Probiotics in Bloating Distention and Irritable Bowel Syndrome – from Clinical Evidence to Guidelines

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Abstract

Research suggests that gut microbiota contribute to symptom generation in irritable bowel syndrome (IBS). The colonic flora appears altered in IBS and ongoing research, including studies involving antibiotics and especially probiotics, further support bacterial microflora as a relevant target in IBS. Probiotics have the potential to influence the stability of the intestinal microbiota, and some probiotic strains and mixtures may therefore influence altered gut sensation, motility, permeability and immune function in IBS. This review considers the current clinical evidence-base for probiotics within IBS management, noting that some probiotics are now recognised within evidence-based position statements and clinical guidelines. The current UK National Health Service (NHS) Map of Medicine treatment pathway for IBS states that there is evidence supporting a role for selected probiotics for IBS management, and the recent German consensus guideline on IBS recommends a role for specific probiotics. These guidelines highlight the importance of selecting and differentiating between probiotics according to species or strain and patient symptoms. For example, in patients with predominant pain and/or bloating, the guidelines support *Bifidobacterium infantis* 35624, *Bifidobacterium lactis* DN-173 010, *Lactobacillus casei* Shirota and *Lactobacillus rhamnosus* GG, and in patients with predominant constipation, probiotic strains *Bifidobacterium lactis* DN-173 010, *Escherichia coli* Nissle 1917 and *Lactobacillus casei* Shirota can be considered.

Keywords

Probiotics, bloating, distention, irritable bowel syndrome, guidelines

Disclosure: Jan Tack has no conflicts of interest to declare. Magnus Simrén has received unrestricted research grants from Danone and AstraZeneca, and served as a Consultant/Advisory Board member for Danone, Novartis, Almirall and Shire/Movetis. Heiner Krammer is a member of the Advisory Board at Danone GmbH and receives/received lecture fees from Danone GmbH, Ardeypharm GmbH and Yakult GmbH.
Received: 3 July 2012 **Accepted:** 6 August 2012 **Citation:** *European Gastroenterology & Hepatology Review*, 2012;8(2):72–6
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Irritable bowel syndrome (IBS) is a highly prevalent condition, seen commonly in specialist and primary care practices. As a functional bowel disorder, IBS is diagnosed on the basis of symptoms and management of the syndrome takes the form of multifactorial, patient-centred care, aimed at improving the most bothersome and impactful symptoms. For a number of years, probiotics were used empirically within IBS management. This situation has changed somewhat in recent years as research and study have provided both rationale and evidence highlighting the importance of gut microbiota in IBS pathophysiology and identifying a role for some probiotics within IBS management. This paper, based on an educational forum held during the United European Gastroenterology Week (UEGW) in Stockholm, Sweden, in October 2011, provides a summary of some of the recent knowledge, insights and data that have led to an increasing number of evidence-based position statements and guidelines recommending specific probiotic strains in the management of IBS.

Defining and Diagnosing Irritable Bowel Syndrome

According to the Rome III criteria for diagnosis of functional bowel disorders, IBS is characterised by recurrent abdominal pain or discomfort that occurs on at least three days each month, associated with two or more of the following features: a change in frequency of stool; a change in appearance of stool; and symptom improvement on defecation.[1,2] Patients who have experienced symptoms with an onset reported at least six months previously, and who have symptoms fulfilling the Rome III IBS criteria over the past three months, can be considered to have IBS.

There is long-standing controversy among IBS researchers over whether symptoms are generated in the brain and driven by psychosocial factors and central nervous system co-morbidities, or whether IBS involves clear pathophysiology in the gastrointestinal (GI) tract. For many years, the prevailing dogma has been that there is no evidence of altered GI morphology in IBS and indeed colonic biopsy samples from patients with IBS would be categorised as normal upon routine pathological review. However, there has been research interest in determining whether gut motility and/or sensitivity are altered in people with IBS, and in recent years, there has been a growing focus on the part played by bacterial flora in IBS symptom-generation.

