

## Treatment of irritable bowel syndrome with probiotics: growing evidence

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Irritable bowel syndrome (IBS) is characterized by abdominal pain or discomfort relieved by defecation or release of gases and by altered bowel habits, over a period of at least three months. No morphological or biochemical cause has been confirmed that links IBS with organic disease. The main symptoms of the syndrome, sensation of incomplete defecation, urgent need to defecate, rectal tenesmus, pain on defecation and mucorrhoea suggest visceral hypersensitivity. Patients often experience extra-intestinal symptoms, including back, head, joint and muscle pain, palpitations, urinary frequency, menstrual irregularities, sleep disturbances and depression. At least 50 per cent of patients have one or more somatic comorbid condition, and this comorbidity has a significant influence on the patient's consultation pattern, diagnostic management, therapeutic plan, and the outcome of treatment<sup>1,2</sup>.

### Aetiology and pathophysiology

The aetiology of IBS seems to be multifactorial. Its pathophysiology is largely unknown, though several of the mechanisms which underlie IBS affect the type and severity of symptoms. Although genetic factors are known to play a minor role, yet these influence symptomatic expression and therapeutic response, at least in some IBS patients. Certain patients show a higher sensitivity to distension of the bowel wall or an increased sense of a central sensitive perception. Psychosomatic disorders are not the cause, but rather the consequence of IBS, and these disorders can modulate and sometimes intensify patients' perception of the severity of their abdominal symptoms<sup>2,3,4</sup>.

Post-infectious IBS (PI-IBS) accounts for about 20-35 per cent of all cases of IBS. There is a six times greater risk of it developing following a gastrointestinal infection. These post-infectious forms of IBS have given rise to new concepts regarding its pathophysiology, with both intestinal flora and alteration of intestinal permeability having been assigned a role in the syndrome<sup>5,6</sup>. The identified risk factors are female gender, a context of stress and anxiety, and duration of episodes for more than five days. It has been shown that genetic factors can promote PI-IBS suggesting that post-infectious IBS is the result of genetic anomalies that affect the immune response to bacteria in the gastrointestinal tract<sup>3,4,7,8</sup>.

### Diagnosis and management

The differential diagnosis of IBS can be difficult. It is particularly important to exclude infections, food intolerances, inflammatory diseases, gastrointestinal tumours, side effects of drugs (antibiotics, tricyclic antidepressants, proton pump inhibitors, *etc.*) and secondary small bowel bacterial overgrowth (diverticula, intestinal stenosis, ileocecal resection, immunological disorders, diabetes mellitus, chronic renal insufficiency, *etc.*)<sup>1,2,3,5</sup>.

This common disorder is clinically managed through varying approaches involving lifestyle changes, and medication to treat the predominant symptom, as no standard therapeutic strategy has been established. Currently available therapies provide symptomatic relief at best and have been shown to be only slightly more effective than placebos (35-45% in IBS). Further, some medicines can cause ischaemic colitis and severe cardiovascular or cerebrovascular events<sup>2,7,9</sup>. Patients often resort to alternative or complementary medicines, but randomized controlled studies with these types of therapy are non-existent or compromised by their low methodological quality.

### Probiotics in the treatment of IBS

Several lines of evidence link symptomatic expression of this syndrome with the intestinal microbiota: (i) IBS patients exhibit subtle differences in their luminal and mucosal-associated intestinal flora when compared with controls; (ii) new-onset IBS symptoms develop in about 30 per cent individuals following recovery from a self-limited episode of infectious gastroenteritis, (iii) small bowel bacterial overgrowth has been reported in a proportion of IBS patients, and (iv) antibiotics such as rifaximin relieve IBS symptoms in some individuals<sup>5,10</sup>.

Probiotics are the focus of considerable interest in relation to the treatment of IBS, though it is important to emphasize that different strains may not necessarily share the same activity. The definition of “probiotic” is: “Live microorganisms that confer a health benefit on the host when administered in adequate amounts”. Probiotics are microbially-derived factors that stimulate the growth of other microorganisms, and are intended to assist the body's naturally occurring gut microbiota. Research into probiotics has accelerated over the last ten years, but clear guidelines regarding the functional and safety aspects (as pharma-food or nutraceutical) are needed if new probiotic strains are to be introduced for human use<sup>6,9</sup>.

