

Part 3

Medical Treatment: What's Round the Corner?

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Probiotics – separating science from snakeoil

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LEARNING POINTS

Probiotics

- Not all probiotics are the same; they have variable efficacy in different indications
- While there is evidence for efficacy in animal models of IBD and in human “pouchitis,” the role of probiotics as a primary therapy for Crohn’s disease or UC is unproven
- There is a critical need for verification of the quality, shelf-life, composition, and stability of many probiotic preparations
- Even if naturally occurring probiotics have suboptimal efficacy in IBD, genetically engineered organisms to deliver anti-inflammatory molecules to the diseased mucosa are promising

Introduction

A probiotic is usually defined as a live microorganism that, when consumed in adequate amounts, confers a health benefit on the host. A prebiotic is a non-digestible food ingredient (frequently an oligosaccharide) that can beneficially influence the health of the host by selectively altering the enteric flora, and a synbiotic is a mixture of pro- and prebiotics. In practice, the definition of probiotics is continually under revision as more is discovered about the mechanism of host–flora interactions. For practical purposes, probiotics are most simply defined in operational terms as commensal organisms that can be harnessed for therapeutic benefit.

Unfortunately, the field of probiotics research has been clouded and probably hindered by exaggerated or unsubstantiated claims for efficacy in a myriad of disorders with little supporting evidence. Simplistic notions of “bowel cleansing” as portrayed in the popular press are conceptually appealing, attractive to patients, and readily exploited commercially. However, the field is beginning to attract rigorous scientific input and two important points have become clear. First, not all probiotics are the same and it is naive to assume that probiotic organisms will behave similarly in different clinical settings. Second, probiotic action is more complex than simply replacing “bad” bacteria with “good” bacteria. Thus, the impact of probiotics or prebiotics is not simply ecologic (“good” for “bad” bacteria) and almost certainly reflects a change in prokaryotic–eukaryotic signaling [1].

The appeal of probiotics to the lay public is the promise of “bugs instead of drugs.” The emphasis has generally been on live microorganisms, but with clarification of mechanisms of action and identification of therapeutic probiotic metabolites, a program of “bugs to drugs” discovery may yield a new generation of biologic control agents that will challenge current definitions. For this reason, the more inclusive term *pharmabiotics* may be more useful in the future.

Background and rationale for probiotics in IBD

Disturbances of host–flora interactions have been implicated in the pathogenesis of IBD. Therefore, manipulation of the enteric flora might be anticipated to emerge as a

plausible therapeutic option. Comparative studies using germ-free and conventionally colonized animals have established that the intestinal microflora is required for optimal development of mucosal and submucosal structure and function. Regulatory influences of the flora on the intestine range from priming mucosal immunity to promotion of gastrointestinal motility, secretory and absorptive capacity, and also include a variety of metabolic properties such as production of folate and B vitamins. In addition, bacterial colonization of the gut has extra-intestinal effects including the regulation of fat deposition. Collectively, the enteric flora comprises over 400 different bacterial strains, accounts for about 1–2 kg body weight in adult humans, and has a metabolic activity equivalent to a hidden inner organ comparable with that of the liver [1].

It appears that the flora exerts a continual regulatory influence on mucosal homeostasis; disruption of this host–flora dialogue renders the intestine vulnerable to injury. Thus, the bacterial flora may be viewed as an important health asset which occasionally may become a liability by participating in the pathogenesis of IBD in genetically susceptible individuals. It follows from first principles that any strategy that promotes microbial assets and/or offsets liabilities represents a therapeutic option. Therein lies the rationale for probiotic/prebiotics and other forms of therapeutic manipulation of gut flora.

Criteria for selecting a probiotic

Probiotics have traditionally been selected from the genera *Lactobacillus* and *Bifidobacterium*, although other bacteria including *Escherichia coli* and non-bacterial organisms such as *Saccharomyces boulardii* have been selected for probiotic potential. Criteria for selection of microorganisms as candidate probiotics include proliferative capacity and capability of transit and survival within the gastrointestinal tract. This requires relative resistance to acid and bile. Most important are safety criteria. Lactobacilli and bifidobacteria have a long history of usage without hazard. In rare or exceptional circumstances, lactobacilli have been linked with systemic translocation but there appears to be no increased frequency of bacteremia with increased usage of probiotics.

Guidelines for probiotic strain identification and functional characterization have been generated by the Joint Food and Agricultural Organization (FAO) of the United Nations and the World Health Organisation (WHO) [2].

At present, there is no biomarker from *in vitro* studies that reliably predicts function *in vivo* for putative probiotic in any clinical condition. It is unlikely that a single microbial agent or microbial product will be effective in each of the diverse clinical conditions for which probiotic efficacy has been claimed. Furthermore, in light of increasing understanding of pharmacogenomics and nutrigenomics, individual variability in composition of the enteric flora might need to be considered as a determining factor for optimal probiotic strain selection. Without resolution of these pivotal issues, probiotic therapy will struggle to become established in the arena of evidence-based medicine.

