Proceedings of the Nutrition Society (2021), **80**, 409–423 doi:10.1017/S0029665121002846
 First published online 23 September 2021

The Nutrition Society Spring Conference 2021 was held virtually 29–30 March 2021

Conference on 'Gut microbiome and health'
Symposium 2: Gut microbiome, nutrition and health: cause and effect

Diet and gut microbiota manipulation for the management of Crohn's disease and ulcerative colitis

Vaios Svolos‡, Konstantinos Gkikas‡ and Konstantinos Gerasimidis*
Human Nutrition, School of Medicine, University of Glasgow, New Lister Building, Glasgow Royal Infirmary, G31 2ER, Glasgow, UK

The aetiology of inflammatory bowel disease (IBD) is multifactorial, with diet and gut microbiota playing an important role. Nonetheless, there are very few studies, particularly clinical research, which have explored the interaction between diet and gut microbiota. In the current review, we summarise the evidence from clinical trials exploring the interactions between the gut microbiota and diet in the management of IBD. Data from the effect of exclusive enteral nutrition (EEN) on the gut microbiota of children with active Crohn's disease (CD), receiving induction treatment, offer opportunities to understand the role of gut microbiota in underlying disease pathogenesis and develop novel dietary and pharmacological microbial therapeutics. In contrast, the evidence which links the effectiveness of food-based dietary therapies for IBD with mechanisms involving the gut microbiota is far less convincing. The microbial signals arising from these dietary therapies are inconsistent and vary compared to the effects of effective treatment with EEN in CD.

Keywords: Enteral nutrition: Inflammatory bowel disease: Crohn's disease: Ulcerative colitis: Gut microbiota: Short-chain fatty acids: Metabolomics: Microbiome

Introduction

Diet and the gut microbiota have long been implicated in the underlying pathogenesis of inflammatory bowel disease (IBD)[1]. Nutritional epidemiology has linked certain nutrients and food components, including *n*-3 PUFA, fibre and meat consumption with the risk of development of Crohn's disease (CD) and ulcerative colitis (UC)[1]. Equally, a dysbiotic microbiota with low diversity, depletion of beneficial species and an overabundance of Proteobacteria are among the most consistent microbial features of IBD. However, most of the current evidence on these two crucially important causes underlying IBD pathogenesis rely on cross-sectional and observational research which in establishing a causal pathway are limited by the inherent limitations of reverse causation and residual confounding. Although the aetiology of IBD is considered multifactorial, where diet and microbiota are of crucial importance, there are very few studies which have explored diet–microbiota interactions, particularly from clinical research. In the current review, we summarise the evidence from clinical trials exploring the interactions between gut microbiota and diet in the management of IBD.

Methods

A comprehensive literature search was carried out, using Medline from inception till June 2021, to identify studies exploring the effect of dietary interventions on the gut

***Corresponding author:** Konstantinos Gerasimidis, email Konstantinos.gerasimidis@glasgow.ac.uk
‡Contributed the same.

microbiota and associated clinical outcomes in patients with IBD. The search terms used were (microbio* OR bacteria) AND ('Inflammatory Bowel Disease' OR IBD OR Crohn OR Colitis) AND (diet OR nutrition OR food) to identify original articles. Additional articles were identified through the reference lists of leading topical review articles.

Inclusion criteria were: (a) human studies with IBD patients of any age and ethnicity, (b) research of either prospective or retrospective design, (c) treatment with exclusive enteral nutrition (EEN) or a food-based dietary intervention, (d) research which explored the impact of dietary interventions on the gut microbiota composition and/or function. Exclusion criteria were: (a) review articles and meta-analyses, (b) papers not in English, (c) studies which included animal models, (d) studies which did not assess changes in gut microbiota characteristics. Studies using nutritional supplements (e.g., probiotics/prebiotics/single nutrient supplements), as the main dietary intervention, were also excluded, as these topics have already been reviewed extensively in the literature[1].

Our search yielded a total of 4,346 papers of which 33 met the inclusion criteria. Evidence was summarised under two main themes: (a) the effect of EEN on the gut microbiota of patients with CD and (b) the effect of food-based dietary interventions on the gut microbiota of patients with IBD.

EEN and gut microbiota composition in patients with CD

In Europe and elsewhere, EEN is the first-line treatment of active CD, in children, achieving clinical remission rates up to 85 % and improving mucosal healing in a substantial proportion of patients [2]. There are currently two main doctrines of how EEN works. The first, by the exclusion of components from the diet of people with CD causing disease, and a second mechanism involving dietary modulation of inflammatory microorganisms of the human gut[3–5]. We identified a total of 24 original articles which investigated the effect of treatment with EEN on the composition or function of the gut microbiota of patients with CD (Table 1). The current literature is comprised predominantly of studies in paediatric patients ($N = 20$)[6–25] with four studies reporting the impact of EEN on the gut microbiota of adults with CD[26–29]. The duration of the EEN course varied from two[26,28,29] to 12[17,18,24] weeks; most of the studies ($N = 19$) used polymeric feeds[6–14,16–23,25,29]. All studies recruited patients with active CD with sample sizes varying from one[8] to 55[21] patients.

Changes in gut microbiota were investigated using an array of molecular methods profiling its composition at the various levels of microbial hierarchy. The most common methods used to characterise the gut microbiota were 16S rRNA sequencing ($N = 10$)[8,10,12,14–16,18,22–24], shotgun metagenomics ($N = 6$)[10–12,17,24,29], quantitative real-time PCR (qPCR) ($N = 3$)[9,26,27], temperature gradient gel electrophoresis (TGGE) or denaturing gradient gel electrophoresis (DGGE) ($N = 4$)[6,7,9,25] and terminal restriction fragment-length polymorphism ($N = 1$)[27]. Fewer studies assessed changes of the gut microbiota function by measuring targeted metabolites, such as short-chain fatty acids (SCFA), lactate, sulphide and ammonia ($N = 3$)[9,13,16] or by performing untargeted metabolomics analysis using liquid chromatography ($N = 2$)[19,20], GC ($N = 1$)[28] or NMR ($N = 1$)[23]. The tissue studied was faeces for the vast majority of the studies with the exception for a single study in which ileal biopsies were used[8] to assess the mucosal-associated microbiota and changes during EEN. In these 24 studies, remission rates varied between 45 % and 100 %, but different groups defined remission using different clinical disease indices and disease biomarkers outcomes (Table 1).

