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CLINICAL PRACTICE GUIDELINES

AGA Clinical Practice Guidelines on the Role of Probiotics in the Management of Gastrointestinal Disorders

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This document presents the official recommendations of the American Gastroenterological Association (AGA) on the role of probiotics in the management of gastrointestinal disorders. The guideline was developed by the AGA Institute's Clinical Guidelines Committee and approved by the AGA Governing Board. It is accompanied by a technical review that provides a detailed synthesis of the evidence from which these recommendations were formulated.[1] To get a better understanding of these guidelines, we recommend reading the accompanying technical review. Development of this guideline and the accompanying technical review was fully funded by the AGA Institute without additional outside funding. Members of the Guideline Panel and Technical Review Panel were selected by the AGA Governing Board in consultation with the Clinical Guidelines Committee with careful consideration of all Institute of Medicine recommendations for clinical guideline development. A patient representative was also included in the development and review process and had no recommended changes. The guideline and accompanying technical review underwent independent peer review, and a 30-day open public comment period; all comments were collated by the AGA staff and were reviewed and carefully considered by the Guideline Panel and Technical Review teams, respectively. Changes were incorporated in revised documents and where changes were not accepted, a thoughtful response document was created. In accordance with the Clinical Guidelines Committee policies, all clinical guidelines are reviewed annually at the AGA Clinical Guideline Committee meeting for new information. The next update for these guidelines is anticipated in 3 years from publication (2023).

Within the last 20 years, there has been increasing recognition and interest in the role of the gut microbiome in gastrointestinal health.[2] Defined by the Food and Agriculture Organization of the United Nations and the World Health Organization as "live microorganisms which when administered in adequate amounts confer a health benefit on the host,"[3] probiotics hold the promise of an effective way to alter the microbiome for our benefit. Enthusiasm and popularity within the community for probiotics has led to a multibillion-dollar industry worldwide.[4] Because probiotics are not considered drugs in the United States or Europe, the regulatory status is not the same as would normally accompany a pharmaceutical product. The industry is largely unregulated and marketing of product is often geared directly at consumers without providing direct and consistent proof of effectiveness.[5,6] This has led to widespread use of probiotics with confusing evidence for clinical efficacy.[7] It is estimated that 3.9 million American adults used some form of probiotics or prebiotics (nutrients that promote growth or beneficial functions of beneficial microbes)[8] in 2015, an amount that is 4 times that in 2007.[9,10] Given widespread use and often biased sources of information, it is essential that clinicians have objective guidance for their patients about the appropriate use of and indications for probiotics.

Although there has been a substantial number of studies examining probiotics in various gastrointestinal diseases, the studies have been extremely varied, including differences in the strain of microbes used, dose, and route of administration, as well as the research methodology, including differences in the reporting of end points and outcomes.[5] Furthermore, most of the studies with probiotics involved a relatively small number of patients compared to trials investigating the effects of pharmacological interventions. Conclusions drawn from meta-analyses or systematic reviews can be misleading if different studies with different patient populations, different reported end points and outcomes, or different strains or combinations of probiotics are grouped together inappropriately.[7] Within species, different strains can have widely different activities and biologic effects. Many immunologic, neurologic, and biochemical effects of gut microbiota are likely to not only

Abbreviations used in this paper: **AGA, American Gastroenterological Association; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IBS, irritable bowel syndrome; MD, mean difference; NEC, necrotizing enterocolitis; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.**

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AGA SECTION

Table 1. Quality of Evidence

Quality	Description
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

be strain-specific, but also dose-specific.[6] Furthermore, combinations of different microbial strains may also have widely different activities, as some microbial activities are dependent on interactions between different strains. In developing this guideline, we have examined the evidence presented in the accompanying technical review with these constraints in mind. We prioritized *Clostridioides difficile*–associated diseases, inflammatory bowel disease, irritable bowel syndrome, infectious gastroenteritis, and necrotizing enterocolitis (NEC) because these were conditions for which probiotics were commonly considered. We focused on patient-important outcomes, such as induction and maintenance of disease, treatment of disease, prevention of sepsis, and all-cause mortality.