Mode of action

Probiotics probably exert their beneficial effects by mimicking normal host–flora interactions [1]. Oral consumption of probiotics is associated with immune engagement and demonstrable systemic immunologic changes [3,4]. Modern techniques, such as laser capture microdissection and gene array analysis of gnotobiotic animals, are now being deployed to probe the molecular events underpinning the regulatory signaling from the lumen and promise to reveal new molecular targets for the design of future therapeutics [5]. Incoming bacterial signals include secreted chemoattractants, such as the formylated peptide f-met-leu-phe, cellular constituents such as lipopolysaccharide and peptidoglycans, and bacterial nucleic acids (CpG DNA). Discrimination of pathogens vs. commensals by the host is mediated, in part, by pattern recognition receptors such as Toll-like receptors (TLRs) which are present on epithelial and immune (dendritic) cells. Engagement of TLRs by ligands from the commensal flora appears to be required for optimal mucosal and immune development and for responses to episodic challenge with pathogens and other forms of injury [6].

Probiotics can also mimic other aspects of the commensal flora including competitive antagonism against pathogens and production of antimicrobial factors such as bacteriocins and other metabolites [7].

Testing the theory – is there evidence for efficacy?

The most compelling evidence for efficacy of probiotics in any clinical condition is in the setting of enteric infections and postantibiotic syndromes where their role is supported

by several recent meta-analyses and a favorable Cochrane review [8,9]. There is also a growing body of support for some but not all probiotics in irritable bowel syndrome and this may involve modulation of cytokines [10].

In IBD, there have been many reports showing the prophylactic effects of probiotic feeding in experimental animal models of IBD [1]. In humans with IBD, the most impressive evidence for the role of probiotics has been in patients with pouchitis where the cocktail of eight bacterial strains (VSL3) has been deployed [11,12]. In UC, a strain of *E. coli* Nissl 1917 has been reported to be equivalent in efficacy to mesalazine in maintenance of remission [13]. Efficacy with other agents including a synbiotic in acute UC has also been reported [14]. In patients with Crohn's disease, the role of probiotics is less clear, with recent negative results in the postoperative setting [15]. It seems the inflammatory process may be too aggressive to expect significant efficacy from probiotics as a primary therapy for Crohn's disease.

Problems, pitfalls, and unresolved issues

The interpretation of different studies of probiotics in IBD and other clinical conditions is confounded by the absence of comprehensive comparisons of probiotic performance using different strains in different specific disease states. More importantly, there are several problems and pitfalls that need resolution before guidelines for routine clinical use of probiotics in Crohn's disease or UC can be formulated.

First, the consumer would benefit from stringent regulation of unsubstantiated health claims on labels of some commercially available probiotic products. Second, there is no international standardized system for verification of probiotic product quality in terms of composition, stability, and shelf-life. Indeed, variability in quality may account for some of the apparent discrepancies between clinical experience and reported efficacy in clinical trials for some probiotics. Third, the dose range for humans has not been determined and may vary with different probiotics, in part influenced by survival during gastric transit. In addition, the optimal vehicle and formulation for delivery of probiotics may be an important variable [3], but remains to be defined in many cases. Fourth, variability in composition of the flora throughout the gut confounds the notion that any given strategy for therapeutic manipulation of the enteric flora will be equally effective for diseases that affect differ-

ent parts of either the small or large bowel. For example, the same probiotic may not be equally suited to different subsets of patients with Crohn's disease, depending on the topographic distribution of the lesions. Fifth, while the use of combinations of probiotic strains may be an appropriate strategy to accommodate different clinical indications and individual variations in host flora, synergy rather than antagonism within any given cocktail of bacteria needs to be demonstrated.

Finally, the use of genetically engineered rather than naturally occurring probiotics has emerged as a plausible strategy to enhance therapeutic efficacy and to deliver anti-inflammatory molecules to the inflamed mucosa. Advantages include direct delivery, avoidance of systemic toxicity, and lower production costs. Proof of principle has already been demonstrated in a murine model of IBD given *Lactococcus lactis* that was engineered to produce either an anti-inflammatory cytokine [16] or trefoil factor to promote healing [17]. Although the use of genetically modified (GM) organisms raises a public health concern, the insertion of the therapeutic transgene into the thymidylate synthase locus means that the GM organism becomes dependent on the enteric microenvironment for a source of thymine or thymidine and this limits its viability when shed in the feces [18]. Controversy surrounding GM foods is widely pervasive, but the concept of engineered probiotics ("turbo probiotics") is likely to be more acceptable, particularly to those who suffer from disabling conditions such as IBD.

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