	p
Male	36 (54.5%)	23 (57.5%)	13 (50%)	0.550
Age at diagnosis, years median (Q1–Q3)	12.3 (9.5–14.7)	12.7 (10.7–14.1)	10.6 (8.4–13.8)	0.089
Disease duration (months)	31 (9–59)	N/A	31 (9–59)	N/A
Disease location				
L1	21 (31.8%)	16 (40%)	5 (19.2%)	0.106
L2	5 (7.6%)	2 (5%)	3 (11.5%)	0.375
L3	35 (53%)	18 (45%)	17 (65.4%)	0.105
Isolated L4a/L4b	5 (7.6%)	4 (10%)	1 (3.8%)	0.641
Concomitant upper GI tract involvement	21 (31.8%)	15 (37.5%)	6 (23.1%)	0.219
Disease behavior				
Inflammatory (B1)	53 (80.3%)	36 (90%)	17 (65.4%)	0.025
Stricturing/Penetrating (B2/B3)	13 (19.7%)	4 (10%)	9 (34.6%)	
Growth Impairment (G1)	17 (25.8%)	11 (27.5%)	6 (23.1%)	0.688
Perianal disease	16 (24.2%)	10 (25%)	6 (23.1%)	0.859
EIM	9 (13.6%)	6 (15%)	3 (11.5%)	1.000
PGA at CDED initiation				
Mild-to-moderate	47 (71.2%)	24 (60%)	23 (88.5%)	0.014
Severe	19 (28.8%)	16 (40%)	3 (11.5%)	
wPCDAI at CDED initiation				
Mild-to-moderate	51 (77.3%)	27 (67.5%)	24 (92.3%)	0.033
Severe	15 (22.7%)	13 (32.5%)	2 (7.7%)	
wPCDAI at CDED initiation	32.5 (15–47.5)	37.5 (22.5–57.5)	15 (12.5–32.5)	<0.001
Hgb at CDED initiation	11.5 (10.7–13)	11.6 (10.7–13)	11.5 (10.8–12.8)	0.995
Albumin at CDED initiation	3.83 (3.40–4.17)	3.7 (3.25–4.15)	3.97 (3.60–4.15)	0.376
CRP (mg/dL) at CDED initiation	1.35 (0.59–4.16)	1.81 (0.75–5.14)	0.90 (0.51–2.94)	0.056
ESR (mm/h) at CDED initiation	35 (22–64)	46 (26–69)	30 (11–54)	0.036
Fecal calprotectin (mg/kg) at CDED initiation	867 (414–1775)	1200 (533–2300)	630 (346–834)	0.003
Concomitant treatment at CDED initiation				N/A
Anti-TNF-α	18 (27.2%)	N/A	18 (69.3%)	
Immunosuppressant	4 (6.1%)	N/A	4 (15.5%)	
Ustekinumab	5 (7.6%)	N/A	5 (19.2%)	

Abbreviations: CDED, Crohn's disease exclusion diet; EIM, extraintestinal manifestations; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; N/A, not applicable; PGA, Physician Global Assessment; TNF-α, tumor necrosis factor-α; wPCDAI, weighted Pediatric Crohn's Disease Activity Index.

$p < 0.01$] and (32.5 vs. 5, $p < 0.01$). We also observed a statistically significant decrease in inflammatory markers between Week 8 and the CDED initiation, as well as fCal (Supporting Information S1: Table 1). At the end of Phase I, 46 (69.7%) achieved clinical remission (defined as a wPCDAI < 12.5). Overall, 27/40 (67.5%) of the patients who were treated at "disease-onset" and 19/26 (73%) of those who received CDED as an "add-on" therapy achieved clinical remission, with no statistically significant differences among the two groups ($p = 0.630$). The rates of CRP normalization (CRP < 0.5 mg/dL) at the end of Phase I were similar between the two groups (28/40, 70% and 16/26, 61.5%, respectively, $p = 0.476$). Median fCal level

