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MODIFICATION OF THE GUT MICROBIOME TO MAINTAIN HEALTH OR TREAT DISEASE

Manipulation of the Microbiota for Treatment of IBS and IBD—Challenges and Controversies

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There is compelling rationale for manipulating the microbiota to treat inflammatory bowel diseases (IBDs). Although studies of animal models of intestinal inflammation produced promising results, trials in humans have been disappointing. In contrast to IBD, the role of the microbiota in the development of irritable bowel syndrome (IBS) only recently has been considered, but early stage results have been encouraging. As pharmaceutical companies develop fewer truly novel agents for treatment of these disorders, consumers seek safer, long-term strategies to deal with chronic symptoms. We assess the rationale for modulating the microbiota for treatment of IBD and IBS, and discuss whether current concepts are simplistic and overstated or simply under-researched. Are claims exaggerated and expectations unrealistic? Difficulties with microbiota terminology and technologies, as well as differences among patients and the heterogeneity of these diseases, pose additional challenges in developing microbiota-based therapies for IBD and IBS.

Keywords: Probiotic; Prebiotic; Fecal Transplantation; Pharmabiotic.

Few areas of biomedical research have developed as rapidly, and offered as much promise, as the microbiota.[1] It is common to see the human microbial biomass emblazoned on the covers of the science journals; the health and economic opportunities from studies of the microbiota frequently are featured in news and business publications. This area of research appeals to a broad range of consumers. As such, there is a need to correct overstatements and inaccurate or unrealistic expectations. Skeptics have dismissed overblown health claims for the therapeutic manipulation of the microbiota as snake oil, whereas others have found hope in several success stories.

Therapeutic manipulations of the microbiota have provided important insights regarding the human microbiota. Successes include the eradication of *Helicobacter pylori* infection to manage peptic ulcer disease and *H pylori*–associated gastric lymphoma and the use of fecal transplantation to treat recurrent *Clostridium difficile* infection. In addition, agents that target enzymes produced by intestinal microbes can reduce the toxicity of chemotherapeutic agents.[2] For example, CPT-11 (irinotecan), which is administered parenterally for treatment of colorectal cancer, is inactivated by glucuronidation in the liver and reactivated by bacterial glucuronidase in the intestine after biliary excretion. This reactivation often causes dose-limiting diarrhea, which can be prevented with inhibitors of this microbial enzyme.

These examples attest to the wisdom of therapeutically targeting the microbiota, but there is also much confusion. We assess the challenges and controversies associated with attempts to therapeutically manipulate the microbiota of patients with inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS). We discuss probiotics and lessons for the future with microbial-based therapies. Many comprehensive reviews of clinical trials and meta-analyses have been published.[3–17] We focus on the rationale for microbial strategies, comment on disparities between findings from animal and human studies, and discuss the impediments to linking scientific research findings with consumers.

Abbreviations used in this paper: **IBD, inflammatory bowel disease; IBS, irritable bowel syndrome.**

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Tyranny of Terminology

Not only politicians, but scientists and clinical researchers would do well to mind George Orwell's[18] refrain "…the slovenliness of our language makes it easier…to have foolish thoughts." Inaccurate thinking can arise when clinicians become captive to errors in nomenclature and imprecise terminology. Neologisms should be used with caution; they often are unnecessary or imply an understanding where none exists. For example, the term dysbiosis is unhelpful if used to merely describe a change in the microbiota that is assumed to be deleterious to the host. Although the change might be adverse to the host, this is seldom shown or proven in all hosts, and in some instances the changed microbiota may be an appropriate response to a change in the host or may represent an epiphenomenon without pathophysiologic implications.

