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TOPIC HIGHLIGHT

2016 Inflammatory Bowel Disease: Global view

Diet therapy for inflammatory bowel diseases: The established and the new

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Abstract

Although patients with inflammatory bowel diseases (IBD) have a strong interest in dietary modifications as part of their therapeutic management, dietary advice plays only a minor part in published guidelines. The scientific literature shows that dietary factors might influence the risk of developing IBD, that dysbiosis induced by nutrition contributes to the pathogenesis of IBD, and that diet may serve as a symptomatic treatment for irritable bowel syndrome-like symptoms in IBD. The role of nutrition in IBD is underscored by the effect of various dietary therapies. In paediatric patients with Crohn's disease (CD) enteral nutrition (EN) reaches remission rates similar to steroids. In adult patients, however, EN is inferior to corticosteroids. EN is not effective in ulcerative colitis (UC). Total parenteral nutrition in IBD is not superior to steroids or EN. The use of specific probiotics in patients with IBD can be recommended only in special clinical situations. There is no evidence for efficacy of probiotics in CD. By contrast, studies in UC have shown a beneficial effect in selected patients. For patients with pouchitis, antibiotic treatment followed by probiotics, like VSL#3 or Lactobacillus GG, is effective. When probiotics are used, the risk of bacterial translocation and subsequent bacteremia has to be considered. More understanding of the normal intestinal microflora, and better characterization of probiotic strains at the phenotypic and genomic levels is needed as well as clarification of the mechanisms of action in different clinical settings. A FODMAP reduced diet may improve symptoms in IBD.

Key words: Enteral nutrition; Parenteral nutrition; Probiotics; Fermentable oligo-, di-, and monosaccharides and polyols; Crohn's disease; Ulcerative colitis

Core tip: Over the last decades various dietary components like milk, fructose, salty foods and sweetened beverages have been implicated to play a role in the pathogenesis of inflammatory bowel disease (IBD), possibly by interacting with gut microbiota and the mucosal immune system. The role of nutrition in IBD is underscored by the effect of various dietary therapies. In paediatric patients with Crohn's disease enteral nutrition reaches remission rates similar to steroids. The use of specific probiotics in patients with IBD can be recommended only in special clinical situations. A FODMAP reduced diet may improve symptoms in IBD.

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INTRODUCTION

Approximately 2 million people worldwide suffer from inflammatory bowel disease (IBD), comprising Crohn's disease (CD), ulcerative colitis (UC) and pouchitis[1].

The exact pathomechanism of IBD is remains unexplained[1]. According to the literature, these diseases may result in part from the mucosal immune response to altered gastrointestinal microbiota in genetically susceptible individuals[1,2]. An abnormal mucosal barrier function in IBD may allow bacterial access to the lamina propria, triggering an inflammatory response[1], though additional environmental factors must be presumed to be involved in the aetiology of IBD[3].

IBD was first recognized as a major health issue in developed countries[4]. Many studies on children and adults in Western Europe and North America over the past 20 years have indicated that the incidence in IBD has increased to the extent that it is no longer a rare condition but affects up to 0.5% of the population[5-7] The incidence is also increasing in Japan or Eastern Europe, where it used to be uncommon[3,8]. Migrants from low prevalence countries take on the prevalence of their adopted high prevalence countries[9]. The incidence of CD appears to increase faster than UC[10]. This increased incidence is due in part to higher awareness and more reliable diagnosis of IBD, but the change to a Western lifestyle also suggests that environmental factors play a role in the development and progression of IBD[3,11].

Environmental factors that may be linked to the Western lifestyle have been implicated as predisposing to IBD[9]: these include smoking, appendectomy, better hygiene and use of oral contraceptives IBD[12,13]. One aspect of Western life style that has changed considerably in parallel with the emergence of IBD is diet[9,14,15]. The early increase in incidence up to the 1960s has been attributed to increased milk consumption[16] and more recently, other dietary components have been implicated. Over the last 20 years fructose intake has increased by more than 20% and intake of salty snacks, pizza, cereals and sweetened beverages has increased by nearly 50%[9]. As dietary antigens along with bacterial antigens are the most common types of luminal antigen, it is reasonable to suppose that dietary factors may play an important role in the pathogenesis of IBD[12], possibly by interacting with gut microbiota and the mucosal immune system.

The aim of therapeutic management is to achieve and maintain remission and prevent disease progression[1]. Pharmacological agents are the main pillar of therapy[17], but have side effects and some patients become refractory to them, necessitating surgery[1]. Nutrition plays a pivotal role in the clinical care of all patients with inflammatory bowel disease[11,18], and the efficacy of diet therapy in IBD was first investigated over 30 years ago[1,19]. In 1984, O'Moráin *et al*[20] reported that patients with acute Crohn's ileitis treatment with an elemental diet achieved remission rates comparable to those treated with corticosteroids, paving the way for an alternative to conventional therapy[18], though the mechanisms responsible are still not well understood[21]. Theories include improved nutritional status, reduced allergenicity of gut contents, avoidance of food additives as well as changes in the nature or quantity of gut bacteria[21]. Intestinal inflammation might be initiated by an aberrant response to the gastrointestinal microbiota, meaning that dietary substances and their metabolites might modify mucosal barrier function[1,22].

Nutrition in IBD as compared to controls

In recent decades a wide range of nutrients and their roles in the etiology of IBD have been investigated[11]. Persson *et al*[23] found an increased relative risk of IBD with consumption of fast food at least twice a week. Epidemiological studies suggest an increased risk of IBD associated with a high intake of the so-called "Western diet", which includes refined sugar and meat and animal fat, along with low fiber intake[14,21]. In contrast, a diet emphasizing vegetables, fruits, olive oil, fish, grains and nuts decreased the risk of pediatric IBD, especially CD[24].

