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Commentary

Probiotics, prebiotics & synbiotics in small intestinal bacterial overgrowth: Opening up a new therapeutic horizon!

The human intestinal microbiota is a complex community comprised a myriad of bacterial species. Disruption of homeostasis in the small intestinal microbial community can lead to significant clinical consequences, most notably small intestinal bacterial overgrowth (SIBO); a situation where bacteria are present, not only in greater numbers, but also in a distribution more commonly associated with the colon. Classically, SIBO was recognized as an important cause of maldigestion and malabsorption; more recently, SIBO has been implicated in a variety of clinical scenarios ranging from non-alcoholic fatty liver disease to unexplained diarrhoea and the irritable bowel syndrome (IBS). Traditionally, SIBO was clinically defined on the basis of quantitative cultures of jejunal aspirates with the presence of more than 10^5 colony forming unit (cfu)/ml of proximal jejunal aspirate being regarded as diagnostic[1]. This approach, due to its invasive nature and resultant costs has fallen into abeyance and, in clinical practice, has been replaced either by cultures of duodenal aspirates obtained via an endoscope or, more commonly, by hydrogen breath tests (HBTs) performed using substrates such as lactulose or glucose. Despite their ease of performance and acceptability to patients, HBTs have been criticized on the basis of considerable variability in sensitivity and specificity, as well as their inability to detect bacterial overgrowth in the more distant reaches of the small intestine and their failure to detect overgrowth by non-H_2-producing bacteria[2,3]. Currently, there is a lack of consensus on how to define an abnormal breath test with no agreement on either the optimal duration of sampling or the best cut-off level to define a positive test[3]. The lack of an accepted "gold standard" for the clinical definition of SIBO, especially, in a non-classical clinical scenario, represents a major challenge for the clinician.

In managing the patient with SIBO attention should first be directed towards the detection and elimination, where feasible, of any underlying cause and, secondly, to the correction of any resultant nutritional deficiencies. In many situations, unfortunately, an underlying cause cannot either be found or, if present, reversed; for many patients, therefore, therapy focuses on the suppression of SIBO *per se*. Traditionally, the latter approach has been based on the use of various, typically broad-spectrum, antibiotic regimens with norfloxacin, tetracycline, ciprofloxacin, metronidazole and doxycycline being popular choices[3]. It must be conceded that antibiotic strategies in SIBO, be it a once-off course, a rotating schedule or continuous therapy, owe more to empiricism than to an evidence base as there have been a few high quality trials of any regimen in this condition. While more recent studies involving the poorly absorbed antibiotic rifaximin have provided more guidance on optimal dosage and treatment duration[2,3], empirical trials of broad-spectrum antibiotics remain the norm in the treatment of SIBO. Not surprisingly, due to the lack of an adequate evidence base, the choice of antibiotic(s), their dose and schedule of administration, as well as the duration of therapy, all lack standardization. Furthermore, long-term treatment with most of the aforementioned broad-spectrum antibiotics may be complicated by poor patient tolerance (and, therefore, compliance issues), disruption of the commensal microbiota, antibiotic-associated diarrhoea (including the risk of *Clostridium difficile*-associated disease), the development of antibiotic resistance, and the potential for rebound colonization once the antibiotic is stopped[1,4].

For all of these reasons and given their ability to repopulate the microbiota, it should come as no surprise that there has been considerable recent interest in the use of probiotics and prebiotics in SIBO. Probiotics

are living organisms, including lactic acid bacteria and nonpathogenic yeasts, that provide health benefits to the host[4]. Based on a considerable volume of laboratory studies, a variety of mechanisms whereby such benefits may be conferred have been identified: competition with pathogens, production of bacteriocins, inhibition of bacterial translocation, enhancement of mucosal barrier function, downregulation of inflammatory responses, metabolic effects, modulation of gut motor and sensory responses and signaling between luminal bacteria, the intestinal epithelium, and the immune system[1,4]. Though high-quality trials of probiotics in any clinical indication remain limited, benefits with specific strains have been described in a number of common disorders such as inflammatory bowel disease, irritable bowel syndrome and antibiotic-associated diarrhoea. Studies on probiotics in SIBO have, however, been limited; yet some encouragement has been provided. For example, Gabrielli and colleagues[5] provided some promising data from a study on *Bacillus clausii* which produced a rate of normalization of hydrogen breath tests that was comparable to antibiotics. In another, albeit small study (N=12), both *Lactobacillus casei* and *L. acidophilus* strains cerela proved effective in treating chronic diarrhoea related to bacterial overgrowth[6]; others showed efficacy in terms of symptomatic benefit among patients with SIBO and functional intestinal distention[7]. These and other studies are, however, difficult to compare due to differences in study populations, probiotic species and clinical outcomes and the interpretation of all studies in the area is hampered by small numbers and shortcomings in study design and interpretation.