Irritable Bowel Syndrome – New Insights into Pathophysiology Linked with Microbiota

In the past 15 years, a number of research groups have provided collective evidence to suggest that compared with otherwise healthy controls, people with IBS have gut mucosa displaying altered permeability that appears to be linked with low-grade inflammation.[3–6] Although the degree of inflammation found in mucosal tissue of patients with IBS is considerably less pronounced than that seen in inflammatory bowel conditions such as Crohn's disease, close investigation of tissue from IBS patients show signs of increased lymphocyte activity, increased cytokine levels and enhanced number of mast cells, with the latter shown to correlate with IBS symptom severity.[5,6] This low-grade inflammation may have an impact on mucosal permeability and is thought to compromise the integrity of the mucosal barrier, potentially affecting tissue sensitivity and altering contractile function.

A pivotal player influencing gut mucosal integrity and contributing to altered GI sensitivity and contractility, may be bacterial gut flora (see *figure 1*). The human GI tract is home to several billion bacteria. Colonisation starts at birth and evolves and changes over a lifetime. While each individual has a unique signature gut flora, recent attempts to sequence and define the composition of human gut microbiota, identifies that there are three robust clusters, or enterotypes, common to all humans, suggesting a limited number of well-balanced host-microbial symbiotic states.[7] In adult faecal samples, the microbiota typically comprises around 40–65 % firmicutes and 15–35 % bacteroidetes, together with smaller proportions of actinobacteria, proteobacteria and fusobacteria.

In terms of the role of gut microbiota, two distinct microbiota ecosystems can be defined in gut homeostasis – the luminal bacteria (which constitutes most gut bacteria) and the mucosa-associated bacteria. It has been proposed that metabolic activity of luminal bacteria in IBS may play a role in bloating and flatulence in IBS through carbohydrate fermentation and gas production, while the mucosal microbiota have the potential to influence host immune responses.[8,9]

Evidence for a role of bacterial flora in IBS comes from a number of lines of research and study.[8] One of the most compelling arguments comes from epidemiological data showing that the prevalence of IBS increases markedly after community outbreaks of acute gastroenteritis. For example, a one-year follow-up of a community cohort in Spain affected by a Salmonella enteritidis outbreak, found that the relative risk for developing IBS was 7.8 (95% confidence interval, 3.1–19.7).[10] Post-infectious IBS has been reported frequently and is a recognised subgroup of IBS. Other evidence for a role of bacterial flora in IBS comes from studies showing that a subset of people with IBS have increased levels of antibacterial antibodies to luminal antigens.[11] More controversial is the hypothesis that IBS may be characterised by small intestinal bacterial overgrowth.[8] In an attempt to study the possible occurrence of bacterial overgrowth in patients with IBS and to examine the impact of antibiotic treatments on overgrowth and on IBS symptoms, Pimentel et al. examined a group of over 200 IBS patients and reported positive lactulose breath tests suggesting bacterial overgrowth in 78 %, with eradication of overgrowth in almost half of all patients followed up after antibiotic treatment.[12] More recently, however, other groups using the gold standard method for estimating bacterial overgrowth (culture of jejunal aspirates) have reported that while there may be mildly increased counts of small bowel bacteria in patients with IBS, these increases do not correlate with the symptom pattern in IBS.[13] Furthermore, the rates of small intestinal bacterial overgrowth can be shown to be higher in patients receiving proton–pump inhibitor therapy, suggesting that there are potential confounders affecting bacterial overgrowth and complicating the study of this aspect of IBS.[14]

Figure 1: Gut Flora may Influence Mucosal Integrity, Cause Low-grade Inflammation and Contribute to Altered Gastrointestinal Sensitivity and Contractility