This guideline was developed utilizing a process outlined previously.[11] Briefly, the AGA process for developing clinical practice guidelines follows the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[11] and best practices as outlined by the National Academy of Science (formerly Institute of Medicine).[12] A priori, the Guideline Panel and methodologist identified and formulated clinically relevant questions about the use of probiotic formulations for the prevention and treatment of gastrointestinal diseases (not prebiotic use). Each research question identified the population, intervention, comparison, and patient-important outcomes. The Technical Review Panel initially reviewed and assessed relevant systematic reviews that addressed the clinical questions, updating high-quality systematic reviews through December 2018 to inform the recommendations when possible.[1] For situations in which there was either no recent systematic review available or the recent systematic review was not deemed high quality, the Technical Review Panel conducted the systematic review de novo. The findings from each systematic review were assessed using the GRADE approach and presented in an evidence profile. The Guideline Panel and the authors of the technical review met face to face on May 9, 2019 to discuss the findings from the technical review. After this meeting, the Guideline Panel independently formulated guideline recommendations; the Technical Review Panel was not involved in the formulating or finalizing of recommendations. Although the quality of evidence (Table 1) was a key factor in determining the strength of the recommendations (Table 2), the Panel also considered the balance between the benefits and harms of the interventions, as well as patients' values and preferences, resource use (ie, cost), health equity, acceptability, and feasibility (the Evidence to Decision Framework). The recommendations, certainty of evidence, and strength of recommendations are summarized in Table 3. The guideline and technical review went through a 30-day public comment period between February 16, 2020 and March 17, 2020. AGA staff collated the comments, the Guideline Panel deliberated in their response and, when appropriate, modified the document text. We hope to provide clinicians with clear guidance regarding the appropriate use of specific probiotics in the context of specific gastrointestinal diseases. The target audience for this guideline includes health care providers, dietitians, and patients. The guidelines include recommendations for specific populations, including adults, children, and neonates.

In addition, we were not able to assess the viability of each formulation reported in the studies, as this information was not routinely available. We recognize that different

Table 2. Strength of Recommendation

Strength of recommendation	For the patient	For the clinician
Strong	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids may be useful in helping individuals in making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.

Table 3. Summary of recommendations[a]

Recommendations	Strength of recommendation	Quality of evidence
1. In patients with *C difficile* infection, we recommend the use of probiotics only in the context of a clinical trial.	No recommendation	Knowledge gap
2. In adults and children on antibiotic treatment, we suggest the use of *S boulardii*; or the 2-strain combination of *L acidophilus* CL1285 and *L casei* LBC80R; or the 3-strain combination of *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, and *B bifidum*; or the 4-strain combination of *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B bifidum*, and *S salivarius* subsp *thermophilus* over no or other probiotics for prevention of *C difficile* infection. Comment: Patients who place a high value on the potential harms (particularly those with severe illnesses) or a high value on avoiding the associated cost and a low value on the small risk of *C difficile* development (particularly in the outpatient setting), would reasonably select no probiotics.	Conditional	Low
3. In adults and children with Crohn's disease, we recommend the use of probiotics only in the context of a clinical trial.	No recommendation	Knowledge gap
4. In adults and children with ulcerative colitis, we recommend the use of probiotics only in the context of a clinical trial.	No recommendation	Knowledge gap
5. In adults and children with pouchitis, we suggest the 8-strain combination of *L paracasei* subsp *paracasei*, *L plantarum*, *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B longum* subsp *longum*, *B breve*, *B longum* subsp *infantis*, and *S salivarius* subsp *thermophilus* over no or other probiotics. Comment: Patients for whom the feasibility and cost of using this combination of bacterial strain is problematic may reasonably select no probiotics.	Conditional	Very low
6. In symptomatic children and adults with irritable bowel syndrome, we recommend the use of probiotics only in the context of a clinical trial.	No recommendations	Knowledge gap
7. In children with acute infectious gastroenteritis, we suggest against the use of probiotics.	Conditional	Moderate
8. In preterm (less than 37 weeks gestational age), low-birth-weight infants, we suggest using a combination of *Lactobacillus* spp and *Bifidobacterium* spp (*L rhamnosus* ATCC 53103 and *B longum* subsp *infantis*; or *L casei* and *B breve*; or *L rhamnosus*, *L acidophilus*, *L casei*, *B longum* subsp *infantis*, *B bifidum*, and *B longum* subsp *longum*; or *L acidophilus* and *B longum* subsp *infantis*; or *L acidophilus* and *B bifidum*; or *L rhamnosus* ATCC 53103 and *B longum* Reuter ATCC BAA-999; or *L acidophilus*, *B bifidum*, *B animalis* subsp *lactis*, and *B longum* subsp *longum*), or *B animalis* subsp *lactis* (including DSM 15954), or *L reuteri* (DSM 17938 or ATCC 55730), or *L rhamnosus* (ATCC 53103 or ATC A07FA or LCR 35) for prevention of NEC over no and other probiotics.	Conditional	Moderate/high

[a]Please see the accompanying technical review for the supporting evidence.[1]

manufacturers use different processes, which may affect the actual content of the probiotic utilized, but this is not within the scope of this guideline and therefore we provided the granular data regarding each strain as specified in the published reports. When the information was available, we considered the strain specificity when evaluating outcomes.