As association of dietary factors and CD has been documented. These factors include the quantity and quality of fat intake, fast food ingestion, total protein and energy intake. Patients with CD consume more sugar or cereals than controls[9,25-28]. Geerling *et al*[29] found that CD patients consumed more carbohydrates than controls, but it was unclear whether this was

actually due to avoidance of other fat or protein sources. They also found that CD patients with a high Crohn's disease activity index (CDAI > 150) had a significantly higher carbohydrate intake than those in remission[29]. The literature is ambiguous on nutrients, as some studies did not confirm a significant association between high sugar intake and the incidence of CD[3,30].

A higher intake of linoleic acid, an n-6 polyunsaturated essential fatty acid found in red meat, various cooking oils and certain margarines, was associated with an increased risk of UC[4,31,32]. Linoleic acid is metabolized to arachidonic acid, which has pro-inflammatory properties and is increased in the mucosa of patients with UC[31].

Possible mechanisms for the association between IBD and nutrition

Possible mechanisms by which diet may cause IBD include a direct effect of dietary antigens, diet-induced alteration of gene expression, alteration of the composition of the enteric flora and an effect on gastrointestinal permeability or the immune system[11].

One hypothetical pathomechanism of CD is increased intestinal permeability, which might in turn increase exposure of the subepithelium to luminal pro-inflammatory molecules and microorganisms[9]. High luminal concentrations of short-chain fatty acids, due to bacterial metabolism of incompletely absorbed carbohydrates[33], can reversibly impair barrier function by inducing apoptosis of epithelial cells[9]. FODMAPs (fermentable oligo-di-monosaccharides and polyols) are a potential source of poorly absorbable carbohydrates[9], but a causal relationship between these foods and IBD remains unclear, as well as the potential confounding factor of socioeconomic status, which is related to food intake. In addition, the role of processing and cooking should be taken into account[34].

Kiss *et al*[35] have shown that some dietary components derived from vegetables interact with intestinal immune receptors influencing intestinal immunity. Vegetables of the Brassicaceae family (*e.g.*, broccoli, cabbage or Brussels sprouts) can activate the aryl hydrocarbon receptor (AhR), which is expressed ubiquitously in vertebrate cells[36]. AhR is highly expressed by intestinal intraepithelial lymphocytes and is involved in the defense against luminal attacks[37]. This receptor is down-regulated in the intestinal inflamed tissue of patients with IBD and activation of AhR can inhibit inflammation and colitis in the gut of mice[38]. The AhR system seems to be a link between external environmental stimuli and the immune system[39]. Dietary factors might interact with the AhR, which affects cytokine expression, synthesis of defensins, antimicrobial peptides and consequently also the microbial composition[36]. Activation of AhR by nutrients might have a beneficial effect in IBD. Clinical trials evaluating the stimulating effect of nutrition on the AhR are still missing.

ROLE OF GUT MICROBIOTA

The colonic microbiota are estimated to comprise 10^{14}[40,41]. Humans harbour 500 to 1000 different bacterial species in the gastrointestinal tract[42], with more than 90% representing *Firmicutes* and *Bacteroidetes*[42], with *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, *Spirochaetae* and *Verrucomicrobia* making up the rest[42]. At birth, the human gut is sterile and colonization by bacteria starts within the first hours of life[40]. The composition of the gut microbiome in infants varies greatly, depending on mode of delivery and infant feeding[43]. During childhood, a more stable, highly individual adult gut microbiome develops out of this diversity[40,44,45], with a symbiotic relationship forming between human host and his/her gut microbes[40]. This complex ecosystem protects against invasion by pathogens by successfully competing with them for nutrients and epithelial binding sites[46]. The human gut provides an ideal environment for the microbiota, which benefit the human host by fermenting indigestible food substances[40]. A balanced microbiota is important for maintaining the health of the host[40], but this balance may be upset by factors like host genetics, antibiotic treatment, intestinal inflammation or diet.

Along with food, microbiota provide the most common luminal antigens in the bowel, and these could influence intestinal inflammation[47]. Different dietary regimens might alter the composition of the gut microbiota and consequently affect the risk of IBD[34], but there are few data to evaluate this issue. In animal models, changes in fat and carbohydrate content in nutrition significantly affect gut microbiota[48]. When Turnbaugh *et al*[49] transfected germ-free C57BL/6J mice with human microbial communities and changed their diet from low-fat, high plant polysaccharide to high-fat, high-sugar "Western-style", their microbiota shifted within a single day. A study in interleukin-10 knockout mice has further shown that a mouse diet high in saturated fat increased the spontaneous rate of colitis as compared to a normal mouse diet[21]. A study in Japan noticed that people living in rural areas, eating typical Japanese food, have different faecal microflora than people living in urban areas, especially as to the number of Bifidobacteria[50]. These data suggest that some kinds of food might alter the intestinal microbiota population[21].

The role of the gut microbiota in inflammatory bowel disease has raised the interest in exchanging presumably abnormal microbiota in patients with IBD with fecal microbiota from healthy persons. However, the available evidence for this is still very weak. A recently published systematic literature review on the use of fecal microbiota transplantation (FMT) in IBD summarized 31 publications with 133 patients,

43% of whom had a Clostridium difficile infection. Improvement of symptoms was reported in 71% of patients with IBD. FMT may have the potential to be helpful in managing patients with IBD, but considerable further efforts are necessary to make this procedure a valid option for these subjects[51].

