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REVIEW ARTICLE

Revolution in diet therapy for inflammatory bowel disease

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Abstract

Until recently, diet as a therapeutic tool to treat inflammatory bowel disease (IBD) has not been proven effective. Nearly a century in the making we are in the grips of a revolution in diet therapies for IBD, driven by emerging data revealing diet as a key environmental factor associated with IBD susceptibility, and observational studies suggesting that dietary intake may play a role in the disease course of established IBD. This review summarizes the current evidence for diets trialed as induction and maintenance therapy for IBD. For Crohn's disease, exclusive enteral nutrition and the Crohn's disease exclusion diet with partial enteral nutrition are supported by emerging high-quality evidence as induction therapy, but are short-term approaches that are not feasible for prolonged use. Data on diet as maintenance therapy for Crohn's disease are conflicting, with some studies supporting fortification, and others suppression, of certain food components. For ulcerative colitis, data are not as robust for diet as induction and maintenance therapy; however, consistent themes are emerging, suggesting benefits for diets that are plant-based, high in fiber and low in animal protein. Further studies for both Crohn's disease and ulcerative colitis are eagerly awaited, which will allow specific recommendations to be made. Until this time, recommendations default to population based healthy eating guidelines.

Introduction

Inflammatory bowel disease (IBD), encompassing ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory conditions of uncertain etiology.[1] The pathogenesis of IBD is purported to relate to susceptible host genetics, immune dysregulation, and gut microbial dysbiosis.[1] There has been an acceleration of incidence and prevalence of IBD in both developed and developing countries over recent decades, implicating the putative influence of environmental factors in IBD susceptibility and pathogenesis.[2–4] Migration studies have clearly demonstrated that migration to a Westernized country imparts risk for developing IBD.[5] Multiple large population-based longitudinal studies have revealed diet as a key environmental factor associated with IBD susceptibility.[6,7] Overall, a Western diet, high in animal protein and refined sugar and low in fiber, fruits and vegetables, is associated with an increased risk of developing IBD.[6] A more nuanced view implicates a carnivorous diet to be more associated with risk of UC development, whereas a higher intake of ultra-processed foods is more associated with risk of

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CD development.[8–10] Beyond susceptibility, dietary intake may also play a role in the disease course of established IBD, with observational studies suggesting that clinical flare is associated with a Western diet, while a plant-based diet may be protective.[11]

Despite signals that diet plays a role in IBD susceptibility and severity, until relatively recently, whole-food dietary strategies have lacked efficacy.[12] Multiple dietary approaches have been trialed in IBD without success, from raw pork diets in the 1940s to milk-free diets in the 1960s.[13] Popularized diets in IBD have lacked a robust evidence base, such as the specific carbohydrate diet (SCD), which despite its restrictive nature, is no better than a Mediterranean diet in ameliorating symptoms of CD.[14] Other popularized dietary approaches, such as a low residue/fiber diet, not only lack evidence but may be harmful, with evidence to suggest that fiber deprivation is associated with clinical flare and risk of gut microbial dysbiosis.[15,16] Nutraceutical approaches have also been trialed in IBD, including omega-3 polyunsaturated fatty acids, which have not been shown to prevent relapse of CD[17] and studies in UC have been conflicting.[18]

Almost a century in the making, we are now witnessing a revolution in diet therapies for IBD. Observed epidemiological trends in IBD have acted as revolutionary forces, as well as an increasing recognition that IBD is at least in part a microbial-driven disease and that dietary intake is the key modulator of gut microbial composition and function.[19] In the era of "treat to target" in IBD, a broader therapeutic armamentarium is required.[20] There is also an acknowledgment that current immune-based therapies for IBD are lacking, demonstrating both incomplete efficacy as well as a significant side-effect profile including malignancy and opportunistic infection.[21] Lack of durability is also a shortfall of current therapies, with high rates of secondary loss of response.[21] Consumer demand has also catalyzed the dietary revolution in IBD; diet has been identified as a key international research priority for both patients and clinicians.[22] In the absence of a robust evidence base, patients can fall prey to internet-based misinformation on dietary approaches in IBD, leaving them at risk of malnutrition and reduced food-related quality of life.[23]

The dietary revolution in IBD has involved a broad recognition of the multifactorial role of diet, not only to manage nutritional needs, but to avoid complications such as sarcopenia and osteoporosis, improve both quality of life and inflammatory disease activity, and prevent disease in offspring.[24] Dietary manipulation in IBD may be used to both induce remission and maintain remission of disease, manage symptoms including concurrent functional symptoms, or as an adjunctive approach to augment response to conventional therapy.[24] There has been an emergence of whole-diet strategies in IBD, with accruing evidence for defined diets in both CD and UC to influence inflammatory activity.[24] Concurrently, there has been an increasing recognition of the important role of excusive enteral nutrition (EEN) for remission induction in CD, both in pediatric and adult cohorts, which is efficacious in inducing both clinical and endoscopic remission, while concurrently augmenting nutritional status, all without the need for immunosuppression.[25]

