Probiotics and Irritable Bowel Syndrome

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While a rationale for the use of probiotics can be developed for a number of gastrointestinal symptoms and syndromes and an experimental basis for their use continues to emerge, irritable bowel syndrome (IBS) has become the focus of much interest in this regard. IBS has also attracted attention because of recent revelations with regard to the potential roles of the enteric flora and immune activation in the pathogenesis of IBS, thereby, leading to a re-awakening of interest in bacteriotherapy in this common and challenging disorder. Some recent, randomized, controlled studies attest to the efficacy of some probiotics in alleviating individual IBS symptoms while selected strains have a more global impact. Evidence for long-term efficacy is also beginning to emerge though more studies are needed in this regard. Several other issues complicate the interpretation of much of the literature in this area: lack of quality control, use of many different species and strains and, above all, significant deficiencies in trial methodology.

Key words: probiotics; intestinal flora; microbiota; irritable bowel syndrome; mucosal immune system

FLORA-HOST INTERACTIONS IN GASTROINTESTINAL HEALTH AND DISEASE

The delicate balance between the indigenous flora (microbiota) of the gut, the epithelium and the gut-associated lymphoid tissues (GALT) plays a central role in intestinal homeostasis, in health and, when disturbed, in the pathophysiology of several gastrointestinal and systemic illnesses (23). Interactions between the host and the flora lead to the induction of systemic immune tolerance and IgA secretion; the enteric flora also helps to sustain the function and integrity of the epithelial barrier and its blood supply, promotes the development of the gut associated lymphoid tissue (GALT) and is essential for the development of gut motility. It is from these such observations, as well as from clinical and experimental studies, that the concept of probiotics (“good” bacteria) emerged; the current interest in these organisms stems from their potential to advance our understanding of the bacterial flora and to serve as new therapeutic options in the management of gastrointestinal (23) and, even non-gastrointestinal (15), diseases.

WHAT IS A PROBIOTIC?

Probiotics, derived from the Greek and meaning “for life”, are defined as live organisms that, when ingested in adequate amounts, exert a health benefit to the host. It is readily acknowledged that studies in a number of animal models have demonstrated efficacy for killed bacteria, or even bacterial products or components (16, 33), in generating a number of anti-inflammatory and anti-infective effects, this strategy has not, as yet, been explored or validated in man. It is critical to emphasize that the current definition of a probiotic insists on the presence of “live organisms” and on the demonstration of a “health benefit”; preparations which do not provide evidence of sustained viability at levels at or above the required dose or whose health claims are to supported by relevant clinical trials in man do not deserve the application of the term probiotic.

Several commercially available products containing viable microorganisms with putative probiotic properties are promoted for their alleged benefits in IBS and related disorders yet few have been validated in controlled clinical trials and fewer still have been tested in head-to-head comparisons. The interpretation of available data on probiotics is further confounded by variability in strain selection, dose, delivery vehicle and evaluation of viability and efficacy. Quality assurance remains a major issue in this field.

The mechanism(s) of action of probiotics is likely to be multifactorial. The conventional and simplistic concept is one of simple displacement: exogenously administered probiotics displace pathogens or otherwise undesirable species or strains; the probiotics increase and multiply,
prosper and thrive where previously unfriendly or frankly hostile bugs plied their evil trade. This notion is almost certainly, and for most clinical scenarios, overly naïve and, quite frankly, implausible. Other more subtle and complex modes of action are more likely and include competitive metabolic interactions with pathogens, production of bacteriocins, inhibition of bacterial translocation, enhancement of mucosal barrier function, and, of particular relevance to any functional disorder where inflammation or immune activation are pertinent, by generating signals with the epithelium (bug-to-gut) and immune system (bug-gut-immune system) to modulate the inflammatory response (23).

WHY MIGHT A PROBIOTIC BE EFFECTIVE IN IBS?

Of all the functional gastrointestinal disorders, irritable bowel syndrome has enjoyed most attention in terms of the possible role of the flora in pathogenesis and of probiotics in therapy. The issue of bacteria and irritable bowel syndrome (IBS) is a complex one and contains several distinct and, even contradictory, strands (28).

Though known on an anecdotal basis to clinicians for decades, the occurrence of IBS following episodes of bacteriologically-confirmed gastroenteritis has now been documented in several studies (37); most recently, post-infectious IBS (PI-IBS) has been described following an outbreak of viral gastroenteritis (20). Interestingly, several studies have documented a link between the development of IBS following prior exposure to an infectious agent and persisting low-grade inflammation or evidence of immune activation. Post-infectious IBS may explain only a minority (perhaps 5–10%) of cases of IBS but does provide a clear link between exposure to an environmental agent, be it bacterial or viral, persistent, albeit subtle, mucosal inflammation and the development of IBS, in predisposed individuals.

