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PROBIOTICS: A NEW AVENUE IN IBS MANAGEMENT, LOOKING BEYOND MOTILITY

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ABSTRACT

Background: Bacterial dysbiosis is considered to be an important contributory factor to the development of IBS.

Methods: A survey was conducted with 91 physicians across India to determine the usage profile of probiotics in IBS patients and to assess their awareness about the importance of maintaining the cold chain for ensuring the viability of the probiotic bacteria and the benefits of indigenous strains of bacteria as probiotics.

Results: Antispasmodics, anxiolytics and laxatives/antidiarrheals were the first line agents used by 66%, 39% and 30% treating physicians respectively. Probiotics are chosen as first line of therapy by almost 60% of the physicians. 97% of physicians opined that probiotics help in restoring the GI flora balance in IBS patients. Probiotics improve stool frequency, consistency, bloating and flatulence in IBS patients as opined by 65%, 61%, 58% physicians respectively. 94% physicians were aware that probiotics are heat labile and have to be refrigerated. 69% physicians confirmed that they are aware about indigenous strains of probiotics being better than foreign strains.

Conclusions: The appropriate use of probiotics offers an opportunity for “The Gut Makeover” in order to restore and optimise the health and diversity of the intestinal microbiome. Probiotics preparations containing lactobacillus and Bifidobacterium are heat labile thus needs to be refrigerated at appropriate temperature. Indigenous bacteria are better adapted due to strong local conditioning effect and have competitor advantage to stay longer with extended transit time in gut, and thereby exerting the prolonged beneficial effects.

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INTRODUCTION

Irritable bowel syndrome (IBS) is characterized by abdominal pain and alterations in bowel habits and is regarded as one of the most common functional gastroenterological diseases. Prevalence of IBS worldwide is reported to range from 10-20%, the prevalence in India is almost 8%.¹ Although the exact pathophysiology underlying IBS is still not known, chronic low-grade mucosal inflammation, alterations in gut epithelial and immune function, and visceral hypersensitivity caused by alterations in intestinal microbiota have been demonstrated to be associated with IBS. The current management of IBS revolves around antispasmodics, laxatives/antidiarrheals and anxiolytics. However, IBS patients often have variant response to these therapies.²

Bacterial dysbiosis is considered to be an important contributory factor to the development of IBS. A bidirectional relationship between the brain function and gut flora has been observed in IBS patients through communication pathways including neural, metabolic (bacterial and host), immunologic, or endocrine pathways.^{3,4,5} Abnormalities in colonic microflora

have recently been suggested in such patients, as has abnormal small intestine bacterial overgrowth (SIBO), or in particular a significant reduction in the amount of intraluminal *Bifidobacteria* or *Lactobacilli*, with consequences like the production of colonic gas, and motility or sensitivity disturbances of the intestinal tract.⁶

Probiotics, defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host”, have the potential to influence the intestinal microbiota. Probiotics may affect intestinal barrier function and exert anti-inflammatory actions. Use of probiotics is a commonly adopted practice in the management regimens of IBS patients.⁷

The objective of this survey was to determine the usage profile of probiotics in IBS patients as per Indian physicians. This survey also intended to assess the awareness of physicians about the importance of maintaining the cold chain for ensuring the viability of the probiotic bacteria and secondly to assess their views regarding the benefits of indigenous strains of bacteria for the management IBS.

MATERIAL AND METHODS

This survey was designed to chronicle the clinical experience of 91 physicians (gastroenterologists, consulting physicians predominantly treating gastroenterological disorders) in their patients with IBS. Equitable inclusion of physicians across India to satisfy a pan-Indian representation of the survey sample was adopted in the survey plan. A *Data Report Form* (DRF) comprising of ten questions related to IBS management and physician perceptions was answered by the physicians who treat patients of IBS with regimens including probiotics. Each physician evaluated at least 50 patients when responding to the survey. The key elements of the questionnaire were as follows: First line of therapy for the management of IBS, rationale for use of probiotics, assessment of symptomatic benefit with probiotics, recommended dose and duration of probiotic therapy, awareness regarding importance of cold chain and indigenous strains of probiotics. The use of probiotics in any other indication apart from IBS was also evaluated.