The dietary revolution in IBD is culminating in high-quality dietary trials, sufficient to provide robust evidence to inform clinical practice. Modern dietary trials in IBD require careful selection of IBD phenotype, as well as measurement of inflammatory burden, beyond symptoms, to interpret true therapeutic efficacy.[26] Dietary trial design also requires consideration of the administration of the dietary strategy, whether by dietary advice alone or as a feeding study, as well as how to approach the placebo arm. Mechanistic insights derived from dietary trials in IBD pose to further shape understanding of the pathogenesis of IBD, unraveling the complex interplay within the intestinal immunological and microbial milieu, and answering the remaining questions relating to diet.[27]

This review provides an overview of the revolution in diet therapy in IBD, with a focus on the use of diet to treat active disease and prevent relapse, including practical recommendations for clinicians.

Diet therapies for CD

Literature describing the relationship between diet and CD is laden with the doctrine proposing that features of a Westernized diet are inflammatory and will drive disease, as elements of this diet have been associated in epidemiological studies with development of disease. Conversely, features of a Mediterranean diet, such as high intake of wholegrains, fruit, vegetables, legumes, and olive oil; moderate intake of fish/seafood, dairy, and wine; and limited in meat, particularly red meat, are purported to be anti-inflammatory and to improve CD activity. This notion, however, does not necessarily translate to evidence that CD may be treated through diet. To date, eight diets have undergone trials to assess their impact as induction and/or maintenance therapy for CD are described in Table 1.

Exclusive enteral nutrition. EEN provided the first evidence that diet can be used to treat inflammation in IBD, specifically CD. Expanding clinical use of EEN has changed attitudes toward the use of diet as a therapeutic agent to target active inflammation in CD. EEN involves using a liquid nutrition formula to meet an individual's nutrition requirements, excluding other food and fluids, usually for a duration of 6–8 weeks. Given the onerous nature of EEN, application beyond this period is unfeasible for long-term or maintenance therapy. EEN is as effective as corticosteroids in inducing clinical remission in pediatric CD, achieving this in up to 80% of patients, with similar rates of biomarker normalization (including CRP and fecal calprotectin).[28,29] Few studies have examined mucosal healing, however, when assessed it is considerably more likely among patients receiving EEN compared to corticosteroids (OR 4.50, [95% CI 1.64, 12.32], OR 5.24, [95% CI 2.06, 13.37]).[28,30] EEN has additional advantages over corticosteroids not only via the avoidance of steroid-related side effects but through improvement in nutritional parameters including improved growth, bone mass, and lean mass accrual in children. As such, it is now recommended as first-line therapy to induce remission of CD in pediatric clinical guidelines.[31]

In adults, the data have been less clear with greater variability in clinical remission rates reported (22–80%), high rates of discontinuation and adherence rates either not reported or poorly described.[29] However, the same premise of efficacy applies to adults as it does to pediatric cohorts, and EEN is likely to be as effective at achieving clinical remission as

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Table 1 Diets investigated for the treatment of Crohn's disease and ulcerative colitis and their composition