Even though, the majority of the studies reported significant effects on microbiota composition, the directions of these effects varied. Few studies observed a decrease in microbial diversity following treatment with EEN proposing that its mode of action may include suppression of either the global gut microbiota or selective bacterial subpopulations causing inflammation[6,9,12,23] (Fig. 1). Leach *et al.* showed that EEN significantly decreased the diversity of global microbiota, and other groups within *Bacteroides-Prevotella* and *Clostridium coccoides*[6]. In accordance to these findings, Gerasimidis *et al.*, also found a decrease in global bacterial diversity, and absolute concentration of *Bacteroides-Prevotella* and *Faecalibacterium prausnitzii*[9]; with the decrease of *F. prausnitzii* being replicated by others[25,26]. This latter observation is counterintuitive and challenges perceptions that *F. prausnitzii* is a critical micro-organism in the pathogenesis of CD and that its diminished abundance increases the risk of post-surgical relapse[30]. A follow-up study of the aforementioned study by Gerasimidis *et al.* using 16S rRNA amplicon and shotgun metagenomics sequencing, also observed a significant decrease of the faecal microbiota Shannon α-diversity; for every 10 days on EEN, 0·6 genus diversity equivalents were lost. This decrease was accompanied by a shift of the microbiota composition to a direction opposite to that of healthy controls[12]. Similarly, Lewis *et al.*, described that EEN shifted the gut microbial community structure of CD children away to that of the healthy reference[11]. In contrast, five other studies reported no significant changes in microbiota diversity during EEN, hence suggesting that the underlying mode of EEN action is less likely to be mediated by such effects and it might be associated with changes in the function or abundance of selective members of the microbial community[15,21,22,24,27]. In previous research, such microorganisms included a decrease of *Bacteroides fragilis*[27], Bacteroidetes, *Bacteroidaceae* and *Porphyromonadaceae*[15], *Haemophilus*, *Veillonella*, *Bifidobacterium*, *Prevotella*, Proteobacteria, *Anaerostipes*, and *Lachnospira*[22]. Only a study by D'Argenio *et al.*, reported that EEN increased the ileal mucosal bacterial diversity and Bacteroidetes abundance in a single paediatric CD patient[8], and Ashton *et al.*, reported increased faecal microbiota richness, diversity, and abundance of

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Table 1. Human studies investigating the effect of exclusive enteral nutrition on the gut microbiota of patients with CD

Study and participants	Intervention	Microbiota outcome measures	Results (microbiota)
Lionetti *et al*. 2005[7] Children Active CD: $N = 9$	• 8 weeks EEN; polymeric feed	• Faecal microbiota composition and diversity (TGGE)	• EEN drastically changed TGGE profile in all patients
Leach *et al*. 2008[6] Children Active CD: $N = 6$	• 8 weeks EEN; polymeric feed	• Faecal total bacteria, *Bacteroides–Prevotella*, *Clostridium coccoides*, *Clostridium leptum* and *Bifidobacteria* (DGGE)	• EEN-treated children had ↓ band counts of total bacteria, *Bacteroides–Prevotella* and *Clostridium coccoides* at 8 weeks compared to healthy children • No significant changes on *Clostridium leptum* and *Bifidobacteria* band counts • Based on similarity analysis EEN induced strong changes for all bacterial groups. Further changes were observed at 16 weeks and 26 weeks follow-up • During EEN: PCDAI changes were positively correlated to *Bacteroides–Prevotella* changes; S100A12 changes were negatively correlated to total bacteria changes • Between the end of EEN and 26 weeks follow-up: PCDAI and S100A12 changes negatively correlated to *Clostridium leptum* changes
Jia *et al*. 2010[26] Adults Active CD: $N = 2$	• 2 weeks EEN; elemental feed	• Quantification of faecal *Faecalibacterium prausnitzii* (A2-165 and M21/2 subgroup) (qPCR)	• *Faecalibacterium prausnitzii A2-165* ↓ during EEN
Shiga *et al*. 2012[27] Adults Active CD: $N = 8$	• 6 weeks EEN; elemental feed	• Faecal microbiota composition (T-RFLP) • Faecal *Bifidobacterium*, *Bacteroides fragilis* group, *Clostridium cocoides* group, *Enterococcus*, *Escherichia coli* and *Lactobacillus* (qPCR)	• Similarity of T-RFLP profiles before and after EEN was not different to the similarity of healthy controls before and after 6 weeks with no food restriction • The number of T-RFs was not different after EEN • *Bacteroides fragilis* group ↓ during EEN • *Bifidobacterium*, *Clostridium cocoides* group, *Enterococcus*, *Escherichia coli* and *Lactobacillus* did not change during EEN
Tjellstrom *et al*. 2012[13] Children Active CD: $N = 18$	• 6 weeks EEN; polymeric feed	• Faecal SCFA and BCFA • Index A: acetic acid minus propionic acid minus butyric acid divided by the total amount of SCFA • Index B: sum of iso-butyric and iso-valeric acid divided by the total amount of SCFA	• Faecal acetic acid and index A ↓ during EEN in children with small bowel/colonic CD • Index B ↑ during EEN in children with small bowel/colonic CD • Index A ↑ during EEN in children with perianal disease
D'Argenio *et al*. 2013[8] Children Active CD: $N = 1$	• 8 weeks EEN; polymeric feed	• Ileum mucosal microbiota composition (16S rRNA next-generation sequencing)	• Ileal Shannon α diversity index score and *Bacteroidetes* ↑ during EEN • Proteobacteria ↓ during EEN
Gerasimidis *et al*. 2014[9] Children Active CD: $N = 15$	• 8 weeks EEN; polymeric feed	• Faecal pH, ammonia, SCFA, BCFA, lactate, free and total sulphide • Faecal microbiota composition and diversity (TGGE) • Quantification of faecal total bacteria, *Bacteroides/Prevotella, Clostridium leptum* cluster, *Clostridium coccoides* cluster, *Bifidobacterium* genus, *Lactobacillus* genus, *Escherichia coli, Faecalibacterium prausnitzii* (qPCR)	• Faecal pH and total sulphide ↑ and faecal butyric acid ↓ during EEN • Global bacterial diversity abundance and *Faecalibacterium prausnitzii* ↓ during EEN • *Bacteroides/Prevotella* ↓ during EEN in patients who responded • Microbiota composition stability was ↓ during EEN • Faecal free sulphide, lactate, ammonia, *Clostridium leptum* cluster, *Clostridium coccoides* cluster, *Bifidobacterium* genus, *Lactobacillus* genus, *Escherichia coli* did not change during EEN

Table 1. (*Cont.*)