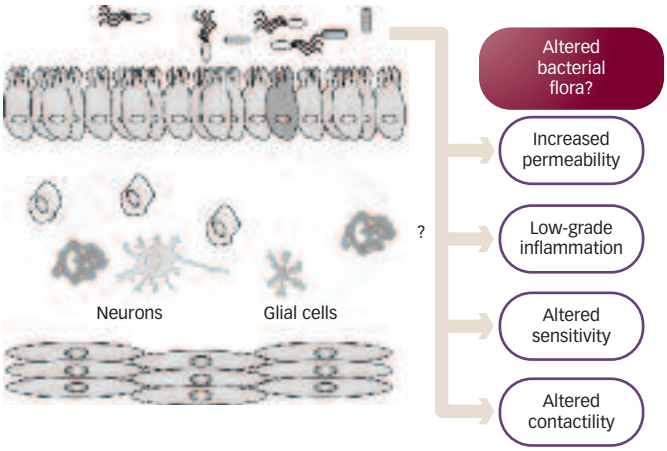
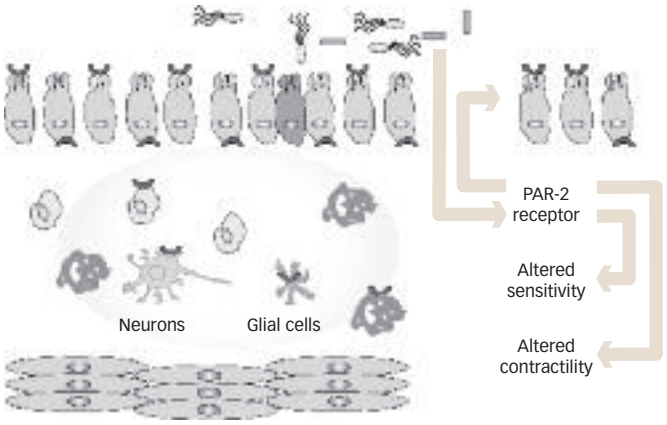


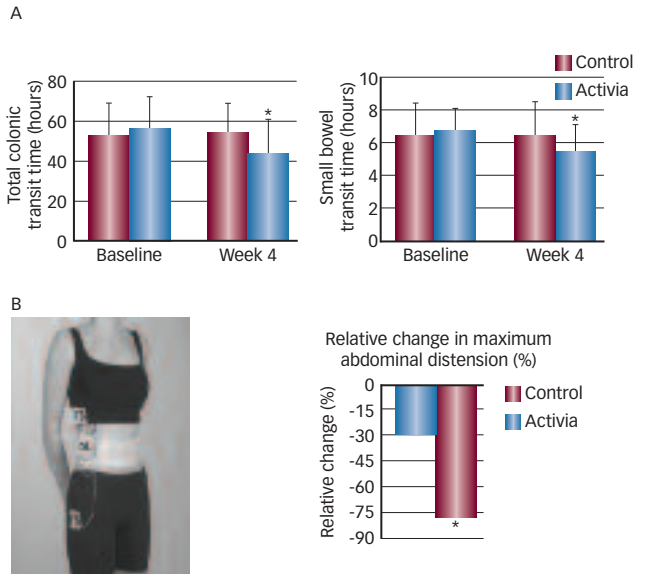
Figure 2: The PAR-2 Receptor is a Candidate Mediator for the Effects of Bacterial Flora on Mucosal Integrity and Altered Gastrointestinal Sensitivity and Contractility



In diarrhoea-predominant irritable bowel syndrome, luminal bacteria appear to be responsible for elevations in colonic luminal serine protease activity, possibly mediated via proteinase-activated receptor-2 (PAR-2) activation and signalling.