Diet	CD or UC	Intent of diet therapy	Meat	Dairy	Additives	Fiber	Highest level of evidence	Practice point
Westernized diet	Reference diet		↑	↑	↑	↓		
Population-based dietary guidelines	Reference diet		↓	↔	↓	↑		
EEN	CD	Induction	↓	↑	↑	↓	RCT[29]	Recommend for remission induction for defined timeframe with monitoring[25]
PEN	CD	Both	↔	↑	↑	↔	RCT[41]	Trial for defined timeframe >50% requirements for remission induction or maintenance
CDED (without PEN)	CD	Induction	↑	↓	↓	↔	Pilot[44]	Trial for defined timeframe, with consideration of nutritional adequacy[45]
CDED + PEN	CD	Induction	↑	↑	↑	↔	RCT[43]	Recommend to induce remission (Phase 1 and 2)
CD-TREAT	CD	Induction	↑	↑	↑	↓	Pre-clinical and pilot[46]	Insufficient data to recommend or trial
SCD	CD	Induction	↑	↔	↓	↓	RCT[14]	Insufficient data to recommend. Trial with consideration of nutritional adequacy
Mediterranean	CD	Induction	↓	↔	↓	↑	RCT[14]	Trial for defined timeframe, due to potential for efficacy and principles in line with population-based dietary guidelines
Semi vegetarian	CD	Maintenance	↓	↔	↓	↑	Observational[49]	Insufficient data to recommend or trial
FACES	CD	Maintenance	↓	↔	↔	↔	Observational[50]	Insufficient data to recommend or trial
Low sulfur	UC	Induction/ maintenance	↓	↔	↓	↓	Pilot[57]	Insufficient data to recommend or trial
4-SURE	UC	Adjunctive	↓	↔	↓	↑	Pilot[58]	Insufficient detail of diet published to trial for defined timeframe
UCED	UC	Induction	↓	↔	↓	↑	Pilot[59]	Insufficient detail of diet published to trial for defined timeframe
Mediterranean	UC	Induction	↓	↔	↓	↑	RCT[60]	Trial for defined timeframe due to potential for efficacy and principles in line with population-based dietary guidelines
Lacto-ovo vegetarian	UC	Maintenance	↓	↔	↔	↑	Pilot[73]	Insufficient data to recommend or trial
AID	UC	Maintenance	↓	↔	↓	↑	RCT[69]	Insufficient data to recommend or trial
IgG4 exclusion	UC	Induction/ maintenance	↓	↓	↓	↔	RCT[61]	Insufficient data to recommend or trial
CMP-free	UC	Induction/ maintenance	↔	↓	↔	↔	RCT[62]	Insufficient data to recommend or trial
Milk-free	UC	Maintenance	↔	↓	↔	↔	RCT[67]	Insufficient data to recommend or trial
Low carrageenan	UC	Maintenance	↔	↔	↓	↔	RCT[66]	Insufficient data to recommend or trial
Low fat, high fiber	UC	Adjunctive	↔	↔	↔	↑	RCT[65]	Insufficient data to recommend or trial
Healthy eating guidelines	UC	Maintenance/ adjunctive	↓	↔	↓	↑	RCT[64,68]	Recommend in line with population-based dietary guidelines

(*Continues*)

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Table 1 (Continued)

Diet	CD or UC	Intent of diet therapy	Meat	Dairy	Additives	Fiber	Highest level of evidence	Practice point
EEN	UC	Adjunctive	↓	↑	↑	↓	RCT[79]	Insufficient data to recommend or trial
FODMAP	UC	Induction	↔	↔	↔	↓	RCT[63]	Insufficient data to recommend or trial

↑ increased; ↔, unchanged; ↓, decreased. Induction therapy: short term: intended to modulate inflammatory pathway or promote healing to induce response or remission in active disease; maintenance therapy: long term: intended to modulate inflammatory pathways and/or barrier function and/or other pathogenic factors (e.g. microbial community structure) to maintain response or remission in quiescent disease; adjunctive therapy: short or long term: intended to work synergistically with conventional therapy to induce or maintain response or remission in either active or quiescent disease.
4-SURE, Four Strategies to Sulphide Reduction; AID, anti-inflammatory diet; CD, Crohn's disease; CDED, Crohn's disease exclusion diet; CD-TREAT, Crohn's Disease Treatment-with-EATing; EEN, excusive enteral nutrition; FACES, Food and Crohn's Disease Exacerbation Study; PEN, partial enteral nutrition; SCD, specific carbohydrate diet; UC, ulcerative colitis.

corticosteroids in adults when adherence is maintained.[25,32] Accordingly, EEN has increasingly been used in adult cohorts, with observational studies demonstrating its ability to treat complications such as strictures and fistulae, reduce post-operative complications and avoid need for surgery altogether.[33] Its application has become more attractive with meta-analyses demonstrating equal efficacy among polymeric, elemental, and formula with altered fat content,[29,34] improving the palatability of the formula offered to patients and the ability to administer EEN orally rather than via a feeding tube.[35]

Predicting patients most likely to respond to EEN therapy is appealing, with some potential candidate markers of response. Male sex, younger age, and milder disease activity have all been associated with EEN response. In a pediatric cohort, males were more likely to achieve remission compared with females (responders 66.7% males *vs* non responders 53.8% males, $P = 0.036$) and there was a trend toward younger patients responding better (responders median 12 years, non-responders 13 years, $P = 0.053$).[36] A lower Pediatric Crohn's Disease Activity Index (PCDAI; 30 *vs* 35, $P = 0.011$) before EEN commencement was also associated with EEN response. Similarly, patients with a weighted PCDAI (wPCDAI) ≤57.5 (OR 3.8 [1.5–9.7], $P = 0.005$) and a fecal calprotectin <500 μg/g (OR 6.9 [1.3–35.4], $P = 0.019$) were more likely to respond to EEN. In contrast, patients with a CRP > 15 mg/L (OR 2.6 [1.01–6.8], $P = 0.047$) responded better to EEN in multivariate analysis, as did those with ileal involvement (OR 6.3 [1.09–36.6], $P = 0.039$).[37] Differences in fecal microbiota prior to EEN in those that responded and those that did not respond to EEN have also been observed, with an individual's microbial signature able to predict response to EEN with 80% effectiveness.[38]