decrease was 550 microg/g (IQR: 1321 microg/g). Twenty-seven (40.9%) patients experienced at least a 50% reduction in calprotectin from baseline (20/40, 50%, in patients treated at disease onset and 7/26, 26.9%, among those who received CDED + PEN as "add-on" strategy, $p = 0.062$). Lastly, 18 (27.2%) patients had calprotectin levels below 150 mg/kg at the end of Phase I, again with no differences between patients treated at disease onset and those who received CDED + PEN as add-on strategy (10/40, 25% and 8/26, 30.8%, respectively, $p = 0.607$). All the patients who received CDED as add-on therapy were treated previously with course of EEN. Nineteen out of 26 (73%) had showed a previous clinical response (defined as a change in wPCDAI > 17.5 points) to the EEN course. Having achieved a previous clinical response to EEN was associated with significantly higher rates of clinical remission when CDED + PEN was used in this setting (17/19 [89.5%] vs. 2/7 [28.6%], $p = 0.026$). Nineteen (28.8%) of the patients in our cohort had severe disease phenotype at CDED + PEN initiation, according to PGA. Patients with severe disease according to PGA were less likely to be in clinical remission than patients with mild-to-moderate disease (50% vs. 80.4%, $p = 0.012$). However, the rates of CRP and fCal normalization were similar between patients with severe disease phenotype and those with mild-to-moderate disease presentation (68.4% vs. 66%, $p = 0.848\%$ and 21.1% vs. 29.8%, $p = 0.554$, respectively). Fifteen patients (22.7%) had severe phenotype at CDED + PEN initiation, according to wPCDAI. Patients with severe disease according to wPCDAI were less likely to achieve clinical remission than patients with mild-to-moderate disease by the end of Phase I (7/15, 46.7% vs. 40/51, 78.4%, $p = 0.017$). Nonetheless, the rates of CRP and fCal normalization did not significantly differ between patients with severe and those with mild-to-moderate disease presentation according to wPCDAI (9/15, 60% vs. 35/51, 68.6%, $p = 0.533$ and 2/15, 13.3% vs. 31.3%, $p = 0.206$, respectively). In addition, when considering only the patients with severe phenotype according to PGA at CDED initiation, clinical (wPCDAI), anthropometric (weight), and biochemical parameters significantly improved after 8 weeks of dietary intervention (Supporting Information S1: Figure 1).

Nine out of 66 (13.6%) patients included in our cohort had at least one extra-intestinal manifestation at the time of CDED initiation. Three out of nine (33.3%) had peripheral arthritis, three (33.3%) had fever (body temperature > 38.5°C for more than 3 days not due for infections), two (22.2%) had erythema nodosum, and one (11.1%) had chronic nonbacterial osteomyelitis. At the end of Phase I patients who did not achieve clinical remission had a trend toward higher wPCDAI values ($p = \underline{0.051}$) and they had more frequently a severe disease phenotype according to PGA, as well as higher baseline ESR levels ($p = 0.043$). Moreover, non-responder patients had more frequently growth impairment and extraintestinal manifestations (EIMs) at the initiation of the dietary treatment ($p = 0.049$ and $p = 0.018$, respectively).

Among the 40 patients who received CDED + PEN at disease onset, no differences in median Simplified Endoscopic Score for Crohn Disease were observed between responders and nonresponders (Table 2). Supporting Information S1: Tables 2 and 3 show baseline characteristics stratified upon CRP and fCal normalization at the end of Phase I. Among the 40 patients who received CDED at disease onset, 13 (32.5%) patients started a concomitant treatment after the Week 4 of Phase I. Seven out of 13 (53.8%) of them received immunemodulator (either methotrexate or azathioprine), whereas the remaining 6/13 (46.2%) were treated with an anti-tumor necrosis factor (TNF) agent (five received Adalimumab and one received Infliximab). Figure 1 shows decrease over time of wPCDAI, CRP and fCal among the 40 patients who received CDED + PEN at disease onset. Median changes of wPCDAI, CRP, and fCAL from baseline did not differ between the patients who started a concomitant treatment and those who continued CDED + PEN alone ($p = 0.359$, $p = 0.736$, and $p = 0.08$, respectively). Similarly, median wPCDAI, CRP, and fCal levels at Week 8 did not differ between patients who continued CDED alone and those who started a concomitant treatment ($p = 0.131$, $p = 0.231$, and $p = 0.570$, respectively).

