VIEWPOINT

The Probiotic Conundrum
Regulatory Confusion, Conflicting Studies, and Safety Concerns

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It is increasingly clear that microbial communities have important functions in immunologic development, infection prevention, and intestinal barrier maintenance. These roles lend credence to the notion that probiotic (ie, live organisms that putatively benefit their host) administration can alter the human gut microbiome. Given that numerous meta-analyses and review articles and marketing are supportive of probiotics, it is easy to understand why medical professionals adopt "can't hurt, might help" attitudes toward these substances. However, the paucity of high-quality data supporting the value of probiotics, concerns about potentially biased reviews of their efficacy, the complex framework in which probiotics are regulated and sold, and the limited but increasingly concerning safety information suggest that this approach may not be appropriate.

To understand the contradiction between enthusiasm for probiotics and the lack of data supporting use of these products, it is helpful to first examine the regulatory environment in which they are sold. In the United States, the primary regulatory authority is the US Food and Drug Administration (FDA), which, despite the size of the industry (annual worldwide revenues expected to exceed US $64 billion[1]), has no central office to oversee probiotics. Nonetheless, physicians and the public may mistakenly assume that probiotics available for purchase are subject to stringent regulatory oversight.

The FDA categorizes products by the type of claims a manufacturer makes on their behalf, not by ingredients or other properties. If a manufacturer claims that any product, including a probiotic, cures, mitigates, treats, or prevents disease, the product is classified as a drug, thereby triggering a costly Investigational New Drug (IND) application process. Similarly, investigator-initiated human studies seeking to determine if a probiotic cures, mitigates, treats, or prevents a disease are considered drug trials and require an IND application, even if the administered intervention has a record of safety in the target population. These requirements pose barriers for researchers who are obliged to provide propriety manufacturing information (ie, Drug Master File, information held by the manufacturer) to the FDA as part of the IND application process. Thus, a company can block a study by simply withholding documentation, such as by not permitting researchers to include proprietary information about a product.

This regulatory framework has led to the marketing of probiotics as dietary supplements. This approach permits their manufacturers to make structure-function claims without FDA approval. Such claims link the probiotic to a body function using words such as "may help" or "promotes." Products that make structure-function claims (such as "helps your digestive system work better" or "promotes health and wellness"), which most consumers find difficult to distinguish from FDA-approved health claims (such as for sumatriptan succinate, "indicated for the acute treatment of migraine attacks with or without aura in adults"), must include a disclaimer indicating that their statements have not been evaluated by the FDA and are not intended to diagnose, treat, or prevent disease. Nonetheless, many consumers erroneously believe that supplements such as probiotics have had their contents analyzed for purity, have been tested for safety and effectiveness, and are approved by the FDA for use as claimed.

Barriers to high-quality clinical research on probiotics are magnified by the "locked-in" provision, which prohibits marketing a substance as a food product if it is first studied under an IND, even if the study is designed to support use of that product as a food rather than a drug. However, the FDA offers a loophole whereby marketing a substance as a dietary supplement or food before seeking an IND (ie, not conducting research that triggers an IND requirement) or beginning any clinical investigation preserves the option to continue to market the substance in those forms after substantial clinical investigations take place, even if the results demonstrate no benefit. These provisions dissuade manufacturers and researchers from rigorously evaluating structure-function probiotic claims. Instead, claims remain subject to the requirements of the food categorization of probiotics. Given all the aforementioned barriers, the FDA has not yet approved any probiotic products as live biotherapeutic agents.[2] However, because the public consumes probiotics under the assumptions of their effectiveness, safety, and government certification, a more stringent regulatory framework is required.

Because high-quality trials that evaluate probiotic efficacy are difficult to conduct, there are few data supporting efficacy claims. Moreover, given the public's perception of structure-function claims, and the successful market for probiotics, manufacturers have little incentive to generate evidence supporting their use. PubMed searches contrast the increasing number of articles on probiotics (3495 in 2019 vs 2658 in 2018, a 31% increase) with the decreasing number reporting human clinical trials of probiotics (185 in 2019, the least since 2012, and a decrease of 92 since 2018 using PubMed search term *probiotic human clinical trial*). There are additional disturbing trends in the literature. Earlier trials, generally with high risk of bias, have favored probiotics for a myriad of conditions, while the preponderance of more recent, low-risk-of-bias trials fail to support earlier positive findings.[3] These sobering reversals of conclusions cast doubt on "might help" premises.

