Editorial

Editorial: Prerequisites for a Successful Probiotic Therapy in Dysbiosis

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This article briefly addresses why many forms of probiotic treatment are unsound and provides a set of prerequisites to increase the effectiveness of improved probiotic delivery. We pay particular attention to why probiotics largely fail, then suggest prerequisite principles that favor successful long-term engraftment.

Probiotic Treatments Are Empirically Ineffective

Since the discovery of probiotic gut bacteria in healthy microbiomes, there has been an explosion in the use of probiotics as a method of improving health and preventing disease. However, the evidence for its efficacy is sparse and deeper analysis suggests that probiotics simply pass through the gut without engraftment.[1] Specifically in *Clostridioides difficile* infection (CDI), well-established probiotics *Saccharomyces boulardii*, *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, and others have been tested in clinical trials and shown to be ineffective in preventing secondary prevention of CDI.[2,3] More broadly, comprehensive systematic reviews of probiotics in the prevention of CDI and resulting diarrhea suggest that a small clinical benefit was achieved with an improvement in merely a 2.5% reduction in risk.[4] This evidence is in stark contrast to the extremely high efficacy rates (93–95%) reported with donor-based fecal microbiota transplantation (FMT)[5,6] by colonoscopy. This stark polarization in efficacy demands a more critical analysis between the two outcomes as the two interventions appear seemingly similar.

Why Probiotics Are Largely Ineffective

A major cause of oral probiotic failure results from the lack of bacterial engraftment in the host's intestines. Engraftment may be defined as the ability of exogenous bacteria, either from probiotics or FMT, to reside permanently in the host in the long-term. Thus, one fundamental flaw in probiotic supplementation relies on the assumption that we orally acquire microbes from our environment which then become part of our microbiome. Vitamins and minerals may be absorbed naturally in this manner from a dietary standpoint. However, the evidence suggests that on the contrary either our cells or the existing microbiome rejects new microbes and their engraftment.[7,8] This makes sense from an evolutionary standpoint as it would become a liability to become infected on every instance when encountering a pathogen, for example, in meals. Furthermore, there is a strong competitive advantage for the preservation of an inherited maternal–infant microbiome[9] or the preservation and stability of the existing microbiome in a healthy individual.

Despite FMT being the gold standard for CDI cure, complete engraftment post-FMT is still rather low. Sequencing data from a host's microbiome a 24 to 48 hours after an FMT shows major shifts in the diversity of microbial species; however, resequencing of the host microbiomes beyond 14 weeks shows a return to original levels of diversity.[10] Yet, the small volumes of bacteria that do engraft are generally responsible for the major clinical changes observed. This minority group appears to be a disproportionally strong predictor of remission and has been termed "Keystone Species," that has been used successfully as a strategy in customizing FMT super donors in recurrent hepatic encephalopathy.[11]

With the understanding that engraftment is critical to the success of microbiome changes, we can identify multiple features of probiotic supplementation that neutralizes bacterial engraftment. First, the data suggests the higher the abundance of a species introduced during a FMT, the more likely long-term engraftment occurs,[8] therefore quantity matters. Probiotic supplementation in its current form with a single oral capsule less than 500 mg limits the final quantities of viable microbes that make it past the low pH of the stomach, oxygen exposure, bile salt exposure, and other

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insults to arrive at the large intestines. Furthermore, from our internal studies, we have also encountered the progressive loss of probiotic strain efficacy when culturing in vitro at each passage. Thus, commercial cultured probiotics having undergone many multiple passages suffer the same loss of strain efficacy given the passaged strains are no longer the original efficacious strains. This is in contrast to a minimum of 30 g of donor stool recommended in colonoscopy-based FMT[12] and in its capsule-based-FMT form, with anywhere from six highly concentrated to forty standard large capsules typically used in one course. Hence, significantly greater volumes arrive in the colon in a viable state comparative to probiotic formulations that in turn lead to greater engraftment levels.