An approval from the Ethics Committee was not required as this survey involved only the physicians' opinion regarding the use of probiotics in IBS patients in their clinical practice and did not involve the direct participation of any patient.

Statistical analysis

Data entry was done in Microsoft Excel 2013 (version Office 365) in a survey (questionnaire) specific excel spreadsheet validated for the survey questionnaire. Validation was done using built-in validation tools in MS excel to minimize data entry errors.

Data for responses to multiple questions were expressed as numbers with percentages (%) for each response. Percentage values were calculated based on the total number of responders for each question independently

RESULTS

The survey questionnaire was sent to 91 participating physicians across India. The results were represented as a percentage calculated based on the response from the survey population of physicians.

In the present survey, antispasmodics, anxiolytics and laxatives/antidiarrheals were the first line agents used by 66%, 39% and 30% treating physicians respectively. Probiotics are chosen as first line of therapy by almost 60% of the physicians. It is evident that, most of the physicians use combination therapy for holistic management of IBS (Figure 1).



Figure 1 First line agents in IBS management

About 97% of physicians opined that probiotics help in restoring the GI flora balance in IBS patients. The other

possible mechanisms of action for probiotics in IBS may include reduction of inflammation (26%), regulation of gastrointestinal motility (19%) and reduction of visceral hypersensitivity (16%).

Probiotics are found to be most useful in patients of IBS-D as opined by 41% physicians. But 33% physicians prefer to use probiotics in all types of IBS, whereas 18% physicians use probiotics in mixed type of IBS.

Most of the physicians were of the opinion that probiotics offer benefit in IBS in multiple ways. They have shown to improve stool frequency, consistency, bloating and flatulence in IBS patients as opined by 65%, 61%, 58% physicians respectively.

About 75% physicians prescribed probiotics twice a day while 24% physicians prefer to use probiotics once a day. About 50% of the physicians use probiotics for an average duration of 2-4 weeks in IBS management while 33% physicians use the same for 4-8 weeks.

Around 94% physicians were aware that probiotics are heat labile and have to be refrigerated, but were not sure whether the cold chain was meticulously followed at all tiers of the delivery chain. About 5% physicians were unaware about temperature sensitivity of probiotics, whereas the rest (1%) were not concerned about the same (Figure 2).

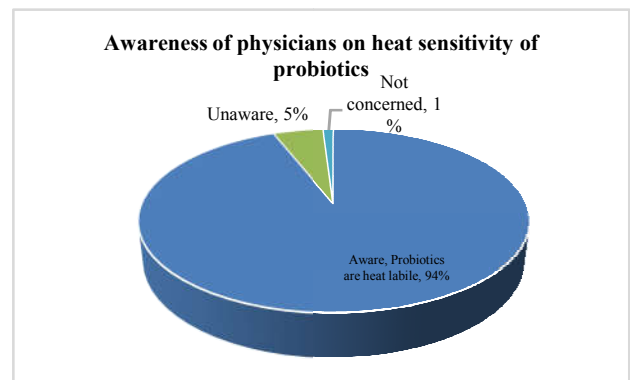


Figure 2 Awareness of Physicians on Heat Sensitivity of Probiotics

Around 69% physicians confirmed that they are aware about indigenous strains of probiotics being better than foreign strains, while 25% were not aware about this concept and 6% were not concerned about the origin of probiotic strains. (Figure 3).

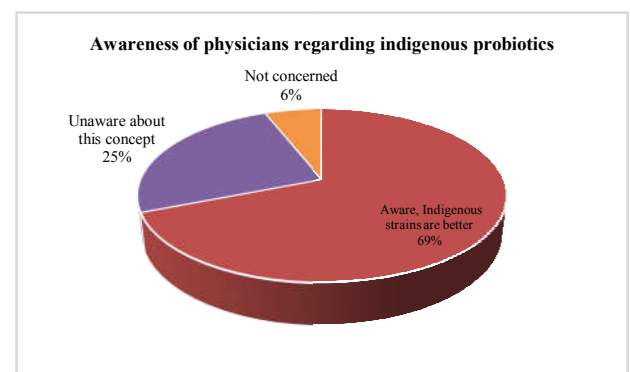


Figure 3 Awareness of physicians regarding indigenous probiotics

Probiotics are used in variety of clinical conditions apart from IBS. The findings from the current survey indicate that probiotics play major role in management of antibiotic associated diarrhoea, inflammatory bowel disease, acute

infectious diarrhoea, small intestinal bacterial overgrowth and hepatic encephalopathy (Figure 4).

