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REVIEW

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Specialized and standard nutritional formulas for the dietary management of pediatric patients with Crohn's disease: a systematic literature review

Richard K. Russell[a], Andrew Fagbemi[b], Jalil Benyacoub[c], Maria E. Capobianco[d], Laura E. Wells[d], Rita Shergill-Bonner[e], Preeti Sharma[c] and Minal Patel[f]

[a]Department of Paediatric Gastroenterology, Clinical Staff Offices, Royal Hospital for Children and Young People, Edinburgh, UK; [b]Royal Manchester Children's Hospital, Manchester University NHS Foundation Trust, Manchester, UK; [c]Medical Affairs, Pediatric Medical Nutrition Nestle Health Science, Vevey, Vaud, Switzerland; [d]Greenway House Larkwood Way, Valid Insight Ltd, Bioscript Group Ltd, Macclesfield, UK; [e]Department of Paediatric Gastroenterology, Evelina London Children's Hospital, London, UK; [f]Department Nutrition and Dietetics, Bart's Health NHS Trust, London, UK

ABSTRACT

Introduction: This systematic literature review (SLR) aims to compare the clinical, humanistic, and economic outcomes associated with specialized and standard nutritional formulas for the treatment of mild-to-moderate pediatric Crohn's disease.

Methods: Search strategies were applied across MEDLINE, Cochrane and Web of Science (January 2000–October 2023) and recent congress proceedings (January 2021–October 2023). PRISMA-P guidelines were followed. Quality assessment evaluated risk of bias.

Results: Twenty-three unique studies met the inclusion criteria. Nineteen studies (754 patients) evaluated specialized formula, 10 assessed standard formula (246 patients). Mucosal healing (7 studies), induction (20 studies) and maintenance of remission (9 studies) were reported over various timeframes. High proportions of patients who received specialized formula achieved mucosal healing (63–89% 8 weeks; 25–74% 10 weeks), and remission (50–100% 8 weeks). Specialized formula sustained remission (34–62.5% 6 months and 24–87.5% 1 year). Results were not directly comparable with standard formula due to significant heterogeneity in study methodology, patient populations, and remission definition.

Conclusions: The evidence predominantly supports the benefits of specialized formula in inducing mucosal healing, remission, and sustaining positive outcomes across multiple timepoints. Direct comparison of nutritional interventions is required to further support the findings of this SLR.

Protocol registration: PROSPERO CRD42023472370.

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Crohn's disease; efficacy; Modulen IBD; Fortisip; SLR; pediatric; nutrition; remission

1. Introduction

Crohn's disease (CD), the most common subtype of inflammatory bowel disease (IBD) in children, is a chronic, complex inflammatory disorder that affects the gastrointestinal tract and is characterized by periods of remission and relapse [1]. In recent decades, the prevalence of IBD, especially CD, has been increasing globally [2], with significant rises in Western countries and a rising incidence noted particularly in pediatric populations [3,4]. CD inflicts a significant clinical burden on patients, in both the short and long term. The dominant symptoms of CD are abdominal pain, chronic diarrhea, weight issues, and fatigue. In children and adolescents, active CD can also affect linear growth and pubertal development [4], has a significant psychosocial burden, and reduces quality of life (QoL) compared to healthy controls [5].

Management of CD considers both the severity and extent of the disease. Key therapeutic goals for adult and pediatric patients with IBD, as identified in the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative, are achieving clinical response and remission, endoscopic healing, normalization of C-reactive protein/erythrocyte, improved QoL and no longer experiencing disease-related disability [6]. A specific treatment goal for pediatric patients is, when applicable, the restoration of normal growth potential and pubertal development. Current strategies for the management of pediatric CD aim to relieve symptoms, promote mucosal healing, induce and maintain clinical remission, plus support nutritional rehabilitation. Guidelines recommend the first-line use of exclusive enteral nutrition (EEN) for the induction of remission in pediatric patients with active mild-to-moderate CD and partial enteral nutrition (PEN) for the maintenance of remission [7]. EEN involves replacing all food and drinks with specialized liquid nutritional formula and water. PEN uses a combination of liquid nutrition and solid foods, with approximately 50% of daily calories from formula and the remainder from regular food. PEN is recommended as one of the maintenance therapy options in mild-to-moderate pediatric patients with CD who have successfully achieved remission predominantly after a course of EEN [7].

CONTACT Richard K. Russell richard.russell@nhs.scot Department of Paediatric Gastroenterology, Clinical Staff Offices, Royal Hospital for Children and Young People, 50 Little France Crescent, Edinburgh EH16 4TJ, UK

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The first-line use of nutritional formulas for the treatment of active CD has increased since the inclusion of nutritional treatment in the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)/ European Crohn's and Colitis Organization (ECCO) guidelines for the medical management of pediatric CD initially in 2014 and reinforced in the subsequent revision [7,8]. In 2023, ESPEN guidelines also recommended a CD exclusion diet plus PEN for the induction of remission as an alternative to EEN in pediatric patients with mild-to-moderate CD [9]. For pediatric patients with severe disease, or those who cannot tolerate EEN, drug treatments including corticosteroids, and anti-tumor necrosis factor (anti-TNF) therapy, are recommended. The threshold for introducing biologics earlier in the disease course are now apparent in both adults and children with CD [7]. This is giving rise to new therapeutic approaches involving combination therapies of EEN or PEN and drug treatments [10].