Study and participants	Intervention	Microbiota outcome measures	Results (microbiota)
Kaakoush *et al*. 2015[10] Children Active CD: *N* = 5	• 8–12 weeks EEN; polymeric feed	• Faecal microbiota composition (16S rRNA next-generation sequencing) • Faecal shotgun metagenomic analysis	• OTU richness ↓ during EEN and this corresponded to disease remission. Disease recurrence corresponded with ↑ of OTU richness • Both 16S rRNA and shotgun metagenomic analysis gave variable results between the 5 EEN-treated children • Changes in *Erysipelotrichaceae*, *Ruminococcaceae*, *Lachnospiraceae, Streptococcaceae*, *Veillonellaceae* and *Peptostreptococcaceae* families were correlated to PCDAI changes
Lewis *et al*. 2015[11] Children Active CD: *N* = 16	• 8 weeks EEN (*N* = 16); polymeric feed	• Faecal shotgun metagenomic analysis	• EEN changed the gut bacterial community structure to a direction opposite to the healthy controls' microbiota within 1 week • Children which clinically respond to EEN had a microbiota further from the healthy centroid compared to those which did not respond • *Dialister*, *Dorea*, *Gordonibacter*, *Haemophilus* and *Streptococcus* ↓ during EEN • *Alistipes* ↑ during EEN • Fungal colonisation (*Candida, Clavispora, Kluyveromyces* and *Cyberlindnera*) ↓ during EEN
Quince *et al*. 2015[12] Children Active CD: *N* = 15	• 8 weeks EEN; polymeric feed	• Faecal microbiota composition (16S rRNA next-generation sequencing) • Faecal shotgun metagenomic analysis	• Microbial diversity ↓ during EEN • The gut bacterial community structure changed to a direction opposite to the microbiota of healthy controls • 34 genera ↓ and 1 ↑ during EEN • FCP correlated with 35 OTUs (14 of them accounted for 78 % of calprotectin variation) • Number of days on EEN correlated negatively to biotin and thiamine biosynthesis and positively to spermidine/putrescine transport system and the shikimic acid pathway (KEGG modules)
Guinet-Charpentier *et al*. 2016[14] Children Active CD: *N* = 19	• 6 weeks EEN; polymeric feed	• Faecal microbiota composition (16S rRNA next-generation sequencing)	• EEN in children with active CD ↓ Proteobacteria phylum, *Escherichia-Shigella*, *Sutterella* and ↑ *Alistipes* • Faecal calprotectin was correlated negatively with *Actinobacteria*, *Clostridia* and positively with β-*Proteobacteria*. • HBI was correlated negatively with Actinobacteria, *Clostridia* and positively with *gammaproteobacteria*
Schwerd *et al*. 2016[15] Children Active CD: *N* = 15	• 6-8 weeks EEN; polymeric feed (*N* = 14); elemental feed (*N* = 1)	• Faecal microbiota composition (16S rRNA next-generation sequencing)	• *Bacteroidetes* phylum, *Bacteroidaceae* family and *Porphyromonadaceae* family ↓ during EEN • *Firmicutes* and *Christensenellaceae* family ↑ during EEN • Microbial diversity did not change during EEN • Clinical and immunological changes after 3 weeks on EEN correlated with the changes on 14 taxonomic groups

Walton *et al*. 2016[28] Adults Active CD: N = 17	• 2 weeks EEN; elemental feed	• Faecal untargeted metabolomics (GC-MS)	• Several faecal volatile organic compounds ↓ during EEN (propionic acid, butyric acid, propionic acid ethyl ester, butyric acid ethyl ester, butyric acid methyl ester, butyric acid 3 methyl, 1-propanol, 1-butanol)
Dunn *et al*. 2016[18] Children Active CD: *N* = 10	• 12 weeks EEN; polymeric feed	• Faecal microbiota composition (16S rRNA next-generation sequencing)	• Microbial diversity during EEN ↓ for patients who sustained remission for 12 weeks post EEN cessation and ↑ for patients who relapsed within 12 weeks post EEN cessation • The gut bacterial community structure of patients who sustained remission for 12 weeks post EEN cessation was more similar to that of healthy controls compared to patients who relapsed within 12 weeks post EEN cessation • Post-EEN community of patients who sustained remission for 12 weeks post EEN cessation had a large component of *Bacteroidetes*, *Firmicutes* and *Verrucomicrobia* and was associated with *Akkermansia muciniphila*, *Bacteroides* (including *Bacteroides fragilis* and *Bacteroides ovatus*), Lachnospiraceae, and Ruminococcaceae • Post-EEN community of patients who relapsed within 12 weeks post EEN cessation had a large component of *Bacteroidetes* and *Proteobacteria* and was associated with Bacteroides (including *Bacteroides plebeius*), *Enterobacteriaceae* (including Klebsiella) and *Prevotella*
Dunn *et al*. 2016[17] Children Active CD: *N* = 15	• 12 weeks EEN; polymeric feed	• Faecal shotgun metagenomic analysis	• Potential gut bacterial community function (KEGG modules) of patients who sustained remission for 12 weeks post-EEN cessation was more similar to that of healthy controls compared to patients who relapsed within 12 weeks post-EEN cessation
van der Hooft *et al*. 2017[19] Children Active CD: *N* = 2	• 8 weeks EEN; polymeric feed	• Faecal untargeted metabolomics (Liquid Chromatography-MS)	• Adenine and guanine substructures ↓ during EEN
Ashton *et al*. 2017[16] Children Active CD: *N* = 3	• 6 weeks EEN; polymeric feed	• Faecal microbiota composition (16S rRNA next-generation sequencing) • Faecal SCFA	• ↑ *Bacteroides & Bifidobacterium*, & ↓ *Prevotella* during EEN • ↑ observed species, Chao1 & Shannon indices during EEN • No change in SCFA during EEN
He *et al*. 2017[29] Adults Active CD: *N* = 14	• 2 weeks EEN; polymeric feed	• Faecal shotgun metagenomic analysis	• No changes in overall microbiota during EEN • ↓ LPS biosynthesis & bacterial secretion system during EEN • ↑ Starch, sucrose metabolism and flagellar assembly during EEN • 2 weeks EEN did not affect abundances of LPS- or SCFA-producing bacteria

Table 1. (*Cont.*)

