Crowd-Sourced Clinical Review

Clearing the air: A crowd-sourced clinical review on the controversies and evidence regarding probiotics for the treatment of the irritable bowel syndrome.

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Keywords: irritable bowel syndrome, probiotics, microbiome

Financial Disclosures & Conflicts of Interest:

DSS has collaborated and received unrestricted educational grants from the Alliance for Education on Probiotics, Nestle Nutrition, BioK+ Intl, P&G Healthcare, Astra-Zeneca, and Boehringer Ingelheim.

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Probiotics are defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.”¹ Patients and providers alike have become increasingly interested in probiotics, contributing to a global industry estimated to reach \$69.3 billion USD by 2023.¹ Nearly 100% of gastroenterologists believe probiotics to be useful in treating gastrointestinal diseases.²

While there is great interest regarding the use of probiotics, there is perhaps an even greater lack of education around the proper selection and usage of probiotics. This even includes health care professionals; as succinctly stated in *Gastroenterology*, “...health care providers do not have the background to critically evaluate the microbiome literature and are ill-equipped to provide competent guidance to their patients.”⁴

There currently exist numerous challenges and limitations surrounding the rapidly expanding probiotic market. In the United States, the Food and Drug Administration (FDA) does not regulate probiotics; this has allowed a lack of oversight, regulation, and accountability, creating an atmosphere of confusion and misinformation. Companies claim myriad health benefits to which they are not held accountable, and there is no guarantee of the quality or composition of a given product. Patients may spend large sums of money on ineffective, counterproductive, or even harmful products. In our experience, up to 95% of patients are taking probiotics inappropriately.

Research on probiotics is limited by the small numbers of study participants, heterogeneity among methodologies (e.g., doses, duration) and study endpoints, and bias such that systematic reviews and meta-analyses are challenging to perform and interpret. Indeed, meta-analyses usually include studies that have evaluated multiple different probiotic strains; given the fact that different strains exert different effects, including strains which may have different, no, or even harmful effect can dilute a potential signal.

Perhaps the most important tenet of probiotic science is that each probiotic strain is unique. A given probiotic comprises a particular strain (or combination of strains), such as *Bifidobacterium longum* 35624 (denoting genus, species, and strain). Different strains have different effects. For example, a recent study found that *Bacillus coagulans* SNZ 1969 improved intestinal motility and increased the frequency of bowel movements in patients with intermittent constipation.⁵ Presumably this strain would be ineffective or even harmful in those with diarrhea. As such, it is crucial that specific strains of probiotic be recommended for specific indications.

There are many other considerations regarding the selection of probiotics. The number of colony forming units (CFU) determines in part the survivability of the organisms within

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the GI tract. In general, 10-100 million CFU/g are required to provide a minimum of the 1-10 million CFU/g needed for therapeutic effect in the colon.⁶ Different strains, based on variables such as susceptibility to stomach acid and bile salts, have varying requirements; for example, *L. reuteri* DSM 17938 requires 0.5 billion CFU to be therapeutic, while *L. plantarum* 299v requires 10 billion CFU. Certain strains require refrigeration, while others are stable at room temperature, and still others are vulnerable to temperature, light, or oxygen. The timing of probiotic ingestion in relation to meals and the composition of the meal may also impact survivability.⁷ Finally, while it is commonly believed that probiotics colonize the gut, this is rarely the case; instead, the effects of probiotics are more likely due to interactions with the endogenous microbiota, and these effects cease upon stopping the probiotic.⁸

Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction characterized by abdominal pain and altered bowel habits. Alterations in the gut microbiota have been documented in IBS, so there is tremendous interest in therapies which target the microbiome to treat IBS. Indeed, IBS is the most common condition for which physicians recommend probiotics, with one survey finding 98% of physicians recommending them.³ However, there is significant variation in prescribing practices (further evidenced by our Twitter survey seen in **Figure 1**), with some providers recommending any probiotic, others recommending specific strains or brands, and still others recommending against altogether.

#TuesdayNightIBS
@TuesdayNightIBS

...

A 29 yo woman w mild-moderate [#IBS](#)-M treated with dietary modification is having inadequate relief of her abdominal pain, bloating, and altered bowel habits which alternate between diarrhea and constipation. She asks about [#probiotics](#). What do you recommend?