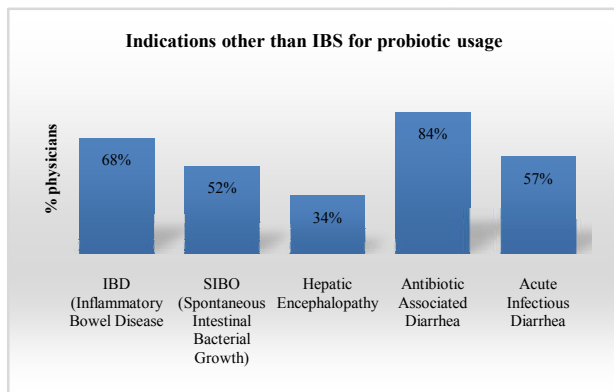


Figure 4 Indications Other Than IBS Where Probiotics Are Commonly Used

DISCUSSION

The intestinal microbiota is a complex ecosystem of microbes inhabiting the intestine. Bacterial dysbiosis is involved in the pathogenesis of IBS through several mechanisms including activation of mucosal immunity, release of serotonin (5-HT) and production of excessive amounts of gas by fermenting poorly absorbable carbohydrates.^{2,4} 97% of physicians opined that probiotics help in restoring the GI flora balance in IBS patients. The other possible mechanisms of action of probiotics accepted by the physicians for justifying probiotics use in IBS include reduction of inflammation, regulation of gastrointestinal motility and reduction of visceral hypersensitivity. The findings of the present study further substantiate data from published literature regarding multimodal action of probiotics in IBS management.⁶

Adequate symptom relief with probiotic treatment has been reported in various placebo controlled trials. Yoon H *et al.* demonstrated that 74.4% patients treated with probiotics had relief of pain, constipation, diarrhoea, and bloating/gas.⁸ In another study it was found that treatment with probiotics offered persistent relief from flatulence.⁹ Two large meta analyses by HuY *et al.* (1700 patients) and Didari T *et al.* (1793 patients) have confirmed the benefits of probiotics in improving the overall symptoms, alleviating abdominal pain/discomfort, relieving abdominal distension and defecation discomfort in patients with IBS.^{10,11} In the current survey, one interesting fact unfurled was the usage of probiotics across the spectrum of IBS patients (IBS-D, IBS-C, mixed type IBS). The key disturbing symptoms of IBS namely bloating and flatulence, altered stool frequency and consistency and abdominal discomfort were reported to be relieved by probiotics in the current survey. These findings of the survey corroborate the findings reported in literature by other researchers of IBS.¹¹

There is a wide variation in the duration of probiotic therapy offered in IBS patients as reported in literature. The meta-analysis by Didari *et al.* has shown the duration of probiotic therapy from 3-21 weeks is effective. In the current survey, 50% physicians use probiotics for 2-4 weeks whereas 33% physicians who use the same for 4-8 weeks. The most common frequency of administration of probiotics adopted by 75% of physicians was twice a day. This is similar to the probiotics regimens reported in clinical trials of IBS by other researchers.^{12,13} A duration of treatment of 4 weeks with probiotics follows the Rome III guidelines.¹⁴ There is

widespread acceptance of the use of probiotics in other disorders such as inflammatory bowel disease, acute infectious diarrhoea, antibiotic-associated diarrhoea, *Clostridium difficile*-associated diarrhoea, and *Helicobacter pylori* infection eradication.¹⁵ Probiotic administration has been reported to improve clinical symptoms in patients with mild to moderately active ulcerative colitis.¹⁶ The mucosal levels of inflammatory cytokines such as IL-8, IL-1 β were found to be lower among patients who received the probiotics.¹⁷ Probiotics restored the mucosal barrier to *E. coli* in patients with pouchitis.¹⁸ The use of probiotics in hepatic encephalopathy has been ratified by the recent Cochrane review. Probiotics improve recovery and may lead to improvements in the plasma ammonia concentrations, may help reduce the development of overt hepatic encephalopathy and may improve the quality of life.¹⁹ Systematic reviews have provided evidence for the efficacy of probiotics in preventing *Clostridium difficile infection (CDI)*. Administration of probiotics closer to the first dose of antibiotic reduces the risk of CDI by >50% in hospitalized adults.²⁰ That probiotics can offer health benefits seems to be well accepted by Indian physicians too. This acceptance is ratified by the prescription of probiotics in other indications such as antibiotic associated diarrhoea, acute infectious diarrhoea, IBD and hepatic encephalopathy. This indicates that the gut microbiome is now being accorded due respect in the pathogenesis of diverse gastrointestinal disorders.