Study and participants	Intervention	Microbiota outcome measures	Results (microbiota)
De Meij *et al*. 2018[21] Children Active CD: $N = 55$	• 6 weeks EEN; polymeric feed	• Faecal microbiota composition (IS-pro)	• No change in Shannon diversity over time, or between EEN responder's and non-responders • Baseline microbiota provided low predictive power of response to EEN
Alghamdi *et al*. 2018[20] Children Active CD: $N = 11$	• 8 weeks EEN; polymeric feed	• Faecal untargeted metabolomics (Liquid Chromatography-MS)	• Based in the log base 2 transformed variable of the OPLS-DA model, the serially collected samples at 15, 30 and 60 days on EEN clustered together • After EEN completion and return to free/habitual diet, the samples appeared between the pre-treatment samples and healthy control groups
Levine *et al*. 2019[22] Children Active CD: $N = 32$	• 6 weeks EEN; polymeric feed	• Faecal microbiota composition (16S rRNA next-generation sequencing)	• No change in Shannon diversity during EEN • ↓ *Haemophilus, Veillonella, Bifidobacterium, Prevotella,* Proteobacteria, *Anaerostipes, Lachnospira* during EEN • ↑ *Oscillibacter, Roseburia, Subdoligranulum, Blautia, Ruminococcus, Erysipelotrichaceae* during EEN • β-diversity moved away from baseline cluster during treatment and rebounded closer to baseline
Pigneur *et al*. 2019[25] Children Active CD on EEN: $N = 13$ Active CD on CS: $N = 6$	• 8 weeks EEN; polymeric feed	• Faecal microbiota composition (TTGE and 454 pyrosequencing)	• At 8 weeks EEN-treated patients had ↑ *Clostridium* XIVa & ↓ *Faecalibacterium* and *Roseburia*, compared with CS-treated • EEN ↑ *Clostridium*, mainly clusters XIVa and IV, *Clostridium symbiosum, Clostridium ruminantium, Ruminococcus torques, Ruminococcus gnavus and Clostridium hathewayi*
Jones *et al*. 2020[24] Children Active CD: $N = 22$	• 12 weeks EEN; type of feed not reported	• Faecal microbiota composition (16S rRNA next-generation sequencing) • Faecal shotgun metagenomic analysis	• Microbial diversity did not change during EEN • Samples with ↓ FCP (<250 μg/g) had ↓ species richness • Samples associated with remission vs severe disease had ↑ relative abundance of 111 functions (KEGG) • ASVs was the only significant taxonomic data set predicting treatment response on their own in RF • An RF model including ASV, species richness & disease location and behaviour was the best for predicting EEN treatment response (AUC of 0·9). Most informative taxa in the top predictive model were *Ruminococcaceae* UCG-002, *Lachnospiraceae* NK4A136, *Bacteroides*, *Parabacteroides* • An RF model including KEGG pathways, species richness & disease location and behaviour was significantly predictive for EEN treatment response (AUC • of 0·8), The 3 top KEGG pathways were: ko4910; insulin signalling, ko03013; RNA transport, & ko02010; ABC transporters

Diederen *et al.* 2020[23] Children Active CD: *N* = 43	6 weeks EEN; polymeric feed	Faecal microbiota composition (16S rRNA next-generation sequencing) Faecal untargeted metabolomics (NMR spectroscopy)	• ASV abundance explained 17 % of the variance in FCP levels. Informative taxa belonged to Firmicutes (*n* = 12), Proteobacteria (n = 4), *Bacteroides* (n = 2), *Fusobacteria* and Actinobacteria (n = 1) • FCP regression and treatment response RF models using MGS functions shared 9 features, including ko00440: phosphonate and phosphonate metabolism (top feature of FCP prediction) • Microbial diversity ↓ during EEN, and increased again 3 weeks post food reintroduction • β-diversity significantly shifted during EEN, but rebounded to baseline at 3 weeks post food reintroduction • *Blautia* and *Subdoligranulum* ↓ during EEN • EEN affected the global faecal metabolome

CD, Crohn's disease; EEN, Exclusive enteral nutrition; TTGE, Temporal temperature gradient gel electrophoresis; DGGE, Denaturing gradient gel electrophoresis; PCDAI, Paediatric Crohn's disease activity index; qPCR, quantitative PCR; T-RFLP, Terminal restriction fragment length polymorphism; SCFA, Short-chain fatty acids; BCFA, Branched-chain fatty acids; RNA, RNA; OTU, Operational taxonomic unit; FCP, Faecal calprotectin; KEGG, Kyoto Encyclopedia of Genes and Genomes; HBI, Harvey Bradshaw index; OPLS-DA, Orthogonal Projections to Latent Structures Discriminant Analysis; CS, Corticosteroids; LPS, Lipopolysaccharide; ASV, Amplicon sequencing variant; AUC, Area under the curve; RF, Random forest; MGS, Metagenomic sequencing.

Bacteroides and *Bifidobacterium* in three children with active CD during EEN[16].

EEN and gut microbiota function in patients with CD

The effect of EEN on gut microbiota function was also investigated but in a smaller number of studies than those which explored compositional shifts. Organic compounds in faeces, including SCFA were consistently found to decrease following treatment with EEN, suggesting a suppressive effect of the therapy on bacterial metabolism, and fermentation capacity in particular[9,13,19,28]. Gerasimidis *et al.*, also reported a substantial increase in faecal hydrogen sulphide levels after 8-week treatment with EEN[9]. Interestingly, the magnitude of changes in faecal bacterial metabolites was larger when in subset analysis patients who did not achieve clinical remission were excluded. In 1H NMR metabolomics analysis, EEN affected the global metabolome with differences noted prior to initiation between treatment responders *v.* non-responders. Following EEN, several metabolites (i.e. leucine, propionate, valine, lactate, alanine, cadaverine, trimethylamine, tyrosine, phenylalanine, isovalerate, urocanate, succinate) were normalised in responders but not in non-responders[23]. These observations contradict the compositional shifts observed during EEN treatment (Table 1) and may suggest that changes in microbiota function might be more relevant in disease improvement.

Microbiota changes during EEN and association with disease activity markers

Several of the studies above also explored relationships between disease activity response to EEN and changes in gut microbiota characteristics. Improvement in disease activity indices, inflammatory and immunological markers correlated with changes in the abundance of bacterial taxa, KEGG modules or pathways[6,9,10,14,15,17,18,24]. Quince *et al.*, found that 35 different OTUs (operational taxonomic unit) correlated with faecal calprotectin changes, 14 of which explained 78 % of the variance in calprotectin levels[12]. In accordance, Kaakoush *et al.* reported that a decreased OTU richness was associated with disease remission, and reversely, disease recurrence was associated with increased richness[10]. Interestingly, clinical response was associated with the distance of the CD microbiota from the centroid of the healthy microbiota; however, paradoxically, as children who clinically responded to EEN moved further away from the healthy reference status, hence their community became even more dysbiotic than those children who did not show improvement[11].

