Published in final edited form as:
Am J Gastroenterol. 2009 April ; 104(4): 809–813. doi:10.1038/ajg.2008.68.

Helping Patients Make Informed Choices About Probiotics: A Need For Research

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Abstract

Applications of probiotics in the treatment of gastrointestinal disorders are gaining acceptance among patients, despite evidence that probiotics can present substantial health risks, particularly for patients who are immunocompromised or seriously ill. Patients will likely formulate their attitudes and beliefs about probiotic therapies with reference to interpretive frameworks that compare probiotics with more familiar therapeutic modalities, including complementary and alternative medicines, pharmacological therapies, and gene-transfer technologies. Each of these frameworks highlights a different set of benefit-to-risk considerations regarding probiotic usage and reinforces extreme characterizations of both the therapeutic promise and peril of probiotics. Considerable effort may be required to help patients make informed choices about probiotic therapies.

BACKGROUND

Many diseases of the gastrointestinal (GI) tract are the result of an imbalance in normally occurring gastrointestinal flora (1). Lacking the microbial flora needed to maintain a healthy ecosystem within the GI tract, deleterious bacteria can overpopulate and disturb normal homeostasis, causing inflammation, producing pH-altering toxins, or interrupting membranous surfaces and thereby increasing susceptibility to microbial pathogens (2).

Probiotics are therapeutic agents containing live microorganisms that are ingested with the intention of restoring the human microbial ecosystem to a healthy functional balance (3). In the past decade, clinical applications of probiotics have gained greater acceptance in gastroenterology, where they have been used extensively to treat gastroenteritis and antibiotic-associated diarrhea (4,5). Although there continues to be much debate about the utility of probiotics in gastroenterology, these agents are attractive for use in patients for whom current therapies are marginally effective, highly burdensome, or have significant side effects that negatively impact quality of life (6).

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Specific author contributions: Richard R. Sharp: primary author, literature review, manuscript preparation; Jean-Paul Achkar: literature review, manuscript preparation; Margaret A. Brinich: literature review, manuscript preparation; Ruth M. Farrell: critical review of content, manuscript preparation.

CONFLICT OF INTEREST

Potential competing interests: None.

A major challenge for physicians in considering the introduction of probiotics into patient care is a paucity of clinical studies characterizing the safety and efficacy of these therapeutic options (7-9). Of importance, however, this lack of clinical data has not curbed patient interest or use of probiotics. This raises difficult challenges for physicians who care for persons with chronic GI diseases. To remain effectively integrated in their patients' care, gastroenterologists must be familiar with common beliefs about probiotics and be prepared to discuss probiotics with patients who express an interest in pursuing these options.

DISCUSSING THE BENEFITS AND RISKS OF PROBIOTICS

The intended result of probiotic therapy is that exogenous bacteria will enter the host GI tract and regulate local immunity (10), modify inflammatory response (11,12), improve the barrier function of the gut epithelium (8), inhibit pathogenic bacteria colonization (13), or otherwise improve physiological function (14). Suggested mechanisms of how these changes occur include alterations to the composition of the host's microbial flora, enhanced biological activity of endogenous bacteria within the human host, production of exogenous proteins that directly benefit the host, regulation of the biological activity of deleterious endogenous bacteria, or stimulation of host (human) cells to produce proteins that restore normal function (15).

The lack of information regarding potential benefits and risks of probiotic interventions raises difficult questions about how gastroenterologists and other physicians can help patients make informed decisions about probiotic usage. Probiotics are seen by many patients as “natural” alternatives to more traditional medical interventions such as pharmacological therapy or surgery. Given this orientation, many patients may regard probiotics as relatively innocuous (16). However, recent evidence suggests that probiotics may present substantial mortality risks for immunocompromised and other seriously ill patients (17-19). An example of this in GI disease comes from a recent study that evaluated probiotic prophylaxis for prevention of infection in patients with predicted severe acute pancreatitis using a preparation that contained six different strains of viable bacteria (17). In this randomized, double-blind, placebo-controlled trial, the authors found no difference in infection rates, but there were significantly higher rates of intestinal ischemia (6% vs. 0%; $P = 0.004$) and mortality (16% vs. 6%; $P = 0.01$) in the group that received probiotic therapy compared with the group that received placebo (17).

Despite these potential risks, several studies suggest that probiotics may be useful in the care of patients with various GI diseases, including inflammatory bowel disease (IBD); irritable bowel syndrome (IBS); antibiotic-associated diarrhea, including *Clostridium difficile* colitis; acute diarrhea in children; and chronic liver disease (7-9,20,21). Evidence supporting the use of probiotics for chronic GI diseases includes studies demonstrating reduction of local gut inflammatory response and symptomatic benefit in patients with IBD using specific strains of *Escherichia coli* (e.g., Nissle 1917), *Lactobacillus, Saccharomyces boulardii*, and *Bifidobacterium* (22-26). Similarly, studies in IBS patients have demonstrated that probiotics have an anti-inflammatory effect, resulting in decreased levels of muscle hypercontractility and pain-related symptoms, and that probiotics can produce more prolonged remissions of IBS-related symptoms as compared with traditional therapies (27-30).