In patients with *Clostridioides difficile* infection, we recommend the use of probiotics only in the context of a clinical trial. *No recommendation, knowledge gap,*

The AGA makes no recommendations for the use of probiotics in the treatment of *C difficile* infection. Incidence of *C difficile* infection is rising and is responsible for almost half a million infections in the United States in 2011,[13] with recurrence rates of up to 19.9%, and leading to 29,000 deaths. Fecal microbiota transplantation is highly effective in treating recurrent *C difficile* infection,[14] but the data supporting the use of probiotics in initial or recurrent *C difficile* infection are less convincing.

The technical review identified 5 placebo-controlled randomized controlled trials (RCTs) evaluating probiotics as adjunct treatment with antibiotics, testing 4 different probiotic formulations. The patient populations across studies differed, including patients with an initial *C difficile* infection, recurrent infection, or both. Probiotics or placebo was administered together with metronidazole or vancomycin at low dose or high doses. Due to these variations in the study design, as well as in clinical outcomes, data were deemed too heterogeneous to be pooled in the analysis. All 5 published studies contained uncertain or high risk of bias regarding blinding of outcome assessment and selective reporting.

The probiotic formulations studied included *Saccharomyces boulardii*, *Lactobacillus plantarum* 299v, *Lactobacillus rhamnosus* ATCC 53103, and the 4-strain combination of *Lactobacillus acidophilus* ATCC 700396, *Lactobacillus paracasei* subsp *paracasei* ATCC 335, *Bifidobacterium animalis* subsp *lactis* ATCC SD5220 and *B animalis* subsp *lactis* ATCC SD5219. The largest study, involving 134 patients, reported that *S boulardii* may have a beneficial effect on cessation (relative risk [RR], 1.33; 95% confidence interval [CI], 1.02–1.74) and recurrence of diarrhea (RR, 0.59; 95% CI, 0.35–0.98), but the quality of evidence was low. The smaller trials with *L plantarum* 299v or the 4-strain combination suggested that these probiotics also may have beneficial effects on diarrhea but the evidence was very uncertain, while the administration of *L rhamnosus* ATCC 53103 resulted in increased recurrence of *C difficile* infection compared to placebo (RR, 2.63; 95% CI, 0.35–19.85). The overall certainty of evidence across all critical outcomes for probiotics used as adjunctive treatment for *C difficile* infection was low. Furthermore, the technical review identified a potential risk of publication bias due to multiple registered trials that were not linked to a published report. While currently available data suggest that some probiotics might be beneficial in treatment of *C difficile,* further studies with standardized study design and larger number of patients are needed to define those probiotics, as well as to identify which patient populations may benefit from this intervention.

In adults and children on antibiotic treatment, we suggest the use of *S boulardii*; or the 2-strain combination of *L acidophilus* CL1285 and *Lactobacillus casei* LBC80R; or the 3-strain combination of *L acidophilus*, *Lactobacillus delbrueckii* subsp *bulgaricus*, and *Bifidobacterium bifidum*; or the 4-strain combination of *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B bifidum*, and *Streptococcus salivarius* subsp *thermophilus* over no or other probiotics for prevention of *C difficile* infection.
Conditional recommendation, low quality of evidence.
Comment: Patients who place a high value on the potential harms (particularly those with severe illnesses) or a high value on avoiding the associated cost and a low value on the small risk of *C difficile* development (particularly in the outpatient setting), would reasonably select no probiotics.

The AGA suggests the use of certain strains and strain combination of probiotics in the prevention of *C difficile* infection. Although there is a large body of literature studying the role of probiotics in preventing antibiotic-associated *C difficile* infection, the studies are very heterogeneous. The technical review identified 39 studies that were previously evaluated by Cochrane review published in 2017.[15] A total of 9955 patients were included but the populations studied were extremely varied, including pediatric, adult, and elderly patients—utilizing a variety of antibiotic regimens in both inpatient and outpatient settings—who have very different risks for the development of *C difficile* infection. The Cochrane review found that probiotics reduced the overall risk of *C difficile* infection vs placebo (RR, 0.40; 95% CI, 0.30–0.52); however, the beneficial effect was driven by the population of patients with high risk of developing *C difficile* infection, with no significant effects observed in patients with low or baseline risk.

The technical review did not identify any new RCTs between the 2017 Cochrane review and November 2018 and thus assessed the certainty of evidence from these 39 trials.[1] The overall certainty of the evidence was downgraded from Moderate to Low due to unclear or high risk of bias in most of the trials across all domains for all outcomes assessed. Several studies were published as abstracts only or referenced unpublished data. Publication bias was considered, as a large number of registered trial protocols on this topic were not associated with subsequent peer-reviewed publications.