Microbiota, immune function and IBD

The human colonic microbiota plays a central role in inducing disorders of immune function and inflammation[52,53] and studies in recent decades have shown that bacteria are involved in the pathogenesis of IBD[53]. The association between *NOD 2/CARD15* gene polymorphisms and CD supports the link between IBD and gut microbiota. This gene has a role in bacterial peptidoglycan recognition and mice deficient in NOD2 show an increased susceptibility to bacterial infection through the luminal route[54-56]. Abnormalities of NOD2 in IBD patients might decrease tolerance to enteric bacteria with secondary inflammation of the gut[54]. In addition, animal models have shown that intestinal inflammation fails to develop when animals are kept in germ-free environment, supporting the role of the microbiota in the pathogenesis of IBD[57]. An imbalance in bacterial function so might play a role in the initiation of IBD[34]. Further, genetic studies have determined that many of the genetic risk alleles for IBD are involved in protecting the host from bacterial invasion of the gut[40]. These risk loci contain genes regulating the epithelial barrier or the innate immune response.

Alterations in the gut microbiome have been associated with IBD[40,58]. Ewaschuk *et al*[59] found that *Bacteroides* spp., *Enterococcis faecalis*, *Enterobacter cloacae*, intestinal *Heliobacter* spp., *Fusobacterium* spp., adherent/invasive *Escherichia coli* strains, *Eubacterium* and *Peptostreptococcus* spp. seem to be harmful intestinal microbes. In contrast, *Lactobacillus* spp., *Bifidobacterium* spp., *Streptococcus salivarius*, *Saccharomyces boulardii* (*S. boulardii*), *Clostridium butyricum*, *Ruminococci* and *Escherichia coli* (*E. coli*) Nissle 1917 seem to be beneficial[59]. Most individuals with IBD, especially CD, are characterized by dysbiosis, in which one or a few potentially harmful microorganisms are dominant[53,60]. In patients with IBD, decreased *Firmicutes*, increased *Proteobacteria* as well as changes in *Bacteroides* compared to healthy controls have been detected[34,61-65]. It has been demonstrated that recurrence of inflammation after ileal resection depends on the exposure of the neoterminal ileum to faecal contents[66,67]. However it is not known which component of faeces triggers this inflammation[40].

NUTRITION AS A THERAPEUTIC OPTION

Although the development of highly active drugs like anti-TNF alpha antibodies has changed the short-term prognosis of severe IBD, there is still a need for low-risk alternative approaches or adjuvant therapies[68]. A number of trials have investigated the efficacy and mechanisms of action of diet in IBD. Historically, nutrition has been seen as an adjunctive therapeutic option and not as a source of therapeutic strategies on its own right[68]. Because of the delivery of high loads of specific nutritional compounds that can affect different targets, nutrition is now not only used as a supportive measure but has also been suggested as primary treatment[18] to induce or maintain remission.

Many studies have shown that clinical remission and mucosal healing in IBD can be achieved with different nutritional regimes. Studies evaluating the effect of enteral nutrition (EN), total parenteral nutrition (TPN), probiotics or FODMAP reduced diet in IBD have been published, but due to the heterogeneity of study protocols, there are as yet no recommendations for routine clinical practice[1]. This review examines concepts of diet therapy in IBD concerning EN, TPN, probiotics and FODMAPs.

Enteral nutrition

Enteral nutrition in CD: The literature includes numerous studies analysing the effect of EN on IBD. EN can be given via the nasogastric tube or by mouth. Generally it is offered in two forms: first, as an elemental diet, containing nutrients in simple forms such as amino acids, mono- or oligosaccharides and medium-chain triglycerides that require little or no digestion prior to absorption[69]; second, as polymeric diets, containing whole proteins and carbohydrates as hydrolysates of starch, which are mostly more palatable[69].

In 2006, the European Society for Parenteral and Enteral Nutrition published guidelines on the role of EN in IBD[70]. In general, EN is indicated in undernourished patients with CD or UC to satisfy nutritional needs[4]. Additionally, in children with active CD, EN is the first line therapy to achieve remission. In adults, however, EN might be a therapeutic option only if treatment with corticosteroids is not tolerated[4]. According to the guidelines of the European Crohn' s and Colitis Organisation ECCO, EN may be an option together with other medications to maintain remission in selected patients[71].

There are meta-analyses and a Cochrane review of randomized controlled trials investigating the effect of EN in CD[72-75]. These studies have mostly shown that EN as sole nutrition can induce clinical remission and mucosal healing in CD[21]. Many trials have evaluated the effect of EN in paediatric CD with the aim of avoiding corticosteroids with their risk of growth suppression[69].

Induction of remission: Paediatric studies give strong support to the role of EN, showing efficacy similar to corticosteroids and better improvements in

growth and mucosal healing[76-81]. In a meta-analysis of paediatric trials comparing the outcome of EN *vs* corticosteroids, there was no significant difference between the two groups[82]. Remission rates were higher with total EN than with partial EN (10/24 *vs* 4/26, RR = 2.7, 95%CI: 1-7.4)[4,82]. Day *et al*[78] evaluated the effect of EN in 27 children with active CD who received polymeric feed for 6-8 wk and no other medication. At the end of the study 80% of the newly diagnosed patients and 58% of the known CD patients were in remission[78].

In most paediatric IBD centres EN is given exclusively for 6 to 8 wk, mostly (90%) as polymeric formulas[21,83]. The mode of reintroduction of food after exclusive EN varies widely, but usually involves an initial low-fibre diet (26%) or gradual re-introduction of normal food, as the formula volume is decreased (56%)[21] .