Meta-analyses, which attempt to clarify decision-making in the face of inconsistent or underpowered trials, can be highly misleading. As has been pointed out, meta-analyses, which include small, unreliable trials, often lend

credence to underpowered, low-quality, single-center trials that can inflate treatment effects. Small, single-center trials have less oversight and are more susceptible to misconduct and at greater risk of bias than multicenter trials. Moreover, because small trials that show large effects are more likely to be published than those that report no benefit, these reports can dominate the results of meta-analyses. The probiotic literature is a classic example of this conundrum.

The few Cochrane reviews that have reported evidence in favor of probiotics, such as a recent analysis of their use in preventing antibiotic-associated *Clostridioides difficile* infection, do not supply convincing data.[4] The review, which analyzed 8672 cases, concluded there was moderate beneficial evidence that probiotics prevent *C difficile*–associated diarrhea (CDAD), but in subgroup analyses this benefit was restricted to those in whom the risk of CDAD exceeded 5%. However, only 4 of the 31 included trials, consisting of only 620 patients (7% of the total analyzed data set), reported any benefit of probiotics. One of these studies was a small (n = 100) study that had high risk of bias, was included as an unpublished abstract from a 2007 conference, and it did not even describe the control group intervention. Nonetheless, this study was assigned a 10% weight in the random-effects model. In contrast, a much larger (n = 2981) trial with low risk of bias that found that probiotics did not prevent CDAD received a weight of 14%, despite studying nearly 30 times the number of patients. Recent reassessments of meta-analyses on probiotic treatment of diarrhea[5] and constipation[6] provide pointed and well-substantiated criticisms of published meta-analyses and conclude that prior meta-analyses were highly misleading and that probiotics offer no benefit.

While "can't hurt" assumptions probably hold true for most probiotics, recent evidence is a good reminder that probiotics are not harmless. Data from a pediatric intensive care unit reported the risk of bloodstream infections caused by *Lactobacillus rhamnosus* GG to be 1.1% among the 522 patients given this probiotic, with whole genome sequencing providing evidence that the administered probiotic translocated from the gut into the blood.[7] In a trial of probiotics in acute pancreatitis involving 296 adults, excess mortality among treated patients (16% vs 6% in the control group) forced early study termination.[8] These studies are the tip of the iceberg, and postmarketing safety surveillance is particularly important in this field because only 2% of probiotic trials adequately report key safety components.[9] Moreover, the long-term safety of microbiome manipulation and the risks of antibiotic resistance gene transfer to other gut microbes, or arising from selective pressure, remain unknown but are a concern.

Two principal reasons might explain the willingness of physicians to suggest probiotics. First, the regulatory framework makes probiotics readily available without compelling their manufacturers to generate sufficient evidence to enable physicians to contradict media and industry encouragement of their use. Second, some professional societies and some journals may be insufficiently critical in reviewing probiotic studies and considering the implications of financial conflicts of interest, a challenge not unique to probiotics.[10] An emphasis on the need for proof of efficacy from high-quality studies with low risk of bias to minimize the influence of poorly conducted trials and conflicts of interest is needed.

In summary, physicians and other health care professionals and regulatory authorities should require the same evidence of efficacy, safety, and cost-effectiveness for probiotics as are required for regulated drugs. Journals should require that meta-analyses and systematic reviews focus on large, multicenter, low-risk-of-bias studies. Regulations must be adapted to enable both manufacturers and independent investigators to test therapeutic and structure-function claims expeditiously and economically. Unless and until new data emerge, the promotion and tacit endorsement of probiotic use is not in the interests of patients, the general public, health care professionals, or the reputations of ethical probiotic manufacturers.

ARTICLE INFORMATION

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