The exact opposite pattern was reported by two other studies that investigated the faecal microbial composition, at EEN completion, as a predictor of remission duration. The authors found that patients who sustained remission for 12 weeks post-treatment with EEN had a more similar gut microbiota to that of healthy controls, than patients who experienced disease relapse sooner[17,18].

https://doi.org/10.1017/S0029665121002846 Published online by Cambridge University Press

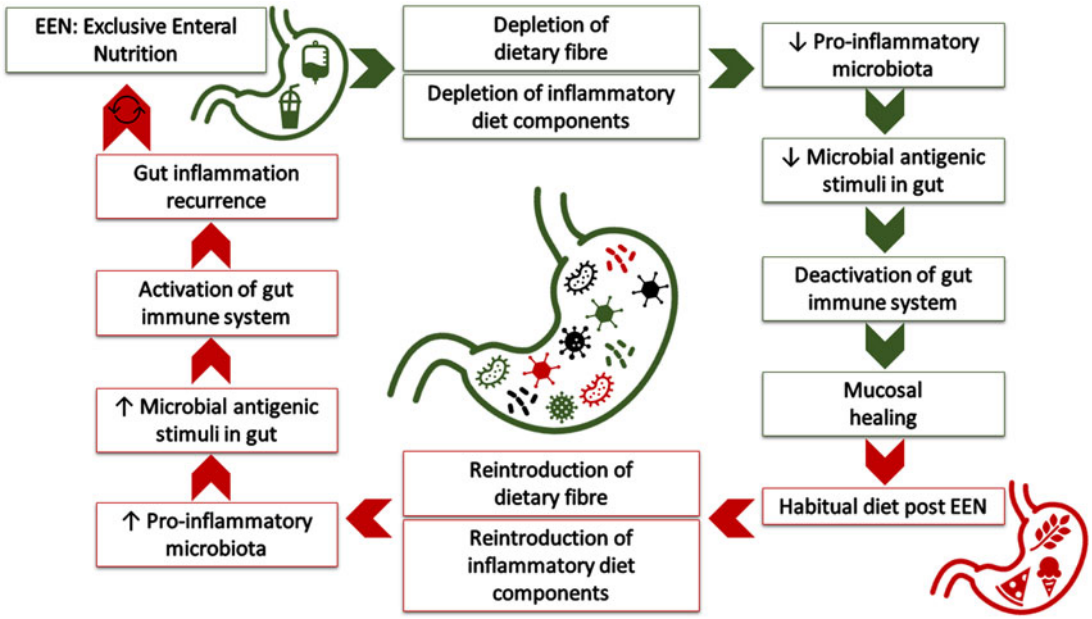

Fig. 1. A proposed microbial mediated mechanism of action of EEN and disease recurrence following habitual diet reintroduction.

Microbiota changes following treatment with EEN and during food re-introduction

There is limited literature about microbiota changes following EEN completion and during reintroduction of habitual diet. Such data are important since they offer insight into the role of diet triggering disease relapse and the mediating role gut microbiota may have in this process. Studies in healthy participants showed that one week of EEN was long enough to significantly decrease total faecal bacterial load and faecal SCFA and influence drastically microbiota composition. In reverse, food reintroduction rapidly reverted these changes to the pre-treatment level[31,32]. Consistent with this observation, recurrence of CD following the end of EEN is associated with a remarkable reversal of microbial shifts to pre-treatment levels, when participants return to the habitual diet[6,9,10,12,22]. It has been proposed that exclusion of dietary components from the habitual diet, rather than enteral nutrition consumption itself, is critical to successful treatment with EEN; underlined by the limited efficacy of partial enteral nutrition in which only a part of the habitual diet has been replaced by enteral nutrition[33]. This is potentially due to the less drastic microbial effects of enteral nutrition when consumed along with a free diet[6,7,11,14]. Monitoring microbiota changes upon food reintroduction following successful treatment with EEN treatment may allow the development of evidence-based advice for maintenance of EEN-induced remission.

Proposed mechanism of EEN mediated by the gut microbiota

Several of the microbial signals observed in previous research may be implicated in the therapeutic action of EEN and may open opportunities to develop novel microbial therapeutics for CD management, such as the CD-TREAT (Crohn's Disease TReatment-with-EATing) diet[32]. The most consistent effects observed in the current literature include a decrease in bacterial diversity[6,9,10,12,18] and the development of a microbial community structure even more dissimilar to that associated with health[11,12]. Paradoxically, the development of such suppressed and dysbiotic microenvironment coincides with mucosal healing, reduction in colonic inflammatory markers, and disease activity improvement[34]. The limited efficacy rates reported for therapeutic strategies aiming to promote or restore a healthy gut microenvironment in patients with CD, including faecal material transplantation[35], probiotics, prebiotics and fibre supplementation[36,37] further support the doctrine that suppression of the global microbiota or selective inflammatory members of the community might be needed to promote disease remission and induce mucosal healing[35,38] (Fig. 1). Opposite to that, microbial suppression with antibiotics has benefitted gut inflammation in CD[39]. The same is also the case for total parenteral nutrition which has been found to ameliorate CD gut inflammation but also to suppress the gut microbial community through substrate depletion for bacterial growth and gut rest[27]. From a nutrition perspective, most of the above microbial effects are to be expected since the composition of feeds used in EEN are of low residue, including fibre, and comprise rapidly absorbed carbohydrates. These factors could modulate the gut microbial dynamics, suppress bacterial growth and activity hence reducing antigenic stimulation, repressing aberrant activation of the gut-associated immune system and consequently promoting mucosal healing[40] (Fig. 1).

Future studies should aim to develop and test strategies to sustain EEN-induced microbial effects by using

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dietary and pharmacological therapies. Should such strategies be successful, they will confirm the hypothesis proposed here that modulation of microbiota is a plausible mechanism of action of EEN. The CD-TREAT diet is a novel dietary therapy for an active CD which has a similar nutritional and food component profile to EEN and effects on gut microbiota characteristics[32]. In animal models of gut inflammation, CD-TREAT improved ileal inflammation, both histologically and in terms of inflammatory biomarkers, and in a pilot trial of 5 children with active CD receiving CD-TREAT, 80 % showed a clinical response, three (60 %) entered remission, with significant 50 % decreases in faecal calprotectin levels[32]. These early signals await confirmation by the results of a major multicentre trial (ClinicalTrials.gov identifier NCT03171246).