In adult patients, a Cochrane meta-analysis of six RCTs including 192 adult patients treated with EN and 160 with corticosteroids indicated that EN is less effective than corticosteroids in inducing remission of active CD[75], but this conclusion was based on an intention-to-treat analysis, and patients who successfully completed EN achieved remission rates comparable to those receiving corticosteroids[4,18]. Compared to placebo treated patients with response rates of 20%-30%, patients with EN reached remission rates up to 60%[11,75,84,85]. Lochs *et al*[86] compared the effect of EN as sole therapy to a treatment with steroids and sulfasalazine in patients with active CD (CDAI > 200). After 6 wk, 53% in the EN group and 79% in the drug-treatment group achieved remission (CDAI decreased by 40% or at least 100 points). In this study EN was less effective than a combination of steroids and sulfasalazine for active CD.

Maintenance of remission: EN might be used not only to achieve but also to maintain remission[87,88]. Several studies in adults and children have assessed the efficacy of EN in maintaining medically or surgically induced remission[89-92]. These studies have shown significantly lower recurrence rates in patients treated with EN than in those on a normal diet[4]. Mucosal cytokines like interleukin-1 beta, interleukin-6 and tumour necrosis factor alpha were significantly lower in patients receiving EN than in those on a normal diet[93], suggesting that EN might alleviate mucosal inflammation and so promote remission[4]. Takagi *et al*[91] randomized 51 CD patients who had recently achieved remission, 26 to receive half their calorie intake as EN and 25 to have a free diet. Over a mean follow-up of 11.6 mo, the relapse rate was 34.6% in the "half enteral" group and 64% in the free diet group (relapse was defined as either a CDAI score of more than 200, or the need for therapy to re-induce remission). This study concluded that EN given as 50% of calories seems to be effective in maintaining remission[21]. Hanai *et al*[94] compared the effect of 6-mercaptopurine (6-MP), an elemental diet and no therapy in patients on CD maintenance. After 24 mo, the clinical remission rates were 60, 47 and 27% for 6-MP, elemental diet and the control group, respectively. The remission rates in the 6-MP and elemental diet groups were significantly higher than in the control group. There was no significant difference between the 6-MP and the elemental diet group[94].

In another prospective study, EN significantly reduced clinical as well as endoscopic recurrence within 1 year in CD patients as compared to patients without any nutritional therapy[93]. This study included 40 adult patients with CD who achieved clinical remission (CDAI < 150). Of them, 20 received continuous elemental diet infusion during the night and a low-fat diet during the day, while the other 20 received neither nutritional therapy nor food restriction[93]. Twenty-five percent in the EN group and 65% in the non-EN group had a clinical relapse during the 1-year observation period, with clinical relapse defined as CDAI > 150.

Yamamoto *et al*[88] evaluated the effect of enteral nutrition on maintenance of clinical remission in patients with CD receiving infliximab (IFX) maintenance therapy. This study showed that concomitant enteral nutrition during IFX maintenance therapy does not significantly increase the maintenance rate of clinical remission in CD patients[88].

Mucosal healing: EN may have a positive effect on mucosal healing[76]. Yamamoto *et al*[95] have shown reduced mucosal cytokine production in adults with CD treated with elemental diet. Besides, some paediatric studies have shown that EN is more effective than corticosteroids in inducing mucosal healing[96,97]. Since along with symptomatic improvement, the main target in the treatment of CD is mucosal healing, this advantage of EN over corticosteroids might be considered in therapeutic decision-making[4,98].

Comparison of different EN formulas: Several studies have compared the effect of different types of enteral formulas in the management of CD: elemental, semi-elemental or polymeric diet[4]. A Cochrane meta-analysis of 10 trials did not show any difference between elemental diet and non-elemental diet[75]. There is no systematic review that shows that one type of enteral formula is better than others[4,18]. This might imply that the therapeutic effect of EN is independent of the type of nitrogen source[18]. There was also no difference in efficacy when EN was compared with low fat or high fat diet, and when foods with high-omega-3 *vs* high-omega-6 fatty acid content were compared[21,75,99]. Whole protein (polymeric) food works comparably well to amino-acid-based food and is generally less hyperosmolar[21]. In summary, the quantity or type of fat and protein does not affect the therapeutic potential of enteral nutrition[75,100-103]. There is no association between the efficacy of EN and locations of CD[21], but the validity of a meta-analysis

covering different feeds would be uncertain because of their variety composition[21].

Potential mechanisms: The mechanism by which EN improves CD is unclear. Hypotheses include altered or reduced gut microbiota, avoidance of long-chain fat, which impairs macrophage function, and avoidance of other harmful components of normal food, like emulsifiers or nano-particles as additives[21]. Malnutrition, which is often a problem in IBD patients, can affect immune function and wound healing. When correction of nutritional status improves wound healing, reduced gut permeability could enhance mucosal healing as well[69].

Gut permeability is thought to play an important role in CD. Abnormalities in tight junctions between enterocytes increase luminal antigen uptake, which might contribute to inflammatory activity[57]. Therapy with an elemental diet was shown to reduce intestinal permeability[104], and the literature also suggests that there is a change in the faecal microbiome following exclusive EN[105,106].

A study with paediatric CD patients looked at the impact of exclusive EN on gut microbiota, which showed reduced diversity and an increase in *Protobacteria*[21,105,107]. Leach *et al*[105] compared the bacteria in the stool in patients with CD under exclusive enteral nutrition to a group of healthy controls under a regular diet. At the start of the study, the diversity of bacteria in the two groups was similar but after 8 wk, the patients treated with exclusive EN had significantly less bacterial diversity than the control group.