Subgroup analyses of individual probiotic strains or strain combinations that may have an effect compared with placebo found that the risk of *C difficile* infection development was reduced by *S boulardii* (RR, 0.41; 95% CI, 0.22–0.79); the 2-species combination of *L acidophilus* CL1285 and *L casei* LBC80R (RR, 0.22; 95% CI, 0.11–0.42); the 3-strain combination of *L acidophilus, L delbrueckii* subsp *bulgaricus*, and *B bifidum* (RR, 0.35; 95% CI, 0.15–0.85); as well as the 4-strain combination of *L acidophilus, L delbrueckii* subsp *bulgaricus*, *B bifidum*, and *S salivarius* subsp *thermophilus* (RR, 0.28; 95% CI, 0.11–0.67), with the overall quality of the evidence rated as Low. It should be pointed out that beneficial effect of probiotics was seen mainly in patients with very high risk of developing *C difficile* infection (>15% baseline risk) and that the analysis of most studies had a wide CI that includes the potential for some benefit, as well as for some harm. Thus, patients who place a high value on avoiding associated financial cost or potential harms (especially those immunocompromised patients) and who have low risk of developing *C difficile* infection (mainly outpatients in the community) may choose not to use any probiotics.

In adults and children with Crohn's disease, the AGA recommends use of probiotics only in the context of a clinical trial. *No recommendation, knowledge gap.*

The AGA recommends use of probiotics on only in the context of a clinical trial for adults and children with Crohn's

disease. Alterations in the gut microbiome in patients with Crohn's disease are being explored increasingly, and interest in microbiota-based therapies, such as probiotics and fecal microbiota transplantation, is growing. However, studies of probiotics for induction or maintenance of remission in Crohn's disease have been limited by small sample sizes, heterogeneity in patient populations, heterogeneity in study design, and differences in the probiotic formulations tested.

The technical review searched for studies of both induction and maintenance of remission in Crohn's disease in adults and children. Only 1 study of 11 subjects was identified for induction of remission in either adults or children. This study found no evidence of benefit for *L rhamnosus* ATCC 53103 compared to placebo for induction of remission (odds ratio [OR], 0.80; 95% CI, 0.04–17.20), with CI that were wide and thus did not exclude the potential for benefit or harm.

Eleven studies of probiotics for maintenance of remission in adults and children with Crohn's disease were identified. The identified studies were heterogeneous in inclusion criteria, the probiotic studied, and study design. The probiotic formulations studied included *Escherichia coli* Nissle 1917; *S boulardii*; *L rhamnosus* ATCC 53103; *Lactobacillus johnsonii* NCC 533; and an 8-strain probiotic combination of *L paracasei* subsp *paracasei*, *L plantarum*, *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *Bifidobacterium longum* subsp *longum*, *Bifidobacterium breve*, *Bifidobacterium longum* subsp *infantis*, and *S salivarius* subsp *thermophilus*. In addition, the studies differed on whether remission was induced by medical or surgical therapy, and only 1 study enrolled children. Lastly, some of the studies used mesalamine as the comparator, or allowed co-therapy with mesalamine in the probiotic arm. There was no overall evidence of benefit from any of the probiotic therapies studied for maintenance of remission.

The overall quality of the evidence was rated as low for induction of remission and maintenance of remission. Given the overall small study samples, as well as heterogeneity in patient populations, probiotic strains studied, and study design, it is unclear whether there is potential for specific probiotic strains to be beneficial for either induction or maintenance of remission in Crohn's disease. Further studies are needed to define specific populations of patients with Crohn's disease who might benefit from probiotics, as well as the most effective probiotic strains.

In adults and children with ulcerative colitis, the AGA recommends the use of probiotics only in the context of a clinical trial. *No recommendation, knowledge gap.*

The AGA recommends the use of probiotics in adults and children with ulcerative colitis only in the context of a clinical trial. As with Crohn's disease, interest in microbiota-based therapies for ulcerative colitis is growing. However, available evidence is limited because of heterogeneity in study design, patient populations, and the specific probiotics that have been studied.

The technical review identified 11 studies on the use of probiotics for induction of remission in adults and children with ulcerative colitis. The probiotic formulations under evaluation included the 3-strain combination of *B breve* Yakult, *B bifidum* Yakult, and *L acidophilus*; *B longum* Reuter ATCC BAA-999; *E coli* Nissle 1917; *Lactobacillus reuteri* ATCC 55730; and the 8-strain combination of *L paracasei* subsp *paracasei*, *L plantarum*, *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B longum* subsp *longum*, *B breve*, *B longum* subsp *infantis*, and *S salivarius* subsp *thermophilus*. The comparators varied among studies, and in some studies included mesalamine.