Second, single-strain probiotics, which are the mainstay of probiotics, may be inherently ineffective due to the lack of species diversity. In successful long remission of ulcerative colitis and recurrent CDI, major shift in the recipient's gut bacteria diversity (as measured by alpha diversity) is a major predictor of long-term remission,[13] and the lack of bacterial diversity changes after FMT is also a predictor of failure and CDI recurrence.[13] This data is also supported by microbial profiling of super donors showing bacterial species richness as a determinant of successful remission in recipient patients.[14] Hence, the modern practice of purification and supplementation of a single probiotic species may be insufficient as it may not be supplementing the "missing" species required by the recipient, eradicating the occult species, nor inductive of the major microbiome diversity changes necessary for long-term remission. Moreover, in many cases, the deficient or superinfecting species in the dysbiotic patient is unknown to the treating physician, and an attempt to guess or trial each probiotic in the happenstance of matching a probiotic strain to the recipient's need is simply an unproductive gamble. All of which may be easily resolved when using super-donor samples with verified species bacterial richness, diversity, and clinical success.[15]

Prerequisites to an Effective Probiotic

Based on the current challenges of probiotics discussed, the future development of probiotics may have an impossibly difficult goal to achieve, yet some strategies may improve efficaciousness. First, the lack of engraftment must be addressed, namely that the engraftment of probiotics needs to substantially increase by several orders of magnitude. While this could be done simply by colonoscopy delivery or major increases in dosage and frequency, the added inconvenience and side effects may simply maintain FMT as the mainstay treatment. However, one area of technological development suggests adjuvants such as smectite clay, which binds to lactic acid bacteria and the intestinal surface of the gut, can be used to significantly promote probiotic adhesion to the gut biofilm.[15] Thus, adjuvants, or along that principle, biofilm adherent compounds, could allow small doses of probiotics to be used that extends the window for engraftment and retention in the microbiome without necessitating large doses.

Second, outside of engraftment issues, species richness and diversity appear to be a clear prerequisite for long-term protective effects. In this regard, a multistrain and species-diverse product may prove more efficacious. It is unlikely that a handful of strains is sufficient despite careful selection. Considering that super-donor diversity can reach into the thousands of different bacterial species not inclusive of virus and fungi species, it is unknown how many species are needed in a probiotic to reach the critical mass needed to truly modify the host microbiome. Pragmatically, it may also be extremely challenging from a regulatory perspective to develop a probiotic product that contains hundreds of unique bacterial strains. Each strain needs individual approval, quality, and purity requirements prior to certification from regulatory bodies.

Pragmatically, the commercial cost of producing hundreds of pure strains of unique bacteria may make such an approach commercially unviable. Nevertheless, if one were to take a rational approach to select the most effective probiotics, 16S sequencing data from successful FMT interventions shows a taxonomical hierarchy to follow. The engraftment of species such as *Bacteroides massiliensis*, *Prevotella copri*, and *Bifidobacterium longum* forms just a few of the identified species highest ranked for the prediction of long-term remission from inflammatory bowel disease (IBD).[10] Equally there is a reverse ranking of microbes that engraft and predict disease relapse, including Proteobacteria, Bacteroidetes, *Roseburia intestinalis,* and *Alistipes putredinis,* among others at the top of the list.[10] A practical probiotic product therein lies in the inclusion of as many positive predictor microbes in the capsule, and the exclusion of as many negative predictors of relapse in order to give the highest chance for the return to species richness in the host.

Conclusion

The prerequisites for the successful "refloralization" of a host's microbiome are highly dependent on engraftment and species diversity, which are deficient in probiotic supplementation. To improve the levels of probiotic efficacy, molecular or technological innovations to raise engraftment are required that may come in the form of biofilm adjuvants. Second, probiotic formulations are currently severely lacking in species diversity that is a strong predictor for efficacy in CDI and UC (ulcerative colitis). Altogether these microbial dynamics favor FMT as the current gold standard, while probiotic supplementation will require further development. Nonetheless, new solutions in probiotics delivery may be of mutual benefit in increasing the efficacy of FMT as well, as engraftment in FMT is far from efficient, and FMT efficacy in conditions such as IBD and obesity shows high variability in patient responses.[1] In light of these comments, it is apparent that *Saccharomyces boulardii*, or for that matter any other probiotic, is unlikely to be efficacious for *C. difficile*.[16]

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