The expected actions of probiotics in the treatment of IBS include: (i) the counteraction of factors that alter balance of the normal intestinal microflora, and the production of bacteriocins to inhibit pathogens; (ii) to stop development of IBS following bacterial gastroenteritis; (iii) the correction of lactose intolerance; (iv) the relief of bloating, flatulence and distension; (v) the local modulation of the functions of the gut-associated lymphoid tissue and cytokine profiles; (vi) to maintain the capacity of deconjugate bile salts; and (vii) the suppression of the local inflammatory response by reducing tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) secretion, which rectifies the imbalance in intramucosal serotonin production, and the anomalous activation of intestinal motility and visceral hypersensitivity<sup>6,8,9,11</sup>.

There is controversy surrounding the subject and it would appear that bacteria contribute to at least some of the symptoms of IBS; however, the effects of probiotics on this gastrointestinal disorder are unclear. Some studies have reported an improvement in IBS symptoms with probiotics, whereas other have failed to detect any benefits. General recommendations from the American College of Gastroenterology (ACG) and expert consensus panels from both Europe and the USA have come to similar conclusions; there is a reasonable rationale for the efficacy of probiotics as a treatment for IBS<sup>2,3,4,6,9,11</sup>. The evidence of their benefits is not strong enough to warrant general recommendation of probiotics as therapy of IBS; however, their effect on single species of lactobacilli and Bifidobacteria is demonstrated, and certain combinations of probiotics appear to be of use. Probiotics may help patients to experience an overall improvement in their symptoms rather than a specific improvement in their bowel function<sup>2,9,11</sup>.

In addition, due to growing evidence of a role for mucosal microinflammation in the pathophysiology of IBS, there has been recent interest in the use of probiotics in this condition. The results of therapeutic trials to date are variable, which may be explained by the heterogeneity of the IBS subtypes included, variation in study design and the diversity of probiotic strains tested<sup>11,12,13,14</sup>.

### One probiotic or several species of probiotics?

It is well established that microorganisms vary considerably in their properties, and so it is inappropriate to combine the results of different trials<sup>2,14,15</sup>. Probiotics are available as single and multispecies formulations, but *Lactobacillus* and *Bifidobacterium* are the most studied microorganisms with respect to IBS. Systematic reviews and meta-analyses show a trend toward an improvement of symptoms with *Bifidobacterium infantis*, *B. brevis* and *B. animalis* (bloating and constipation), and with *Lactobacillus plantarum*, *L. casei*, *L. reuteri*, *L. acidophilus* and *L. rhamnosus* (abdominal pain, bloating, diarrhoea and constipation). The most common combinations are *Lactobacilli* and *Bifidobacteria*, administered in the form of yoghurt or nutraceuticals<sup>11,13,15</sup>. As probiotics are safe to consume (as well as having beneficial properties), these are ideal adjuncts to IBS therapy. In time, these are likely to assume an adjunctive therapeutic role in the treatment of IBS, but for the moment there are fundamental aspects that need to be resolved. Many of the studies published to date have been carried out in small and/or specific populations (children; women; young, not elderly people, *etc.*), or over short periods, so further research is needed.

It should be emphasized that probiotics are viewed as food and not drugs by the medical community. In addition to the need for a robust evidence-based approach to convince the clinical community of the health benefits of probiotics<sup>11,15</sup>, these agents will need to demonstrate their effectiveness within existing regulatory frameworks: (i) the traits that underlie probiotics' function will need to be understood; (ii) different strains must be compared at gene level *in vitro*; (iii) natural strains should be selected for specific gene products to improve probiotic function; (iv) optimal natural strains need to be determined; and (v) clinical documentation of the effect of probiotic strains must be provided. The clinical evidence needs to be appraised in a different manner to that concerning drugs and therapeutics in order to demonstrate that can enhance the proliferation of beneficial microbes and thus produce sustainable changes in the human microbiome<sup>13</sup>.

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