Four studies compared the 8-strain probiotic combination to mesalamine or balsalazide for induction of remission, suggesting potential for benefit but with very low certainty of the evidence (RR, 1.72; 95% CI, 0.78–3.32). Two studies examined the effectiveness of oral *E coli* Nissle 1917 compared to mesalamine for this indication, again with uncertain benefit (RR, 0.86; 95% CI, 0.49–1.49). One of these studies also allowed adjunctive treatment with steroids and gentamicin, while the other allowed co-therapy with topical prednisolone. One study of rectally administered *E coli* Nissle 1917 did not show any clear evidence of benefit compared to placebo. Rectally administered *L reuteri* ATCC 55730 was tested in children, with suggestion of an increased clinical response rate compared to placebo (RR, 1.83; 95% CI, 1.14–2.92). Other probiotics were tested in single studies only, with no demonstrated benefit for induction of remission.

The technical review identified 6 studies of probiotics for maintenance of remission in ulcerative colitis. Two studies of *E coli* Nissle 1917 and 1 study of *L rhamnosus* ATCC 53103 (RR, 0.82; 95% CI, 0.60–1.11) did not show clear benefit of the probiotic compared to mesalamine for maintenance of remission. In addition, compared to placebo, the 2-strain combination of *L acidophilus* LA-5 and *B animalis* subsp *lactis* Bb12; the 2-strain combination of *B breve* Yakult and *L acidophilus*; and the 3-strain combination of *Enterococcus faecalis* T-111, *Clostridium butyricum* TO-A, and *Bacillus mesentericus* TO-A did not show any evidence of benefit for this indication, although these formulations were tested in single studies only.

The overall quality of evidence for probiotics for induction or maintenance of remission in ulcerative colitis was rated as low. Available evidence is limited by small sample sizes, differences in patient populations, variability in study design, and heterogeneity in the probiotic formulations used. The most extensively tested formulation was the 8-strain combination of *L paracasei* subsp *paracasei*, *L plantarum*, *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B longum* subsp *longum*, *B breve*, *B longum* subsp *infantis*, and *S salivarius* subsp *thermophilus* for induction of remission, although even here the available studies were limited by potential for bias and pooled results did not show evidence of benefit. Further research is needed to identify specific

patient populations that might benefit most from treatment with probiotics and to define the most effective probiotic formulations.

In adults and children with pouchitis, the AGA suggests the use of the 8-strain combination of *L paracasei* subsp *paracasei*, *L plantarum*, *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B longum* subsp *longum*, *B breve*, *B longum* subsp *infantis*, and *S salivarius* subsp *thermophilus* over no or other probiotics.
Conditional recommendation, very low quality of evidence.
Comment: Patients for whom the feasibility and cost of using this combination of bacterial strain is problematic may reasonably select no probiotics.

The AGA suggests the use of the 8-strain combination of *L paracasei* subsp *paracasei*, *L plantarum*, *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B longum* subsp *longum*, *B breve*, *B longum* subsp *infantis*, and *S salivarius* subsp *thermophilus* over no or other probiotics in patients with pouchitis. Pouchitis is a frequent post-surgical complication after total proctocolectomy and ileal pouch–anal anastomosis for ulcerative colitis, and a role for the gut microbiota has been suggested in its pathogenesis. The possibility of microbiota-directed therapy for this condition has been suggested.

The technical review identified 7 studies of probiotics for treatment or prevention of pouchitis in adult patients with an ileal pouch–anastomosis for management of ulcerative colitis. The 8-strain probiotic formulation for maintenance of remission in chronic pouchitis was tested in 2 studies including a total of 76 patients, with a potential benefit in the proportion of patients who maintained remission at 12 months compared to placebo (RR, 20.24; 95% CI, 4.28–95.81, low certainty of evidence). Two additional studies suggested a benefit of the same 8-strain combination for prevention of an initial episode of acute pouchitis, but with very low certainty of evidence (RR for no episodes of pouchitis, 1.29; 95% CI, 1.03–1.61). Single trials of *L rhamnosus* ATCC 53103, *B longum* Reuter ATCC BAA-999, and *C butyricum* CBM 588 did not show clear evidence of benefit for treatment or prevention of pouchitis, although samples sizes were extremely small in all available studies.

The overall quality of evidence was rated as very low due to risk of bias, small sample sizes, and heterogeneity in the patient populations and interventions tested. The majority of evidence came from studies of the 8-strain probiotic combination of *L paracasei* subsp *paracasei*, *L plantarum*, *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B longum* subsp *longum*, *B breve*, *B longum* subsp *infantis*, and *S salivarius* subsp *thermophilus*. Other probiotic formulations need further testing for this indication. It also unclear whether these results would apply to children or to patients who underwent an ileal pouch–anal anastomosis for conditions other than chronic ulcerative colitis, such as familial adenomatous polyposis.