There are a range of different nutritional formulas available for EEN or PEN in pediatric patients with active mild-to-moderate CD [11]. These formulas vary considerably in terms of the composition of ingredients and nutrients, making selection of the optimal formula a potential challenge. Evidence-based research that demonstrates the clinical outcomes of specific formulas can be a valuable resource for healthcare providers when determining the most appropriate treatment plan for individual patients. Moreover, understanding all of the outcomes associated with specific formulas can support informed decision-making by healthcare administrators and payers. The objectives of this systematic literature review (SLR) were thus to identify, quality-assess and extract data on the clinical, humanistic and economic outcomes of a specialized formula e.g. Modulen IBD, Nestlé Health Science, and standard oral nutritional formulas e.g. Ensure Plus and Osmolite (both Abbott), Fortisip, Neocate and Nutrison (all Nutricia) in the management of pediatric patients with mild-to-moderate CD.

2. Methods

2.1. Research questions

Research questions included:

(i) What is the clinical efficacy and effectiveness of specialized formula and standard formulas in the management of pediatric patients with mild-to-moderate CD?
(ii) What is the QoL of patients using a specialized formula and standard formulas?
(iii) What are the direct and indirect costs associated with specialized formula and standard formulas
(iv) What is the strength and extent of evidence supporting each formula?

2.2. Search strategy

This SLR was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines [12]. Databases searched included MEDLINE (via PubMed.com), Cochrane Database of Systematic Reviews & Cochrane Controlled Register of Trials (via Cochrane Library). Select conference proceedings were also searched including ESPGHAN, ECCO, American College of Gastroenterology (ACG), European Society for Clinical Nutrition and Metabolism (ESPEN) and Professional Society for Health Economics and Outcomes Research (ISPOR). Articles published between 2000 and 2023 and conference presentations published between January 2021 and October 2023 were included. The initial search was conducted on 16 October 2023. Results were limited to English language and the SLR protocol was registered on PROSPERO (identifier CRD42023472370).

2.3. Selection criteria

Retrieved publications were identified using pre-specified Population, Intervention, Comparators, Outcomes, Study design and Timeframe (PICOS-T) criteria. These criteria were generated based on the research questions outlined above (Table 1).

2.4. Literature screening

Titles and abstracts identified from the database searches were reviewed by two independent reviewers to assess suitability for inclusion in the SLR. Data from the identified studies was then extracted into a data extraction template. Bibliographies of the included studies were reviewed to obtain further relevant references.

2.5. Study outcomes assessed

This SLR focused on three primary outcomes to assess the clinical efficacy and effectiveness of specialized and standard nutritional formula: induction of remission, mucosal healing, and maintenance of remission. Mucosal healing was measured as the percentage of patients who achieved healing of the mucosa through endoscopic and/or histologic scores that assessed inflammation status. Endoscopic and histologic scoring systems were derived from previously published evidence [13–15], with a scale ranging from 0 to 3, with 0 indicating no inflammation (endoscopic), or normal or minor chronic inflammation (histologic), to 3 indicating severe inflammation, with extensive deep ulceration (endoscopic), or inflammation with ulceration (histologic) [13–15]. Maintenance of remission was defined as the percentage of patients maintaining remission at a given time point after the induction period. Additional clinical, humanistic and economic outcomes were extracted as secondary outcomes.

2.6. Quality assessment and data collection

The quality of evidence from randomized controlled trials (RCTs) was assessed using the Cochrane Risk-of-Bias Tool v2.0. The Newcastle-Ottawa Scale was used to assess the quality of non-randomized studies [16]. The Consolidated

Table 1. Full PICOS-T criteria for the SLR.

Criteria	Inclusion criteria	Exclusion criteria
Population	Pediatric patients aged 5 to 18 years with CD*	• Patients aged >18 years or <5 years • Animals/*in vitro* studies
Intervention	Specialized formulas and standard formulas used as EEN or PEN: Alicalm, Altrajuce, Altraplen, Aymes, Boost, Calshake, Complan, Compleat, Elemental 028, Enshake, Ensure, Foodlink Complete, Fortisip, Fresubin, Modulen IBD, Modulife, Nourish, Nutilis, Nutren Junior, Nutricrem, Nutrison, Osmolite, PediaSure, PediaSure Harvest, Pediasure Sidekicks, Peptamen Junior, Real Food Blends, Scandishake, Soy Pediatric Drink, Vital, Vivonex	Studies not evaluating any of the listed interventions
Comparator	Any comparator or no comparator	None
Outcomes	Primary outcomes: • Mucosal healing (%) • Induction of remission (%) • Maintenance of remission %) Secondary outcomes: • Additional clinical outcomes • Humanistic outcomes (HRQoL) • Economic outcomes (direct and indirect costs)	Studies not reporting at least one of the outcomes of interest
Study design	• Randomized and non-randomized controlled trials • Observational studies (e.g. cross-sectional studies, cohort studies, case-control studies, patient surveys, patient registries, patient records, medical chart reviews)	• Preclinical studies • Reviews, letters, comments and editorials • Case reports
Timeframe	• Full texts published from 2000 to the present day • Congress/meeting abstracts published from the last three years (2020–2023)	• Full texts published before 2000 • Abstracts published before 2020

CD, Crohn's disease; EEN exclusive enteral nutrition; HRQoL, health-related quality of life; PEN, partial enteral nutrition. *Studies that assessed both adults and children were included if data provided for children are reported separately.

Health Economic Evaluation Reporting Standards (CHEERS) checklist scored the methodological quality of economic evaluations [17].

3. Results

3.1. Study selection

A total of 688 references were initially identified using the search strategy (Figure 1). Title and abstract screening resulted in the inclusion of 68 full texts, of which 28 publications (of 23 unique studies; Table A1 in the supplementary material) were included for data extraction, including four conference abstracts.

