



## Conference on ‘Diet, gut microbiology and human health’ Symposium 4: Manipulating the microbiome: health and therapeutic opportunities

### Irritable bowel syndrome: the problem and the problem of treating it – is there a role for probiotics?

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The aim of this review is to highlight the impact of irritable bowel syndrome (IBS) in those patients who consult the medical profession and examine the therapeutic potential of probiotics in this condition, where there is a strong need for new treatment options. Traditionally, IBS is frequently regarded as a trivial condition which is certainly not life threatening and mainly psychological in origin. However, these preconceptions are misplaced, as in some patients the condition can be devastating with the pain being as severe as that of childbirth coupled with incapacitating bowel dysfunction. In addition, patients suffer from a variety of non-colonic symptoms such as low backache, constant lethargy, nausea and genito-urinary problems, all of which lead to these patients having extremely poor quality of life. Unfortunately, the treatment of IBS is very unsatisfactory with only one new medication being developed for this condition in the last 25 years. It is now recognised that IBS is a multifactorial condition with symptoms being triggered by a variety of factors, some of which appear to be influenced by probiotics, resulting in speculation that they may have therapeutic potential in this condition. There have been over thirty controlled clinical trials of probiotics in IBS with approximately two-thirds of these studies showing evidence of an improvement in symptoms. However, not all probiotics appear to be effective with different symptoms being improved by different strains and some improving symptoms more than others. Consequently, the ideal probiotic for the treatment of IBS has yet to be defined, but the evidence is good enough to encourage further research with the aim of identifying an optimal strain or strains.

#### Irritable bowel syndrome: Impact: Microbiota: Probiotics

##### The problem

Irritable bowel syndrome (IBS) is often viewed as a relatively mild condition which is psychological in origin and certainly not life threatening. Approximately 10–15% of the population are affected<sup>(1)</sup> and it is certainly true that in a proportion of these individuals the condition is more of a nuisance than being anything serious and they seldom, if ever, have to consult their doctor. However, the condition can be much more severe in a substantial minority necessitating repetitive consultation both in the primary and secondary care setting and placing a significant burden on healthcare systems

because the treatment is so unsatisfactory<sup>(2,3)</sup>. The principal symptoms are abdominal pain, abdominal bloating and some form of bowel dysfunction which can be either diarrhoea (IBS-D), constipation (IBS-C) or an alternation between the two (IBS-A). Over the years, a number of diagnostic criteria for IBS have been developed of which the Rome III criteria<sup>(4)</sup> are the most widely used, although a further update is in development. These criteria are extremely useful for ensuring homogeneity of patient groups for research purposes but rather cumbersome for use in the clinical setting. In the more severe cases of IBS, many women liken the pain to that of childbirth and can experience this on a regular,

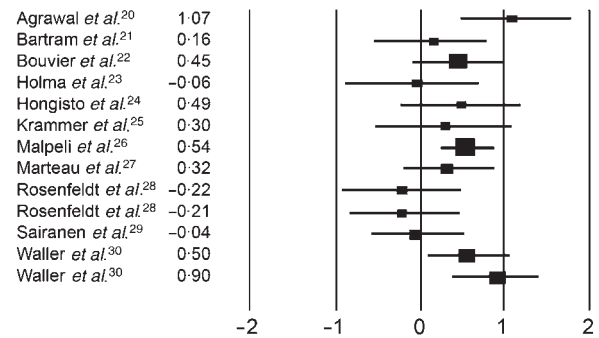
**Abbreviation:** IBS, irritable bowel syndrome.

