Probiotics in the Management of Irritable Bowel Syndrome and Inflammatory Bowel Disease
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Abstract and Introduction

Abstract

Purpose of review There is direct evidence that the pathogenesis of inflammatory bowel disease (IBD) involves the gastrointestinal microbiota and some evidence that the microbiota might also play a similar role in irritable bowel syndrome (IBS). The aim of this article is to review the emerging evidence for the mechanisms and effectiveness of probiotics in the management of these disorders.

Recent findings The composition of the gastrointestinal microbiota is strongly influenced by factors including age, diet and disease. Probiotics may be effective through their impact on the host gastrointestinal microbiota and promotion of mucosal immunoregulation. Probiotics are considered to be well tolerated, although the quality of studies and health claims has been variable. There are many short-term studies demonstrating the effectiveness of probiotics in IBS, although recommendations should be made for specific strains and for specific symptoms. Within IBD, a number of trials have shown the benefits of a range of probiotics in pouchitis and in ulcerative colitis, although current evidence in Crohn's disease is less promising.

Summary Clearly, some probiotics have considerable potential in the management of IBS and IBD; however, the benefits are strain specific. High-quality trials of probiotics in gastrointestinal disorders as well as laboratory investigations of their mechanism of action are required in order to understand who responds and why.

Introduction

The gastrointestinal microbiota are a complex and metabolically active ecosystem that play an important role in health and disease. Genotypic sequencing studies have been used to demonstrate that the human gastrointestinal tract can be populated by any of 1000–1150 different species, with individuals harbouring at least 160.1 Despite this diversity, a core of 18 species was found in all individuals and 57 species were found in 90% of individuals, indicating considerable dominance and interindividual stability of these species across humans.1

Many of these bacteria cluster within individuals. In a recent study across four countries, the sequenced metagenomes were shown to fit into three distinct clusters ('enterotypes'), each characterized by variations in numbers of Bacteroides (enterotype 1), Prevotella (enterotype 2) and Ruminococcus (enterotype 3).2 The abundance of these genera correlated positively or negatively with other genera, indicating a propensity for coexistence or avoidance of other species, respectively. Overall, this describes a microbial ecosystem whose structure is determined, at least in part, by the abundance of species that together contribute to a limited number of preferred compositions.

The composition of the microbiota is strongly influenced by factors including age, disease and diet. In one study,3 the microbiota of people aged 65–96 years was different from younger adults, with higher Bacteroides and Clostridia cluster IV, as well as some signature sequences that were present only in older people. Numerous diseases have been associated with alterations in the microbiota (dysbiosis), ranging from gastrointestinal disorders such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) to extra-intestinal disorders such as obesity and diabetes.4 In terms of diet, the impact of food intake on the microbiota is only recently being explored in depth. Habitual long-term diet has been shown to strongly associate with enterotype, with protein/animal fat being associated with enterotype 1 and carbohydrate being associated with enterotype 2.5 Meanwhile, acute feeding of diets differing in fat and nonstarch polysaccharides alter the microbiota in humans,6 and this has been examined in detail in gnotobiotic mice in whom manipulation of dietary macronutrients was shown to account for the majority of the change in microbiota.6

Approaches to modulating the gastrointestinal microbiota have been investigated as a method of promoting health and in some cases treat disease, in particular the use of probiotic organisms.
Probiotics

The Food and Agriculture Organization of the WHO provides the most widely accepted definition of a probiotic as 'a live organism that, when ingested in adequate amounts, exerts a health benefit to the host'. The most commonly used probiotics are lactobacilli, bifidobacteria and nonpathogenic yeasts such as *Saccharomyces boulardii*. Products that are labelled 'probiotic' are now widely available; however, few fulfil this definition. From a microbiological perspective, some may not contain sufficient live organisms following commercial or domestic storage or have not been adequately tested to ensure they will survive transit through the gastrointestinal tract. From an application perspective, some may not confer a claimed health benefit either because they have not undergone efficacy testing in humans or because what evidence is available is inadequate or negative.

In the future, the definition of a probiotic may require modification, as there is experimental evidence that dead bacteria, bacterial components and substances secreted by bacteria (e.g. bacteriocins, conjugated linoleic acid) have physiologically relevant effects. The more inclusive term 'pharmabiotic' has also been proposed to encompass entities that exert these potentially important effects.

Many probiotics have been used for decades, and yet, definitive data on safety are limited. In the largest ever systematic review of probiotic safety, the Agency for Healthcare Research and Quality concluded that 'the available evidence in randomised controlled trials does not indicate an increased risk; however … despite the substantial number of publications, the current literature is not well equipped to answer questions on the safety of probiotic interventions with confidence'. Most would agree that probiotics should be used with caution in certain patient groups. There have been a small number of notable complications of probiotics in the acute clinical setting, the first reporting septicaemia in infants with short bowel syndrome and the second reporting increased mortality among patients with severe acute pancreatitis administered a novel probiotic mix as a result of intestinal ischaemia of unclear cause.