3.2. Study characteristics

Of the 23 studies (Table A1 in the supplementary material), there were 6 RCTs [18–23], 8 prospective observational studies [13,24–30], 8 retrospective observational studies [14,31–37], and 1 economic evaluation [38]. Most studies were conducted in Europe (17 studies), with the majority from the United Kingdom (6 studies) [13,24,27,32,35,38]. Studies predominantly evaluated the use of nutritional treatment over 8 weeks (11 studies) [13,21,27,30,33,35,37,39–42]. The longest follow up was one year which was reported in six studies [22,27,29,34,38,40]. Twenty-two studies reported clinical outcomes, 8 studies humanistic outcomes, and 2 studies reported economic outcomes (note that several studies reported multiple outcomes).

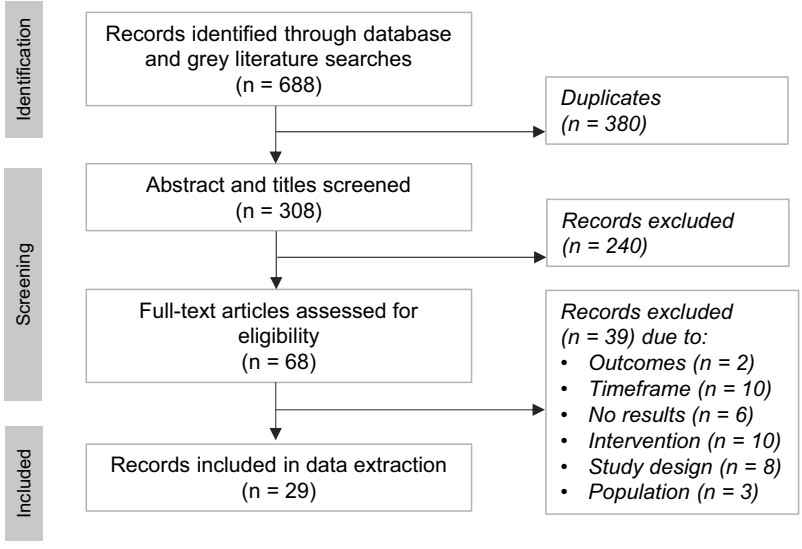

Figure 1. PRISMA flow diagram.

3.3. Study population and intervention

This SLR included 1,000 patients, of which 754 were treated with specialized formula across 19 studies. The use of standard formulas (such as Elemental 028, Ensure Plus and Osmolite, Fortisip, Neocate, Nutrison, and Pregomin), were evaluated in 246 patients across 7 studies [14,20,25,30,32,33,36]. In the studies of standard formula, there were 4 retrospective study designs, 2 prospective observational studies and 1 RCT.

In terms of age, the lowest reported mean age (standard deviation) was 10.2 years (4.5) [25] and the highest mean age was 14.9 years (2.7) [20]. There was a male predominance reported in 17 studies (median 63%, range, 42–83%). Due to the heterogeneity in the reporting of baseline age and sex in the included articles, results could not be combined. Eleven studies specified the severity of IBD, which ranged from mild to severe [18,19,23,25,28–30,33,36–38]. Most studies included patients with moderate disease (12 studies); patients with mild and severe disease were reported in 9 and 7 studies, respectively. Seventeen studies reported the use of nutritional formulas through EEN; 1 for PEN, 4 for both PEN and EEN and 2 studies did not specify the regimen used. Several studies reported multiple routes of administration, both standard and specialized formula, and different severities of disease so the number of studies may not always total 23.

A network meta-analysis was planned but could not be conducted due to the limited evidence for standard formulas.

3.4. Primary outcomes

3.4.1. Induction of clinical remission

Induction of clinical remission was the most common primary outcome (20 studies). Specialized formula demonstrated effectiveness in achieving remission in 16 studies, across multiple time points and regardless of the method of administration (Figure 2). At 8 weeks, patients who achieved remission ranged from 50% to 100% [13,21,27,33,35,37,39–42]. At 6 months, 63–100% of patients achieved remission with specialized formula [25,31,34]. Induction of remission with standard formula was reported in 6 studies [20,25,30,32,33,36]. At 8 weeks, 63% (standard formula, Fortisip) [33] and 70% (standard formula, Osmolite) [30] of pediatric patients achieved remission (Figure 2). At 6 months, 83% of patients achieved remission with standard formula (Osmolite) in a single-center observational study of 6 patients [25] (Table 2).

Overall, Pediatric Crohn's Disease Activity Index (PCDAI) scores were lower following treatment with both standard and specialized formula compared to baseline. PCDAI at baseline ranged from a mean of 54.2 in patients treated with specialized formula [31] to 26.3 in patients treated with standard formula (Osmolite) [25]. Following 8 weeks of treatment, PCDAI score ranged from a mean of 5 in patients treated with specialized formula [37] to 10 in patients treated with standard formula (Osmolite) [30] (Table A2 in the supplementary material) showing improvements for both standard and specialized formula.