There is slightly more evidence to suggest that colonic flora may be altered in IBS.[15,16] A recent review noted that many of the available studies of colonic microbiota in IBS have been performed in small patient populations and have used widely differing methodologies, making it difficult to draw clear conclusions.[8] Nevertheless, most individual studies reported altered colonic flora; and for example reported changes such as that in diarrhoea-predominant IBS there are decreased *Lactobacillus* species and in constipation-predominant IBS there are increased levels of *Veillonella*. A recent study using phylogenetic micro-array and realtime polymerase chain reaction (PCR) measurement of stool samples noted upregulation of some species and downregulation of other species in IBS as compared with controls; and correlated the presence of certain strains with IBS symptom severity scores and the involvement of several groups of firmicutes and proteobacteria in the pathogenesis of IBS.[17]

Figure 3: Clinical Trial Evidence has Linked Symptomatic Improvements in Abdominal Bloating Following Use of Probiotics for Four Weeks, with Effects on Gut Motility and Gut Transit Times (A), and an Objectively Demonstrated Reduction in Abdominal Girth (B)



*A: gastrointestinal motility; B: change in abdominal distention. * p<0.05.*

Pathophysiological studies also suggest a contribution of gut microbiota to IBS. For example, research in patients with diarrhoea–predominant IBS has identified that elevated colonic luminal serine protease activity in these patients, is not related to endogenous epithelial cell or inflammatory activity, but is linked with production of proteases by luminal bacteria, and further, that these proteases alter colonic permeability and sensitivity, possibly via proteinase-activated receptor-2 (PAR-2) activation and signalling (see *Figure 2*).[18]

Antibiotics and Probiotics

Another piece of evidence in support of a role for gut microbiota in IBS pathophysiology comes from therapeutic studies with antibiotic agents.[19–21] Clinical studies have shown that use of antibiotics can provide some symptomatic relief in IBS. For example, two recent phase III studies, Targeted Non-systemic Rifaximin Gut-selective Evaluation of Treatment for Non-constipation IBS (TARGET)1 and TARGET2, which each compared the effects of two weeks of treatment with rifaximin in patients with IBS without constipation, reported that the antibiotic was superior to placebo in relieving both global symptoms of IBS and in providing relief of bloating during a 10-week follow-up period, results which the authors suggest is related to the ability of this antibiotic to affect an underlying cause of IBS linked to an alteration in intestinal microbiota.[21] It has to be noted, however, that the superiority of rifaximin over placebo was found to be modest.

Probiotics and Irritable Bowel Syndrome

Probiotics have been described as living micro-organisms that confer a health benefit to the host when administered in adequate amounts.[22] It is thought that probiotics may exert their effects through a variety of mechanisms, and studies suggest that the effects of probiotics on immunity, intestinal barrier integrity, visceral hypersensitivity and motility may be strain specific.[23,24]

The evidence for, and understanding of how, probiotic species and probiotic mixtures impact on IBS has advanced in recent years as a growing number of clinical studies have sought to elucidate the effects of these agents in clinical settings.[24]

Growing Body of Clinical Evidence for Probiotics

A search of the medical literature performed in July 2011, highlights that the past 10 years have seen both a growing number of clinical trial reports relating to probiotics in IBS and an increase in the number of reviews and meta-analyses on this topic.

While early studies of probiotics were often of poor quality, most studies did nevertheless indicate a degree of efficacy for certain probiotics, encouraging further study of single species and mixtures in clinical settings.[25] Indeed, the more recent studies highlight that different symptoms respond to different probiotics, and identify that some probiotics are much more effective than others. It appears that the choice of strain may depend on which symptom is being targeted. For instance, some probiotic organisms and products mainly affect bloating and flatulence, whereas others improve bowel frequency, and some have a positive effect on a global symptom score. When evaluating the individual clinical trials in IBS, the results seem to be somewhat better and more convincing for a number of bifidobacteria, including *Bifidobacterium infantis* 35624, *Bifidobacterium lactis* DN–173 010, as well as for some probiotic mixtures.[26,27]

Among key studies reported in recent years are a six-month randomised placebo-controlled study of a probiotic mixture in over 100 patients with IBS, which found a median reduction of 42 % in a symptom score comprising abdominal pain, distension, flatulence and borborygmi,[28] and a large-scale multicentre study comparing a probiotic containing *Bifidobacterium animalis* DN-173 010 with placebo in primary care patients with IBS, which found that by week three and continuing to week six, over 60 % of patients responded with improved quality of life scores as assessed by the functional digestive disorders quality of life questionnaire in terms of discomfort.[29] Moreover, convincing evidence supports clinical efficacy for *B. infantis* 35624, through two well-executed randomised placebo-controlled trials.[30,31]