Food-based dietary therapies and the gut microbiota in IBD

There is a high interest from patients with IBD and healthcare professionals to develop dietary therapies for the management of CD and UC. A recent review identified a total of 24 food-based dietary therapies for the management of CD and UC with variable proposed modes of action[1]. Nine clinical trials met the inclusion criteria of the current review (Table 2). Of these, six studies recruited only patients with CD[22,41–45], one study recruited only patients with UC[46] and two studies[47,48] had a mixed IBD population. Most studies recruited adult patients ($n = 6$)[41–43,45–47], while children and young adults were recruited in the other three studies[22,44,48].

Like in EEN, the composition of the gut microbiota was examined in most cases using high-throughput sequencing ($n = 8$)[22,41,43–48], with one study using qPCR[42]. Microbial metabolic activity was assessed in five studies using gas ($n = 4$)[41,42,47] and liquid ($n = 1$)[46] chromatography, while meta-proteomic analysis was performed in one study using liquid chromatography and MS[44]. All studies used faecal samples for profiling the gut microbiota.

CD exclusion diet and partial enteral nutrition

The CD exclusion diet (CDED) in combination with 50 % partial enteral nutrition (CDED + PEN) is a new dietary regime which aims to alleviate gut inflammation through modification of inflammatory gut microbiota[22]. The premise behind the CDED + PEN dietary regime is the exclusion of food constituents (i.e. animal fat, food additives) thought to aggravate gut inflammation and cause dysbiosis, solely based on evidence from preclinical and epidemiological research. This hypothesis has recently been challenged in the literature[49] since the inclusion of 50 % PEN, an integral component in the CDED + PEN dietary regime, inevitably increases the consumption of food components (e.g. emulsifiers and maltodextrin) and nutrients (milk fat) that the authors aim to avoid with CDED. The authors also recommend the consumption of foods, such as fruits and vegetables, thought to provoke beneficial effects on the gut microbiota including production of SCFA. Improvements in disease activity and quality of life indices were observed after a 6-week, multicentre intervention in children with active CD. Some microbial compositional shifts were similar between patients on the CDED + PEN and the EEN group. CDED + PEN decreased *Haemophilus, Veillonella, Bifidobacterium, Prevotella,* and *Anaerostipes,* and increased *Oscillibacter and Roseburia* whereas during EEN more bacteria were influenced including a decrease in *Lachnospira* and increases in *Subdoligranulum*, *Blautia*, *Ruminococcus*, and *Erysipelotrichaceae*. Both diets decreased Proteobacteria, with this effect lost when EEN patients returned to their habitual diet but sustained in patients on CDED + 25 %PEN. Irrespective of dietary intervention, non-responders had a lower overall change in microbiota composition but more *Gammaproteobacteria*. Interestingly, although the rationale behind CDED + PEN is to increase consumption of dietary fibre through fruits and vegetables, *Bifidobacterium*, whose levels are positively influenced by fermentable fibre, were decreased following both dietary interventions, most likely indicating that not only was it not possible for patients to increase fibre intake, but on average they had a lower consumption compared to prior treatment initiation[50].

Low FODMAP diet

A diet that limits the intake of low fermentable, oligo-, di-, monosaccharides and polyols (FODMAP) has been tested as an option for alleviating functional gastrointestinal symptoms in patients with IBD. Two studies assessed the impact of low FODMAP diets on the gut microbiota of patients with CD. In the first pilot cross-over study in eight patients with CD in remission, Halmos *et al.* showed that a 3-week low FODMAP diet reduced the concentration of *Clostridium XIVa* cluster, *Akkermansia muciniphila* and increased levels of *Ruminococcus torques*, compared to a FODMAP containing diet[42]. No significant differences were observed in total bacteria or faecal SCFA between the two groups.

In the second RCT, patients with CD and UC in remission following a 4-week low FODMAP diet, experienced a decrease in the relative abundance of *B. adolescentis*, *B. longum* and *F. prausnitzii*, compared to a sham diet[47]. No differences were observed neither in the microbiota α- and β-diversity between the two groups, nor in the functional metagenomic capacity using KEGG orthologues, or SCFA levels. The abundance of *F. prausnitzii, A. muciniphila* were negatively impacted by the low FODMAP diet in both studies, species which are considered to exert favourable effects on host immunity[30,51]. Importantly, the effects observed in the IBD microbiota, were similar to the effects of a low FODMAP diet on the microbiota of healthy people or of patients with irritable bowel syndrome, hence stressing that the underlying mechanism might be disease independent[42]. In both studies, low FODMAP diets

https://doi.org/10.1017/S0029665121002846 Published online by Cambridge University Press

Table 2. Human studies investigating the effect of food-based diets on the gut microbiota of patients with CD or UC

Study and participants	Intervention	Microbiota outcome measures	Results (microbiota)	Results (clinical data)
Walters *et al*. 2014[43] Adults CD remission, $N = 5$	• SCD crossover vs LRD for 30 days	• Faecal microbiota composition (16s rRNA – PhyloChip DNA microarray)	• Microbial diversity ↑ in SCD vs LRD (no specific metrics used) • SCD: Relative abundance ↑ in 134 species (> 20 species from *Clostridia*), ↓ in 6, • LRD: Relative abundance ↑ in 11 species, ↓ in 13 • No association of microbiota changes with changes in clinical activity	• Not reported
Halmos *et al*. 2016[42] Adults CD remission, $N = 8$	• Low-FODMAP diet crossover vs Australian, normal FODMAP diet for 3 weeks	• qPCR for faecal total bacteria and *Clostridium* cluster IV, *F. prausnitzii, Clostridium* cluster XIVa, *Roseburia, Lactobacilli, Bifidobacteria, A. muciniphila, R. gnavus, R. torques, Clostridium* cluster IV • Faecal SCFA (GC) • Faecal pH	• ↑ *Clostridium* cluster XIVa, *A. muciniphila* ↓ and *R. torques* in low-FODMAP diet vs Australian diet • No differences: total bacteria, faecal SCFA, faecal pH	• Symptoms worsened with Australian diet vs low-FODMAP diet • No differences in FCP
Suskind *et al*. 2018[48] Children, young adults Active CD, UC $N = 9$	• SCD for 12 weeks	• Faecal shotgun metagenomic analysis	• No changes in Shannon α-diversity • No significant changes in abundance of microbial taxa • Inter-individual variability in responses • Relative abundance of Proteobacteria lower in 7/9 patients, but median change NS	• ↓ disease activity scores • No change in FCP
Levine *et al*. 2019[22] Children Active CD $N = 38$	• 50 %CDED + 50 %PEN for 6 weeks (induction) and another 6 weeks (maintenance)	• Faecal microbiota composition (16S rRNA next-generation sequencing)	• Week 6: ↓ Actinobacteria, Proteobacteria, *gammaproteobacteria, Bifidobacteria, Haemophilus, Pasteurellales, Prevotella* • Week 6: ↑ *Clostridia, Oscilibacter, Romboutsia, Intestinibacter, Anaerotruncus* • Week 12: ↑ *Clostridia,* ↓ Proteobacteria, minor rebound in Actinobacteria • No changes in Shannon α-diversity • Trend for increased β-diversity at week 6	• ↓ disease activity indices • ↓ FCP
Cox *et al*. 2020[47] Remission CD, UC Adults $N = 52$	• Low-FODMAP ($n = 27$) vs sham diet ($n = 25$) for 4 weeks	• Faecal microbiota composition (Ion proton sequencing) • Faecal SCFA (GC – MS), metagenomic pathways, faecal pH	• ↑ *B. dentium,* ↓ *B. adolescentis, B. longum, F. prausnitzii* in Low-FODMAP vs sham diet • No differences: Shannon α-diversity, β-diversity, faecal pH, faecal SCFA, KEGG orthologs • Total faecal SCFA and acetic acid lower in low-FODMAP diet in per protocol analysis	• ↑ in quality of life scores in low-FODMAP diet, in symptoms score (UC only) in low-FODMAP diet • No differences in disease activity, FCP