3.4.2. Mucosal healing

Mucosal healing was reported in 7 articles [13,14,18,21,22,28,37]. Specialized formula achieved mucosal healing across multiple time points, including 8 weeks (63–89% of patients) [28,37] and 10 weeks (25–74% of patients) [18,28]. Following 8 weeks of treatment, endoscopic scores ranged from 0.74 to 1.35 [13], and histological scores from 1.28 [13] to 1.42 [14]. One single-center study of 47 pediatric patients with CD reported endoscopic and histological scores for standard formula (Neocate and Pregomin) at 8 weeks [14]. Endoscopic scores were 0.75 and 0.82 for standard formula (Neocate and Pregomin, respectively);

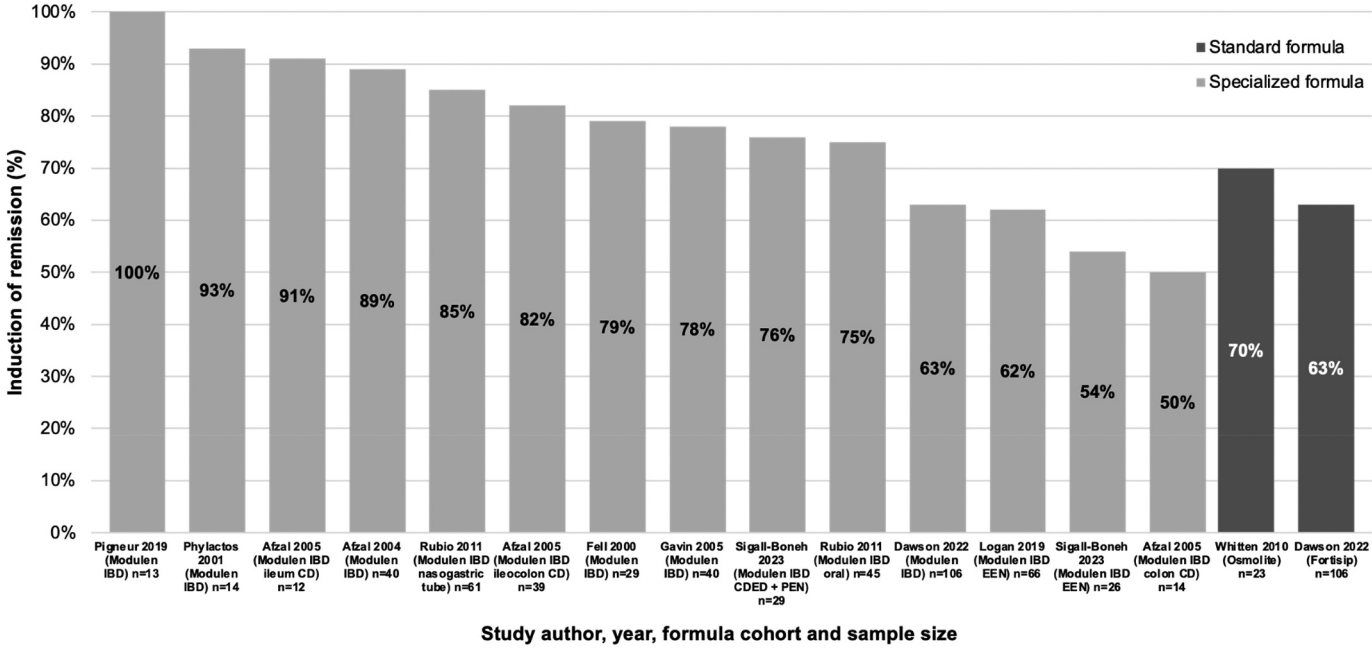

Figure 2. Percentage of pediatric patients with CD who achieved remission when treated with specialized or standard formula in clinical studies in this SLR at 8 weeks*.

Table 2. Induction of remission – results from the included studies.

Author, year	Sample size	Cohort, intervention	Time of assessment	Induction of remission, n (%)	Definition of remission	P-value
Afzal et al. [13]	65	Ileocolon, Modulen IBD	8 weeks	32 (82.1%)	PCDAI <20	$p = 0.021$*
		Colon, Modulen IBD		7 (50%)		
		Ileum, Modulen IBD		11 (91.7%)		
Agin et al. [31]	73	Modulen IBD	1 month	1 (6%)	Absence of clinical symptoms and PCDAI < 10	$p = 0.235$
		No intervention		0 (0%)		
		Modulen IBD	3 months	14 (88%)		$p = 0.001$
		No intervention		8 (42%)		
		Modulen IBD	6 months	16 (100%)		$p = 1.00$
		No intervention		19 (100%)		
Arpe et al. [32]	50	Ensure Plus/Paediasure Plus/ Paediasure	6 weeks	70%	wPCDAI <12.5	NA
Borelli et al. [18]	41	Modulen IBD	10 weeks	15 (79%)	Absence of clinical symptoms and PCDAI < 10	$p = 0.40$
		Corticosteroid		15 (79%)	Absence of clinical symptoms and PCDAI < 10	
Dawson et al. [33]	171	Modulen IBD	8 weeks	41 (63%)	NA	$p = 0.89$
		Fortisip		67 (63%)		
Faiman et al. [34]	39	Standard food reintroduction, Modulen IBD	6 months	13 (65%)	Physician's global assessment	NA
		Rapid food reintroduction, Modulen IBD		12 (63%)		
Gavin et al. [35]	40	Overall, Modulen IBD	8 weeks	31 (78%)	CRP <2 mg/L	NA
Gerasimidis et al. [24]	17	Overall, Modulen IBD	53 days (median)	8 (47.1%)	NA	NA
			56 days (median)	7 (41.2%)		
Hartman et al. [36]	28	Modulen IBD	Baseline	2 (7%)	PCDAI <15	$p = 0.0001$
			5.3 months	16 (57%)		
		Ensure Plus	Baseline	3 (17%)		$p = 0.03$
			4.5 months	4 (22%)		
		Non-supplemented group	Baseline	0 (0%)		$p = 0.03$
			5.5 months	4 (22%)		
Leach et al. [25]	6	Osmolite	26 weeks	5 (83%)	PCDAI <15	NA
Levine et al. [19]	78	EEN, Modulen IBD	6 weeks	25 (73.5%)	PCDAI <10	$p = 0.51$
		CDED+PEN, Modulen IBD		32 (80%)		
Lionetti et al. [26]	9	EEN, Modulen IBD	2 weeks	8 (89%)	PCDAI ≤15	NR
			4 weeks	9 (100%)		
Logan et al. [27]	66	Modulen IBD	8 weeks	41 (62%)	wPCDAI <12.5	NA
Ludvigsson et al. [20]	33	Elemental 028	6 weeks	11 (69%)	PCDAI <10 or a decrease in PCDAI of 40%, or 15 points, of the initial level	$p = 0.438$
		Nutrison		14 (82%)		
Matuszczyk et al. [28]	20	Modulen IBD	10 weeks	13 (65%)	PCDAI <10	NA
Pigneur et al. [21]	19	Corticosteroid	8 weeks	5 (83%)	HBI <5	$p < 0.05$
		EEN, Modulen IBD		13 (100%)		
Rubio et al. [37]	106	Nasogastric tube, Modulen IBD	8 weeks	52 (85%)	PCDAI <10	$p = 0.157$
		Oral, Modulen IBD		34 (75%)		
Sigall-Boneh et al. [42]	55	EEN, Modulen IBD	8 weeks	14 (54%)	NA	$p = 0.08$
		CDED+PEN, Modulen IBD		22 (76%)		
Werkstetter et al. [29]	10	Overall, Modulen IBD	12 weeks	8 (80%)	PCDAI <10	NA
Whitten et al. [30]	23	EEN, Osmolite	8 weeks	16 (70%)	PCDAI <15	NA

