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ONLINE EXCLUSIVE

Probiotics as a Tx resource in primary care

While probiotics have not been marketed as drugs, clinicians can still recommend them in an evidence-based manner.

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PRACTICE RECOMMENDATIONS

› *Consider specific probiotics to prevent antibiotic-associated diarrhea, reduce crying time in colicky infants, and improve therapeutic effectiveness of antibiotics for bacterial vaginosis.* (A)

› *Consider specific probiotics to reduce the risk for* Clostridioides *(formerly* Clostridium*)* difficile *infections, to treat acute pediatric diarrhea, and to manage symptoms of constipation.* (B)

› *Check a product's label to ensure that it includes the probiotic's genus, species, and strains; the dose delivered in colony-forming units through the end of shelf life; and expected benefits.* (C)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

We are in the age of the microbiome. Both lay and scientific press proliferate messages about the importance of the microbiome to our health even while they often remain unclear on how to correct microbiota patterns associated with different diseases or suboptimal health states. Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host."[1]

Certain probiotics have been shown to prevent and treat specific diseases or conditions, inside or outside the gut. But the level and quality of evidence varies greatly. In addition, the health claims allowed by government regulators depend on making discrete distinctions (food vs drug, maintaining health vs treating disease, and emerging evidence vs significant scientific agreement) along dimensions that are increasingly recognized as continuous and complex.[2] This leads to confusion among doctors and patients about whether to trust claims on product labels and what to make of the absence of such claims.

Find out which probiotic is effective for a patient's condition. Simply recommending that a patient "take probiotics" is not particularly helpful when the individual wants a product that will aid a specific condition. While probiotics, to date, have not been marketed as drugs in the United States, clinicians can still approach recommending them in an evidence-based manner.

In this article, we review diseases/conditions for which probiotic products have good efficacy data. We discuss probiotic efficacy and safety, offer relevant information on regulatory categories of probiotics, and give direction for proper usage based on the current evidence base. Although this review is meant to be an easy-to-use resource for clinicians, it is not a comprehensive or detailed review of the numerous probiotic products and studies currently available.

Regulatory and commercial variances with probiotics

In the United States, probiotics have been marketed as dietary

supplements, medical foods, or conventional foods, all of which require different levels of evidence and types of oversight than drugs. The efficacy of some probiotics in treating or preventing certain diseases and conditions is similar to, if not better than, effects observed with traditional drug interventions (**TABLE 1**[3-32]). However, unlike drugs, which are subject to premarket oversight, the probiotic marketplace contains products with uneven levels of evidence, from well substantiated to greatly limited. Currently, no probiotics are sold in the United States as over-the-counter or prescription drugs, although probiotic drugs will likely enter the US market eventually.

What to consider when recommending a product. When considering probiotics, remember that strain, dosage, and indication are all important. Just as we know that not all antibiotics are equally effective for all infections, so, too, effectiveness among probiotics can—and often does—vary for any given condition. Effectiveness also may vary from patient to patient. Most recommendations made in this review are tied to specific probiotic strains and doses. In some cases, more than one probiotic may be efficacious, likely due to the same or similar underlying mechanism of action. For example, most probiotics produce short-chain fatty acids in the colon, providing a common mechanism supporting digestive health.[33-35]

Contrary to the blanket recommendation preferring higher dosages or a greater number of strains,[36] our recommendations are based on levels shown to be effective in clinical trials, which in some contexts can be as low as 100 million colony-forming units (CFU) per day.[37,38] Indeed, a survey we conducted previously of retail dietary supplement products indicated that products with lower CFUs or fewer strains could more readily be linked to evidence of efficacy than multistrain, high-CFU products.[39]

Understanding probiotic product labels is a good start. Information shown on the label of a probiotic dietary supplement in the United States should include the genus, species, and strains contained in the product, the dose delivered in CFU (the most common measure of the number of live microbes in a probiotic product) through the end of shelf life, and expected benefits. (For help in deciphering these labels, see the label schematic developed by the International Scientific Association for Probiotics and Prebiotics[40] at https://isappscience.org/infographics/probiotic-labelling/.)

Per guidelines from the Food and Agricultural Organization of the United Nations and the World Health Organization, all probiotic products should have this type of information clearly displayed on the product packaging.[41] However, some probiotic foods display less information; for example, they may not specify the product's strains or recommended dosage levels. Product Web sites may or may not disclose details missing from the food label. The absence of such information makes it impossible to make evidence-based recommendations about those products.