A better understanding of factors influencing adherence to EEN is crucial to identifying patients most at risk of failing EEN induction treatment. Pediatric studies have demonstrated that patients with colonic involvement were significantly less adherent (adherents 72.5% colonic involvement *vs* non-adherents 87.8% colonic involvement, $P = 0.035$) than those without colonic involvement, as are those with more severe disease (higher PCDAI score 30 *vs* 32.5, $P = 0.035$, higher fecal calprotectin 987 *vs* 588 μg/g, $P = 0.001$).[36] Predicting and optimizing adherence in adult cohorts are imperative for successful EEN therapy. In adults, adherence and completion of EEN have been associated with a greater mean conscientiousness score (35.57, 95% CI = 32.88–38.25 in the adherent group compared to 30.13, 95% CI = 26.53–33.73 in the non-adherent CD group [$P = 0.014$]).[39] Those who are adherent to EEN are more likely to go on to complete EEN therapy.[32] Other characteristics and enablers for the completion of EEN therapy include patient self-efficacy, health system support, supplement characteristics and access, and social support.[25]

While the efficacy of EEN is well-accepted in CD, attention has now shifted to understanding the mechanism of action of EEN, which is not only crucial to the design of future diets to treat IBD but also reveals insights as to underlying disease pathogenesis. Currently, the mechanism of action of EEN is believed to be a complex interplay between luminal environment and host mucosal immune response.[40] EEN eliminates exposure to table foods and dietary antigens and has been shown to alter gut microbiota, immunological indices, luminal metabolome, intestinal epithelium, and nutritional status.[40] There are in fact a number of paradoxical findings when examining the effects of EEN. For example, while EEN excludes table foods and many dietary components, the formula itself contains multiple putatively detrimental components such as emulsifiers and maltodextrin. When examining changes in fecal microbiota, EEN consistently results in a reduced microbial diversity and a reduction in species such as *Faecalibacterium prausnitsii*, believed to in fact be protective in CD.[40] Ultimately, achieving a greater understanding of how EEN works will pave the way for food-based dietary treatments for CD.

Other diets as induction therapy for CD. Given the success of EEN, the logical next step to both improve understanding of its mechanism and to ease the burden of the treatment is the assessment of partial enteral nutrition (PEN), providing only a proportion of estimated requirements through enteral formula and allowing unrestricted food for the remaining intake. Studies have assessed PEN for at least 50% of nutritional requirements, with clinical remission rates varying between 15% and 64%, if based on CD activity indices.[41] However, there are

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generally poor rates of remission with PEN monotherapy when using fecal calprotectin as a marker, with only 14% of patients achieving <250 μg/g despite improved disease activity scores.[41] As an adjunct to biologic therapy, at least 50% PEN can enhance therapeutic effects, even in complicated disease.[42] It would seem that a higher proportion of PEN correlates with efficacy. This may relate to the impact of PEN on the luminal environment, which is enhanced with higher intakes, with one study in adult patients receiving either EEN or PEN demonstrating that PEN at >50% is comparable to EEN in terms of fecal metabolites and pH. PEN has advantages in terms of adherence rates, which may allow for a longer duration of diet therapy; however, more evidence is required before its use can be routinely recommended in practice.

Crohn's disease exclusion diet (CDED) is the only diet looking at controlling the food component alongside PEN therapy, using 50% PEN and restricting the food proportion of the diet to 14 foods. The CDED with PEN induced clinical remission and reduced fecal calprotectin in up to 75% of pediatric patients with CD in a randomized trial ($n = 40$), which was similar to the EEN comparator but was better tolerated.[43] Similar results were seen in adults receiving CDED with and without PEN in a pilot open-label study ($n = 44$).[44] The rationale for the CDED treating disease is that it removes putative inflammatory food components of a Westernized diet, however, this is at odds with the nutritional composition of the CDED with PEN, which appears high in total and saturated fat, sugar and additives, albeit mostly from the PEN component. Nutritional analysis of the CDED with and without PEN have identified adequate total fiber, but deficiencies in calcium and excesses in protein (mainly of animal source; Table 1).[45] Total fat and sugar intake were not assessed, nor were fiber types.