Other words outlive their usefulness, or their meanings have drifted or require re-definition because of scientific progress. For example, the term *antibiotic*, once restricted to metabolites of microbial origin, now includes sulfonamides and synthetic agents. Similarly, probiotics most commonly are defined as "live microorganisms, which when administered in adequate amounts confer a health benefit on the host."[19] However, this definition excludes dead organisms or bioactive molecules produced by bacteria such as proteins, polysaccharides, nucleotides, or peptides. The term *prebiotic* also is problematic. It is used in reference to dietary ingredients, usually of a carbohydrate nature, that exert a beneficial influence on the composition of the microbiota. This is too vague with the increasing evidence that almost all dietary ingredients affect microbiota. The term *pharmabiotic* might be preferable to describe any biological entity mined from or influencing the microbiota with potential therapeutic benefit.

The imperative for precision in nomenclature will be exacted by regulatory authorities. This already has occurred in Europe and increasingly in the United States, where unqualified use of the words probiotic or prebiotic is no longer acceptable on food labels because of implied health claims. Furthermore, many consumers have been misled to erroneously believe that all probiotic products are the same or that all probiotic strains have the same effect.

Manipulation of the Microbiota to Treat IBD and IBS

The intestinal microbiota is involved in the pathogenesis of Crohn's disease and ulcerative colitis, but it is unclear whether tissue damage results from an abnormal immune response to a normal microbiota or from a normal immune response against an abnormal microbiota. Animal models provide evidence for each possibility, and show that immune deficits can change the microbiota toward one with a colitogenic capacity.[5]

Animal models also illustrate the complexity and heterogeneity of microbes that contribute to chronic inflammatory disorders. Because the microbiota is required for full development and maturation of the immune system, it is also necessary for an inflammatory response regardless of the stimulus. In one particularly informative study, genetic susceptibility and the indigenous microbiota were required for the pathogenesis of chronic inflammation, but the timing of onset depended on environmental factors such as chemicals and viruses.[20] Studies of acute intestinal infections have provided insight into the mechanism by which environmental factors contribute to intestinal inflammation.[21] Temporary disruption of the mucosal barrier by infectious or other environmental agents exposes the host immune system to the resident microbiota, which leads to proliferation of commensal-specific and pathogen-specific T cells. These long-lived cells migrate to other mucosal sites where they react with the commensal microbiota and may tip the balance from physiologic to pathologic inflammation. Furthermore, because the common mucosal immune system enables lymphocytes to migrate among different mucosal tissues, it is possible that commensal-specific T cells generated by infection at an extraintestinal site might migrate to the gut. This might account for some patients developing relapses of IBD with respiratory and other infections (Figure 1).

Less well appreciated is a role for the microbiota and, consequently, manipulation thereof, at other phases of the disease (Figure 2). For example, investigators have linked bacterial products with spontaneous or postoperative fibrotic processes, adhesions, and cicatrization,[22–25] and there is evidence for the involvement of microbes in spontaneous and colitis-associated colon carcinogenesis.[26] There is also evidence for the direct involvement of the microbiota in translocation and sepsis and, as an indirect or competitive influence, on risk of complicating infections such as *C difficile*–associated disease.[5] The microbiota has been linked with obesity-related and other metabolic disorders, and therefore might be involved in the changing phenotype of IBD as the prevalence of obesity increases.[1]

By comparison with IBD, the rationale for altering the microbiota in patients with IBS is less well substantiated. IBS is the best characterized and most widely studied functional gastrointestinal disorder; it is a source of considerable discomfort for many and potentially disabling for some. Progress in studies of its pathophysiology has been elusive. IBS presents several challenges for the clinical investigator: it does not have a validated and universally applicable biomarker, there is considerable heterogeneity in its presentation and progression, and its symptoms are nonspecific. It therefore has been a challenge to develop drugs to treat IBS—particularly in light of the low or zero threshold imposed by regulatory agencies for serious adverse events. Patients with IBS have sought help from complementary and alternative medicines and have been consuming products purported to contain probiotics or prebiotics for decades.

The pathogenesis of IBS has been proposed to involve dysmotility, visceral hypersensitivity, aberrant cerebral representation of visceral events, and abnormal responses to stress. Although combinations of these factors might contribute to the development of symptoms, none is sufficient to cause all of them. There is considerable evidence that different pathophysiological processes operate in the various subtypes of IBS (diarrhea-predominant,