[#TuesdayNightIBS](#)

102 votes · Final results

10:22 AM · May 4, 2021 · Twitter Web App

Figure 1

A 2018 systematic review found that combination probiotics as a class may benefit global IBS symptoms, abdominal pain, persistence of symptoms, and the specific symptoms of bloating and flatulence. For combination probiotics, the number needed to treat (NNT) was 7. *Lactobacillus plantarum* 299v (DSM 9843) had an NNT of 3.⁹ The most recent ACG guidelines for IBS recommend against probiotics citing small and inconsistent studies, heterogeneity and bias, and the challenge of interpreting meta-analyses.¹⁰ The British IBS guidelines, on the other hand, recommend as a first-line therapy an up to 12 week trial of probiotics, though say that there is not enough data to recommend specific strains. However, their own review found a benefit for combination probiotics, and single strain probiotics of the genus *Lactobacillus*, *Bifidobacterium*, and *Escherichia*. An AGA technical review on probiotics found low certainty of evidence for probiotics in IBS given that much of the research comes from single randomized control trials.¹¹

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Given the numerous challenges involved in probiotic research and the lack of medical education dedicated to interpreting the literature, there is great need for educational resources to assist clinicians and patients. One such resource is the Clinical Guide to Probiotic Products Available in the US (and equivalent Canadian guide) developed by the Alliance for Education on Probiotics (AEProbio), a grant-funded initiative which supports an annual critical review and publication of the summary of the research regarding safety and efficacy of probiotic products.¹² **Table 1** features a list of probiotic strains and combinations of strains with evidence of benefit in IBS, compiled from the four aforementioned reviews.

AP&T systematic review	<p>Effect on persistence of symptoms</p> <ul style="list-style-type: none">• Combination probiotics• <i>Lactobacillus plantarum</i> DSM 9843• <i>Escherichia</i>, specifically <i>Escherichia coli</i> DSM17252• <i>Streptococcus faecium</i> <p>Global IBS or abdominal pain scores</p> <ul style="list-style-type: none">• Combination probiotics <p>Individual symptom scores</p> <ul style="list-style-type: none">• Combination probiotics for bloating and flatulence
AGA technical review	<p>Improvement of global IBS symptoms:</p> <ul style="list-style-type: none">• <i>L. plantarum</i> 299v• <i>Saccharomyces cerevisiae</i> CNCM I-3856• <i>E. coli</i> DSM 17252• combination <i>S. salivarius</i> ssp. <i>thermophilus</i>, <i>L. delbrueckii</i> ssp. <i>bulgaricus</i>, <i>L. acidophilus</i>, and <i>B. longum</i> ssp. <i>longum</i>• 7-strain combination <i>L. acidophilus</i> KCTC 11906BP, <i>L. plantarum</i> KCTC 11876BP, <i>L. rhamnosus</i> KCTC 11868BP, <i>B. breve</i> KCTC 11858BP, <i>B. animalis</i> ssp. <i>lactis</i> KCTC 11903BP, <i>B. longum</i> ssp. <i>longum</i> KCTC 11860BP, and <i>S. salivarius</i> ssp. <i>thermophilus</i> KCTC 11870BP• <i>B. bifidum</i> MIMBb75• 3-strain combination of <i>L. plantarum</i> CECT7484, <i>L. plantarum</i> CECT7485, and <i>Pediococcus acidilactici</i> CECT7483• 14-strain combination of <i>Bacillus subtilis</i> PXN 21, <i>B. bifidum</i> PXN 23, <i>B. breve</i> PXN 25, <i>B. longum</i> ssp. <i>infantis</i> PXN 27, <i>B. longum</i> ssp. <i>longum</i> PXN 30, <i>L. acidophilus</i> PXN 35, <i>L. delbrueckii</i> ssp. <i>bulgaricus</i> PXN 39, <i>L. casei</i> PXN 37, <i>L. plantarum</i> PXN 47, <i>L. rhamnosus</i> PXN 54, <i>Lactobacillus helveticus</i> PXN 45,