3.4 | Predictors of response to CDED Phase I

Table 3 shows univariate and multivariate analysis of predictors of clinical, biochemical and fCal remission at the end of Phase I. At univariate analysis, severe disease phenotype (according to PGA), baseline ESR and CRP levels and the presence of an EIM at CDED initiation were associated with lower rates of clinical remission at the end of Phase I. Clinical response at Week 4 of Phase I was an independent predictor of both higher clinical remission rates and of higher rates of fCal normalization at the end of Phase I in the multivariate model ($p = 0.012$) (Table 3).

4 | DISCUSSION

We have presented a "real-world" cohort of pediatric patients treated with CDED + PEN, both at disease onset and as an "add-on therapy" in the unfortunately common setting of secondary loss of response to biologics and immunomodulators. We have shown that CDED coupled with PEN is effective in patients who were treated at diagnosis but also in those who

TABLE 2 Baseline characteristics stratified upon clinical remission to Phase I.

Characteristic	Overall (N = 66)	Clinical remission (N = 46)	No clinical remission (N = 20)	p
Male	36 (54.5%)	26 (56.5%)	10 (50%)	0.625
Age at diagnosis, years median (Q1–Q3)	12.3 (9.5–14.7)	12.5 (8.7–14.7)	12.1 (10.2–13.6)	0.859
New-onset disease	40 (60.6%)	27/40 (67.5%)	13/40 (32.5%)	0.630
Add-on treatment	26 (39.4%)	19/26 (73%)	7/26 (27%)	
Disease duration, months, median (Q1–Q3) (only add-on cohort)	31 (9–59)	27 (8–57)	45 (13–69)	0.644
Disease location				
L1	21 (31.8%)	13/21 (62%)	8/21 (38%)	0.347
L2	5 (7.6%)	3/5 (60%)	2/5 (40%)	0.635
L3	35 (53%)	25/35 (71.4%)	10/35 (28.6%)	0.745
Isolated L4a/L4b	5 (7.6%)	5/5 (100%)	0/5 (0%)	0.312
Concomitant upper GI tract involvement	21 (31.8%)	15/21 (71.4%)	6/21 (28.6%)	0.834
Disease behavior				
Inflammatory (B1)	53 (80.3%)	36/53 (67.9%)	17/53 (32.1%)	0.527
Stricturing/penetrating (B2/B3)	13 (19.7%)	10/13 (76.9%)	3/13 (23.1%)	
Perianal disease	17 (25.8%)	11/17 (64.7%)	6/17 (35.3%)	0.603
Growth impairment	16 (24.2%)	8/16 (50%)	8/16 (50%)	0.049
EIM	9 (13.6%)	3/9 (33.3%)	6/9 (66.6%)	0.018
PGA at CDED initiation				
Mild-to-moderate	47 (71.2%)	37/47 (78.7%)	10/47 (21.3%)	0.018
Severe	19 (28.8%)	9/19 (47.3%)	10/19 (52.7%)	
wPCDAI at CDED initiation				
Mild-to-moderate	51 (77.3%)	40/51 (78.4%)	11/51 (21.6%)	0.017
Severe	15 (22.7%)	7/15 (46.6%)	8/15 (53.4%)	
wPCDAI at CDED initiation	32.5 (15–47.5)	25 (15–42.5)	40 (20–57.5)	0.051
Hgb at CDED initiation	11.5 (10.7–13)	12 (10.9–13.2)	11 (10.7–12.1)	0.067
Albumin at CDED initiation	3.83 (3.40–4.17)	3.91 (3.40–4.29)	3.75 (3.49–4.10)	0.695
CRP (mg/dL) at CDED initiation,	1.35 (0.59–4.16)	1.27 (0.59–2.32)	2.7 (0.61–5.67)	0.261
ESR (mm/h) at CDED initiation,	35 (22–64)	33 (18–56)	55 (32–70)	0.043
Fecal calprotectin (mg/kg) at CDED initiation,	867 (414–1775)	900 (420–1692)	650 (393–1890)	0.874
SES-CD score, median (Q1–Q3) (only disease-onset cohort)	21 (17–28)	21 (17–28)	23 (17–28)	0.762

Note: Clinical remission: weighted Pediatric Crohn's Disease Activity Index below 12.5.