In the current survey, the concept of greater benefits of using indigenous strains of probiotics was accepted by 69% of the physicians. The data on probiotics available today are chiefly related to probiotics obtained from the Western population. Currently researchers have proposed that using indigenous local probiotics would be likely to offer better outcomes as viability and concentrations of probiotics can vary.²¹ It is observed that, gut flora of a specific community is well adapted to the environment of their intestine. Foreign probiotic bacteria face tough competition from these microbes as they have originated from the gut of a population having different food habits. Indigenous bacteria, however, can become part of the Indian gut very easily since they have been isolated from a similar gut environment and are well adapted to survive therein. Indigenous bacteria are better adapted due to strong local conditioning effect and have competitor advantage to stay longer with extended transit time in gut, and thereby exerting the prolonged beneficial effects.²² The proponents of use of indigenous strains of probiotics argue in favour of local strains based on several emerging facts. First, there is a significant difference in the gut flora of Western and Indian / Asian population. A 25 % loss in bacterial diversity is seen in the gut flora of the Western population due to the use of antibiotics. The local probiotic strains may differ from the Western strains and may not offer similar or expected benefits.²¹ Secondly specific nutritional health requirements vary from region to region. The use of probiotics which promote the breakdown of non nutritive factors such as phytic acid which inhibit the absorption of iron would be useful in developing countries such as India and in elderly.²¹ Thirdly, Asian food is rich in herbs and spices. Locally sourced probiotics would be more resistant to herbs and spices available locally and would have the advantages of viability, stability and functionality after consumption.²¹ Fourth, there may be differences in immune response to the indigenous and Western bacteria and this will further determine their survival

and subsequent beneficial effect. Understanding the role of indigenous intestinal bacteria and their ecological interactions would be critical to improve outcomes with the use of probiotics²³

Finally, the proper storage of probiotics and maintenance of the cold chain are critical to ensure viability of the probiotics. Probiotic strains lose viability over time at room temperature. Over 1/3rd of commercial probiotic products tested contained less than 1% of the expected number of viable organisms.²⁴ While a number of factors can adversely affect probiotic viability, lack of refrigeration often plays a major role in the premature destruction of organisms. A high degree of awareness (94% physicians) was observed amongst the survey physicians regarding the need to maintain the cold chain in order to preserve the viability of the probiotic microorganisms. Globally, it has been observed that a major limitation to producing efficacious probiotic formulations is the tendency of the probiotics microorganisms to lose their viability during storage and gastrointestinal transit.^{25,26,27,28} Hence a robust protective technique is required to ensure the viability of probiotics and their ability to withstand temperature changes.

CONCLUSION

Intestinal microbiota can play a substantial role in the pathogenesis of IBS. A multi factorial role has been proposed for the altered intestinal microbiome in the pathogenesis of IBS. The altered metabolic activity of the intestinal microbiome caused by stress and psychological disturbances activates mucosal immunity and inflammation, increases epithelial permeability, and reduces barrier function. This activates the sensory-motor dysfunction responsible for the diverse symptoms of IBS. Our current knowledge of the link between the alterations in the indigenous bacteria microbiota and IBS may enable us to treat IBS with probiotics based on a sound rationale. The widespread acceptance by Indian physicians of the benefits of probiotics in Indian patients with IBS is based on the positive outcomes in terms of the relief of symptoms of IBS. The appropriate use of probiotics offers an opportunity for “The Gut Makeover” in order to restore and optimise the health and diversity of the intestinal microbiome.

Declaration

Conflict of interest: This survey and scientific publication was conceptualized, edited, designed and funded by Abbott India Ltd. Please consult full prescribing information before prescribing any of these products mentioned in this publication.

Ethical approval: Not required

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