Recent evidence suggests that it may well be possible to extend the concept of luminal triggering, by bacteria, and other microorganisms, of mucosal inflammation, to IBS, in general. While it is possible that asymptomatic, or forgotten, episodes of enteric infection could contribute on a larger scale to the pathogenesis of IBS, one could also invoke either qualitative or quantitative changes in the colonic or small intestinal flora, or, as has been proposed in inflammatory bowel disease, a dysfunctional interaction between elements of the flora and the host (31).

Support for an inflammatory basis for IBS comes from both the enteric and systemic compartments and the immune system in man. Direct evidence for a role for mucosal inflammation was first provided by Chadwick and colleagues who described microscopic inflammation, or evidence of immune activation, in all 77 IBS patients that they evaluated (8). Is this subtle inflammatory state really of any relevance to the basic pathogenesis of IBS? A direct linkage between immune activation and symptom development has been provided by a number of disparate sources. Firstly, Barbara and colleagues demonstrated, not only an increased prevalence of mast cell degranulation in the colon in IBS, but also a direct correlation between the proximity of mast cells to neuronal elements and pain severity (4). Secondly, further work from the Bologna group (4) as well as a study by Cenac and colleagues (7), have shown that mediators released by mucosal mast cells from IBS patients are capable of activating sensory nerves. The latter, for example, demonstrated that protease activity in colonic biopsies is increased in IBS patients, that these proteases signal to sensory nerves and generate visceral hypersensitivity through PAR2 and that trypsin and tryptase, products of mast cells, are the most likely contributors to this increased proteolytic activity (7). The concept that inflammation and immune activation can promote visceral hypersensitivity, a phenomenon regarded by many as pervasive among IBS subjects, is supported by a considerable amount of data from experimental animal models.

The cellular and humoral elements of the mucosal immune compartment have also been further studied in IBS and while results are, as yet, far from uniform, they do provide evidence for immune dysfunction in the colon in IBS (1, 13, 19). In general, such studies have demonstrated altered chemokine and/or cytokine production in the colonic mucosa; whether these abnormalities represent a response to the luminal flora or are a basic defect which, in turn, alters the host response to the indigenous flora, is as yet unclear.

Others have focused their attention on the systemic compartment and demonstrated either increased release of pro-inflammatory cytokines from peripheral blood mononuclear cells (18, 24) or elevated levels in serum (9).

While these disparate findings support the inflammatory hypothesis in IBS several gaps remain. Firstly, correlations between the mucosal, enteric and systemic immune compartments have not been examined. Secondly, while it is attractive to impugn the enteric flora as the initiator of these mucosal and systemic immune changes this has not been established and a role for a central “driver” of immune activation or even bidirectional effects, along the brain-gut axis, cannot be discounted. It is also distinctly possible that other factors such as allergic responses to dietary constituents could
also be involved. Finally, it is also possible that these changes are secondary to bowel dysfunction. These observations notwithstanding it is clear that, for the first time, the mucosa and its interactions with its environment, has become a major focus of research and therapeutic interest in IBS; it has been suggested, for example, that gender differences in mucosal responses to stress could explain the female predilection to IBS (3).

For some time, various studies have suggested the presence of qualitative changes in the colonic flora in IBS patients: a relative decrease in the population of bifidobacteria being the most consistent finding. It should be noted, however, that these findings have not always been reproduced and the methods employed have been subject to question. Specifically, many of these studies relied on culturing of fecal samples, an approach that will, not only provide a poor reflection of the distribution of bacteria within the colon as well as across its diameter, but will certainly fail to detect many metabolically active species that remain unculturable by current methods. Such species may comprise as much as 60% of the entire microbiota! The recent application of genomic technologies to this issue is already beginning to yield some interesting results and to confirm abnormalities in the flora in IBS (17); future studies combining this approach with metabolomics and metagenomics should provide a more comprehensive picture of the status of the colonic flora in IBS (35). More recently, the role of the gut flora in IBS has been taken a stage further with the suggestion that some IBS patients may harbor quantitative changes in the indigenous flora in the small intestine: small intestinal bacterial overgrowth (SIBO).