Potential Mechanisms by which Probiotics May Affect Irritable Bowel Syndrome Symptoms

A number of recent randomised controlled clinical studies of probiotics in patients with IBS provide information on how probiotics may act to help improve IBS symptoms.[25] For example, in a study involving patients with IBS with constipation, it was shown that after four weeks of consuming a probiotic containing *B. lactis* DN-173 010, patients had significantly decreased colonic and small bowel transit times compared with placebo, which were accompanied by significant, measurable reductions in maximal abdominal distention and a trend towards reduced mean abdominal distention during the day.[32] This study links control of symptomatic bloating with effects on transit times and gut motility seen within four weeks of using this probiotic (see *Figure 3*). In another randomised trial, a probiotic containing *B. infantis* 35624, but not a probiotic containing *Lactobacillus salivarius* UCC4331 was reported to alleviate IBS symptoms in a manner that was associated with normalisation of pro-inflammatory cytokine levels over an eight-week study period, suggesting anti-inflammatory, immune-modulating actions for this bifidobacteria.[31] There are also reports from a clinical trial with a multi–species probiotic mixture containing *Lactobacillus*

Table 1: Probiotics in Irritable Bowel Syndrome According to German Guideline 2011

Probiotic Strain	Trademark Name	IBS Pain/Bloating Type	IBS Pain Type	IBS Constipation Type
Bifidobacterium infantis 35624	Bifantis®	B		
Bifidobacterium animalis ssp. lactis DN-173 010	Activia®	B		C
Lactobacillus casei Shirota	Yakult®	B		B
Lactobacillus plantarum		C		
Lactobacillus rhamnosus GG	Culturelle® LGG® Gefilus®		B	
Escherichia coli Nissle 1917	Mutaflor®			C
Combination preparations	VSL#3		C	
Levels of Evidence of Various Probiotic Strains Depending on the Predominant IBS Symptom				
Level of evidence A Randomised controlled clinical trial, cohort study				
Level of evidence B Retrospective cohort, exploratory cohort, ecological study, outcomes research, case-control study, or extrapolations from level A studies				
Level of evidence C Case-series study or extrapolations from level B studies				

IBS = irritable bowel syndrome.

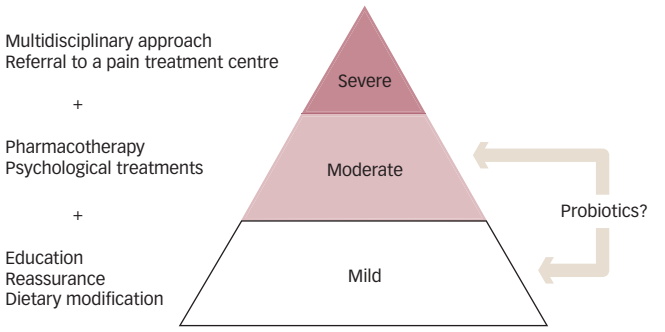
rhamnosus GG, *Lactobacillus rhamnosus* Lc705, *Propionibacterium freudenreichii ssp. shermanii* JS and *Bifidobacterium breve* Bb99, of changes in IBS-associated microbiota towards those seen in subjects without IBS that were detected and measured using realtime PCR assay of faecal samples in subjects given the probiotic mixture over a six-month period.[28,33]

Clinical Guideline Recommendations for Use of Probiotics within Irritable Bowel Syndrome Management