In symptomatic children and adults with irritable bowel syndrome, we recommend the use of probiotics only in the context of a clinical trial. *No recommendations, knowledge gap.*

The AGA makes no recommendations for the use of probiotics in children and adults with irritable bowel syndrome (IBS). While there are many studies examining this question, they are marked by significant heterogeneity in study design, outcome, and probiotics used.

The technical review found a total of 76 RCTs that used 44 different probiotic strains or combinations of strains.[1] For the majority of studies that reported a benefit, the data were derived from a single RCT. Only 2 formulations (*S boulardii* and the 8-strain combination) had more than 1 RCT that measured the same outcome, allowing for combined analysis. Three studies tested *S boulardii* in 232 adults with IBS and while the studies used different outcome measures, all reported an abdominal pain score that was not different between those treated with *S boulardii* and those treated with placebo. Two RCTs tested the 8-strain combination (*L paracasei* subsp *paracasei*, *L plantarum*, *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B longum* subsp *longum*, *B breve*, *B longum* subsp *infantis*, and *S salivarius* subsp *thermophilus*) in 73 adults with IBS and abdominal pain and although this demonstrated a decrease in the abdominal pain score using the visual analog scale (mean decrease, 3.78; 95% CI, 4.93–2.62), the overall sample size was small and there was unclear risk of selection, reporting, and detection bias. In addition, the patients enrolled were of variable IBS subtypes.

In the remainder of the studies, the majority of the single RCTs using different probiotic and probiotic combinations of variable duration reported some benefit, but the sample sizes were all relatively small and had significant differences in study subjects and designs. The overall quality of evidence was very low. There was also significant concern for publication bias, as the Technical Review team found numerous registered protocols that yielded no peer-reviewed publications or results that were publicly available. Although there has been significant interest and potential for the use of probiotics in IBS, further studies are needed to clarify this important question.

In children with acute infectious gastroenteritis, we suggest against the use of probiotics.
Conditional recommendation, moderate quality of evidence.

The AGA suggests against the use of probiotics in children with acute infectious gastroenteritis in the United States and Canada. The majority of the data supporting the use of probiotics in children with acute infectious gastroenteritis were from studies performed outside of United States and Canada, while 2 high-quality studies performed in the United States and Canada did not show any benefit.

The technical review identified 89 studies, 58 were included in a Cochrane Review published in 2010 and 31 additional studies were published after 2010. Most of the studies that showed a benefit of probiotics were published in India, Italy, Poland, Turkey, and Pakistan and had 1 or more concerns regarding risk of bias.[1] Of the 89 studies, 58 reported duration of diarrhea as an outcome. Combining these 58 studies that utilized various strains of probiotics, the mean duration of diarrhea was reduced by 21.91 hours (95% CI, 16.17–27.64 hours), but the level of evidence was low. The most commonly studied probiotic was *S boulardii*, which was utilized in 21 RCTs. Only 9 studies reported on the mean duration of diarrhea, which was reduced by 28.9 hours (95% CI, 16.78–41.03 hours), but the level of evidence was very low. The second most commonly used strain was *L rhamnosus* ATCC 53103, which was evaluated in 19 RCTs. Of these 19 RCTs, 14 studies reported mean duration of diarrhea as an outcome, which was reduced by 23.13 hours (95% CI, 12.33–33.94 hours).

While some strains of bacteria improved diarrhea duration in children, few of the studies were performed in North America until 2 recent multicenter, randomized, double-blind, placebo-controlled trials conducted by the Pediatric Emergency Care Applied Research Network and the Pediatric Emergency Research Canada. These studies enrolled 943 and 827 children from 10 and 6 emergency departments in the United States and Canada, respectively. The US study used *L rhamnosus* ATCC 53103 and the Canadian study used a combination of *L rhamnosus* R0011 and *Lactobacillus helveticus* R0052 for 5 days. Neither showed any benefit in the occurrence of moderate-to-severe gastroenteritis between placebo and probiotics groups. Two additional studies in the United States and Canada using the same strains of bacteria confirmed the lack of benefit. Given likely differences in host genetics, diet, sanitation, and endemic enteropathogens between North America and the other global regions, as well as different causes of acute infectious gastroenteritis in children, we do not feel that the studies conducted in other regions can be generalized to the population served by the AGA and thus suggest against the use of probiotics for acute infectious gastroenteritis in children.