Along the same theme of simulating EEN is the CD-TREAT (Crohn's Disease Treatment-with-EATing) diet, a novel diet aimed to mimic EEN composition with real food. Data supporting the CD-TREAT as an induction therapy is in its infancy, with pre-clinical models showing that the diet induces EEN-like microbial effects and improved inflammatory markers. This was replicated in five pediatric patients with active CD, achieving clinical remission and reduced fecal calprotectin following the diet.[46] Larger controlled trials in humans are underway.

A change in approach was to compare two contrasting diets in a head-to-head trial of patients with CD receiving the SCD, a diet eliminating lactose (but not dairy), sucrose, starchy vegetables including most legumes and all grains, to the Mediterranean diet, a plant-based diet, which is abundant in the vegetables, legumes, and grains restricted on the SCD. A large randomized controlled trial (RCT) in symptomatic CD patients showed that both diets reduced symptoms by half with a concurrent reduction in fecal calprotectin in a third, although less than 20% of participants had elevated fecal calprotectin on study entry.[14] While the diets may improve symptoms seen in CD, the likely mixed population of patients with inflammatory and functional symptoms makes the clinical utility of the diets uncertain.

To date, only EEN and CDED with PEN are supported by high-quality evidence to treat active CD, but promising results of longer-term diets are awaited. The inferences from the data of successful and potential induction diet therapies in CD are that a diet low in fiber and high in dairy protein, fat and food additives treat disease (Table 1 and Fig. 1), which is in contrast to dietary patterns that appear to influence development of disease. Our lack of mechanistic studies to understand which components of these diets are involved in the reduction in inflammation prevents the ability for recommendations to modulate specific food components outside of the context of these specific dietary strategies.

Diets as maintenance therapy for CD. Diets assessed for supporting remission in quiescent CD are less studied. Trials assessing 50% PEN in adult patients with CD for 6–24 months have indicated feasibility in its long-term application and reduced risk of flares compared to unaltered eating or thiopurine therapy. Retrospective pediatric studies have shown similar effects at 12 months.[47] As suggested by the evidence of PEN in active CD, a higher percentage of PEN is probably important as sustained

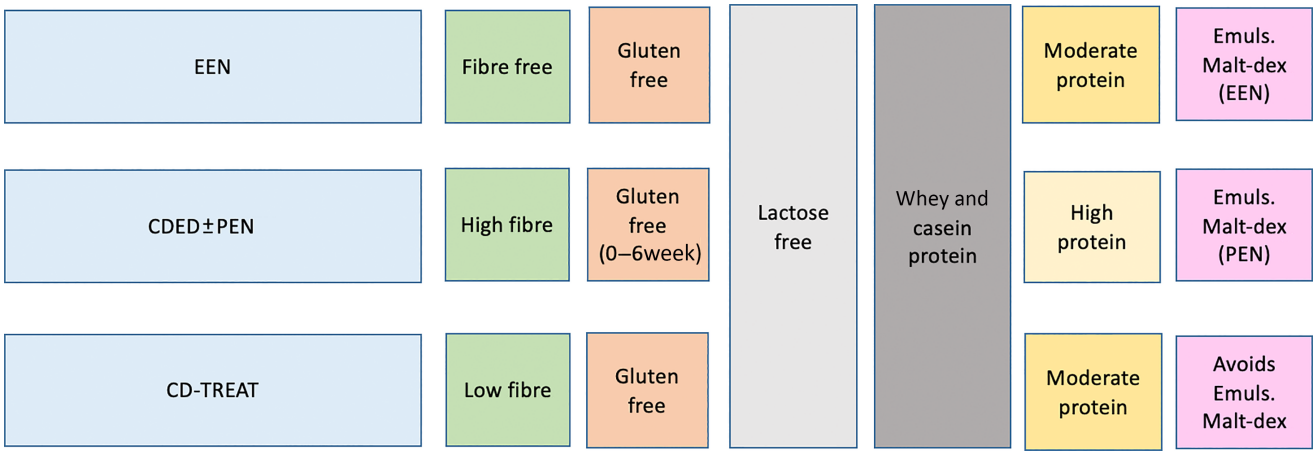

Figure 1 Dietary profiles of prospectively trialed emerging diet strategies as induction therapy for Crohn's disease. Emuls., emulsifier; Malt-dex, maltodextrin.

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remission from 20% to 30% PEN was not achieved.[48] The speculation from these data is that extending the diets used for induction therapy would prevent disease relapse. However, this concept is conflicting with a study associating a reduced risk of flare with a semi-vegetarian diet (SVD), high in fiber and low in animal protein and fat (Table 1), over 2 years.[49] Survey data of patients with quiescent CD also refutes that idea, as those consuming at least 23 g fiber were 40% less likely to flare over 6 months, compared to those with an intake of 10 g fiber.[16] Lastly, the FACES internet-based trial of over 200 patients with clinically quiescent CD randomized to limiting red and processed meat to less than once monthly or consuming at least two servings per week showed no difference in symptomatic relapse between the cohorts. However, adherence in the low meat group was only 57% compared to 99% adherence in the high meat group.[50]

It seems that there is more confusion on the role of diet to maintain remission in patients with CD, with conflicting data on fiber, animal protein and fat. In the absence of clear information, the default messaging should be to follow healthy eating guidelines while the field awaits robust evidence to indicate otherwise.

