

AGA Issue Brief for Media: Probiotics

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There is a growing recognition of and interest in the role of the gut microbiome in human health and disease, particularly as it relates to common gastrointestinal (GI) disorders. Given the enthusiasm and popularity of probiotics among the general public, probiotics have become a multi-billion-dollar industry worldwide. In the U.S., probiotics currently are marketed as foods and dietary supplements. Yet, patients living with GI symptoms or disorders take probiotics with hopes of mitigating, treating, curing or preventing disease – which meets the Food and Drug Administration’s criteria for a drug.

AGA’s upcoming guideline and technical review on the role of probiotics in the management of GI disorders puts probiotics front and center of the evidence base. This is a different approach from previous guidelines from AGA and other professional societies, which may have addressed probiotics but as one of several interventions available for a particular disease.

What are probiotics?

The Food and Agriculture Organization of the United Nations and the World Health Organization defines probiotics as “live microorganisms which, when administered in adequate amounts, confer a health benefit on the host.” Although most probiotics being studied are bacteria, yeast (such as *Saccharomyces boulardii*) are also being studied as probiotics.

Why is it important to go beyond probiotic species to consider probiotic strains?

Research has shown that biological functions of bacteria are specific to the strain, not the species. For example, most strains of *Escherichia coli* are harmless and exist naturally in the gut, while others such as shiga-toxin producing *E. coli* and enteropathogenic *E. coli* are pathogenic. In contrast, *E. coli* Nissle 1917 is an example of a probiotic strain that has been shown to promote beneficial effects.

Why did AGA develop a guideline on probiotics?

Patients routinely ask clinicians whether they should be taking probiotics and if so, which products. To date, clinicians have not had rigorous evidence-based guidance regarding the use of probiotics for digestive disorders.

What is the difference between the guideline and technical review?

The guideline includes AGA’s official recommendations for clinicians regarding the role of probiotics in the management of GI disorders. The guideline recommendations are based on the rigorous review of evidence presented in the technical review.

Why is this guideline unique?

This guideline is the first to focus on probiotics across multiple GI diseases. Clinical guidelines are typically focused on a single disease and discuss probiotics as one of multiple possible interventions for that disease.

This guideline also considers the effect of each single-strain or multi-strain formulation of probiotics independently. This is different from previous guidelines, which have grouped data from different formulations under the single umbrella of “probiotics.”

The technical review that accompanies the AGA guideline updated existing high-quality systematic reviews with evidence from recent randomized, placebo-controlled trials, or conducted a new systematic review when none existed to match the clinical question. AGA’s guideline also uses the “GRADE” (Grading of Recommendations Assessment, Development and Evaluation) approach, which is considered the standard in guideline development.

What products does the guideline cover?

Probiotics, including single-strain and multi-strain formulations. These include probiotics taken orally or rectally (for ulcerative colitis). The guideline and technical review only refer to the probiotic strain(s) rather than brand names of products.

The guideline and technical review do not cover:

- Antibiotics
- Fecal microbiota transplantation (FMT)
- Prebiotics
- Synbiotics

What conditions does the guideline cover?

The guideline includes eight recommendations across seven conditions. Most of the recommendations are applicable to both adults and children, with exceptions noted as follows:

1. *Clostridioides difficile* (*C. difficile*, or *C. diff*) infection.
 - a. Treatment of symptomatic adults only.
 - b. Prevention in adults and children receiving antibiotics.
2. Crohn’s disease: Induction or maintenance of remission in adults and children.
3. Ulcerative colitis: Induction or maintenance of remission in adults and children.
4. Ileal pouch-anal anastomosis in chronic ulcerative colitis: Prevention or maintenance of remission of pouchitis in adults and children.
5. Irritable bowel syndrome (IBS): Treatment of symptomatic adults and children.
6. Acute infectious gastroenteritis: Reduction of duration or severity of diarrhea in children only.
7. Necrotizing enterocolitis (NEC), sepsis, and all-cause mortality: Prevention in preterm, low birth weight newborns only.

Are there any recommendations in AGA’s guideline that are different from existing guidelines?