In preterm (less than 37 weeks gestational age), low-birth-weight infants, we suggest using a combination of *Lactobacillus* spp and *Bifidobacterium* spp (*L rhamnosus* ATCC 53103 and *B longum* subsp *infantis*; or *L casei* and *B breve*; or *L rhamnosus*, *L acidophilus*, *L casei*, *B longum* subsp *infantis*, *B bifidum*, and *B longum* subsp *longum*; or *L acidophilus* and *B longum* subsp *infantis*; or *L acidophilus* and *B bifidum*; or *L rhamnosus* ATCC 53103 and *B longum* Reuter ATCC BAA-999; or *L acidophilus*, *B bifidum*, *B animalis* subsp *lactis*, and *B longum* subsp *longum*), or *B animalis* subsp *lactis* (including DSM 15954), or *L reuteri* (DSM 17938 or ATCC 55730), or *L rhamnosus* (ATCC 53103 or ATC A07FA or LCR 35) over no and other probiotics.
Conditional recommendation, moderate/high quality of evidence.

The AGA suggests the use of certain probiotic strain or strain combination for the prevention of NEC in preterm infants less than 37 weeks gestational age and low birth weight. Preterm birth is common, affecting 10% of newborns in the United States and 15 million pregnancies worldwide each year. Premature infants have increased risk of mortality and multiple morbidities, including NEC. NEC is the most important gastrointestinal emergency among preterm neonates, characterized by mucosal or even deeper intestinal necrosis of the bowel with common long-term sequelae, including short bowel syndrome and impaired neurodevelopment. Microbiota differs in infants with NEC compared to healthy infants providing a rationale for microbiota-oriented treatments.

The technical review presented results from a recent systematic review and network meta-analysis that assessed the role of probiotics in the prevention of mortality and morbidity in preterm infants.[16] In total, 63 studies comparing single- and multiple-strain probiotics to placebo in patients with severe NEC were included and multiple outcomes, such as all-cause mortality, severe NEC (stage II or greater), culture-proven sepsis, and duration of hospitalization were assessed.

Combinations of *Lactobacillus* spp and *Bifidobacterium* spp (*L rhamnosus* ATCC 53103 and *B longum* subsp *infantis*; or *L casei* and *B breve*; or *L rhamnosus*, *L acidophilus*, *L casei*, *B longum* subsp *infantis*, *B bifidum*, and *B longum* subsp *longum*; or *L acidophilus* and *B longum* subsp *infantis*; or *L acidophilus* and *B bifidum*; or *L rhamnosus* ATCC 53103 and *B longum* Reuter ATCC BAA-999; or *L acidophilus*, *B bifidum*, *B animalis* subsp *lactis*, and *B longum* subsp *longum*; or *B animalis* subsp *lactis* [including DSM 15954], or *L reuteri* [DSM 17938 or ATCC 55730], or *L rhamnosus* [ATCC 53103 or ATC A07FA or LCR 35]) reduced all-cause mortality compared to placebo (OR, 0.56, 95% CI, 0.39–0.80), while severe NEC was reduced by combinations of *Lactobacillus* spp and *Bifidobacterium* spp (*L rhamnosus* ATCC 53103 and *B longum* subsp *infantis*; or *L casei* and *B breve*; or *L rhamnosus*, *L acidophilus*, *L casei*, *B longum* subsp *infantis*, *B bifidum*, and *B longum* subsp *longum*; or *L acidophilus* and *B longum* subsp *infantis*; or *L acidophilus* and *B bifidum*; or *L rhamnosus* ATCC 53103 and *B longum* Reuter ATCC BAA-999; or *L acidophilus*, *B bifidum*, *B animalis* subsp *lactis*, and *B longum* subsp *longum*; OR, 0.35; 95% CI, 0.20–0.59), *B animalis* subsp *lactis* (including strain DSM 15954; OR, 0.31; 95% CI, 0.13–0.74), *L reuteri* (DSM 17938 or ATCC 55730; OR, 0.55; 95% CI, 0.34–0.91), or *L rhamnosus* (ATCC 53103 or ATC A07FA or LCR 35; OR, 0.44; 95% CI, 0.21–0.90), all supported by moderate- or high-quality evidence.

There was low to very low quality of evidence to support beneficial effects of combinations of *Lactobacillus* spp, *Bifidobacterium* spp, and *Enterococcus* spp (*L acidophilus*, *B longum* subsp *longum*, and *E faecalis*; or *L gasseri* PTA-5845, *B longum* subsp *infantis* PTA-5843, and *E faecium* PTA-5844; or *L acidophilus*, *B longum* subsp *longum*, and *E faecium*; or *L acidophilus*, *B longum* subsp *infantis*, and *E faecalis* (OR, 0.28; 95% CI, 0.16–0.49), combinations of *Bifidobacterium* spp and *S salivarius* subsp *thermophilus* (*B longum* subsp *infantis*, *B bifidum*, and *S salivarius* subsp *thermophilus*; or *B longum* subsp *infantis* DSM 33361, *B animalis* subsp *lactis* DSM 15954, and *S salivarius* subsp

thermophilus TH-4) (OR, 0.38; 95% CI, 0.19–0.75) or a *B subtilis* and *E faecium* (OR, 0.23; 95% CI, 0.08–0.63) in severe NEC reduction compared to placebo.