CD, Crohn's disease; CDED, Crohn's disease exclusion diet; CRP, c-reactive protein; EEN exclusive enteral nutrition; HBI, Harvey-Bradshaw Index; IBD, inflammatory bowel disease; NA, not available; PCDAI, pediatric Crohn's disease activity index; PEN, partial enteral nutrition; wPCDAI, weighted PCDAI. *P-value refers to the difference (chi squared test) between the isolated colonic group vs the ileal and ileocolonic groups.

histological scores were 1.08 and 1.38 for standard formula (Neocate and Pregomin, respectively) [14] (Table 3), thus showing improvements in mucosal healing for both standard and specialized formula. No publications reported the percentage of patients achieving mucosal healing for standard oral nutritional supplements (ONS).

3.4.3. Maintenance of clinical remission

Maintenance of remission was reported in 9 articles that evaluated specialized formula [19,22,26,27,29,34,40,42,43]; no studies were identified for standard formula. The use of specialized formula maintained patients in remission over the long term with 34–62.5% of patients maintaining remission at 6 months [29,42] and 24–87.5% at 1 year [22,27,29,40] (Table 4). No additional treatments were used in Pigneur et al. [22] and Fell et al. [40], although it should be noted that at the time of the Fell et al. study [40], alternative treatments were limited, with steroids being the primary option available. Pharmacological interventions such as immunomodulators, thiopurines, proton-pump inhibitors, methotrexate, azathioprine, and 5-amino-salicylic acid were utilized in three studies [27,29,42].

Table 3. Mucosal healing – results from the included studies.

Author, year	Sample size	Cohort	Intervention	Time of assessment	Mucosal healing, n (%) or mean (SD)	P value
Afzal et al. [13]	65	Ileocolon	Modulen IBD	Baseline	ES, mean (SD): 1.67 (0.86) HS, mean (SD): 2.00 (0.86)	ES: $p = 0.01$ HS: $p = 0.008$
				8 weeks	ES, mean (SD): 0.74 (0.65) HS, mean (SD): 1.28 (0.75)	
		Colon	Modulen IBD	Baseline	ES, mean (SD): 1.57 (0.68) HS, mean (SD): 1.78 (1.0)	ES: $p = 0.322$ HS: $p = 0.238$
				8 weeks	ES, mean (SD): 1.35 (1.0) HS, mean (SD): 1.39 (0.85)	
Berni Canani et al. [14]	47	EEN	Modulen IBD	Baseline	ES, mean (SD): 2.58 (0.51) HS, mean (SD): 3.33 (0.78)	ES: $p < 0.001$ HS: $p < 0.001$
				8 weeks	ES, mean (SD): 0.83 (0.72) HS, mean (SD): 1.42 (01.16)	
			Neocate	Baseline	ES, mean (SD): 2.67 (0.49) HS, mean (SD): 3.25 (0.75)	ES: $p < 0.001$ HS: $p < 0.001$
				8 weeks	ES, mean (SD): 0.75 (0.62) HS, mean (SD): 1.08 (0.67)	
			Pregomin	Baseline	ES, mean (SD): 0.82 (0.64) HS, mean (SD): 1.38 (1.04)	ES: $p < 0.001$ HS: $p < 0.001$
				8 weeks	ES, mean (SD): 2.85 (0.38) HS, mean (SD): 3.38 (0.77)	
Borelli et al. [18]	41	Modulen IBD Corticosteroid	Modulen IBD Corticosteroid	10 weeks	14 (74%); 95% CI, 51%–89% 6 (33%); 95% CI, 16%–57%	$p < 0.05$
Matuszczyk et al. [28]	20	Overall	Modulen IBD	10 weeks	5 (25%)	NR
Pigneur et al. [21]	19	EEN	Modulen IBD Steroids	8 weeks	8 (89%) 1 (17%)	$p < 0.005$
Pigneur et al. [22]	100	Daily supplement Cyclic EEN	Modulen IBD	12 months	18 (35%) 25 (51%)	NR
Rubio et al. [37]	106	Nasogastric tube Oral	Modulen IBD	8 weeks	5 (63%) 7 (89%)	NR

ES, endoscopic score; EEN exclusive enteral nutrition; HS, histological score; IBD, inflammatory bowel disease; NR, not reported; SD, standard deviation.