Diet therapies for UC

To date, there is no diet therapy to treat inflammation in UC with sufficient data to support translation into clinical practice. However, there is a compelling rationale for diet therapy, supported by emerging data on the role of diet for microbial manipulation in UC. The pathogenesis of UC points toward compounding interactions between gut barrier function, gut microbes, and a dysregulated immune response. Inflammation begins in the rectum and extends proximally, correlating with colonic fermentation patterns and a bacterial density gradient.[51] Diet is a key player in modulating the intraluminal environment, and the large bowel is the primary site for fermentation of fiber (carbohydrate) and excess, or resistant proteins, which are metabolized into vitamins, gases, and enzymes as part of normal digestive processes.[52] In UC, fermentation of carbohydrate and protein appears defective, with inadequate fermentation of carbohydrate (reduced short-chain fatty acids [SCFA]) and excess fermentation of protein (increased gaseous metabolites, specifically hydrogen sulphide [H_2S]).[53–55] At high levels, H_2S impairs the production of SCFA and energy to colonocytes, starving the epithelial cell and causing metabolic injury and inflammation in the epithelial lining, as seen in UC.[56] Evidence for this microbial-driven H_2S hypothesis, proposed as a pathogenic mechanism of UC, underpins the potential of using diet as a microbial-driven therapeutic agent for UC.

Diet as induction therapy for UC. Six trials have examined diet as an induction therapy, with three pilot studies focusing on the reduction of H_2S as the therapeutic target (Table 1).[57–59] These pilot studies are of particular interest as, though uncontrolled open-label studies, the dietary profiles of each strategy are similar (Fig. 2) and clinical data are comparable. Roediger *et al.* were the first to trial a low sulfur diet in four participants with active UC.[57] Participants were induced with 3 weeks of oral prednisolone, Salazopyrin and instructed to follow a low sulfur amino acid diet, avoiding a select few animal-based foods. Excellent self-reported compliance was reported (100%) with all patients achieving histological and symptomatic remission without relapse at 52 weeks. A second pilot dietary advice trial reported outcomes of the Four Strategies to Sulphide Reduction (4-SURE) diet in 28 adults with mild–moderately active UC for 8 weeks. Clinical response (reduction in partial mayo ≥2) was achieved in 14/28, endoscopic response (reduction in endoscopic sub score ≥1) was achieved in 10/28, and histological response (reduction in Nancy Histological Index ≥1) was achieved in 12/28.[58] The third trial examined the UC exclusion diet (UCED) in 23 pediatric-adolescents with mild–moderately active refractory UC. Participants were prescribed a 6-week whole food exclusion diet advice with a 14-day triple antibiotic regimen if they failed to go into clinical remission. Of those who received diet alone, 9/24 achieved clinical remission (PCUAI < 10) and 17/24 had a clinical response.[59]

Other defined dietary strategies trialed as induction therapy for UC include the Mediterranean diet,[60] IgG exclusion diet,[61] cow's milk protein (CMP)-free diet,[62] and the low FODMAP diet.[63] Of these, the Mediterranean diet and IgG4 exclusion diet trial had positive outcome as induction and maintenance therapy over 3- and 6-month timeframes. Compared to a regular diet, the Mediterranean diet yielded a significant reduction in PUCAI