These results have been the target of much criticism, on several grounds (30). Firstly, IBS symptoms are non-specific and may be mimicked by SIBO, regardless of etiology; patient selection is, therefore, an issue. Secondly, the hydrogen breath test, which has been most widely used in the diagnosis of SIBO in this context, is subject to considerable error, especially in relation to altered small bowel transit, and, thirdly, studies of the impact of eradication have, for the most part, been short-lived. Finally, others have failed to confirm these findings (5, 27). While arguments will continue regarding the accuracy, relevance and appropriateness of various diagnostic tests in the detection of overgrowth in the context of IBS, it appeals to this author that diagnostic shortcomings, patient selection and symptomatic overlap have contributed greatly to the overgrowth iceberg in IBS whereas in reality it is, for the most part, no more than a mirage. In contrast, evidence for a role for the colonic flora in IBS continues to accumulate (26).

**ARE PROBIOTICS EFFECTIVE IN IBS?**

Given their safety profile, probiotics, if effective would, at first sight, appear to be an attractive option as potential manipulators of the gut flora in IBS. Are probiotics effective in IBS? Several factors complicate the interpretation of clinical trials of probiotic preparations in IBS: many studies have been underpowered and some earlier studies were even uncontrolled and not blinded. Furthermore, results between studies are difficult to compare because of differences in study design, use of non-validated and differing endpoints as well as variations in probiotic dose and strain. Nevertheless, there has been some, but by no means consistent, evidence of symptom improvement (21, 22, 29, 39). In reviewing more recent studies some patterns emerge [individual studies detailed in refs (29, 32)]; some probiotics, or probiotic cocktails, seem to exert their beneficial effects on bloating and flatulence alone, others relieve pain or discomfort (Lactobacillus acidophilus 2012,2013), others (Bifidobacterium animalis) are effective primarily among those with constipation and one strain, Bifidobacterium infantis 35624, has provided global symptom relief. In the first of our studies with the latter organism, we compared, for the first time, the effects of two probiotic strains on symptoms in seventy-five patients with irritable bowel syndrome. We demonstrated superiority for Bifidobacterium infantis 35624 over both a Lactobacillus and placebo for each of the cardinal symptoms of the irritable bowel syndrome (abdominal pain/discomfort, distension/bloating and difficult defecation), as well as for a composite score (24). More recently, we have replicated these results in a much larger, dose-ranging, primary care-based study involving 360 IBS subjects, where B. infantis, in an encapsulated formulation and in a dose of 10^8, was associated with significant improvements in the cardinal symptoms of IBS and in the subjects global assessment (SGA) of all symptoms; at study end, over 60% of subjects randomized to the Bifidobacterium felt better than before therapy, a therapeutic gain of over 20% over placebo (38). In both studies, a positive impact on IBS symptomatology occurred independent of any effect on stool frequency; indicating that observed effects were not attributable to either a laxative or an anti-diarrheal effect.

To date, most studies have been short-term, the duration of therapy typically lasting from 4 to 12 weeks (10, 11, 29, 32, 36). Given the chronic and relapsing natures of IBS and the failure of externally administered probiotics to persist in the human intestine for more than a few weeks beyond the cessation of administration,
longer-term studies are sorely needed (21, 22, 39) and more studies are required in certain populations such as males and children (14).

How do probiotics work in IBS? Are these symptomatic improvements merely a reflection of the displacement of more gas-producing, bile salt-deconjugating species or is there a more fundamental effect? That the immune modulating properties of strains such as *Bifidobacterium infantis*, may be relevant to IBS in man is suggested by our demonstration of the normalization of a baseline pro-inflammatory state (24). Animal models provide further insights demonstrating the ability of a variety of probiotic strains to reduce visceral hypersensitivity, spinal afferent traffic and the stress response (6); one species, *L. Acidophilus* has even been shown to induce the expression of μ-opioid and cannabinoid receptors in human intestinal epithelial cells (34). These and other (12) studies also raise the tantalizing possibility that bacterial products, including small molecules, may mediate the beneficial effects of probiotics in IBS, thereby, opening the way to new therapeutic avenues. Indeed, the mechanisms whereby mucosal inflammation and/or irritation can generate the intestinal and brain-gut axis phenomena that are now recognized as hallmarks of IBS are now well characterized (2, 25, 31, 40).

Probiotics have clearly emerged as potential therapies for IBS; for some selected strains evidence of benefit continues to emerge, for others impact is limited to the alleviation of individual symptoms, for all, more studies of long term impact are needed (21, 22, 29, 39).

CONCLUSION

Probiotics offer considerable potential in the treatment of IBS and a considerable body of evidence now exists to support their use in this disorder. While good quality clinical trials are, belatedly, now being performed in IBS with probiotics, evidence to date indicates that, here, as elsewhere, effects of probiotics are highly strain specific and endure only for as long as the organism is administered.

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REFERENCES


The d-alanine content of lipoteichoic acid is crucial for Lactobacillus plantarum-mediated protection from visceral pain perception in a rat colorectal distension model. Neurogastroenterol Motil 20: 843–850.