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sometimes daily, basis<sup>(5)</sup>. In the diarrhoea group of patients, there can be significant urgency and some patients experience faecal incontinence which can have an extremely restricting effect on their lifestyle<sup>(5)</sup>. The constipation variety is characterised by infrequent defecation and it is not uncommon for some patients to fail to open their bowels for up to 1–2 weeks. The gastro-colonic reflex is a response to eating where a healthy individual experiences a desire to open their bowels shortly after eating their first meal of the day and not with any subsequent intake of food. In IBS this reflex is exaggerated, so that patients with the diarrhoea predominant form of the condition often need to open their bowels after every meal whereas in those with constipation, abdominal pain or bloating is made worse by eating. Bloating is another extremely common feature of IBS which can take the form of a feeling of pressure within the abdomen which, in some individuals, can be accompanied by an actual increase in girth usually referred to as distension<sup>(6,7)</sup>. In addition, IBS patients often suffer from a variety of non-colonic symptoms such as low backache, constant lethargy, nausea and a range of urological and gynaecological symptoms such as frequency of micturition and pain on intercourse<sup>(8)</sup>. Not surprisingly, the latter can profoundly affect sexual activity in women suffering from this problem<sup>(9)</sup>. These non-colonic symptoms are important as on some occasions the patients find them more intrusive than the traditional symptoms of IBS. Furthermore, they can lead to inappropriate referral to gynaecological, urological and even orthopaedic clinics where the outcome is poor because they actually have IBS rather than a condition relating to these specialities<sup>(10,11)</sup>. Altogether, these features of IBS lead to the erosion of the quality of life of sufferers to the extent that it can be equal to or worse than that of diseases such as diabetes and chronic renal disease<sup>(12)</sup>. All these issues coupled with the inadequacies of current treatment options can lead to a sense of hopelessness and it has been shown that suicidal ideation is worryingly high in many of these patients<sup>(13)</sup>. Consequently, there is a strong need for the development of new treatment strategies for IBS.

### The pathophysiology of irritable bowel syndrome and the influence of probiotics

It is now recognised that there is no single cause of IBS with disturbances of gastrointestinal motility and sensitivity, the central processing of painful stimuli from the gut, inflammation, diet, genetic and psychological factors all being important<sup>(14)</sup>. Furthermore, there is an accumulating body of evidence that the microbiota of the gut is disturbed (dysbiosis) in at least a proportion of patients<sup>(15)</sup> although no particular phenotype characteristic of IBS has yet been identified. The presence of dysbiosis, coupled with accumulating evidence that some of the pathophysiological mechanisms involved in IBS can be modified by probiotics, has led to speculation that probiotics might be effective in treating the condition<sup>(16)</sup>.



**Fig. 1.** A comparison of studies measuring the effect of a variety of different probiotics on gastrointestinal transit time. A positive value equates to an acceleration of transit.

The administration of probiotics can influence motility<sup>(17,18)</sup> which is known to be abnormal in IBS<sup>(19)</sup>, and in particular, there is convincing evidence that gastrointestinal transit can be accelerated by some organisms (Fig. 1)<sup>(20–30)</sup> suggesting those that have this effect would be better suited to IBS-C<sup>(31)</sup>. Visceral hypersensitivity of the gastrointestinal tract is one of the most consistent abnormalities in patients with IBS<sup>(32,33)</sup> and is usually assessed by balloon distension of the rectum. Although the effect of probiotics on visceral hypersensitivity has not yet been assessed in IBS, it has been shown that they can reduce this abnormality in experimental animals<sup>(34,35)</sup> using balloon distension techniques. Brain scanning techniques, such as positron emission tomography or functional MRI, have been utilised to provide good evidence that the central processing of painful stimuli applied to the gut is abnormal in IBS<sup>(36,37)</sup>. It is therefore of interest that it has been shown that the administration of a probiotic can reduce the reactivity of areas in the brain associated with this abnormal processing<sup>(38)</sup>. It has been known for many years that some patients with IBS date the onset of their symptoms to an episode of gastroenteritis<sup>(39)</sup> and this condition is sometimes referred to as post-infective IBS. It remains to be determined whether IBS-D and post-infective IBS are similar entities, although a recent study has suggested that the microbiota in these two conditions is very similar<sup>(40)</sup>. It has been shown that in a proportion of individuals with post-infective IBS and other forms of IBS, there is evidence of a persisting, low grade, inflammation in the gastrointestinal mucosa<sup>(41,42)</sup>. This abnormality might be amenable to modulation by some species of probiotic organisms that have been shown to elaborate a variety of proteins and metabolites that have anti-inflammatory and immunomodulatory activity<sup>(43,44)</sup>. For instance, it has been shown that in some patients with IBS the ratio between IL10 (an anti-inflammatory cytokine) and IL12 (a proinflammatory cytokine) is in a pro-inflammatory state and this can be normalised by the administration of *Bifidobacterium infantis* 35624<sup>(43)</sup>. In addition to having dysbiosis<sup>(15)</sup>, it is a common clinical observation that patients with IBS frequently give a history of repeated or prolonged antibiotic consumption. This is supported by a prospective