Zhang *et al*. 2020[41] Remission CD Adults $N = 40$	• Diversified diet ($N = 15$) based on principles of Mediterranean diet and epidemiology on CD risk. • Intervention group: Patients consuming ≥ 3 servings of red & processed meat / week and ≤ 15 g of fibre or ≤ 3 servings of fruit and vegetables / week. • Control group: all other patients (conventional treatment)	• Faecal microbiota composition (16S rRNA next-generation sequencing) • Faecal SCFA (GC)	• ↑ *F. prausnitzii* (4, 12 weeks), ↓ Proteobacteria (4, 8 weeks), *Escherichia/Shigella* (4 weeks) in intervention group vs baseline • No differences: Shannon α-diversity, faecal SCFA levels • Relative abundance of *Escherichia/Shigella* at 12 weeks negatively associated with vegetable intake at baseline • 5 diet principal components affected 35/93 bacteria (genus) and 9/45 metabolites	• No differences in FCP
Suskind *et al*. 2020[44] Active CD Children $N = 10$	• SCD vs modified SCD (addition of oats and rice) vs whole foods diet (excluding wheat, Maize, sugar, milk, food additives) for 12 weeks. • Firstly 2 weeks all patients on SCD	• Faecal microbiota composition (shotgun metagenomics) • Faecal metabolomics (Liquid chromatography – mass spectometry) • Faecal meta-proteomics	• Results available for $n = 3$ (modified SCD) and $n = 2$ (whole foods diet) • Metagenomics (week 0 – week 12): shift in β-diversity in each patient (inter-individual variability in direction of shift) • No change in species richness • ↑ *Blautia species, Lachnospiraceae species, F. prausnitzii, R. hominis, R. intestinalis, Eubacterium eligens, Anaerobutyricum hallii* in 4/5 patients • ↓ *E. coli*, strain of *F. prausnitzii* • Metabolomics: ↓ 1,2-propandiol, sterol metabolites, maltose; ↑ fatty acids, amino acid precursors (week 0 – week 2); changes after week 2 less pronounced • Meta-proteomics: ↓ enzymatic activity of starch breakdown and sugar metabolism; shift towards catabolism of amino acids (week 0 – week 2); changes after week 2 less pronounced.	• All patients completing the trial achieved clinical remission. • Normalisation of CRP only at SCD, modified SCD. • FCP decreased in modified SCD and whole foods diet group, increased in SCD (no p value)
Lewis *et al*. 2021[45] Active CD Adults $N = 191$	• SCD vs Mediterranean diet for 12 weeks.	• Faecal microbiota composition (16S rRNA next-generation sequencing + shotgun metagenomics)	• No differences in richness, Shannon α-diversity between the two groups at week 6/12. • Shifts in β-diversity independent of diet. • Gradient of ↑ *Bacteroides vulgatus, Enterobacteriaceae* and ↓ *Eubacterium rectale, Eubacterium eligens, F. prausnitzii* from baseline to week 12. Analysis not specific for each diet arm.	• No differences in symptomatic remission rates, FCP, CRP levels between two groups. • FCP levels significantly decreased only in SCD group.

Table 2. (*Cont.*)

Study and participants	Intervention	Microbiota outcome measures	Results (microbiota)	Results (clinical data)
			• Significant association between β-diversity and FC levels at week 6; lost after adjustment for multiple comparisons. • No other association between microbiota characteristics and clinical outcomes.	
Fritsch *et al.* 2021[46] Remission UC Adults *N* = 17	• LF/HF diet (10 % of energy intake) crossover vs iSAD (addition of fruit and vegetables to American diet) for 4 weeks	• Faecal microbiota composition (16S rRNA next-generation sequencing) • Faecal SCFA (Liquid chromatography – mass spectometry)	• LF/HF vs baseline: ↑ *Bacteroidetes, F. prausnitzii, Prevotella*; faecal acetate, faecal tryptophan; ↓ *Actinobacteria*, lauric acid • iSAD vs baseline: ↓ *Clostridia* • LF/HF vs iSAD: ↑ *F. prausnitzii* in LF/HF • β-diversity: trend for increased diversity in LF/HF vs baseline • No difference in α-diversity	• ↑ in quality of life with both diets vs baseline • No differences in disease activity or FCP

CD, Crohn's disease; SCD, Specific carbohydrate diet; LRD, Low residue diet; RNA, RNA; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides and polyols; qPCR, quantitative PCR; SCFA, Short-chain fatty acids; FCP, Faecal calprotectin; UC, ulcerative colitis; CDED, Crohn's disease exclusion diet; PEN, Partial enteral nutrition KEGG, Kyoto Encyclopedia of Genes and Genomes; LFHF, Low fat high fibre; iSAD, improved Standard American diet; CRP, C-reactive protein.

improved certain functional symptoms and these effects were not associated with recurrence of intestinal inflammation, as measured with faecal calprotectin levels.