Long-term perspective of enteral nutrition: Compared to corticosteroids, EN has no long-term adverse effects[18], though there are many other factors that can potentially influence its efficacy[4]. The palatability of feeds and the length of time without solid food, as well as the social inconvenience, contribute to high dropout rates and reduced patient compliance[108]. Additionally, the high cost of enteral formulae has to be considered. A major problem of EN as primary therapy for CD is the high relapse rate, approximately 50% within 6 mo, when patients return to normal diet[21,103]. There is evidence to advocate an exclusion and re-introduction diet following successful induction of remission with EN, rather than an immediate return to a normal diet[11,18]. At 2 years, the remission rate was 59%[18,109] when patients were weaned off EN for 2-4 wk, and, before normal diet was re-introduced, given a limited range of foods generally tolerated by CD patients. After achieving clinical remission, patients with good compliance might receive a half elemental diet with approximately half of their calories derived from an elemental diet[18]. A return to normal feeding nonetheless often leads to relapse[110] and a lower efficacy of dietary therapy in distal disease (colonic/perianal) has been described[111].

Enteral nutrition in UC

There is no evidence that EN is an effective therapy for active UC[21]. One prospective randomized trial compared the effect of TPN and total EN as an adjunct therapy in patients with acute UC on intensive steroid therapy[112]. Remission rates as well as need for colectomy were similar in these two groups.

TOTAL PARENTERAL NUTRITION

Since dietary antigens may be important stimulants for the mucosal immune system, bowel rest with total parental nutrition (TPN) has been considered as a therapeutic option in IBD. The aim of TPN as primary therapy for IBD is to achieve bowel rest, to correct nutritional deficits[11,18,113] and to remove antigenic mucosal stimuli[110]. Various studies have analysed effect of TPN and in the 1980´s especially, TPN was used to treat patients with moderate to severe CD[40].

Müller *et al*[114] prospectively evaluated the effect of TPN in 30 patients with CD, whereby 83% achieved remission, but relapse was common. Surgery could be avoided in 25 of 30 complicated CD patients on 3 wk of inpatient TPN followed by 9 more weeks at home[114]. Greenberg *et al*[115] compared the effect of TPN, partial parenteral nutrition (PPN) with supplementary nutrition with a defined formula *via* NG tube, or PPN with supplementary normal diet. There were no significant differences in the remission rates of 71% in the TPN group, 58% in the PPN with defined formula diet group and 60% in the group with PPN and normal diet[115]. Ostro *et al*[116] evaluated the effect of TPN in 100 patients with CD refractory to conventional medical management. In their study, 90 patients received complete nutrient replacement and 10 received protein-sparing therapy; Seventy-seven patients achieved clinical remission. The remission rate was not influenced by the location of the intestinal involvement. Additionally, TPN was shown to play a role in the healing of post-operative enterocutaneous fistulas arising from surgical anastomosis or complicated fistulas in CD[18,113,117]. When TPN and EN are compared, TPN is associated with higher costs and significant risks including line sepsis and should be restricted to patients who cannot take adequate nutrition enterally[21].

TPN had no effect on severe acute UC in two short-term studies of patients with severe disease[118,119].

PROBIOTICS

There is growing evidence for an association between IBD and an alteration in the gut microbiota but due to the complexity of the gut microbiota, research on this is still in its early stages. Studies have shown a disbalance in the gut between protective *vs* harmful intestinal bacteria[120] with, *e.g.*, an increase in mucosa-associated Escherichia coli and a reduction

in bifidobacterium and lactobacillus species[21,120]. Strategies modulating this dysbiosis might be a therapeutic option in IBD[33]. Antibacterial treatment has been used, but with limited effect[120]. Probiotics may improve intestinal microbial balance, enhancing gut barrier function and improving local immune response[59]. Probiotics are live microorganisms, which when administered in adequate amounts, confer a health benefit on the host[121]. Their effects are strain specific, so that comparisons and meta-analyses of studies using different probiotics are problematic.

Bacteria associated with probiotic activity like lactobacilli or bifidobacteria have been used as well as non-bacterial organisms such as *S. boulardii*[122], but it is a challenge to manipulate the highly individual gut microbiota. Potential mechanisms of probiotics are competitive interactions with the gut microbiota, production of antimicrobial metabolites, and interaction with the epithelium or immune modulation[122,123]. Cells involved in both the innate and adaptive immune responses, like B cells, T cells and dendritic cells as well as macrophages, might be affected[120,124,125]. Probiotic bacteria are able to antagonize pathogenic bacteria by reducing luminal pH[126,127] and inhibiting bacterial adherence and translocation[123]; they can also produce antibacterial substances and defensins[120,128]. For example, invasion of an epithelial cell line by invasive *E. coli* isolated from patients with CD was prevented by pre- or co-incubation with *E. coli* Nissle 1917[129]. Pre-treatment of IL-10 deficient mice with *Lactobacillus reuteri* and *L. casei* can reduce Heliobacter hepaticus-induced colitis[130]. A decrease in mucosal secretion of inflammatory cytokines was shown to be induced by *E. coli* (Nissle 1917) in models of experimental colitis[131]. Probiotics also influence cell-cell interactions and stability through modulation of intestinal barrier function[120]. Alterations in mucus, chloride secretion or changes in tight junction protein expression by epithelial cells might be mechanisms for improved gut mucosal barrier function[120,132].