**Table 1.** Comparison of the change in symptom scores (negative value equals improvement) in various irritable bowel syndrome (IBS) bowel habit subtypes\* following treatment with *Bifidobacterium infantis* or placebo

	IBS-D	P value	IBS-C	P value	IBS-A	P value
<i>B. infantis</i>	49	–	18	–	18	–
Placebo	56	–	18	–	23	–
Abdominal pain/discomfort	–0.29	0.099	–0.58	0.036	–0.24	0.403
Bloating/distension	–0.33	0.056	–0.15	0.622	–0.25	0.362
Urgency	–0.29	0.075	0.01	0.978	–0.12	0.623
Incomplete evacuation	–0.45	0.008	–0.07	0.834	–0.11	0.730
Straining	–0.39	0.007	0.08	0.799	–0.34	0.263
Passage of gas	–0.28	0.073	–0.00	0.995	–0.35	0.169
Bowel habit satisfaction	–0.37	0.014	–0.59	0.047	0.24	0.355
Overall assessment	–0.36	0.028	–0.48	0.078	–0.21	0.456
Composite score	–0.99	0.027	–1.32	0.074	–0.15	0.838

\* The principal symptoms of IBS are abdominal pain, abdominal bloating and some form of bowel dysfunction. The latter can take the form of diarrhoea, constipation or an alternation between the two and these different types of IBS are usually referred to as IBS-D, IBS-C and IBS-A respectively.

study showing that 4 months after receiving antibiotics, 48 % of patients experienced functional bowel symptoms compared with only 22 % of controls not receiving such a medication<sup>(45)</sup>. There is also some evidence that a proportion of patients with IBS have small-bowel bacterial overgrowth<sup>(46)</sup> although this finding remains somewhat controversial because of dispute over what is the optimum method for detecting this abnormality<sup>(15)</sup>. Furthermore, some of the medications that are commonly used in IBS can affect the microbiota and this is particularly true for proton pump inhibitors and laxatives or anti-diarrhoeal medications<sup>(15)</sup>. Consequently, the observation that probiotics have been shown to be beneficial in antibiotic diarrhoea and that some species even have anti-microbial activity<sup>(47,48)</sup> suggests a possible role in targeting the dysbiosis in IBS. There is growing evidence that a defect of the gastrointestinal barrier, which helps to confine a variety of bacterial and other antigens to the gut lumen, plays an important role in the pathogenesis of a number of gastrointestinal diseases, including IBS<sup>(49)</sup>. Consequently, there is considerable interest in understanding how this barrier is maintained coupled with the fact that there is experimental support for the notion that probiotic bacteria enhance barrier function<sup>(50,51)</sup>. We have shown in a number of studies that the prevalence of depression is not especially high in patients with IBS, although anxiety is a consistently common finding in this condition<sup>(52)</sup>. Therefore, it is noteworthy that the administration of probiotics has been shown to lead to a reduction in anxiety and depression behaviour in animals<sup>(53)</sup>, as well as reduced anxiety scores in human subjects<sup>(54,55)</sup>.