The manner in which the production, advertising and sale of probiotics is regulated has varied considerably between countries. There has been a regrettable trend for some products to claim benefits for their strain(s) on the basis of evidence from other strain(s). Probiotic effects are strain specific and cannot be extrapolated from one strain to another, no matter how closely related. Regulation in this area is changing, especially where health claims are involved, as indicated by the recent pronouncements of the European Food Safety Authority, which now demands robust data to support health claims.

A major advance in probiotic research has been the greater understanding for their mechanisms of action. The gastrointestinal microbiota and some probiotics have considerable metabolic activity, including the fermentation of nondigested carbohydrates and their conversion into short-chain fatty acids, the deconjugation of bile salts and vitamin synthesis. A number of probiotics modify the inflammatory response to some enteropathogens. For example, a specific strain of *Bifidobacterium* infantis 35624 has been shown to prevent nuclear factor-kappa-B and interleukin (IL)-8 activation and also inhibit the secretion of chemokine ligand 20 in response to *Salmonella typhimurium*, *Clostridium difficile* and *Mycobacterium paratuberculosis*.

Some probiotics have been shown to produce chemicals (e.g. neurotransmitters, neuromodulators) that can modify gastrointestinal functions such as motility or sensation and some have been shown to enhance mucosal barrier function and modulate inflammation. These mechanisms suggest potential roles for probiotics in the management of IBS and IBD. Within the preceding year, numerous mechanistic studies, randomized controlled trials (RCTs), systematic reviews and meta-analyses relating to this area have been published. The aim of this article is to review the recent evidence for the mechanisms and effectiveness of probiotics in the management of IBS and IBD.

Irritable Bowel Syndrome

IBS is characterized by abdominal pain, bloating and change in stool frequency/consistency in the absence of an organic cause. It is a problematic disorder resulting in impaired quality of life, and with prevalence between 10 and 20% in developed countries, there are considerable economic consequences through increased absenteeism and utilization of healthcare services.

The pathogenesis of IBS is multifactorial, including roles for genetics, abnormal pain processing, behavioural pathways and the gastrointestinal microbiota. Regarding the microbiota, a large case–control
study demonstrated that infectious gastroenteritis resulted in almost a four-fold increase in the odds of developing IBS within the subsequent 2 years (odds ratio 3.7). Meanwhile, numerous studies report a luminal dysbiosis in IBS, with many showing that patients have lower lactobacilli and bifidobacteria, the genera frequently used in probiotic products. However, more studies are now investigating the mucosal microbiota in IBS, with recent evidence of lower bifidobacteria in diarrhoea-predominant IBS patients than in controls, together with a negative correlation between mucosal bifidobacteria and the number of days patients experienced pain or discomfort. With all such studies, identifying whether alterations in microbiota are primary events that lead to the development of IBS or merely secondary effects of the syndrome is difficult to determine.

There is also increasing evidence of low-grade mucosal inflammation in IBS. Toll-like receptors (TLRs), the pattern recognition receptors that regulate microbial tolerance, are deregulated with increased TLR-4 and TLR-5 expression and decreased TLR-7 and TLR-8 expression compared with controls.

A recent Rome Foundation group report identified 28 RCTs of probiotics in adults with IBS and four RCTs in children. This report provides considerable details of these older RCTs that are not the focus of the current review. Furthermore, at least six systematic reviews (five of which included meta-analysis) have been published on probiotics in IBS. The six systematic reviews included RCTs in children only, adults only, and children or adults.

Most of the meta-analyses indicated a beneficial impact of probiotics on global symptoms, abdominal pain and flatulence, whereas the impact on bloating was equivocal. However, aggregating the effects of different probiotics into a meta-analysis should be undertaken with caution. Different probiotics have different microbiological characteristics that will inevitably impact on their efficacy. Therefore, converting the findings from meta-analyses into clinical guidelines (e.g. `probiotics improve global symptoms of IBS`) implies that all probiotics will result in a similar benefit, which may not be the case. Recent guidelines have therefore made strain-specific recommendations, including limited weak evidence for Bifidobacteria lactis DN 173010 in improving overall symptoms, abdominal pain and urgency in constipation-predominant IBS and limited weak evidence for VSL#3 (a probiotic mixture containing eight different strains) in reducing flatulence in IBS. Although these are guidelines from the UK focusing only on UK available probiotics, these highlight the need for health professionals to refer to individual RCTs and base their advice on the probiotic and the symptom most relevant to each patient.