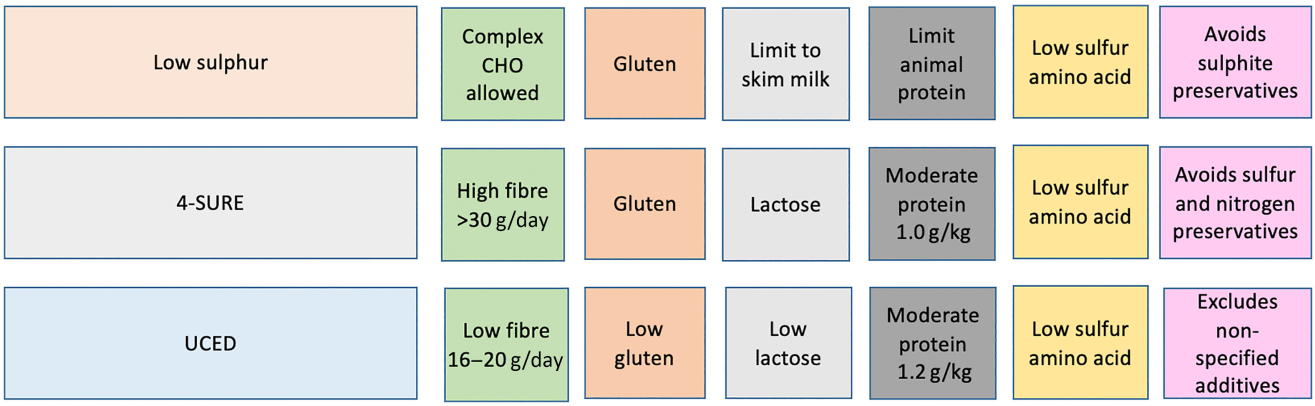

Figure 2 Dietary profiles of prospectively trialed emerging diet strategies as induction therapy for ulcerative colitis.

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Table 2 Supplementation with fermentable fibers to augment response to oral therapy in adults with ulcerative colitis

Fiber	Therapeutic intent	Dose	Duration	Adjunctive oral therapy	Treatment outcomes	Practice points
Germinated barley	Induction	20 g/day	12 months	Prednisolone	Sustained remission[80]	Insufficient data to recommend as an adjunctive therapy; however, supplemental to habitual diet may provide putative benefits to bowel function and microbial activity through optimization of fiber intake. Clinician-directed trial with dose titration and monitoring of symptoms recommended
	Induction	30 g/day	4 weeks	5-ASAs or corticosteroids	Clinical and endoscopic response[81]	
	Induction	20–30 g/day	4 weeks	5-ASAs or corticosteroids	Clinical response[82]	
Psyllium	Maintenance	20 g/day	12 months	Mesalamine	Lower rates of relapse[83]	Trial for defined timeframe
Oat bran	Maintenance	60 g/day	3 months	5-ASAs, IMM, corticosteroids	Nil relapse[84]	Insufficient data to recommend as an adjunctive therapy; however, supplemental to habitual diet may provide putative benefits to bowel function and microbial activity through optimization of fiber intake. Clinician-directed trial with dose titration and monitoring of symptoms recommended
Inulin	Induction	15 g/day	9 weeks	5-ASAs	Clinical and endoscopic response[85]	
	Induction	12 g/day	1 week	Mesalazine	Clinical response[86]	

5-ASAs, five aminosalycylic acid; IMM, immunomodulator.

(Mediterranean diet week 0: 30.5 ± 3.7 *vs* week 12: 7.6 ± 11.2; regular diet week 0 29 ± 6.1 *vs* week 8 9.2 ± 7.5, $P < 0.05$) with 22 in clinical remission compared to 18 on regular diet.[60] A small but significant reduction in total Mayo score was observed in participants following IgG exclusion diet compared to those following a sham diet (2.41 ± 0.89 *vs* 3.52 ± 1.15, $P < 0.05$). However, the interpretation of the induction phase of this study is limited by a lack of appraisal of objective inflammatory activity at baseline.[61]

Diet as maintenance therapy for UC. Seven prospective trials have examined dietary strategies for the maintenance of remission of UC, mostly examining variations of healthy eating.[57,61–68] The efficacy of differing dietary strategies as a maintenance therapy beyond population-based healthy eating guidelines is inconclusive.

A novel and complex diet termed the anti-inflammatory diet (AID) was compared to habitual Canadian diet as a strategy to maintain clinical remission in 43 adults with UC. The AID was designed to increase plant-based foods rich in fiber, antioxidants and polyunsaturated fats, and reduce red and processed meats. No differences in relapse rates as defined by a 2-point increase in partial Mayo score were observed between diets (AID 5/26 [19.2%]; Canadian diet 8/27 [29.6%], $P = 0.38$), though increased fecal calprotectin was observed in the Canadian diet group ($P = 0.002$).[69] As with CD, the Mediterranean diet was compared to the habitual Canadian diet in 32 adults with quiescent disease and there was no observed difference in clinical outcomes between diets. Interestingly, nutritional deficits were found for both diets suggesting a lack of adherence to dietary recommendations.[64]