Combinations of *Lactobacillus* spp, *Bifidobacterium* spp, and *S boulardii* (*L rhamnosus*, *L acidophilus*, *B longum* subsp *longum*, and *S boulardii*; or *L acidophilus*, *B bifidum*, and *S boulardii*) reduced days to reach full enteral feeds (mean difference [MD], –3.30; 95% CI, –5.91 to –0.69), supported by moderate- or high-quality evidence. Similar effects, although based on low or very low quality of evidence, were shown with combinations of *Lactobacillus* spp and *Bifidobacterium* spp (*L casei* and *B breve*; or *L rhamnosus*, *L acidophilus*, *L casei*, *B longum* subsp *infantis*, *B bifidum*, and *B longum* subsp *longum*; or *L acidophilus* and *B bifidum*; or *L acidophilus*, *B bifidum*, *B animalis* subsp *lactis*, and *B longum* subsp *longum*; MD, –2.15; 95% CI, –3.78 to –0.51), or with *L reuteri* (DSM 17938 or ATCC 55730 (MD, –2.62; 95% CI, –4.53 to –0.71). Finally, *B animalis* subsp *lactis* and *L reuteri* (DSM 17938 or ATCC 55730) significantly shortened hospitalization based on moderate- or high-quality evidence (MD, –13.00; 95% CI, –22.71 to –3.29 and MD, –7.89; 95% CI, –11.60 to –4.17, respectively).

Discussion

The gut microbiome plays an important role in gastrointestinal health and disease and probiotics represent a promising modality for therapeutic intervention. As outlined in the accompanying technical review,[1] the current evidence suggests that the use of certain probiotic strains or probiotic strain combinations may prevent *C difficile* infections for adults and children on antibiotic treatment. However, the quality of evidence was low and the reporting of potential harms was not always consistent. Thus, for patients who place a high value on avoidance of potential harms, particularly those with severe illnesses or immunosuppression, it would be reasonable to select not to use probiotics. While there was evidence for probiotics in the prevention of *C difficile*, the technical review found significant knowledge gap in the use of probiotics in treatment of *C difficile* and recommend this as an area for further study. Similar knowledge gaps exist in the use of probiotics in irritable bowel syndrome and inflammatory bowel disease (Crohn's disease and ulcerative colitis). In the subset of patients with pouchitis, current evidence supports the use of the 8-strain combination (*L paracasei* subsp *paracasei*, *L plantarum*, *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B longum* subsp *longum*, *B breve*, *B longum* subsp *infantis*, and *S salivarius* subsp *thermophilus*) if feasibility of obtaining the combination is not a barrier. In preterm infants less than 37 weeks gestational age, the probiotic strains *B animalis* subsp *lactis* or *L reuteri* (DSM 17938 or ATCC 55730) or *L rhamnosus* (ATCC 53103 or ATC A07FA or LCR 35) or combination of *Lactobacillus* spp and *Bifidobacterium* spp (*L rhamnosus* ATCC 53103 and *B longum* subsp *infantis*; or *L casei* and *B breve*; or *L rhamnosus*, *L acidophilus*, *L casei*, *B longum* subsp *infantis*, *B bifidum*, and *B longum* subsp *longum*; or *L acidophilus* and *B longum* subsp *infantis*; or *L acidophilus* and *B bifidum*; or *L rhamnosus* ATCC 53103 and *B longum* Reuter ATCC BAA-999; or *L acidophilus*, *B bifidum*, *B animalis* subsp *lactis*, and *B longum* subsp *longum*) may prevent the development of NEC. For children with acute gastroenteritis in North America, however, the current evidence does not support the use of probiotics. While other society guidelines[17–19] have previously recommended the use of probiotics in this population, these guidelines were developed prior to the publication of two large multi-center studies from North America, which became available after their recommendations were made. This is an area that will require further study and recommendations evolve as more direct high-quality data become available.

We identified that significant knowledge gaps exist in this very promising and important area of research due to the significant heterogeneity between studies and variability in the probiotic strains studied. The lack of consistent harms reporting makes it difficult to assess true harms. The lack of product manufacturing details prohibits true comparisons and decreases the feasibility of obtaining certain products by patients. Future high-quality studies are urgently needed that address these pitfalls. These guidelines will undergo a review and consideration for an update within 3–5 years or earlier if practice-changing evidence becomes available.

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