3.5. Secondary outcomes

3.5.1. Clinical

Twenty studies reported at least one secondary clinical outcome of interest including PCDAI, weight, weight z-score, weight gain, height, height z-score, height gain, body mass index (BMI), BMI z-score, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin, hemoglobin, hematocrit, platelets and number of nasogastric tubes inserted (Table A2 in the supplementary material; calprotectin was not extracted into the data extraction template).

3.5.2. Humanistic

Eight studies reported humanistic outcomes, including QoL and adherence to treatment [13,19,23,24,27,33,37–40]. A prospective cohort showed significantly improved QoL following 8 weeks of treatment with EEN specialized formula ($p < 0.05$), evaluated using the IMPACT II questionnaire [39]. A cost-effectiveness analysis estimated similar quality-adjusted life years (QALYs) for specialized and standard formulas over a 1 year time horizon [38]. This was the only study that reported QoL outcomes for standard formulas. The effectiveness of nutritional formula can vary due to patient adherence to treatment. In the only study

Table 4. Maintenance of remission – results from the included studies.

Author, year	Sample size	Intervention	Cohort	Time of assessment	Maintenance of remission at follow-up,* n (%)	P-value
Faiman et al. [34]	39	Modulen IBD	Standard food reintroduction	12 months	10 (77% of those achieving remission)	$p = 0.58$
			Rapid food reintroduction		10 (83% of those achieving remission)	
Fell et al. [40]	29	Modulen IBD	Overall	8 weeks 12 months	96% 14 (61%)	NA
Levine et al. [19]	78	Modulen IBD	EEN CDED and PEN	12 weeks	45.1% 75.6%	$p = 0.01$
Lionetti et al. [26]	9	Modulen IBD	EEN PEN	4 weeks From 2 to 8 months	8 (100%) 9 (100%)	NA
Logan et al. [27]	66	Modulen IBD	Overall	14 months	12 (29% of those achieving remission)	NA
Pigneur et al. [22]	100	Modulen IBD	Daily supplement Cyclic EEN	12 months	12 (24%) 25 (51%)	$p =$ 0.004
Sigall-Boneh et al. [42]	55	Modulen IBD	EEN CDED and PEN	14 weeks	16 (61.5%) 20 (69%)	$p = 0.56$
			EEN CDED and PEN	24 weeks	9 (34%) 16 (55%)	$p = 0.12$
Werkstetter et al. [29]	10	Modulen IBD	Overall	24 weeks 52 weeks	5 (62.5%) 7 (87.5%)	NA NA

CDED, Crohn's disease exclusion diet; EEN exclusive enteral nutrition; IBD, inflammatory bowel disease; NA, not available; PEN, partial enteral nutrition. *Percentages refer to initial samples unless specified.

that reported adherence with both specialized and standard formula, 4% and 7% of patients did not adhere to treatment with specialized formula and standard formula (Fortisip), respectively [33]. There is acknowledgment that the exclusion of regular food is a key factor that drives the benefit of formulas used in EEN and adherence is key in achieving this benefit, thus this difference between standard and specialized formula is important. In the eight studies that reported adherence with specialized formula, between 4% and 29% of patients did not adhere to treatment [13,19,24,27,28,33,37,40].

3.5.3. Economic

Two articles reported economic outcomes. A 2022 UK observational study compared the costs of specialized and standard nutritional formula over 8 weeks of treatment, which considered formula costs only. The direct cost of specialized formula was £17.15 per day (£960 per treatment course, 2017 costs), whilst standard formula was £8.22 per day (£460 per treatment course, 2017 costs) [33]. The study concluded that there were potential cost advantages associated with the use of standard formula compared to specialized formula. In contrast, a 2023 UK cost-effectiveness analysis that compared specialized and standard nutritional formula and included all related costs in the analysis, estimated savings of £746 with the use of specialized formula over 1 year. The probabilistic sensitivity analysis showed that specialized formula was 83% more likely to be cost-effective versus standard formula at a £20,000/QALY willingness-to-pay threshold [38].

3.6. Quality assessment

When assessing the quality of evidence, four RCTs showed a risk of bias [19,20,22,23] due to lack of information on the patient randomization process (2 studies, supplemental Table A7), patient awareness of assigned intervention (4 studies) and selected reporting of results (2 studies). Two RCTs showed considerable risk of bias due to missing outcome data [18], and deviation from an intended intervention. Of the 16 observational studies (supplemental Table A6), seven were judged to be of high quality [13,14,30,31,34,36,37]; six of these studies assessed specialized formula and one standard formula. The remaining observational studies were of fair quality as they often did not report how control groups were derived. Finally, the only economic evaluation fulfilled 50% of CHEERS items as it was an abstract with limited information [38] (supplemental Table A8). The second article that included economic information was an observational study, hence was assessed using the Newcastle-Ottawa Scale [33].

3.7. Validation of SLR findings

Primary research was conducted with five healthcare professionals (HCPs) in the UK to validate the findings from the literature and assess how they translate into real-world clinical practice, given the lack of real-world evidence identified in this review. All interviewees (three gastroenterologists and two dieticians) had experience prescribing specialized and standard nutritional formulas for the treatment of pediatric patients with CD in either community or tertiary care settings. The most commonly prescribed nutritional formulas were specialized formula and standard formulas (Fortisip, Ensure Plus, Osmolite and PaediaSure). Interviewees confirmed that results from the literature were mostly aligned with real-world clinical practice. The majority of interviewees used PCDAI score to define remission (<10 or < 20). Specialized formula was considered superior to standard formula in terms of mucosal healing by one HCP however, the remaining interviewees considered them broadly comparable. Three HCPs (1 gastroenterologist and 2 dieticians) considered specialized formula better than standard in the induction of remission; the remaining 2 gastroenterologists considered them comparable. It was noted by one respondent that specialized formula was unlikely to induce remission in 100% of patients; 80% was considered more realistic in clinical practice. Both dieticians suggested lower remission rates (approximately 65%) with standard formula. There was no consensus on the percentage of patients maintaining remission at 1 year with specialized formula. One gastroenterologist agreed with results from the literature (80%), a second considered 60% achievable, and the third suggested 30–40%. No data for standard formulas was available in the literature.