Abbreviations: CDED, Crohn's disease exclusion diet; EIM, extraintestinal manifestations; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; PGA, Physician Global Assessment; SES-CD, Simplified Endoscopic Score for Crohn Disease.

experienced a clinical and biochemical relapse while on maintenance therapy. We have also provided data on patients with severe disease, showing that CDED + PEN may be an effective strategy also in this subset of patients. Lastly, we have also provided some clues on the characterization of the CDED + PEN responders. Indeed, on one hand, the achievement of an early clinical response was associated with higher clinical remission rates as well with higher rates of fCal normalization. On the other, we have shown that a higher inflammatory burden at diagnosis (higher CRP, ESR, and wPCDAI) as well as the presence
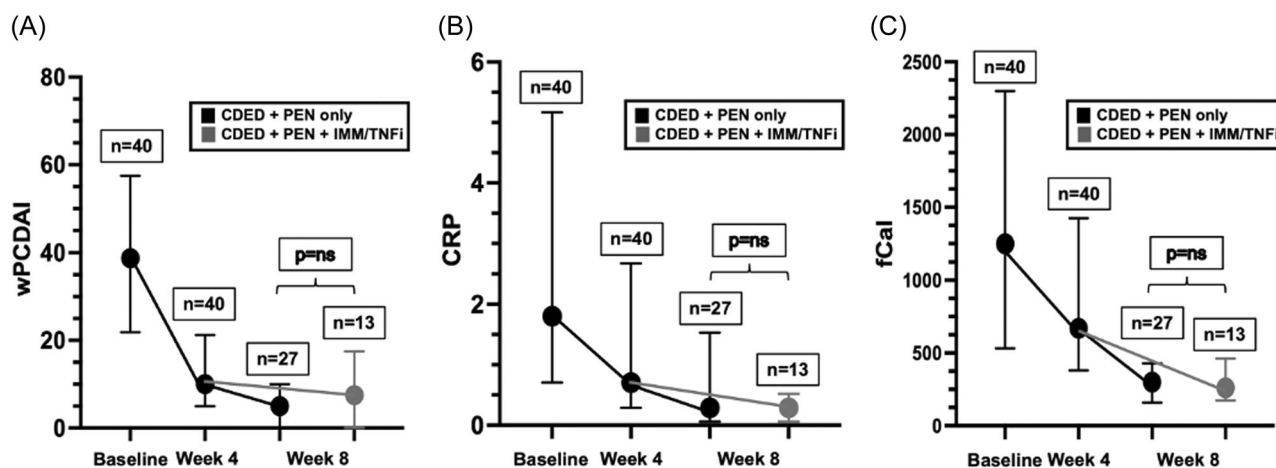
FIGURE 1 Longitudinal changes in weighted wPCDAI (A), CRP (B), and fCal (C) in newly diagnosed patients who received CDED + PEN (n = 40). At Week 4, seven patients introduced an immunemodulator (six azathioprine, one methotrexate) and six received an anti-TNF. All the patients were assessed at Week 8, at the end of Phase I. No statistically significant difference in wPCDAI, CRP, and fCal between the 13 patients who received an additional treatment and the 27 patients who continued only the dietary intervention at Week 8. CDED, Crohn's disease exclusion diet; CRP, C-reactive protein; fCal, fecal calprotectin; PEN, partial enteral nutrition; TNF, Tumor necrosis factor; wPCDAI, weighted Pediatric Crohn's Disease Activity Index.

of EIM tend to be associated with lower remission rates.

In the pediatric RCT,[8] 40 patients with mild-to-moderate CD were allocated in the intervention arm and then received CDED coupled with PEN, 75.6% of which achieved sustained remission at Week 12. Our data are consistent with those presented in the pathfinder RCT. Indeed, in a real-world setting, the clinical remission rate at Week 8 in our cohort was 69.7%. As such RCT results have been published, CDED has been widely utilized as induction strategy for luminal CD in clinical practice. It is worth noting that in the real-life setting the patients' features might slightly differ from the inclusion/exclusion criteria of the RCTs. Indeed, in our cohort, we also included patients with severe phenotype at disease presentation, as well as patients with isolated colonic disease. Moreover, we included in our cohort patients who received CDED + PEN in the setting of secondary loss of response to biologic agents (either anti-TNF alpha or anti-interleukin [IL] 12/23), who were excluded from the pediatric RCT. Lastly, CDED + PEN Phase I in our study had a duration of 8 weeks in contrast with the 6 weeks of the dietary protocol of the RCT. This different practice at our center derived from previous experience with EEN.