Some probiotics are as effective as, if not better than, drugs traditionally used to treat or prevent certain diseases and conditions.

Probiotics are generally safe, with caveats

The overall safety of typical probiotics (*Lactobacillus* species, *Bifidobacterium* species, and *Saccharomyces cerevisiae* var. boulardii) has been well documented.[42,43] Many probiotic strains have been granted Generally Recognized as Safe status for use in foods in the United States.[44,45] Many traditional probiotic species have been evaluated by the European Food Safety Authority (similar to FDA, except jurisdiction is only over foods, not drugs) and are considered safe for use in food in the European Union.

Be aware that probiotics delivered in dietary supplements and foods are intended for the general population and not for patient populations. Manufacturers therefore are not required to assure safety in vulnerable populations. Nevertheless, probiotics are often stocked in hospital formularies.[46,47] Probiotic usage in vulnerable patient groups has been considered by an expert working group from the standpoint of quality assurance for microbiologic products used to treat and prevent disease, with the experts recommending that health care professionals (including pharmacists and physicians) seek quality information from manufacturers and that manufacturers participate in programs providing third-party

9 questions patients frequently ask about probiotics

Q. Is a higher dose and greater number of strains better?

A. Not necessarily. The best approach is to recommend products that have been tested in human studies with positive outcomes. Sometimes these products are single strain and have doses lower than other commercial products. If your patient's goal is to simply add live, potentially beneficial microbes to a diet, and he or she is not presenting with any specific health complaints, then fermented foods or any probiotic supplement should be sufficient.

Q. Is yogurt a good choice for managing antibiotic-associated diarrhea (AAD)?

A. In patients at high risk, recommend a probiotic from **TABLE 1**.[3-32] Simply recommending "yogurt" is not a strong recommendation, since few yogurts contain specific probiotics that are known to help with AAD. Yogurt usually contains live cultures, but the only cultures required in yogurt (*Lactobacillus bulgaricus* and *Streptococcus thermophilus*) do not survive intestinal transit and, with the exception of improving lactose digestion, are not likely to promote digestive health. Yogurts stipulating the strain and dose of added microbes are more likely to be supported by evidence.

Q. Does the sugar in probiotic yogurts negate the benefits of probiotic yogurt?

A. Most studies testing the health benefits of yogurt have been conducted on sweetened yogurts. Therefore, the sugar present in these products does not negate the probiotic effects. However, sweetened yogurts should be consumed as part of a balanced diet.

Q. Are probiotics beneficial for healthy people?

A. Studies have shown that probiotics can modestly decrease the incidence and duration of some common infectious symptoms such as those occurring in the gastrointestinal and upper respiratory tracts. These studies have been conducted on healthy subjects. But like multivitamins, improving health in healthy people is difficult to demonstrate.

Q. Are probiotic products unregulated?

A. Most probiotic products in the United States are marketed as foods or dietary supplements. These products are regulated by the US Food and Drug Administration (FDA), but not in the same way drugs are regulated. The FDA does not conduct premarket review of data on safety or health benefits. However, the FDA requires that these products are manufactured under current Good Manufacturing Procedures. Further, products are required to be labeled in a truthful (and not misleading) fashion. Enforcement of these standards requires action by the FDA, and limited resources within the agency result in products on the market that may not comply with standards.

Q. Are refrigerated products better than nonrefrigerated?

A. The stability of the live microbes in a probiotic product depends on product formulation and conditions of storage. Some products may require refrigeration, but others do not. Responsible product manufacturers make certain that their probiotic is able to meet the label claim through the end of shelf life if stored as recommended.

Q. Is it better to take probiotics as supplements or foods?

A. It is important to take the product tested for the specific effect, whether it is in food or supplement format. If products with equivalent efficacy are available in different formats, then have patients take the product that best fits with his or her diet and lifestyle.

Q. What is the difference between probiotics and prebiotics?

A. Probiotics are live microorganisms beneficial to one's health. Prebiotics are not live microbes, but are substances that are used by beneficial, resident microorganisms. Simply put, prebiotics are food for the beneficial bacteria in your gut. Most prebiotics are a type of fiber.

Q. The body already has so many bacteria, how can we expect the comparatively small number of live microbes in a probiotic product to have any benefits?