Specific carbohydrate diet

The specific carbohydrate diet (SCD) is a diet which excludes complex carbohydrates which in principle could escape absorption and lead to bacterial fermentation, bacterial overgrowth and intestinal inflammation. Although popular among the IBD community, until recently, there was a lack of robust scientific evidence to recommend the SCD for the induction or maintenance of remission in IBD[52]. Four clinical trials on SCD and its effects on the gut microbiota were identified and included in this review. In the first pilot, cross-over study, five patients with CD in remission followed the SCD or a low-residue diet for 30 days[43]. SCD appeared to increase bacterial diversity and the abundance of over 100 species, of which, more than 20 species were *Clostridia*. These microbial signals compared to a more stable bacterial composition following a low-residue diet. Nonetheless, alterations in the gut microbiota were not linked to changes in clinical activity suggesting that any effect of SCD might be independent of microbial modification. Similar results were also observed in another open-label trial in nine children and young adults with active IBD where considerable inter-individual variation in microbial changes was observed, potentially reflecting the diversity of the dietary regime or normal biological variation[48].

Suskind *et al.* investigated the effect of the SCD and a modified version of SCD (with added oats and rice), on the gut microbiota of children with mild to moderate CD and in comparison, to a food-based exclusion diet for 12 weeks[44]. Comprehensive 'omics analysis, examining the effect of the different diets on the faecal metagenome, metabolome and metaproteome was performed; albeit in only 5/10 patients (modified SCD, $n = 3$, food-based exclusion diet, $n = 2$). Although species richness did not change throughout the 12-week intervention, inter-individual shifts in the microbiota community structure were observed. The relative abundance of various taxa (i.e. *F. prausnitzii* and *R. hominis*) increased in 4/5 patients, whereas *E. coli* decreased in 3/5 patients although it is unclear how these signals related to disease activity. A decrease in 1,2-propandiol, and sterol metabolites was observed, while certain fatty acids and metabolites involved in amino acid biosynthesis decreased after the initial 2 weeks of SCD intervention. Meta-proteomics analysis revealed a reduced enzymatic activity linked to starch catabolism and sugar metabolism, after 2 weeks of SCD, and highlighted the decreased enzymatic functionality related to amino acid biosynthesis, complementing the metabolomics findings. All patients achieved clinical remission, while normalisation of CRP levels was achieved in patients following the SCD and modified SCD. Faecal calprotectin levels decreased with the modified SCD and the food-based

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exclusion diet, while a non-significant increase was observed after the SCD.

In a large recent study of 191 patients, Lewis *et al.* compared the efficacy of the SCD against a Mediterranean diet on clinical outcomes and their effects on the faecal microbiota, in adults with mild-to-moderate active CD for 12 weeks[45]. There were no significant differences in clinical remission or faecal calprotectin normalisation rates between the two groups, although very few patients had raised faecal calprotectin levels at study enrolment. None of the two diets had a significant effect on microbiota α-diversity. Bacterial richness and Shannon diversity were comparable between the groups and remained stable throughout the study period. Beta diversity changed slightly over the course of the study. This was not related to the diet or symptomatic remission but was weakly associated with FC concentration; an effect which was no longer significant following adjustment for multiple comparisons.

Other dietary interventions and their effect on the gut microbiota of patients with IBD

Fritsch *et al.* assessed in a randomised, crossover trial, the impact of a catered, low-fat, high-fibre diet (LF/HF) compared to a typical American diet enriched with fruit, vegetables and fibre on the gut microbiota of patients with quiescent UC[46]. Microbial α-diversity was not impacted by either of the two diets, while a trend for increased β-diversity was observed only after the LF/HF diet. Adherence to the LF/HF was associated with a higher abundance of Bacteroidetes, *Prevotella* and fewer Actinobacteria, compared to baseline. The relative abundance of *F. prausnitzii* was also higher after the LF/HF compared to the improved standard American diet. The increase in the relative abundance of Bacteroidetes and *Prevotella* are in accordance with the effects of plant-based diets on the gut microbiota composition[53,54]. Faecal metabolome profiles showed a clear separation between the two dietary interventions and a significant increase in levels of acetate and tryptophan was noted, along with a reduction in lauric acid after the LF/HF. Using regression models, dietary changes had more pronounced effects on the faecal microbiota compared to the metabolome. Significant improvements in quality of life scores and serum amyloid A were observed only following the LF/HF compared to baseline, while faecal calprotectin levels remained low following both diets suggesting that in patients in remission with conventional medication a LF/HF does not exacerbate gut inflammation.

Zhang *et al.* assessed the impact of a Mediterranean-style diet, which is believed to protect from the development of CD, on the faecal microbiota of patients with quiescent CD[41]. Patients who followed a diet enriched in red and processed meat and low in fibre, fruit and vegetables were allocated to the intervention arm, while every other patient followed their standard of care medication and unrestricted diet. Although the dietary intervention did not influence α-diversity, the baseline differences observed in β-diversity between patients on the intervention arm and those on the control group were no longer significant after 12 weeks. In the dietary intervention group, an increase in *F. prausnitzii* levels was observed after 12 weeks, along with a significant reduction in *Escherichia/Shigella* and overall Proteobacteria, compared to baseline. Although these changes represented a shift towards a less dysbiotic microbiota in CD, there was no effect of the diet on faecal SCFA levels. Faecal calprotectin levels remained in normal ranges over the course of the intervention in both groups.

Conclusions

Several studies have explored the effects of dietary therapies on the gut microbiota of patients with IBD. The most consistent data come from studies exploring a mediating role of the gut microbiota in the underlying mechanism of action of EEN. Although the exact mechanism is still elusive future research should explore ways to mimic the effects of EEN on the gut microbiota as well as devise strategies to control the reversal of EEN-induced changes which may have consequent benefits to prolongation of disease remission and reduce risk of relapse. The current evidence from EEN studies does not support that SCFA or certain beneficial species such as *F. prausnitzii* are of key importance to disease management. Currently, the microbial signals which mediate the effectiveness of food-based dietary therapies for the management of quiescent or active IBD remain inconsistent; with the most prominent finding being a reduction in levels of Proteobacteria.

Acknowledgements

None.

Financial support

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflict of interest

K Gerasimidis received research grants, consultancy fees, honoraria and hospitality from Nestle Health Sciences, Danone-Nutrition, Abbott, Baxter, Servier, Dr Falk, Mylan. K Gkikas is funded by a PhD scholarship from Nestle Health Sciences. The rest of the authors have no conflict of interest to declare.

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