There are no human data showing any effect of probiotics on dysplasia or colon cancer; however, in animal studies probiotics also seem to reduce the progression from inflammation to dysplasia and finally to colon cancer[130]. Oral administration of Lactobacillus salivarius UCC118 was shown to reduce the incidence of colon cancer as well as the severity of mucosal inflammation in IL-$10^{-/-}$ mice *vs* placebo[130]. Oral administration may not be required for certain probiotic effects: Il-$10^{-/-}$ mice had fewer proinflammatory cytokines after subcutaneous injection of *L. salivarius* UCC18[133].

Consequently, probiotics might improve IBD by regulating the inflammatory response or modulating gut microbiota composition. Many studies have tried to determine the effect of various probiotics in IBD and there will surely be more to come.

Probiotics in CD

There is no strong scientific evidence to justify the use of any of the probiotic strains that have been tested in the past in the management of CD[134,135]. The ECCO guidelines do not recommend probiotics to maintain remission in adult or paediatric CD patients[71]. The use of probiotics in patients with CD has produced ambiguous results and the available trials are small, with very few double blind, randomized, controlled trials[54].

The only positive study, by Guslandi *et al*[136], found that the yeast *S. boulardii* had an effect in CD. Thirty-two patients with CD in remission were treated with either mesalazin 3 g per day alone or mesalazin 2 g per day with *S. boulardii*. In the group treated with S. boulardii, significantly fewer patients relapsed than in the mesalazin only group (6.25% *vs* 37.5%, $P < 0.05$).

Fujimori *et al*[137] treated 10 patients with active CD unresponsive to 5-ASA or steroids with a therapy consisting of Bifidobacterium and Lactobacillus and the prebiotic psyllium for longer than 12 mo. Six patients achieved remission, 1 showed partial remission and there were 3 nonresponders. There were no significant differences when C-reactive protein and erythrocyte sedimentation values were compared before and after therapy. Malchow *et al*[129] treated 28 patients with active CD with prednisone and either E. coli Nissle or placebo. *E. coli* Nissle 1917 is a non-pathogenic *E. coli* that colonizes the intestine and inhibits the growth of enteropathogenic and other enteric bacteria[54]. This probiotic bacterium develops antagonistic activity against enterobacteria such as *Salmonella enteritidis*, *Shigella dysenteriae*, *Yersinia enterocolitica* and *Vibrio cholera*[138,139]. In this study, *E. Coli* Nissle was given in an increasing dosage over 24 d to a final dose of 5×10^{10} bacteria per day for one year. There was no statistically significant difference between the two groups in the time needed to induce remission[129]. In a placebo-controlled randomized study in children with CD treated with *Lactobacillus GG vs* placebo, there was also no significant difference in remission maintenance[140]. Seventy-five children were randomized to receive either *Lactobacillus GG* or placebo for 2 years, and the study concluded that *Lactobacillus GG* does not prolong time to relapse in children with CD when given as an adjunct to standard therapy. Schulze *et al*[138] determined the effect of *Lactobacillus GG vs* placebo in a controlled trial including 11 patients with mild to moderate CD. These patients received antibiotics (ciprofloxacin, metronidazole) for 2 wk, a tapering steroid regime over 12 wk and after 1 wk of antibiotic therapy they were randomized to receive either *Lactobacillus GG* or placebo for 6 mo[141]. The two groups did not differ as to relapse during the study period and mean time to relapse.

Recurrence of CD after surgical resection: For 1 year, Prantera *et al*[142] treated 45 patients who had undergone a curative ileocecal resection with either *Lactobacillus GG* or placebo but saw no benefit from the probiotic therapy. Marteau *et al*[143] studied the effect of *Lactobacillus johnsonii* (*L. Johnsonii*) in 98 patients with CD who had undergone a resection of less than 1 m of small bowel within 21 d prior to study enrolment. Patients were randomized to receive either *L. Johnsonii* or placebo for 6 mo, with no difference between the two groups. Van Gossum *et al*[144] also studied the effect of *L. Johnsonii vs* placebo in a 3-mo trial and again with the same result of no difference between the two groups.

Probiotics in UC

There are data that suggest that certain strains of probiotics are effective in the management of UC[145,146]. Tursi *et al*[147] studied the effect of the probiotic mixture VSL#3™. This contains 450 billion colony forming units of 8 lactic acid bacteria (*B. breve*, *B. longum*, *B. infantis*, *L. acidophilus*, *L. casei*, *L. delbrueckii*, *L. plantarum* and *Streptococcus salivarius subsp. thermophilus*). Seventy-one patients were treated with this probiotic for 8 wk and compared to an untreated control group of 73 patients[147]. VSL#3 ™ was significantly superior to placebo in reducing the activity of mild-to-moderate UC. Other factors like the reduction in rectal bleeding as well as the reintroduction of remission in relapsing UC patients after 8 wk of treatment did not reach statistical significance[147]. Bibiloni *et al*[148] treated 34 patients with active UC unresponsive to conventional therapy with VSL#3™ daily for 6 wk and achieved a response rate up to 77%.

Twenty-four patients with mild to moderate UC flares were treated with *S. boulardii* for 4 wk and showed a response rate of 68%[149]. Zocco *et al*[150] evaluated the effect of *Lactobacillus GG* in a randomized study of 187 patients with quiescent colitis. For 12 mo they received either *Lactobacillus GG* alone, *Lactobacillus GG* and mesalazine 2400 mg/d or mesalazine 2400 mg/d alone. They concluded that Lactobacillus GG has efficacy similar to mesalazine in maintaining remission in UC. After 12 mo of treatment, remission was maintained of 85% in the Lactobacillus GG group, 80% in the mesalazine group and 84% in the combined treatment group.