Probiotics are increasingly considered to have a role within the management of mild to moderate IBS (see *Figure 4*).[2] One of the first mentions of probiotics within clinical guidelines on IBS was in 2001 when a group of European doctors developed recommendations on the management of IBS that highlighted the need for the objective study of probiotics and their potential role in symptom management.[34] There then followed a decade of research assessing specific probiotic strains and their clinical benefits in IBS. Today, a role for probiotics in the management of IBS is recognised within an increasing number of evidence-based position statements and clinical guidelines produced, for example, in the UK by the British Society of Gastroenterology 2007, the National Institute for Health and Clinical Excellence (NICE) 2008,[35] and the Map of Medicine (MOM) 2010,[36] and more recently in Germany by the German Society of Digestive and Metabolic Diseases (DGVS) and German Society of Neurogastroenterology and Motility (DGNM) 2011.[37] Other international guidelines that support a role for probiotics include the American College of Gastroenterology 2009 guidance and the World Gastroenterology Organisation (WGO) guidelines of 2009.[38]

The NICE guidance of 2008[35] states that some probiotics are effective in people with IBS while others are not, noting that the probiotic strain, the dose and the method of ingestion are factors that may influence effectiveness of available products. While NICE did not feel able to recommend named bacteria or probiotic products on the basis of evidence from single trials, the guidance highlighted the case for including probiotics within diet and lifestyle management and stressed the safety of probiotics from reliable sources. More recently, the 2010 UK MOM on IBS management[36] accredited by the Royal College of Physicians, identified that some specific strains such as *B. lactis* DN-173 010 and the probiotic cocktail VSL#3® have clinical trial evidence for relieving bloating distention and flatulence, and others such as *B. infantis* 35624 to reduce bloating and other cardinal symptoms of IBS.

Figure 4: Role for Probiotics in the Graduated Treatment Approach for Patients with Irritable Bowel Syndrome



Source: Khan, Chang, 2010,[2] with permission from Nat Rev Gastroenterol Hepatol.

The most recent German consensus guideline on IBS also reflects the growing number of randomised controlled trials, which have added to the evidence-base in the past years[37] (see *Table 1*). The S3 IBS German Guideline of 2011 was developed following an evidence-based evaluation of all available publications. The guideline provides clear statements and recommendations each of which are characterised by a level (or class) of evidence, the degree of evidence and the power of consensus regarding a given recommendation. Classes of evidence are based on accepted evidence-based grading of data, with degree of evidence A based on studies of evidence class 1 (i.e. systematic reviews of randomised controlled trials or single randomised trials), B class 2 or 3 evidence or indirect evidence from class 1, C class 4 evidence or indirect evidence from class 2 and 3, and D class 5 evidence or indirect class 4 evidence. The degrees of recommendations range from strongly in favour, weakly in favour, weakly against, to strongly against. Current German guidelines state that, "Selected probiotics can be used in

the treatment of IBS, with the strain being selected according to the symptoms. (Level of evidence A, grade of recommendation [weakly in favour, strong consensus] >95 % agreement.)" Current German guidelines on IBS make clear that a general statement on a role for probiotics in the treatment of IBS is not appropriate but rather that there needs to be a differentiation between choice of probiotic species or strain, depending on the patient group. As shown in *Table 1*, depending on the predominant IBS symptom, different probiotic strains are recommended. For example, in patients with predominant pain and/or bloating, the guidelines note there is level B evidence to support *B. infantis* 35624, *B. lactis* DN-173 010, *Lactobacillus casei* Shirota and *L. rhamnosus* GG. In patients with predominant constipation, probiotic strains *B. lactis* DN-173 010 (level C), *Escherichia coli* Nissle 1917 (level C) and *L. casei* Shirota (level B) have evidence of benefits based on German guideline evaluation of available evidence.

Conclusions

Understanding of the pathophysiology of IBS has increased in recent years, leading to new approaches and strategies for the management of cardinal symptoms of the condition. Appreciation of the role of gut microbiota in IBS has seen some probiotics find a role and place within evidence-based guidelines. Ongoing research and study will continue to identify pathways, mechanisms and management approaches to ensure better symptom control for the many people affected by this condition. ■

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