More research must be done to delineate appropriate indications for probiotic usage and to establish the long-term safety and efficacy of probiotics for the treatment of chronic GI diseases. Areas of active research include the use of “probiotic cocktails” such as VSL#3, in which multiple microorganisms are combined into a single therapeutic agent in hopes of enhancing benefit (31). The simultaneous use of multiple species raises additional questions of host-microbe interactions that may affect safety and efficacy. Other technological

innovations in the field of metagenomics may allow probiotic treatments to be tailored to individual disease phenotypes, potentially increasing their efficacy (32-34).

INFORMED DECISION MAKING ABOUT PROBIOTICS

As with all medical interventions, steps should be taken to ensure that patients have the opportunity to make well-informed decisions about the personal use of probiotics. The challenge of obtaining meaningful informed consent is heightened, however, when patients consider the use of innovative therapies with unproven efficacy or incompletely characterized safety profiles. When robust clinical data are unavailable for the purpose of characterizing the potential benefits and risks of a therapy, as currently is the case with probiotics, additional efforts must be made to ensure that patients understand the range of known and unknown risks associated with the use of that agent. Using that information, patients can then weigh the potential benefits against possible harms and make an informed decision that is consistent with their health-care goals, personal values, and expectations.

If patients are to make informed choices about the use of probiotics, they must consider a set of safety-related issues that have not been well characterized (Box 1). Patients who are unfamiliar with these or other concerns about the safety of probiotics may have an incomplete appreciation of the full set of risks associated with their use and thus cannot make well-informed choices about probiotic therapies.

A critical first step in preparing patients to make informed decisions about probiotics is for health-care providers to understand how patients conceptualize the potential benefits and risks of these therapeutic options. Many patients will formulate their initial attitudes and beliefs about probiotics with respect to several broad interpretive frames for understanding new developments in medicine and science. These interpretive frames place probiotic options within the context of other, more familiar therapeutic modalities, including comparisons of probiotics with (i) complementary and alternative medicines, (ii) traditional pharmacological therapies, and (iii) gene-transfer technologies. Each of these interpretative frames highlights a different set of benefit-to-risk considerations that patients may consider in making personal decisions about the use of probiotics.

A key challenge in presenting probiotic options is that patients who conceptualize probiotics through a single one of these interpretative frames will have an incomplete understanding of the full range of potential benefits and risks associated with their use. For example, patients who view probiotics as similar to pharmacological interventions or dietary supplements may fail to appreciate potential risks associated with microbe-host interactions resulting from the ingestion of living microorganisms (35) This potential for misunderstanding highlights the need to clarify both the specific interpretive frames that patients may use to conceptualize probiotics and the types of misconceptions that might be perpetuated as a result of viewing probiotics through these interpretive lenses

Will patients see probiotics as a form of complementary and alternative medicine?

Some patients may view probiotic interventions as a form of complementary and alternative medicine (CAM), because many probiotics are composed of naturally occurring bacteria. From this perspective, probiotics may be seen as a “natural” alternative to traditional drugs, and thus patients may regard probiotics as safer, more effective, and less likely to pose significant health risks. The current marketing of probiotic-containing food products reinforces this perception of probiotics, as does the over-the-counter availability of probiotic-containing yogurts and other probiotic foods available in grocery stores. For many patients, CAM therapies are preferable to traditional drugs because these non-conventional therapies involve a more holistic approach to the management of disease, are readily available, and do not require the additional

costs of a physician visit (16). For these reasons, the perception of probiotics as a form of CAM may encourage broad probiotic usage.

Unfortunately, the perception of probiotics as a form of CAM may mask important safety and efficacy issues. For example, viewing probiotics as a form of CAM may lead some patients to overestimate their benefits because many patients have unrealistic expectations regarding the benefits of CAM therapies (36,37). This concern is reinforced by results from a national survey of patient perceptions of CAM, where the authors found that 21% of patients who have used a CAM therapy believe it to be superior to conventional medical care (36). Conversely, viewing probiotics as a form of CAM may lead patients to underestimate the degree of risk associated with the use of probiotics because many patients assume that CAM therapies are safer and have fewer side effects than traditional therapies because they typically do not contain “man-made” chemicals. This perception may in turn lead to improper use or dosing of probiotics. Misperception of risks associated with CAM therapies has been observed in the use of black cohosh and St. John's wort, alternative therapies that have potentially serious side effects and drug interactions (38,39).