Since these systematic reviews, meta-analyses and clinical guidelines, a number of RCTs have been published that investigate the effectiveness of probiotics in IBS. Within the previous year, at least two have been undertaken in large samples (>100). In an RCT of 122 patients with IBS, Bifidobacterium bifidum MIMBb75 resulted in a greater reduction in global IBS symptoms, with more patients consuming the probiotic (47%) than the placebo (11%) reporting adequate relief of their symptoms. However, in an RCT of 120 patients with IBS, there was no difference in symptom response rates or quality of life between patients consuming Escherichia coli Nissle 1917 or placebo following 12 weeks, in part due to large placebo responses (although there was significantly greater response rates in the probiotic group at weeks 10 and 11). Interestingly, following subgroup analysis of those who developed IBS following gastroenteritis or antibiotics, more patients had symptom response to the probiotic (60%) compared with placebo (14.3%). However, this subgroup included only 17 patients and the statistical analysis was only one-sided. Despite these clear limitations, this study alludes to the possibility of greater efficacy of probiotics in patients in whom the pathogenesis of their IBS is known to involve the gastrointestinal microbiota and raises hypotheses for testing in future studies.

The evidence from clinical trials and systematic reviews are largely supportive of the use of probiotics in IBS, but only for specific strains. This is important given that focus groups suggest that patients view probiotics as appealing alternatives to drugs and a natural, low-risk management strategy.

**Inflammatory Bowel Disease**

IBD refers to a group of disorders characterized by chronic inflammation of the gastrointestinal tract of unknown cause. Two principal phenotypes are described: ulcerative colitis wherein inflammation is typically continuous, limited to the mucosa and confined to the colon, and Crohn’s disease wherein inflammation is often discontinuous, transmural and may involve any part of the gastrointestinal tract. Both tend to affect adolescents and young adults, and though they vary in disease extent and severity, they can inflict a tremendous impact on quality of life and have considerable socioeconomic consequences for the individual and society.
The rationale for the therapeutic use of probiotics in IBD is derived from the hypothesis that the endogenous intestinal microbiota plays a crucial role in its pathogenesis. These include the genetic predisposition to IBD resulting from polymorphisms in genes coding for molecules involved in bacterial recognition (e.g. nucleotide oligomerization domain-2). In addition, a dysbiosis of the microbiota in ulcerative colitis and Crohn's disease has been described, including altered microbiota in smokers, a risk factor for Crohn's disease. Furthermore, Faecalibacterium prausnitzii, an organism with proven anti-inflammatory properties, is lower in people with IBD. However, microbiota–host interactions are highly complex and likely bidirectional, as evidenced by the impact of inflammation per se on the microbiota.

An extensive literature supports the impact of various probiotics in experimental models of IBD. For example, a specific strain of B. infantis produces a marked reduction in caecal and colonic inflammation in the IL-10 knockout model of colitis, with a parallel suppression of the proinflammatory cytokines interferon-gamma (IFN-γ), tumour necrosis factor-alpha (TNF-α) and IL-12. These effects on host immunoregulation are thought to be mediated through direct interactions with host dendritic cells or by the induction of vitamin A or tryptophan metabolic pathways. Furthermore, this same organism has been shown to induce IL-10 secretion and enhance Foxp3 expression in peripheral blood in healthy volunteers.

Genetic manipulation of probiotics can result in profound changes in their immunomodulation, further elucidating the mechanism through which these effects are exerted. For example, genetic engineering a defect in techoic acid (a component of the bacterial cell wall) biosynthesis in Lactobacillus plantarum, converted what was a proinflammatory response to the wild type to an anti-inflammatory response in the mutant, featuring greatly enhanced IL-10 production. In another example, a protein derived from Lactobacillus rhamnosus GG reduced epithelial apoptosis and suppressed inflammation in mouse models of IBD by activating epithelial growth factor receptor.

Despite a convincing rationale and a deluge of convincing animal data, clinical data on probiotics in IBD are rather scanty and far from convincing. One exception is in pouchitis, a variant that occurs in the neo-colon following a total colectomy and ileo-anal pouch procedure for ulcerative colitis. Here, a systematic review has indicated that VSL#3 is effective in the primary prevention and maintenance of remission in pouchitis.

With regard to ulcerative colitis, a systematic review of controlled trials has suggested efficacy for probiotics such as nonpathogenic E. coli, S. boulardii, as well as Lactobacillus reuteri (by enema) and VSL#3 in maintaining remission in ulcerative colitis and in treating mild to moderately active disease. However, other studies have been less favourable and large longer term studies are required. Importantly, in this systematic review, only data from the same probiotics were meta-analysed, avoiding the heterogeneity of aggregating data for different probiotics.