4. Discussion

This SLR comprehensively assessed clinical, humanistic, and economic outcomes reported by studies that evaluated the use of specialized and standard formulas for the treatment of pediatric active CD. Overall, specialized formula demonstrated benefits across all primary outcomes. A high proportion of pediatric patients with CD who received specialized formula achieved mucosal healing at 8 (63–89% of patients) and 10 weeks (25–74% of patients). A possible explanation for the low percentage at 10 weeks (25%) is that the measurement of calprotectin was completed 4 weeks following completion of EEN; measuring immediately after the end of the EEN would have been likely to have yielded a higher percentage of patients [27,28]. The largest body of evidence supported the use of specialized nutritional formula for induction of clinical remission in 50–100% of patients (16 studies; Figure 2), while six studies reported this outcome in 63–70% of patients with standard formula [30,33].

No publications reported the percentage of patients achieving mucosal healing for standard ONS. One article for standard ONS was identified but was excluded as the results were not reported separately for the two interventions [44]. In patients who received specialized formula, between 50–100% of patients achieved remission at 8 weeks. The lower range (50%) refers to a subset of patients suffering from colonic CD; however, percentages for ileocolonic and ileal groups in the same study were significantly higher (82% and 92%, respectively) [13]. Evidence from studies identified suggests that EEN may not be as effective for isolated colonic CD as it is for ileal or ileocolonic disease [45], which may explain the lower percentage of patients achieving remission in this study [13]. However, other studies have not replicated this finding [46,47].

For maintenance of remission, specialized formula showed a sustained benefit at 6 months (34–62.5%) [23,29], and at 1

year (24–87.5%) [22,29,40]. Of these studies, no additional treatments were used in Pigneur et al. [22] and Fell et al. [40], however pharmacological interventions such as immunomodulators (thiopurines and methotrexate), and 5-aminosalicylic acid were utilized in three studies [27,29,42]. In patients treated with specialized formula, QoL also showed improvements across all QoL domains [39]. Mean (standard deviation) QoL scores improved from 0.56 (0.18) to 0.74 (0.16) which was considered clinically significant ($p < 0.01$). However, QoL was only assessed in this one small study of 26 patients [39] which utilized a QoL measure (IMPACT II) which has now been superseded by the IMPACT III questionnaire [48]. IMPACT III has been available since 2008 and has been included in over 30 publications on QoL of children with inflammatory bowel disease, but these did not meet the criteria for this review. IMPACT III is likely to provide data more suitable to contemporary disease cohorts and allow easier comparison between treatments than IMPACT II.

It is broadly accepted that corticosteroids are effective at inducing remission in patients with active CD [14,18,49]. However, they should not be used to maintain remission [49] and do not heal the mucosa as well as nutritional therapies, as supported by 3 publications in this SLR, which showed significantly improved mucosal healing with nutritional therapy versus steroids [14,18,21]. Borelli et al. found that significantly more patients treated with specialized formula demonstrated mucosal healing versus steroids over 10 weeks (74% versus 33%, $p < 0.05$) [18], and this finding was confirmed in Pigneur et al. over 8 weeks (89% versus 17%, $p < 0.005$) [21]. In Berni Canani et al., significant improvements in mucosal inflammation were observed after 8 weeks in 64.8% of patients who received nutritional therapy (specialized or standard formula) versus 40% of patients who received steroids ($p < 0.05$) [14]. Additionally, 19% of patients who received nutritional therapy achieved complete mucosal healing at the end of the treatment compared with none who received steroids ($p < 0.005$) [14]. The side effect profile of steroids is also inferior to nutritional therapies [49]. Moreover, pediatric patients with CD may experience growth delay and low bone mineral density following use of corticosteroids [50], thus reduced use or avoidance of steroids in this patient group may be beneficial. It is also important to consider strategies to maintain remission after discontinuation of nutritional therapy. Whilst not considered in this SLR, this is an area of interest for future research.

Notably, there were limitations in the review of the literature. There is a general lack of robust evidence for standard formulas in the treatment of pediatric CD, with only 7 studies identified in this review. Additionally, there were only four head-to-head studies that directly compared standard and specialized formula. To establish whether specialized formula offer significant advantages over standard formula, there is a need for further randomized, controlled comparative trials. Results were not directly comparable due to significant heterogeneity between studies including methodology, patient populations and the definition of remission. Some studies used endoscopic scores to define mucosal healing, whilst others relied on calprotectin or histological markers. These different scales and definitions mean results of mucosal healing are not directly comparable. Providing a standardized definition of mucosal healing across clinical studies would improve clarity and allow for more accurate comparison.

Other limitations based on the study design included short duration of follow-up and small sample size in many studies, and the predominance of observational studies. There was often a short duration of follow-up, typically 6 to 8 weeks, with some studies reporting outcomes at only 2 weeks [23,26]. Eight of the 27 studies reporting clinical outcomes were RCTs [18–23,42,43], and the remaining were prospective observational (11 studies) [13,24–30,39–41] or retrospective evaluations (8 studies) [14,31–37]. The sample size was small (20 patients or less) in seven studies, with only three studies including more than 100 patients [22,33,37]. In terms of patient characteristics, mean age was similar across the studies, ranging from 10.2 to 14.9 years and the research protocol specified mild-to-moderate CD. However, there was variation in disease localization and proportion of males to females across the studies. These differences in study design and patient characteristics introduce potential confounding factors and make direct comparisons challenging. It should be noted that meta-analysis/meta-regression was not planned as part of this research but could be beneficial for future research.