The study by Khalighi and colleagues[8] in this issue represents a valuable addition to the literature and also serves to shed some new light on the role of probiotics and prebiotics in the treatment of SIBO. In this study, patients with symptoms suggestive of SIBO were tested for its presence using a lactulose HBT. Thirty patients with a positive HBT were identified, all treated for three weeks with an oral broad-spectrum antibiotic. At the end of this treatment period they were randomized in what was described as a double-blinded fashion into two groups, one to receive a synbiotic preparation (Lactol; a proprietary formulation that combined the probiotic *Bacillus coagulans* with prebiotics in the form of fructo-oligosaccharides) for 15 days of each month followed by minocycline for the remaining 15 days and the other to receive minocycline for the first 15 days of each month with no treatment for the remaining 15 days; each group was treated and followed for six months. At the end of the six months HBT and symptom assessments were repeated and compared to baseline. Those in the probiotic group were noted to have significant reductions in pain, bloating, belching and diarrhoea in comparison to the control group. Indeed, all of those in the probiotic group reported complete resolution of abdominal pain in comparison to only 7 of 15 in the antibiotic only group. Other symptoms assessed were nausea, vomiting and constipation which were similarly improved in both groups. Lastly, post-treatment HBT was noted to be negative in 93.3 per cent of those in the probiotic group in comparison to 66.7 per cent in the antibiotic only group; a difference that, in contrast to the symptom responses, was not significantly different. One could speculate that this may have been a Type II error.

There are several novel aspects to this study that render it of interest: use of a synbiotic, rotation of the synbiotic with the antibiotic and a long duration of follow up. Empirically, in an effort to minimize antibiotic exposure and counteract the impact of broad spectrum antibiotics on the commensal microbiome, clinicians have followed a course of antibiotics with a probiotic; this study now provides a sound basis for this approach. It is also apparent that the inclusion of the synbiotic augmented the clinical impact of the antibiotic and may have increased the likelihood of eradication of SIBO. Furthermore, and in contrast to many prior studies, that by Khalighi and colleagues[8] involved well-matched study groups and was prospective and randomized. The double-blinding of the groups could be questioned, however, as only one of the two groups received any form of treatment in the second half of each month. Other limitations include a relatively small study population of only 30 patients, the apparent heterogeneity of the subjects included which presents somewhat of a challenge in the application of this study to other populations and a reliance on the lactulose breath hydrogen test to diagnose SIBO. Given the high false-positive rate associated with this test[2], it is possible that some of the patients did not actually have SIBO at the initiation of the study. The lack of detailed information on the antibiotics used in the "three weeks of aggressive therapy with broad-spectrum antibiotics" is also problematic as it is theoretically possible that the final results of the various maintenance therapies reflected the efficacy of the initial three-week course of antibiotics and not the subsequent six months of either minocycline alone or in combination with the

synbiotic; a breath test at the end of the initial three-week period would have helped to address this issue, as would information on the exact antibiotic regimens used.

Despite, these shortcomings, the study by Khalighi *et al*[8] has demonstrated, not only improvement in, but resolution of, clinically relevant gastrointestinal symptoms of SIBO with a regimen that incorporated a synbiotic product. This, for the first time, bolsters the empirical approach of following antibiotic therapy with a probiotic, prebiotic or synbiotic in the treatment of patients with, or suspected to have, SIBO[9]. Though this was a pilot study but as such it does point the way towards larger and more definitive studies, which could include additional objective markers of the impact of SIBO. Biomarkers of inflammation, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) or faecal calprotectin, of gut barrier function such as measures of permeability, or a direct evaluation of the impact of the various therapies on the gut microbiota would be of interest and could complement the rather subjective data derived from questionnaires which may also be subject to recall bias. Furthermore, it would be interesting and clinically important to define the relative risk, between the various treatment strategies, for rebound colonization or symptom recurrence at the end of the treatment period.

Given the various potential adverse effects associated with the use of antibiotics and prolonged courses of antibiotics, in particular, the definition of a therapeutic role (whether in initial therapy, maintenance of eradication/suppression of SIBO, or in the prevention of undesired effects of antibiotics) for probiotics and prebiotics in SIBO would represent a major step forward.

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