In contrast to these somewhat encouraging findings in ulcerative colitis, the literature on probiotics in the maintenance or treatment of Crohn's disease provides little encouragement. Despite these findings, one study reported that over one-third of patients with IBD were currently using probiotics or had done so within the previous year, indicating a need for the health professionals to question patients regarding probiotic use.

**Conclusion**

As the composition and functions of the gastrointestinal microbiota are revealed, their critical role in health and disease will be defined. These discoveries open new therapeutic avenues and have the potential to explain the benefits of probiotics. Although many products masquerade as probiotics, only those that contain live organisms and have been shown in high-quality human studies to confer a health benefit can actually claim this title. We need more high-quality trials of probiotics in gastrointestinal disorders as well as laboratory investigations of their mechanism of action. Ultimately, such studies should allow us to understand, not only who responds, but why.

**Sidebar**

**Key Points**

- There is direct evidence that the pathogenesis of IBD involves the gastrointestinal microbiota and some evidence that they also play a similar role in IBS, as evidenced by alterations in the luminal and mucosal microbiota and activated mucosal immune system, especially in IBD.
• Most of the meta-analyses of probiotics in IBS report a beneficial impact on global symptoms, abdominal pain and flatulence, whereas the impact on bloating is equivocal. However, any benefit is likely to be strain specific.

• The most convincing evidence for probiotics in IBD lies with pouchitis; however, a range of probiotic products have been shown to be successful in maintaining remission and in treating mild to moderately active ulcerative colitis. Data for the use of probiotics in Crohn's disease do not yield promising results.

References


** The first ever evidence that humans develop one of three distinct clusters of gastrointestinal microbiota, which do not relate strongly to age, sex or BMI.


* A large cross-sectional study in older people using pyrosequencing to indicate differences in the abundance of some species and core signature sequences compared with controls. It also includes a smaller longitudinal study indicating relative stability over 3 months.


* A detailed review of the gastrointestinal dysbiosis occurring in a range of disorders.


** The most detailed investigation of dietary and microbiota interactions to date, consisting of both a large cross-sectional study and an acute feeding study indicating numerous dietary associations with the microbiota.


* A murine feeding study examining the impact of varying ratios of protein (casein), fat (corn oil), complex carbohydrate (cornstarch) and simple carbohydrates (sucrose) on microbiota compositions.


* An excellent review of the background on the regulation of probiotics and their labelling.


** The largest ever systematic review of probiotic safety. Numerous analyses are undertaken, including the effect of population, probiotic and disease on the safety profile, as measured by adverse events.


* A review of the studies of immune modulation of B. infantis 35624, focusing on response to enteropathogens and immunoregulation in models of colitis.


* Recent evidence in a large sample of US military, indicating the impact of an episode of gastroenteritis on the risk of developing IBS in the short term.


** A detailed report by the Rome Foundation group relating to the microbiota and functional bowel disease, reviewing a range of old and recent probiotic trials in IBS.


* A study utilizing fluorescent in-situ hybridization to investigate differences in mucosal-associated microbiota in IBS subgroups and healthy controls.


* A study demonstrating altered colonic TLR expression in patients with IBS compared with controls. This study provides insights into dysregulation of the mucosal immune function in IBS that may involve interaction with the gastrointestinal microbiota.

* A detailed review of the systematic reviews of probiotic use in IBS, including details of the odds ratios and relative risk of symptom improvement reported in each of the meta-analyses.


* National guidelines for the dietary management of IBS in the UK, including the recommendation for the use of specific probiotics.


* A recent, large RCT of a bifidobacteria probiotic in the management of global symptoms in patients with IBS.


* A recent, large RCT of a nonpathogenic E. coli Nissle in the management of symptoms in patients with IBS, indicating efficacy in only those patients with a history of gastroenteritis or antibiotic therapy.


* A rare qualitative study that used focus group of patients with IBS or IBD and found that patients were keen to use probiotics, as they were viewed as natural and well tolerated additions to medical therapy.


The first evidence for differences in the gastrointestinal microbiota between smokers and nonsmokers with Crohn's disease, statistically adjusted for background inflammation.


** Deep pyrosequencing of the gastrointestinal microbiota in IBD demonstrating the association between inflammation, genetics and environmental factors (e.g. smoking) on strains of bacteria.


* Recent evidence for the effect of a specific strain of bifidobacteria on Foxp3 T regulatory cells in healthy individuals.


** An excellent systematic review of probiotics in IBD, in which pooled odds ratios were only calculated for a specific probiotic and for a specific patient group.


* A small RCT in children with active distal ulcerative colitis in which the probiotic was delivered by rectal enema and improved mucosal inflammation and increased mucosal expression of IL-10.


Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest
Acknowledgements

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