A. Our bodies are home to trillions of microbes. But remember that we are not uniformly colonized, even throughout the digestive tract. Orally consumed probiotics travel through some sparsely colonized regions of the upper digestive tract, and may become dominant in those segments. But even as minor components of the lower digestive tract, probiotics can impact the gut environment and clinical outcomes.

TABLE 1

Commonly used probiotics supported by good evidence[3-32]

These recommendations are based either on strength of recommendation taxonomy (SORT) Grade A/Level 1 or on evidence that has been systematically reviewed by select expert panels. All products are dietary supplements unless otherwise indicated.

Condition (study effect)	Probiotic strain(s) / Product brands[a]	Dosage (CFU/d, unless otherwise specified); always check product label	Estimated NNT (95% CI), or effect size	Comments
Acute pediatric diarrhea (treatment)	S boulardii lyo CNCM I-745 / Florastor[b]	10 billion	Reduced duration of diarrhea, mean 19.7 h	22 included studies for a total of 2440 patients[3]
	L reuteri DSM 17938 / BioGaia ProTectis	100-400 million	NNT: Day 1 cure, 8 (5.5-14.8); Day 2 cure, 2.5 (2.0-3.6); mean difference in diarrhea duration, –24.8 h (–38.8 to –10.8 h)	NNT based on 3 SORT Level 2 RCTs,[4-7] N = 256.[c]
	L rhamnosus GG (also known as LGG) / Culturelle	≥ 10 billion	Reduced duration of acute gastroenteritis in children; MD –0.85 day (–1.15 to –0.56)	18 RCTs (n = 4208) were included. Compared with placebo or no treatment, LGG use had no effect on stool volume but was associated with a reduced duration of diarrhea (15 RCTs, n = 3820, MD –0.85 day, [–1.15 to –0.56]). LGG use was associated with a reduced duration of hospitalization.[8]
Antibiotic-associated diarrhea (AAD) (reduced incidence)	*L rhamnosus* GG / Culturelle	1-40 billion	6.6 (4.5-12)	SORT Grade A for pediatric AAD: 3 studies are consistent and 2[9,10] were rated high quality in a systematic review.[11] Estimate based on meta-analysis (MH estimate of fixed risk difference) of data from the 3 trials[9,10,12] reported in the Cochrane systematic review.[11]
	S cerevisiae var boulardii lyo CNCM I-745 / Florastor[b]	226-1000 mg/d[d]	10 (9-13)[13]	NNT reported in a systematic review of 21 RCTs that involved pediatric or adult AAD.[13]
	L casei DN-114 001, *S thermophilus*, *L bulgaricus* / DanActive (aka Actimel)	20 billion *L casei* DN-114 001; 20 billion *S thermophilus*; 2 billion *L bulgaricus*	5 (3-15)[14]	Results from a single RCT including 135 hospitalized older adults (age 50+).[14] Cochrane review[15] scored this study as low risk of bias, although some elements were unclear, including allocation concealment.[14]
	L acidophilus CL1285, *L casei* LBC80R, *L rhamnosus* CLR2[e] / Bio K+ Bio K+ CL1285	50[16-18]-100 billion[18]	9 (5.6-21.9) for 50 billion CFU/d; 3.5 (2.4-6.3) for 100 billion CFU/d	Based on 3 RCTs,[16-18] SORT Level 1 or 2, with consistent results. Study weaknesses: (1) allocation concealment is not explicitly described in the reports for 2 studies and (2) a total of 35 of 472 (7%) of randomized patients are excluded from the primary analysis in 1 study. Dose-specific NNT and Miettinen-Nurminen-Mee score–based CIs reported here based on raw data from the 3 cited studies, all in adult hospitalized patients.

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(eg, United States Pharmacopeia [USP] or Underwriters Laboratories [UL]) verification of probiotic products to assure products meet applicable purity standards.[48,49]

Published case studies have reported that probiotics may be a rare cause of sepsis.[43] Recently, *Lactobacillus rhamnosus* GG was linked to bacteremia in 6 critically