We have shown that CDED + PEN is effective also in patients with severe disease presentation. Indeed, both clinical and biochemical parameters significantly reduced over time in patients with severe phenotype according to PGA. On the other hand, we have shown that a higher inflammatory burden at baseline (higher CRP and ESR), as well as the presence of EIM such as arthritis, erythema nodosum, and fever tend to be associated with poorer response to this dietary regimen.

Identifying nonpharmacological strategies to induce remission in patients whose disease is partially responding to medications, or refractory to conventional therapies, is an unmet need.[18,19] CDED coupled with PEN has been also utilized as a salvage regimen in the setting of secondary loss of response to biological therapy. Sigall-Boneh et al.[13] gathered data of 21 patients (10 children and 11 adults) failing to respond to biologics, showing that CDED coupled with PEN was able to induce remission in 61.9% of them. To the best of our knowledge, we presented the largest cohort of pediatric patients treated with CDED in the setting of biological therapy failure. Compared to Sigall-Boneh et al.[13] we have shown slightly higher clinical remission rates. One possible explanation could be the longer duration of Phase I in our practice (8 weeks rather than 6 weeks) as well as the fact that disease duration was significantly lower in our cohort (2.5 years vs. 7 years). Interestingly, in our cohort, as opposed to those presented by Sigall-Boneh et al.,[13] we had five patients with previous failure of both anti-TNF-α and anti-IL12/23 agents (Ustekinumab).

More recently, the concept of "dietary-responder" was introduced to identify those patients who present an early response to dietary regimens (either CDED or EEN) and who are more likely to be in clinical remission at the end of the treatment.[20] Sigall-Boneh et al.[13] showed that patients who responded to dietary regimens (either CDED or EEN) at Week 3 (at the first half of Phase I) achieved more frequently clinical remission at the end of Phase II (Week 12). In our cohort, we have confirmed that there is a subset of patients (those showing a clinical response at Week 4) more likely to achieve clinical remission, already at the end of Phase I. Moreover, we observed that achieving

TABLE 3 Univariate and multivariate predictors of clinical remission, CRP, and fCal normalization at the end of Phase I.

Characteristic	Univariate analysis OR (95% CI)	p	Multivariate analysis OR (95% CI)	p
Clinical remission (n = 46)				
Age (A1a vs. A1b)	1.50 (0.46–4.91)	0.503		
Colonic localization (L1 vs. L3–L2)	0.59 (0.20–1.78)	0.349		
Inflammatory vs. noninflammatory phenotype	1.57 (0.38–6.47)	0.529		
Severe phenotype (according to PGA)	0.24 (0.08–0.76)	0.015	0.12 (0.01–1.29)	0.081
CRP	0.85 (0.75–0.99)	0.040	0.98 (0.77–1.24)	0.851
ESR	0.98 (0.96–1.00)	0.039	0.99 (0.96–1.03)	0.760
fCal	1.00 (1.00–1.01)	0.862		
UGI tract involvement	1.13 (0.36–3.52)	0.834		
Growth impairment	0.73 (0.23–2.37)	0.604		
Perianal disease	0.32 (0.10–1.02)	0.055		
EIM	0.16 (0.04–0.74)	0.019	0.500 (0.08–2.99)	0.449
Add-on vs. disease onset	0.77 (0.26–2.28)	0.630		
Clinical response at Week 4	3.63 (0.93–14.32)	0.063	21.7 (1.95–241.5)	0.012
C-reactive protein normalization (n = 44)				
Age (A1a vs. A1b)	1.47 (0.49–4.41)	0.486		
Colonic localization (L1 vs. L3-L2)	0.40 (0.14–1.18)	0.097		
Inflammatory vs. noninflammatory phenotype	1.86 (0.46–7.61)	0.386		
Severe phenotype (according to PGA)	0.89 (0.28–2.80)	0.848	0.85 (0.18–4.07)	0.841
ESR	0.98 (0.97–1.00)	0.185		
fCal	1.00 (1.00–1.01)	0.876		
UGI tract involvement	1.36 (0.46–4.02)	0.576		
Growth impairment	0.53 (0.15–1.87)	0.324		
EIM	0.34 (0.08–1.42)	0.140	0.40 (0.08–2.08)	0.279
Perianal disease	0.59 (0.17–2.11)	0.420		
Add-on vs. disease onset	0.69 (0.24–1.94)	0.477		
Clinical response at Week 4	5.60 (1.06–29.59)	0.043	4.46 (0.78–25.5)	0.092
fCal normalization (n = 18)				
Age (A1a vs. A1b)	0.53 (0.17–1.69)	0.283		
Colonic localization (L1 vs. L3-L2)	3.00 (0.76–11.8)	0.116		