Ishikawa *et al*[151] investigated the effect of daily Bifidobacteria supplemented fermented milk, (containing *Bifidobacterium bifidum*, *Bifidobacterium breve* and *Lactobacillus acidophilus*), *vs* standard therapy with 5-ASA and steroids in 20 patients for 12 mo. The probiotic group had significantly fewer disease exacerbations than did the placebo treated control group.

Kruis *et al*[152] evaluated the effect of *E. coli* Nissle 1917 *vs* mesalazine 1500 mg per day in a 12-wk randomized trial with 103 patients with UC in remission. Relapse rates were similar in both groups, supporting the use of E. coli Nissle 1917 as a non-toxic treatment for ulcerative colitis. This result was confirmed by a larger study of the same group[139]. Rembacken *et al*[153] evaluated the effect of *E. coli* Nissle in maintaining remission in 83 patients with active UC at the start of the trial. At the beginning of the study patients received standard therapy to induce remission and were then randomized to either *E. coli* Nissle 1917 or mesalazine. There was no difference concerning relapse rates between the two groups.

Unlike other probiotics, the ECCO guidelines recommend *E. coli* Nissle as an effective alternative to 5-ASA for maintaining remission in UC[154].

Pouchitis

The most convincing data so far on the effect of probiotics in IBD have been found in the treatment of pouchitis[131]. The ECCO guidelines recommend probiotics as a therapeutic option for maintaining antibiotic-induced remission in recurrent pouchitis in pediatric UC[155]. Several probiotic strains are beneficial in preventing and treating pouchitis after surgery for UC[59].

Pouchitis is an idiopathic inflammatory disease of the ileal pouch that occurs in 15%-53% of UC patients following total abdominal colectomy with ileal pouch-anal anastomosis[54,156]. As faecal stasis with immunologic reactivity seems to be important in the pathogenesis of pouchitis, several studies evaluated the effect of probiotics in this disease. In a study with 40 patients with chronic relapsing pouchitis, Gionchetti *et al*[157] compared the effect of VSL#3 and placebo for 9 mo following one month's antibiotic therapy with rifaximin and ciprofloxacin. Eighty-five percent in the probiotic group stayed in remission *vs* 0% in the placebo group, as was confirmed by an international multicentre study[158]. In a different group of 31 patients with antibiotic dependent pouchitis, Shen *et al*[159] studied the effect of VSL#3. After 8 mo, 25 patients (71%) stopped therapy because of recurrence of symptoms or side effects.

Gionchetti *et al*[160] evaluated the effect of prophylactic probiotic therapy to prevent pouchitis. When 40 patients were randomized within a week after surgery to receive either VSL#3 or placebo for 12 mo[160], 10% in the probiotic group developed acute pouchitis compared to 40% in the placebo group. The VSL#3 treated group also showed a significantly lower stool frequency than the placebo group.

Similar results were shown in a study by Gosselink *et al*[161] with *Lactobacillus GG* in which 39 patients treated with Lactobacillus GG were compared to a placebo group for 3 years. In the probiotic therapy group significantly fewer patients developed pouchitis within those 3 years than in placebo group; however there is no current evidence that early intake of

prebiotics or probiotics can protect against the development of pouchitis, or even of IBD. Kuisma *et al*[162] evaluated the effect of Lactobacillus GG *vs* placebo in 20 patients in the treatment of active pouchitis for 3 mo and found no improvement in the probiotic group as compared to the control group.

Safety aspects

Although probiotics are considered safe, there have been case reports of bacteraemia and endocarditis associated with probiotic therapy[163]. In addition, the antibiotic resistance transferred from the probiotic bacteria to other bacteria in the gastrointestinal tract might also be of clinical relevance, and the risk of translocation of probiotics across the inflamed colonic mucosa in severely ill IBD patients has to be considered[54]. As mentioned above, the manipulation of the gut microbiota presents a challenge and the probiotic strain, dose, and frequency as well as the duration of the probiotic therapy have to be defined[120], taking into account that the highly individual variety of bacteria in the gut might cause bacteria-host interactions[120]. Further studies have evaluated the effect of nonviable bacteria. Since some of the beneficial effects of probiotics might be mediated by their DNA, live bacteria might not be needed at all[131].

FODMAP

Along with increased fast food and total protein and energy intake fructose consumption has also increased dramatically. Since the incidence of IBD has also increased in recent decades, an association between ingestion of incompletely absorbed fermentable carbohydrates (FODMAPs) and IBD has been postulated[9]. In the 1980s and 1990s, evidence was building for the role of poorly absorbed short-chain carbohydrates in the induction of gastrointestinal symptoms. These incompletely absorbed carbohydrates and polyols are summarized in the acronym FODMAPs. They include fructo-oligosaccharides (found in wheat, onions, legumes), lactose (found in milk and milk products), fructose (found in apples and many other fruits and vegetables, or honey), galactans (found in legumes) and sorbitol (found in stone fruits, artificial sweetener)[164]. Ingested FODMAPs are poorly absorbed in the small intestine. Due to their molecular size and osmotic effect, they draw fluid into the small and large bowel lumina[33,165]. FODMAPs can also induce gastrointestinal symptoms when they are fermented by intestinal bacteria and produce large amounts of gas[33,164,166].

Several trials have demonstrated the effect of a FODMAP-reduced diet in the treatment of irritable bowel syndrome (IBS). This diet restricts FODMAPs, as in wheat, onions, beans, many fruits and vegetables, and sorbitol and other sweeteners[21,167]. Dietary studies have demonstrated that reduction of FODMAPs reduces symptoms in up to 50% of patients[164]. In one case, the effect of a FODMAP reduced diet was determined in a placebo-controlled, cross-over rechallenge in patients with IBS[168]. Patients had fewer symptoms on the FODMAP reduced diet and symptoms recurred in 70%-80% of them when FODMAPs were reintroduced.