TABLE 1

Commonly used probiotics supported by good evidence[3-32] *(cont'd)*

Condition (study effect)	Probiotic strain(s) / Product brands[a]	Dosage (CFU/d, unless otherwise specified); always check product label	Estimated NNT (95% CI), or effect size	Comments
C difficile diarrhea (reduced incidence)	*S cerevisiae* var boulardii lyo CNCM I-745 / Florastor[b]	10-30 billion	41.2 (25.2-108.1)[15]	Pediatric and adult patients. NNT based on MH estimate of common risk difference, using raw data from 9 RCTs of variable quality reported under the title "Analysis 1.9" in a recent Cochrane review.[15]
	L acidophilus CL1285, *L casei*, *L rhamnosus* CLR2[d] / Bio K+ Bio K+ CL1285	50[16-18]-100 billion[18]	30.3 (16.3-211.5) for 50 billion CFU/d 4.3 (3.0-7.1) for 100 billion CFU/d	Raw primary data, as reported in Analysis 1.8 in recent Cochrane review[15] of 3 RCTs of variable quality. These are the same 3 trial reports described earlier for AAD outcome for this same product. These trials were not powered for the CDAD outcome. Same adult hospitalized patients as for AAD trials. The 3-arm study by Gao et al[18] found a very high incidence of *C difficile* in the placebo arm; 20 of 84 patients (23.8%). Dose-specific NNT and Miettinen-Nurminen-Mee score–based CIs are based on trial data as summarized by Cochrane.[f,g]
	L casei DN-114 001, *L bulgaricus*, *S thermophilus* / DanActive	20 billion *L casei* DN-114 001; 20 billion *S thermophilus*; 2 billion *L bulgaricus*	5 (3-15)[14]	Based on a single RCT,[14] the same trial report as described earlier for AAD outcome for this same product.
Colic in breastfed infants (reduced symptoms and crying time)	*L reuteri* DSM17938 / BioGaia ProTectis	100 million	2.6 (2-3.6)[19]	SORT Grade A: Consistent evidence from high-quality RCTs included in individual patient data meta-analysis.[19] Commence once colic is diagnosed/suspected (5 drops, one straw, or one tablet daily).
Constipation (management of symptoms)	*B lactis* BB-12 / See footnote[h]	1-10 billion CFU Placebo = 453 1 billion, n = 343 10 billion, n = 452	Risk difference CI, 10.4 (4.7-16); percentage points and a corresponding NNT (95%) of 9.6 (6.2-21.2)	SORT Level 1,[20] but positive result found only in per-protocol analysis.[i]
	B lactis DN-173010, *L bulgaricus*, *S thermophilus*, *Lactococcus lactis* / Activia	13 billion *B lactis* DN-173010, 1 billion total of *L bulgaricus*, *S thermophilus*, *Lactococcus lactis*	40% increase in stool frequency by Week 1 and 58% by Week 2	Effect size based on one SORT Level 2 study.[21]

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ill patients, but all cases resolved without complications.[50] Further, the death of a premature infant was linked to administration of a probiotic contaminated with an opportunistic pathogenic mold.[51] A randomized controlled trial (RCT) of a multispecies probiotic product in critically ill pancreatitis patients showed higher mortality in the group given the multispecies probiotic.[52] However, additional examination of the data suggests that the observed higher mortality was due to problems with randomization for disease severity and other concerns, and not to the probiotic.[53] Much more frequently, probiotics have been administered orally in at-risk patient groups, including premature infants, cancer patients, and critically ill patients, with no significant increases in adverse events.[54-56]

Taken together, clinical trials have re-

TABLE 1

Commonly used probiotics supported by good evidence[3-32] *(cont'd)*

Condition (study effect)	Probiotic strain(s) / Product brands[a]	Dosage (CFU/d, unless otherwise specified); always check product label	Estimated NNT (95% CI), or effect size	Comments
Lactose intolerance (reduction of symptoms associated with lactose maldigestion)	*L bulgaricus*, *S thermophilus* / Yogurt with ≥ 100 million live, active cultures/gram yogurt	10 billion/100 g yogurt	One study showed the ingestion of 18 g lactose in yogurt resulted in one-third as much hydrogen excretion as a similar load of lactose in milk or water. Twenty percent of yogurt group reported diarrhea or flatulence compared with 80% of milk group.[22]	Recommendation based on numerous studies, although not systematically reviewed.[23] The European Food Safety Authority approved the claim "Live yoghurt cultures in yoghurt improve digestion of lactose in yoghurt in individuals with lactose maldigestion" for yogurts containing 10 billion live yogurt cultures/100 g yogurt.[24] Choose yogurts that are labeled "contains live and active cultures."
Vaginal health (improved therapeutic efficacy of antibiotic treatment of bacterial vaginosis)	*L rhamnosus* GR-1, *L reuteri* RC-14 / Fem-Dophilus RePhresh ProB	4 billion	3.7 (2.5-6.6)	SORT Grade A, based on 2 RCTs, which are consistent, SORT Level 1.[25,26] Miettinen-Nurminen-Mee score–based CIs computed using raw data reported in studies. Start probiotic before or as soon as possible after starting antibiotic. Continue at least 1 week after antibiotics have been stopped.