Yes. Differences from existing recommendations for the prevention of *C. difficile* infection, treatment of IBS, acute infectious gastroenteritis, and prevention of necrotizing enterocolitis (NEC), sepsis, and all-cause mortality are highlighted below.

Prevention of C. difficile infection in adults and children receiving antibiotics. A [2017 guideline](#) from the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America noted that there was “insufficient data at this time to recommend administration of probiotics for primary prevention of [*C. difficile* infection] outside of clinical trials (no recommendation).” In contrast, AGA’s guideline recommends four different probiotic

formulations for prevention of *C. difficile* infection, but this recommendation is conditional, and is based on low quality of evidence.

Treatment of IBS in symptomatic adults and children. A [2018 monograph](#) from the American College of Gastroenterology and a [2019 guideline](#) from the Canadian Association of Gastroenterology recommended probiotics, as a group, to improve IBS symptoms. In both cases, the recommendations were rated as “weak” or “conditional,” and the quality of evidence as “low.” In contrast, AGA’s guideline makes no recommendations for the use of probiotics in adults and children with IBS. Given the lack of evidence to make a recommendation, AGA suggests that patients consider stopping probiotics, as there are associated costs and not enough evidence to suggest lack of harm.

The conclusions may be different because AGA considered the evidence for each individual formulation of probiotics, rather than grouping the evidence for a variety of probiotics as was done by other societies for previous guidelines.

Acute infectious gastroenteritis in children. A [2014 guideline](#) from the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and European Society for Pediatric Infectious Diseases, a [2014 position paper](#) from ESPGHAN, and a [2017 guideline](#) from the Infectious Diseases Society of America have recommended the use of probiotics in children with acute gastroenteritis. In contrast, AGA’s guideline suggests against the use of probiotics in children with acute gastroenteritis in North America.

The conclusions may be different because the previous guidelines relied on data almost exclusively outside of North America, where the endemic pathogens, host genetics, and dietary traditions are different. AGA’s guideline incorporates evidence from more recent multi-center trials conducted in pediatric emergency rooms within North America, and determined that studies conducted in other regions of the world in different medical settings might not be generalizable to the North American population that AGA serves.

Prevention of NEC, sepsis and all-cause mortality in preterm, low-birth-weight newborns. A [2020 position paper](#) from ESPGHAN conditionally recommended one single-strain and one multi-strain formulation for the prevention of NEC in preterm infants. In contrast, AGA’s guideline conditionally recommends several single- and multi-strain formulations of probiotics based on moderate/high quality of evidence.

The conclusions may be different as AGA performed a network meta-analysis, which is different from a conventional (treatment vs placebo) meta-analysis as it performs head-to-head comparisons of multiple (three or more) interventions simultaneously.

What was the key challenge in reviewing clinical studies of probiotics?

There currently is no standard for how to report data from clinical studies of probiotics. To ensure that the evidence base was as rigorous as possible, AGA only included data from published randomized controlled trials in updating existing high-quality systematic reviews on probiotics. However, there remained challenges with assessing clinical studies of probiotics; among the studies considered in AGA’s technical review, there were differences in:

- Dosing and duration of treatment.
- Study population.
- Inclusion and exclusion criteria.

- Use of adjunctive therapies.
- Clinical endpoints (outcome measurements).

Furthermore, many studies did not report details on manufacturing conditions, probiotic strain viability, or product shelf life. Altogether, these inconsistencies make it difficult to compare data from different manufacturers, even if the studies tested the same probiotic strain.

Key references

- Su, G.L., Ko, C.W., Bercik, P. *et al.* American Gastroenterological Association Institute Guidelines on the Role of Probiotics in the Management of Gastrointestinal Disorders. *Gastroenterology* 2020 [add link when in-press]
- Preidis, G.A., Weizman, A.V., Kashyap, P.C. *et al.* American Gastroenterological Association Institute Technical Review on the Role of Probiotics in the Management of Gastrointestinal Disorders. *Gastroenterology* 2020 [add link when in-press]
- Khoruts, A., Hoffmann, D.E., Britton, R.A. Probiotics: promise, evidence and hope. *Gastroenterology* 2020 [add link when in-press]
- AGA patient info sheet on probiotics: <https://www.gastro.org/practice-guidance/gi-patient-center/topic/probiotics>