As 57% of patients with CD and 33% of patients with UC experience IBS-like symptoms[169,170], a FODMAP reduced diet might also be a therapeutic option in IBD[9,164]. In addition to relief from IBS-like symptoms in IBD, there are three observations that support the hypothesis that FODMAPs may also be involved in the pathogenesis of IBD[9]. First, the intake of FODMAPs in general and fructose specifically have increased in Western societies in recent decades. Second, there is an association between increased intake of sugars and the development of CD[9]. Third, excessive intake of FODMAPs creates conditions in the bowel like increased intestinal permeability that may predispose to CD[9]. To follow this up, studies have investigated the effect of a FODMAP reduced diet in IBD[164]. Barrett *et al*[165] treated 12 patients with ileostomy with either a low or high FODMAP diet for 4 d. Due to the osmotic effect[33] of FODMAPs, there was a 20% increase in ileal effluent on the high FODMAP diet as compared to the low FODMAP diet. It has been suggested that an increased inflow of FODMAPs into the distal small intestinal and proximal colonic lumen might underlie susceptibility to Crohn's disease. The passage of FODMAPs and their subsequent rapid fermentation might lead to expansion of bacterial populations with a secondary increase in intestinal permeability. Croagh *et al*[171] retrospectively determined the effect of a FODMAP reduced diet in patients with IBD. Seventy percent of patients who received instruction on a FODMAP reduced diet remained adherent to diet after 3 mo and reported a significant improvement of symptoms like pain, bloating, and diarrhea[171].

The role of bacteria in mediating the effects of FODMAP on intestinal inflammation was investigated by Zhou *et al*[172] in mice treated with low or high FODMAP diet or regular chow for 2 wk. Mice receiving the high FODMAP diet developed dysbiosis in the gut as well as mucosal inflammation and impaired intestinal permeability[172]. Pedersen *et al*[173] investigated the effect of a FODMAP-reduced diet in 89 patients with IBD (CD: 28 and UC: 61) suffering from IBS symptoms. They found a significant reduction in IBS-like symptoms in patients with IBD and a further reduction in disease activity for UC. In this study 70% of IBD patients with IBS symptoms were dysbiotic at the start of the diet and 50% after 6 wk on the diet. There were no significant changes in the microbiota in these patients after the 6 wk of reduced FODMAP diet[174].

It must, however, be borne in mind that most of the studies on the effect of a low FODMAP diet in IBD

Table 1 Summary of effects of nutritional interventions in inflammatory bowel disease

	Crohn's disease			Ulcerative colitis			
	Induce remission	Maintain remission	Postop.	Induce remission	Maintain remission	Postop.	Pouchitis
Enteral nutrition	Children: ++ Adults: +	++	+	No effect	No effect	No effect	Not tested
Total parenteral nutrition	+	No effect	Not tested	No effect	No effect	No effect	Not tested
Probiotics	No effect	No effect	No effect	+	+	Not tested	++
Low-FODMAP- diet	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested

are limited due to their retrospective and uncontrolled nature and lack of objective data on inflammatory changes associated with dietary intervention[14]. The FODMAP diet also greatly restricts consumption of many fruits and vegetables[175] and recurrence of symptoms after reintroduction of FODMAPs has to be expected.

CONCLUSION

Pharmacological therapy remains the mainstay of treatment of IBD. However, patients with IBD have a strong interest in dietary modifications as part of their therapeutic management. Unfortunately, dietary advice plays only a minor part in published guidelines for the management in IBD. The scientific literature shows that dietary factors might influence the risk of developing not only IBD but also intestinal mucosal inflammation. In addition, diet may serve as a symptomatic treatment for IBS-like symptoms in IBD. A "Westernized diet" rich in animal fat and protein and low in fiber may increase the risk of IBD. Dysbiosis induced by nutrition contributes to the pathogenesis of IBD.

Table 1 shows a summary of the effects of nutritional interventions in IBD. Due to the lack of large prospective controlled studies, no strong recommendations can be made at this point. The different protocols of many studies evaluating the effect of nutritional interventions in IBD, like EN, TPN, probiotics or a FODMAP reduced diet, are not comparable. Still, the role of nutrition in IBD is underscored by the effect of various dietary therapies, especially in paediatrics. In paediatric patients with CD, EN is an accepted therapeutic option. In this group EN has been shown to reach remission rates similar to steroids. Although some studies have shown similar benefits in adult patients with CD treated with EN compared to corticosteroids, a number of meta-analysis have shown that in adult patients, EN is inferior to corticosteroids. The protein or fat content of enteral formulae does not seem to affect clinical outcome. EN is not a successful therapeutic option in UC.

The efficacy of TPN in IBD is not greater than that achieved in other trials with steroids or EN.

The use of specific probiotics in patients with IBD can be recommended only in special clinical situations. There is no sound evidence to justify the use of probiotics in the management of CD. By contrast, studies on UC have shown a beneficial effect in selected patients. For patients with pouchitis, antibiotic treatment followed by probiotics, like VSL#3 or Lactobacillus GG, is effective in maintaining remission, though when probiotics are used, the risk of bacterial translocation and subsequent bacteremia has to be considered. Fulfillment of the therapeutic potential of probiotics requires more understanding of the normal intestinal microflora, and better characterization of probiotic strains at the phenotypic and genomic levels is needed as well as clarification of the mechanisms of action in different clinical settings. A FODMAP reduced diet may improve symptoms in IBD. More randomized controlled trails are necessary to evaluate the efficacy of these diet forms in IBD.

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