AAD, antibiotic-associated diarrhea; *B*, *Bifidobacterium*; *C*, *Clostridioides* (formerly *Clostridium*); CDAD, *C difficile*-associated diarrhea; CDI, *Clostridium difficile* infection; CFU, colony-forming units; CI, confidence interval; FDA, Food and Drug Administration; *L*, *Lactobacillus*; MH, Mantel-Haenszel; MD, mean difference; NNT, number needed to treat; RCT, randomized controlled trial; *S*, *Saccharomyces*; SORT, Strength of Recommendation Taxonomy.

[a]Other commercial products may contain the same strains and doses as the example products listed. *L rhamnosus GG*, *B lactis* BB-12, and *Saccharomyces cerevisiae* var. boulardii lyo CNCM I-745 may be available in products other than those listed. We do not advocate for a specific commercial brand, only the strain. Ingredient statement should indicate the strain and dose. Follow manufacturer usage and storage instructions.

[b]Florastor is labeled in mg, not CFU. This is contrary to recommended practices. Manufacturer indicates that Florastor contains 5 billion CFU/capsule through end of shelf life. Some experts recommend use with caution in severely immunocompromised patients.

[c]These estimates are based on a Mantel-Haenszel (fixed-effects) estimate of the common risk difference across the 3 RCTs. On Days 3-7, there was significant between-study heterogeneity.

[d]An error in the meta-analysis[27] was made regarding the dose used in 1 included study.[28] It listed the dose used in this study as 50 mg, but the total daily dose was actually 6 50-mg tablets, or 300 mg/d. Therefore, we indicate in this table the actual smallest dose, 226 mg, which was used in Lewis et al.[29]

[e]Although *L rhamnosus* CLR2 was not labeled before 2014, it has always been included in Bio-K+ and Bio-K+1285.[30]

[f]One hospital in Canada gave Bio-K+ to all adult patients on antibiotics for 10 years. During this time, 44,835 inpatients received Bio-K+, and the CDI rate declined from 18 cases per 10,000 patient-days to 2.3 cases per 10,000 patient-days.[31]

[g]For trials reporting on both AAD and CDAD outcomes, cases of AAD that lacked *C difficile* testing results are excluded from the denominator in Analysis 1.8 of Cochrane review.[15]

[h]Strain *B lactis* BB-12, when indicated on a product label, is present at 1 billion CFU/serving or dose in many different foods and supplements, including Trubiotics (Bayer), YoBaby (Stonyfield), Nancy's yogurt and kefir, and LaYogurt yogurts by Johanna Foods. Available products vary over time and by geographical region.

[i]This study involved 1248 healthy adults who defecated only 2 to 4 days per week during a 2-week baseline (pre-randomization), including n = 453 placebo control subjects. The primary outcome for this study was that weekly stool frequency improve from baseline for at least half of the follow-up weeks. For this outcome, it appears that 656 of 791 (82.9%) treated subjects responded and that 355 of 451 (78.7%) placebo subjects responded, for a risk difference of 4.2 (–0.4 to 8.8) percentage points for the primary stool defecation outcome, which is not statistically significant. However, the trial report also included a posthoc analysis of a more restrictive version of the outcome, one based on FDA[32] guidance issued after the study began data collection, which when applied posthoc, resulted in the statistically significant risk difference indicated.

ported more adverse events in the placebo than probiotic group.[42] Infection data collected in these trials have been used in subsequent analyses to demonstrate that in some settings, certain probiotics actually reduce the risk of infections. One notable example was a meta-analysis of 37 RCTs that showed that probiotics reduce the incidence of late-onset neonatal sepsis in premature infants.[57]

At the present time, risk of probiotic use is low but still demands awareness, especially in unusual circumstances such as use in particularly vulnerable patients not yet studied or use of a product with limited available safety data. Any recommended product should be manufactured in compliance with applicable regulatory standards and preferably assured through voluntary quality audits.[49]