Furthermore, QoL and economic outcomes were reported, but the data was limited. As noted previously, the effectiveness of nutritional formula can vary due to patient adherence to treatment, however data on adherence was limited, with 8 studies reporting adherence to specialized formula [13,19,24,27,28,33,37,40], and only one to standard formula [33]. From the studies included in this review, it is not clear whether a better adherence improves remission rates, with only one study suggesting that greater patient compliance correlates with increased remission [37]. The primary research that was conducted to supplement the findings of this SLR investigated factors related to adherence of pediatric patients. The key factors included family support, education, palatability of the formula and nutritional strategies that involve the consumption of regular food alongside nutritional formulas, such as PEN and CD exclusion diet. Additional tools to support adherence may be of benefit. The specialized formula reported here is accompanied by an App to enhance patient engagement and improved adherence to treatment.

An observational study reported potential short-term economic advantages of standard formula [33]; however, this publication only considered the daily costs of the nutritional supplements, but did not account for differences in patient outcomes and other healthcare costs, such as additional pharmacological treatments or HCP costs [33]. It is important to consider all direct medical costs in any economic evaluation. Furthermore, the retrospective and prospective cohorts in this study were not well matched with significant differences in the proportion of patients receiving an initial course of EEN ($p < 0.001$) [33], and the study used different methods to assess disease activity. One economic study (published in abstract) indicated the potential cost-effectiveness of specialized formula over 1 year when considering wider treatment-related costs [38]. However, the cost-effectiveness analysis had limitations due to its reliance on

assumptions as there are no head-to-head trials of specialized and standard formulas [38]. These limitations may thus affect the ability to draw firm conclusions from the economic evidence in both the short and long-term [33], and highlight the need for a more comprehensive analysis that includes real-world clinical and economic data to support clinical decision-making.

The effectiveness of various formulas for managing CD in children was systematically assessed by McVeigh and Payne in 2020 [51]; however, this evaluation did not compare specialized and standard nutritional formulas and did not locate any evidence directly comparing the two. The current SLR also did not identify any head-to-head trials comparing specialized and standard formulas. Primary research was thus conducted with HCPs to help validate the findings from the literature. HCPs expressed varied perspectives of real-world clinical practice with some suggesting that specialized formula achieve higher rates of mucosal healing, induction and maintenance of remission versus standard formulas and others considering the two comparable. HCPs also noted that criteria used to select a nutritional formula are often based on contractual reasons, local guidelines, and price. However, understanding the outcomes associated with specific formulas can support informed decision-making by healthcare professionals, administrators and payers.

5. Conclusion

Numerous nutritional formulas are used for the treatment of pediatric patients with CD, however, specialized formula is the only formula designed and positioned specifically for the dietary management of the active phase of CD. Overall, 75% of studies screened in this review evaluated specialized formula. Nutritional formulas vary considerably in terms of their composition of nutrients and ingredients, accessibility, taste and price, making the optimal selection of formula an ongoing clinical challenge. The majority of published evidence supports the efficacy of specialized formula in promoting mucosal healing, remission, and sustaining positive outcomes across multiple time points. This SLR confirms the clinical efficacy, real-world effectiveness, potential QoL gains, and benefits of specialized formula when used to treat pediatric patients with active CD up to 1 year. A direct head-to-head trial of specialized and standard nutritional formula in pediatric patients with CD would help to confirm the findings of this SLR and add to the current body of published evidence to improve current clinical practice.

6. Expert opinion

The current data support the use of specialized formula being used as EEN with less support for standard formula. An obvious next step would be to undertake a head-to-head RCT of standard versus specialized formula using agreed outcome response measures for comparison [52]. However, these types of studies, while good in theory, are difficult to conduct, expensive, and may struggle to recruit patients e.g. if endoscopies were required at the start and end of treatment to compare rates of mucosal healing.

There are quicker and easier ways to enhance the available literature and use pragmatic outcomes that are aligned with studies in children and adolescents. Fecal calprotectin has been underrepresented in studies in this SLR, but this alone can act as a broad proxy for outcomes in nutritional studies without the need for endoscopy [53]. Using fecal calprotectin and additional information to generate the Mucosal Inflammation Noninvasive Index (MINI) could be used to assess mucosal healing in future studies [54]. MINI and fecal calprotectin could be assessed with ease at numerous timepoints during a course of EEN to identify the optimal length of treatment, and these outcomes have the practical benefit of negating the need for endoscopy [54].

More studies that assess QoL using contemporary methods, such as the IMPACT III questionnaire, are needed in pediatric patients with CD. Studies should also evaluate how different feeding routes (oral or tube) and different formulas (specialized versus standard) benefit patients directly, compared to the clinical measures favored by HCPs. In this SLR, the rudimentary assessment of compliance to nutritional formulas was a major limitation. Recent advancements in objective measures of compliance, such as fecal calprotectin and gluten immunogenic peptides [55], could be used to more accurately assess compliance across different formulas. Thus, conducting future studies using up-to-date assessment tools would provide an easy, yet accurate and more practical way to advance the evidence supporting the nutritional treatment of children with CD.

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Author contributions

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Data availability statement

Data for the systematic literature review were obtained from published sources.

Ethical approval and consent statements

As this was a systematic literature review, no ethical clearance or informed consent was required.

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