In a 4-week parallel-group crossover study of 17 adults with clinically quiescent or mild UC, participants were fed a low fat high fiber and an improved standard American diet. No differences in clinical relapse were observed in each arm ($P = 0.08$), although there were likely minimal compositional difference between the two diets, which were both similar to healthy eating guidelines.[65] Indeed, patients with quiescent UC had improved disease activity scoring when given dietary advice specific for UC derived from evidence-based practice guidelines compared with those given control diet advice in line with population-based guidelines. No objective markers of inflammation were measured. Lastly, relapse rates were assessed in 12 adults with quiescent UC who followed either a no-carrageenan diet (habitual American diet with avoidance of carrageenan food additive) or a re-supplemented no-carrageenan diet (no-carrageenan diet with carrageenan capsules) for 12 months or until relapse.[66] Three of five participants who consumed carrageenan capsules relapsed compared to 0/7 in the placebo arm, where relapse was defined as a ≥2 point increase in SCCAI (carrageenan 4.20 ± 3.70 *vs* placebo 0.86 ± 1.46, $P = 0.05$). An earlier trial of a milk-free diet showed no change in relapse rates compared to a "dummy" milk-free gluten-free diet.[67]

Diet to augment response to therapy in UC. Diet to improve the efficacy of pharmacological and microbial therapies is an exciting and rapidly evolving area of the dietary revolution in UC. The core concept of these augmentation strategies is optimizing dietary fiber and a plant-based approach to eating. The mechanism of effect is less clear, presumed to be related to the presence or absence of fiber-fermenting microbes. Two studies provide insight. One study observed abnormal fermentation patterns in quiescent UC after supplementing with resistant starch

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and wheat bran. A 2-fold lower fermentation of fibers into starch was observed in UC compared to healthy controls ($P = 0.002$), suggesting either an absence or defect in fiber-fermenting microbes.[70] Working from a similar hypothesis, another study identified bidirectional changes in the production of inflammatory cytokines after supplementation with β-glucan fibers in vitro and in vivo, concluding when fiber-fermenting microbes are present, an anti-inflammatory effect is observed but when absent, unfermented fibers fuel inflammatory pathways.[53]

Conversely, other clinical studies have shown positive mechanistic effects of modulating dietary fiber. Examining luminal pH changes after high (13 g/meal) and low (<2 g/meal) fiber meals, one study demonstrated fiber-derived changes in pH affect 5-aminosalicylaic pH-controlled drug delivery matrices.[71] The clinical relevance of this is important as the habitual diets of adults with UC lack dietary fiber and may be limiting efficacy of oral therapy.[72] Smaller studies indicate supplementation of habitual diet with different fermentable fibers augments response to oral therapy, with clinical and endoscopic response and sustained remission observed (Table 2).

In keeping with a similar emerging dietary pattern in the revolution of diets for UC, plant-based diets are increasingly being evaluated as a dietary strategy to augment response to biologic and microbial therapies. In a Japanese study, prescribed Infliximab and a lacto-ovo SVD to 92 patients admitted with a flare of UC. Cumulative relapse rates were observed to be lower at 1 and 5 years than previously reported using conventional therapy.[73] This same diet was examined as a first-line combination induction therapy (lacto-ovo SVD and Infliximab) for severe UC, with impressive rates of remission (76%).[74]

Plant-based diets have also been used in two RCTs and several case studies as a strategy to augment and maintain response to fecal microbiota transplantation (FMT). A plant-based anti-inflammatory diet was trialed alongside FMT in 66 adults with mild–moderate UC who were assigned to either standard medical therapy (SMT) or FMT with diet (FMT-AID) for 8 weeks. FMT-AID was superior to SMT in achieving clinical and deep remission at 8 weeks and AID alone was superior to SMT in sustaining deep remission at 48 weeks.[75] Similar cases of deep remission have been reported at 6- and 12 months using a combination of FMT and 4-SURE diet in severe UC.[76,77] In a similar trial that was ceased early, UCED without FMT was superior at achieving clinical remission and mucosal healing than single donor FMT with or without diet.[78]

These data suggest that fiber supplementation and plant-based, low animal protein diets may be effective therapeutic strategies to augment pharmacological and microbial therapies in UC; however, further evaluation is required in well-designed prospective trials.

Conclusion

Diet therapy is rapidly becoming an essential component in the management of IBD with multiple diets demonstrating efficacy for ameliorating inflammation, either as a standalone therapy or in combination with other treatments. Currently, EEN and CDED with PEN can be recommended for remission induction in CD, although further evidence is required to support whole food strategies. In UC, diets aiming to reduce H_2S show promise for remission induction, as well as plant-based and high fiber diets, although further evidence is required for any definitive recommendations. In the absence of strong evidence to the contrary, recommendations for maintenance of remission defaults to population-based healthy eating guidelines. The use of diet to augment response to therapies is also showing promise in early trials. For the revolution of diet therapies to continue its current trajectory, future high-quality trials are needed with careful trial design, clear intent of diet therapy and objective measurement of disease activity as well as consideration of the dietary intervention itself. Furthermore, mechanistic studies are required to further understand which components of efficacious diets are important in the modulation of inflammation to enable the application of these more broadly.

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