TABLE 2

Sample probiotic recommendations from global medical organizations[68-71]

Source	Recommendations
World Gastroenterology Organisation	Practice Guideline on Probiotics and Prebiotics Graded (using Oxford Centre for Evidence Based Medicine grading system[68]) evidence for probiotic use for GI conditions. The introduction to this guideline provides useful basic information about probiotics (and prebiotics), culminating in 2 tables (Table 8 for adult indications; Table 9 for pediatric indications) that summarize the gastrointestinal conditions for which there is evidence from at least 1 well-designed clinical trial.[69]
European Society for Paediatric Gastroenterology Hepatology and Nutrition[70,71]	The use of *Lactobacillus rhamnosus* GG may be considered in the management of children with acute gastroenteritis as an adjunct to rehydration therapy. Quality of evidence: Low. Recommendation: Strong. The use of *Saccharomyces cerevisiae* var boulardii may be considered in the management of children with acute gastroenteritis as an adjunct to rehydration therapy. Quality of evidence: Low. Recommendation: Strong. The use of *Lactobacillus reuteri* DSM 17938 may be considered in the management of children with acute gastroenteritis as an adjunct to rehydration therapy. Quality of evidence: Very low. Recommendation: Weak. If the use of probiotics for preventing AAD in children is considered, the working group recommends using: • *L rhamnosus* GG. Quality of evidence: Moderate. Recommendation: Strong. • *S cerevisiae* var boulardii. Quality of evidence: Moderate. Recommendation: Strong. If the use of probiotics for preventing *Clostridioides difficile*-associated diarrhea in children is considered, the working group suggests using *S boulardii*. Quality of evidence: Low. Recommendation: Conditional.

AAD, antibiotic-associated diarrhea; GI, gastrointestinal.

Evidence of effectiveness is strong for many conditions

Probiotics have been studied for clinical benefit in numerous conditions (**FIGURE**[3,8,11,15,19,23,54,58-65]), and systematic reviews of the clinical trials have found the overall results to be sufficiently strong to warrant recommendations, even though some individual trials were of low quality.[66] Some evidence may require confirmatory studies to clarify which specific product should be recommended.

Admittedly some of the indications are for diseases that most family physicians do not typically manage. For example, the evidence for probiotics for preventing necrotizing enterocolitis in premature infants was reviewed in a Cochrane analysis, which gave an estimated number needed to treat (NNT) of 41 and concluded, "our updated review of available evidence strongly supports a change in practice."[54] A recent study of > 4500 infants in India found a probiotic/prebiotic supplement resulted in a 40% reduction in clinical sepsis compared with placebo.[67] Another common use of probiotics is as adjunctive therapy for mild to moderately active ulcerative colitis, where the current estimated NNT is 4.[63] Probiotics may also address gut and non-gut conditions and serve different functions throughout the lifespan.

Probiotic applications most relevant to primary care

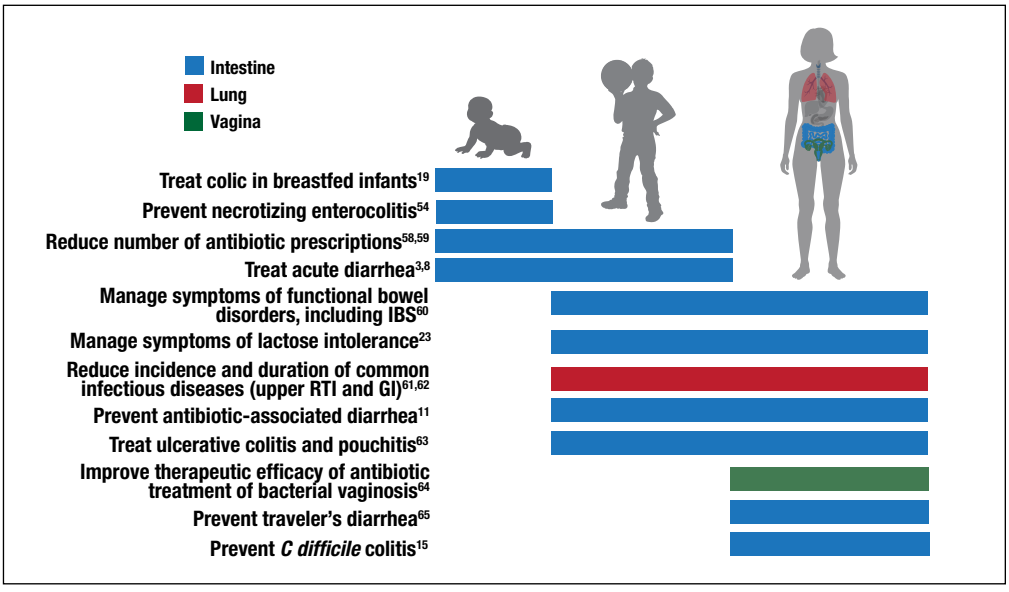
We summarize in **TABLE 1**[3-32] probiotic uses supported by good evidence for indications of general interest in primary care medicine. This table includes endpoints with actionable evidence (including many strength of recommendation taxonomy [SORT] Level 1 studies) that allow us to make strong recommendations. Not all evidence is SORT Grade A, but we agree with the expert groups that deem evidence to be sufficient to warrant recommendations.