Despite the fact that a substantial proportion of patients with IBS give a history of antibiotic usage, it is interesting to note that some non-absorbable antibiotics may actually have a beneficial effect. Originally this observation was noted for neomycin but this medication can have side effects and more recently, attention has focused on rifaximin<sup>(56)</sup>. The beneficial effects of this antibiotic have been well documented in large-scale clinical trials although some questions remain about how often such an antibiotic should be given and whether repeated courses could lead to drug resistance.

However, the observation that this antibiotic can have beneficial effects in IBS lends further support to the notion that targeting the microbiota in this condition has therapeutic potential.

### Treating irritable bowel syndrome with probiotics

Most of the drugs in development for the treatment of IBS target a specific receptor and consequently are aimed at a particular subgroup of the condition, such as IBS-C or IBS-D, whereas the more traditional medications, such as antispasmodics, tend to be given to all patients irrespective of the pattern of their symptomatology. Similarly, because probiotics potentially modulate a number of the pathophysiological mechanisms involved in IBS, they are usually given to all subtypes of the condition both in the clinical setting as well as in therapeutic trials. There have been twenty-eight controlled trials assessing the efficacy of probiotics in adults suffering from IBS with twenty (71 %) showing a positive effect<sup>(43,57–75)</sup>, seven showing no effect<sup>(43,76–81)</sup> and one leading to a deterioration of symptoms<sup>(82)</sup>. In addition, four trials in children all gave positive results<sup>(83–86)</sup>. However, the quality of some of these trials has not been optimal and there is always the problem of the possibility of publication bias. In addition, formulation is critical with efficacy not necessarily improving with a higher concentration of bacteria. For instance, a liquid probiotic preparation containing  $10^{10}$  colony-forming units of *B. infantis* was effective in IBS, whereas the same dose in a capsule had no effect because in this form, it solidified on contact with moisture<sup>(61)</sup>. Although many trials show an improvement in symptoms, different preparations appear to improve different symptoms with some helping pain, others reducing flatulence and some relieving a range of symptoms<sup>(14)</sup>. A meta analysis of probiotic trials would be inappropriate, as for instance, different strains of bifidobacteria will have unique properties not necessarily shared by other closely related organisms. However, it is entirely acceptable to compare different therapeutic trials assessing the efficacy of the same organism or product.

As the majority of studies have been undertaken on IBS, irrespective of bowel habit subtype, it is difficult to know whether some may be more suited to one subtype or another. In one trial on *B. infantis*, although all subtypes were included<sup>(61)</sup>, the results were broken down according to subtype (Table 1) and it can be seen that the preparation was equally effective in all three groups. However, in those studies where transit was accelerated (Fig. 1), it might be anticipated that those products might be more suited to constipation type IBS. An increase in abdominal girth, sometimes referred to as distension, is an extremely common feature of IBS and has been shown to be associated with constipation and delayed gastrointestinal transit<sup>(87,88)</sup>. Consequently, it might be expected that this symptom might be improved by relieving constipation or accelerating gastrointestinal transit and this has been confirmed using a probiotic yoghurt that has been shown to reduce transit times<sup>(20)</sup>.

Despite the evidence that probiotics may be potentially useful in the treatment of IBS, a number of questions remain to be answered. For instance, it is still not known whether preparations containing single organisms or mixtures are preferable or whether there are any contraindications to their use, such as administration to immunocompromised patients. Those patients most likely to respond, such as possibly individuals with a history of excessive antibiotic consumption, have also yet to be defined but it might be anticipated that these products are going to be more effective in combination with other approaches such as dietary manipulation, rather than being stand-alone treatments. Their beneficial effects seem to evolve quite slowly and symptoms start to return when treatment is discontinued<sup>(61)</sup> indicating that it is likely that long-term maintenance treatment will be required when a particular preparation is found to be effective.

In conclusion, there is reasonably good evidence that probiotic organisms have activity in the treatment of IBS but the best organism(s) for this purpose have yet to be defined. The availability of products for which there are data to support their use in IBS is patchy and varies from country to country. Consequently the best advice that can be given at the present time, is to try and source an evidence-based product and take it for at least 4 weeks.

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