T A B L E 3 (Continued)

Characteristic	Univariate analysis OR (95% CI)	p	Multivariate analysis OR (95% CI)	p
Inflammatory vs noninflammatory phenotype	0.420 (0.08–2.12)	0.294		
Severe phenotype (according to PGA)	0.63 (0.18–2.23)	0.473	0.17 (0.02–1.33)	0.092
CRP	0.79 (0.61–1.02)	0.072		
ESR	0.98 (0.95–0.99)	0.037		
UGI tract involvement	0.91 (0.29–2.89)	0.871		
Growth impairment	0.59 (0.18–1.95)	0.391		
EIM	0.73 (0.14–3.91)	0.715		
Perianal disease	0.86 (0.24–3.11)	0.815		
Add-on vs. disease onset	1.33 (0.44–4.00)	0.608		
Clinical response at Week 4	12.50 (2.19–71.36)	0.004	20.54 (2.95–142.91)	0.002

Note: CRP normalization: CRP < 0.5 mg/dL. fCal normalization: fCal < 250 microg/g.

Abbreviations: CI, confidence interval; CRP, c-reactive protein; EIM, extraintestinal manifestations; ESR, erythrocyte sedimentation rate; fCal, fecal calprotectin; OR, odds ratio; PGA, Physician Global Assessment.

clinical response at week 4 is also a predictor of fCal normalization at the end of Phase I of the dietary regimen. Our findings reinforce the idea that a close monitoring in the early phases of the dietary regimen may allow the identification of patients who will be more prone to respond and on the other hand avoiding unsuccessful restrictive diets in patients who are likely to be "dietary refractory." On the top of that, when considering patients who used CDED + PEN as add-on strategy, a previous successful course of EEN was predictive of clinical remission. The latter observation may offer a further clue to the selection of the ideal patient who will more likely respond to this dietary regimen.

Our study certainly has several limitations to be acknowledged, mostly related to the retrospective nature of our study. Indeed, we had some missing data to deal with, especially concerning the achievement of Phase II. However, the study was focused to outcomes at the end of Phase I of the CDED. Moreover, remission was based on clinical activity indices and no data on endoscopic outcomes were available, although objective biomarkers (including fCal) were provided.

Lastly, some of the patients in the "disease-onset" group had a maintenance drug introduced at Week 4, before the end of Phase I. This may have biased our 8-week clinical remission rates. However, it is worth considering that more than half of them received an immunomodulator (azathioprine), which is unlikely to have played a significant clinical impact after only 4 weeks of treatment. On the other hand, when comparing wPCDAI, CRP, and fCal between those who added a maintenance drug before Week 8 and those who did not, we did not observe any statistically significant difference.

5 | CONCLUSIONS

Our study confirmed the effectiveness of such dietary regimen in inducing clinical and biochemical remission in diverse clinical setting: at disease onset, as add-on therapy in patient's refractory to biologics (even to second-line ones), in clinically severe disease and in isolated colonic disease. Furthermore, we have confirmed that identification of patients with and without a rapid response to diet might help identify those who will be in clinical remission by the end of Phase I, both at disease onset and when CDED + PEN has been used as add-on strategy. The main advantages of such strategies are to reduce exposure to further drugs while targeting the environmental mechanism of disease without additional toxicity. This issue is of utmost importance for children and adolescents with decades of life with the disease ahead.

CONFLICTS OF INTEREST STATEMENT

Paolo Lionetti has received speaker fees from Takeda, Dr. Falk, Nestlé Health Science, and Nutricia. The other authors have no conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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