The granular data we provide can help shape recommendations of a product for a specific indication. Numerous probiotics have been tested on suboptimal gastrointestinal health, including managing functional bowel symptoms ranging from occasional gas, bloating, or constipation through diagnosed irritable bowel syndrome (IBS). Sup-

FIGURE

Conditions treatable or preventable with probiotics[3,8,11,15,19,23,54,58-65]

Sufficiently strong evidence from systematic reviews and meta-analyses of clinical trials supports the use of probiotics in several conditions.



C, *Clostridiodes* (formerly *Clostridium*); GI, gastrointestinal; RTI, respiratory tract infection.

Base your probiotic dosages on levels shown to be effective in clinical trials, which can be as low as 100 million CFU/d.

plements such as *Bifidobacterium infantis* subsp. *longum* 35624 (the probiotic in Align), *Lactobacillus plantarum* 299V (the probiotic in NatureMade Digestive Probiotic Daily Balance), and foods such as Activia yogurt, Yakult cultured milk, or Good Belly juice can be recommended for digestive symptoms.

For patients experiencing gut symptoms unrelated to diagnosed disease, it may be reasonable for them to try a well-documented strain for 3 to 4 weeks. Currently it is difficult to predict success *a priori*; this may change as we learn more about how an individual's microbiome, diet, and genetics affect response to specific probiotics. **TABLE 2**[68-71] presents sample recommendations from international expert panels for select contexts.

The popular press today commonly recommends consuming more fermented foods. Although we agree in general with this recommendation, physicians should be clear that fermented foods may be a source of live cultures, but not all fermented foods retain live microbes. Further, many fermented foods lack evidence documenting health effects, and therefore are not a source of probiotics. If the patient's goal is to support regular diet with live microbes, any number of probiotic products or fermented foods that retain viable cultures may suffice. However, when patients request probiotics for specific needs, recommendations should be based on available evidence for specific studied products. (See also, "Questions patients frequently ask about probiotics" on page E3.)

What to look for in the future

Basic research, human trials, and market development in the field of probiotics are progressing rapidly. Probiotics at this time are primarily from the genera *Lactobacillus*, *Bifidobacterium,* and *Saccharomyces*. But the potential of probiotics has spurred research into previously untapped microbial members of the healthy human microbiota. Microbes such as *Akkermansia*, *Faecalibacterium,* and *Rosburia* may comprise "next-generation probiotics" that will likely be developed as drugs.[72]

Active areas of research holding some promise involve microbiome-driven components of intractable problems such as metabolic syndrome (obesity,[73] diabetes, and lipid dysregulation) and brain dysfunction[74] (depression, anxiety, cognition, autism). A guide to the clinical use of probiotic products available in the United States, updated yearly, may be a useful reference (but the reader may want to examine the referenced studies as their level of evidence is different than the SORT method).[75] Science-based videos, infographics, and other resources are available from the International Scientific Association for Probiotics and Prebiotics, (mentioned earlier; www.isappscience.org/).

It appears that probiotics will continue to be widely used and hopefully in a more evidence-based manner. As we learn more about individual microbiome variations, recommendations will likely be more patient specific. Probiotics that have robust evidence represent the strongest recommendations. Even so, since the risks of using traditional probiotics (such as *Lactobacillus*, *Bifidobacterium* and *Saccharomyces* strains) are low, trial and error may be warranted at times. JFP

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Since the risks of using traditional probiotics are low, trial and error may be warranted at times.

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