	<p><i>Lactobacillus salivarius</i> PXN 57, <i>Lactococcus lactis</i> PXN 63, and <i>S. salivarius</i> ssp. <i>thermophilus</i> PXN 66</p> <ul style="list-style-type: none"> • <i>C. butyricum</i> • 4-strain combination .<i>animalis</i> ssp. <i>lactis</i> Bb12, <i>L. acidophilus</i> LA-5, <i>L. delbrueckii</i> ssp. <i>bulgaricus</i> LBY-27, and <i>S. salivarius</i> ssp. <i>thermophilus</i>. <p>Abdominal pain</p> <ul style="list-style-type: none"> • <i>L. plantarum</i> 299v • <i>L. rhamnosus</i> ATCC 53103 • <i>Bacillus coagulans</i> MTCC 5856 • 2-strain combination of <i>L. acidophilus</i> SDC 2012 and SDC 2013 • <i>E. coli</i> DSM 17252 • 4-strain combination of <i>S. salivarius</i> ssp. <i>thermophilus</i>, <i>L. delbrueckii</i> ssp. <i>bulgaricus</i>, <i>L. acidophilus</i>, and <i>B. longum</i> ssp. <i>longum</i> • 4-strain combination of <i>L. rhamnosus</i> NCIMB 30174, <i>L. plantarum</i> NCIMB 30173, <i>L. acidophilus</i> NCIMB 30175, and <i>Enterococcus faecium</i> NCIMB 30176 • 3-strain combination of <i>B. longum</i> ssp. <i>infantis</i> M-63, <i>B. breve</i> M-16V, and <i>B. longum</i> Reuter ATCC BAA-999 • 2-strain combination of <i>B. longum</i> ssp. <i>longum</i> and <i>L. acidophilus</i>
British Society of Gastroenterology	<p>Global IBS symptoms</p> <ul style="list-style-type: none"> • Combination probiotics • <i>Lactobacillus</i> • <i>Bifidobacterium</i> • <i>Escherichia</i>
AEProbio Probiotic Guide (US)	<ul style="list-style-type: none"> • <i>B. (animalis) lactis</i> CNCM I-2494 • <i>B. longum</i> 35624 • Combination <i>L. acidophilus</i> CL1285, <i>L. casei</i> LBC80R, <i>L. rhamnosus</i> CLR2 • Combination <i>Bacillus subtilis</i> PXN 21, <i>B. bifidum</i> PXN 23, <i>B. breve</i> PXN 25, <i>B. infantis</i> PXN 27, <i>B. longum</i> PXN 30, <i>L. acidophilus</i> PXN 35, <i>L. delbrueckii</i> ssp. <i>bulgaricus</i> PXN 39, <i>L. casei</i> PXN 37, <i>L. plantarum</i> PXN 47, <i>L. rhamnosus</i> PXN 54, <i>L. helveticus</i> PXN 45, <i>L. salivarius</i> PXN 57, <i>L. lactis</i> ssp. <i>lactis</i> PXN 63, <i>Streptococcus thermophilus</i> PXN 66 • Combination <i>L. acidophilus</i> NCFM, <i>B. animalis</i> ssp. <i>lactis</i> Bi-07 • Combination <i>L. acidophilus</i> CUL-60, <i>L. acidophilus</i> CUL-21, <i>B. animalis</i> ssp. <i>lactis</i> CUL-34, <i>B. bifidum</i> CUL-20

	<ul style="list-style-type: none"> • <i>L. plantarum</i> 299v • Combination <i>L. rhamnosus</i> R0011 and <i>L. helveticus</i> R0052 • Combination <i>L. rhamnosus</i> NCIMB 30174, <i>L. plantarum</i> NCIMB 30173, <i>L. acidophilus</i> NCIMB 30175, <i>Enterococcus faecium</i> NCIMB 30176 • Combination <i>L. acidophilus</i> NCFM and <i>B. lactis</i> Bi-07
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ssp. = subspecies

Table 1

Clearly there is still much that needs to be elucidated in probiotics research. Especially in IBS, which is a heterogeneous condition to begin with, more work is required to ascertain which strain or combinations of strains are beneficial for which subsets of patients. While there are limitations in probiotics research, this does not mean that there is no role for probiotics in IBS. Based on our research, interpretation of the literature, and practice, we suggest the following regarding probiotics in IBS:

- Probiotics should be considered as a reasonable first line therapy option for IBS
- When recommending probiotics, advise a particular strain(s) based on available evidence and the patient's specific symptoms (i.e., pain, bloating, diarrhea, constipation)
- It is reasonable to trial a probiotic for up to 12 weeks, and discontinue if there is no effect (in some cases it may be appropriate to recommend a different probiotic)

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12. D. Skokovic-Sunjic Clinical Guide to Probiotic Products Available in the USA 2021, 13th ed, Jan 1st 2021 ISBN 978-1-7775181

http://www.usprobioticguide.com/PBCIntroduction.html?utm_source=intro_pg&utm_medium=civ&utm_campaign=USA_CHART