To improve patient communication about the potential benefits and risks of CAM therapies, physicians are encouraged to discuss CAM within the context of the patient's primary symptoms, frequency of symptoms, and treatment expectations (40). By constructing a more complete account of patient motivations and prior medical experiences, physicians may be in a better position to assess understandings of CAM-related risks and benefits. Because of the difficulty of precisely estimating CAM-related risks, physicians also are encouraged to remind patients about the possible unknown consequences of using CAM therapies, either alone or in combination with conventional pharmacological interventions (41). These approaches may be useful in exploring patient interests in probiotic therapies as well.

Will patients perceive probiotics as a form of pharmacological therapy?

Patients may also view probiotic therapies as similar to traditional pharmacological interventions. Although pharmaceuticals are not living organisms, both drugs and probiotics seek to alter cellular function and response. Individual drugs and probiotic agents also have their own unique pharmacodynamic and pharmacokinetic profiles pertaining to absorption, metabolism, and distribution within the body, which may suggest to patients that these therapeutic options are broadly analogous to each other.

Unfortunately, viewing probiotics as a pharmacological therapy may cause misunderstandings about how probiotics work. Unlike drugs, probiotics are composed of thousands of living microorganisms whose mechanism of action as therapeutic agents involves the activation of host-mediated factors. Probiotics are not metabolized or excreted in the same manner as pharmaceutical products, and thus the duration of action is difficult to predict. In addition, the resulting probiotic effects, both beneficial and potentially harmful, may persist throughout a probiotic organism's existence within the human viscera. Once established within the body, implanted probiotic microorganisms may be difficult to remove (42). Lacking these perspectives on critical differences between probiotics and pharmacological therapies, patients may not appreciate the full range of risks posed by the use of probiotic agents.

A number of techniques have been shown to increase patient appreciation of therapeutic risks and benefits (43). To help patients appreciate estimates of therapeutic risk, it may be useful to compare risk probabilities with those of more familiar events, such as the likelihood of being in a car accident or being struck by lightning (44). To redirect patients away from a natural inclination to focus primarily on adverse outcomes, it may also be helpful to alternate between presentations of therapeutic risks and potential benefits (45). These approaches may also be

useful in discussing probiotics with patients who view these agents as a form of pharmacological therapy.

Will patients perceive probiotics as a form of gene therapy?

Other patients may view the use of probiotics as a form of gene therapy, because probiotics work by introducing foreign DNA into a human host and expressing this DNA within the host's organ systems. As a result of recent media coverage, gene-transfer technologies are not unfamiliar to many patients. Some patients may be aware that clinical trials involving gene therapy have been largely unsuccessful. One of the most widely known and controversial attempts at human gene therapy resulted in the death of a research volunteer at the University of Pennsylvania who suffered a catastrophic immune reaction in response to an experimental therapy (46). For many, this story stands as a caution regarding the use of gene-transfer technologies. Other patients may be familiar with gene-transfer technologies used to engineer more robust food crops and may have concerns about the safety of genetically modified foods.

Viewing probiotics as a gene-transfer technology may cause ambivalence or concern about the potential benefits and risks of probiotic agents, particularly with regard to probiotics containing genetically modified microorganisms. This frame of reference may also prompt unwarranted levels of concern about safety and unforeseen consequences of introducing foreign DNA into a human host. Patients who view probiotics through the lens of gene-transfer technologies, or who see parallels with genetically modified foods, may have a heightened sense of the need for governmental regulation or have unrealistic expectations about the therapeutic promise of genetically engineered probiotics.

LOOKING AHEAD: THE NEED FOR RESEARCH

Introducing novel therapeutics in a responsible way requires that patients have the capacity to make well-informed decisions about their use. Each of the three interpretive frameworks reviewed above highlights a different set of risk-to-benefit considerations that patients may weigh in deciding about the use of probiotics. Considered individually, each framework presents an incomplete picture of key considerations in the use of probiotic therapies. To the extent that these interpretive frameworks also reinforce extreme characterizations of both the therapeutic promise and peril of probiotics, it will be critical to develop more balanced strategies for discussing probiotics options with patients. These considerations suggest a need for a more comprehensive conceptual framework integrating these divergent perspectives in a manner that helps patients to appreciate the full range of potential benefits and risks associated with probiotics.

Effective physician-patient communication about probiotics requires an understanding of both the conceptual frameworks that patients use in interpreting probiotic options and the manner in which these conceptual frameworks influence personal decisions about probiotics. Research studies examining the salience of the interpretive frameworks described above are thus critically important in promoting informed patient decision making. By characterizing patient understandings of probiotics, gastroenterologists and other physicians can make informed choices about how best to discuss probiotics with their patients and to help place them in a position to make informed decisions about probiotic options.

CONCLUSIONS

Patients' initial perceptions of treatment efficacy, mechanism of action, and safety directly shape the ways that patients conceptualize new therapeutics and, ultimately, determine their willingness to accept these therapeutic options. Once these initial attitudes and concerns are in the public sphere, well founded or not, they have a resilience that highlights the importance of

"first messages" about new therapies. For this reason, it is critical to characterize patient understandings of probiotics before these emerging therapies become more commonplace in medicine. Of particular importance is the identification of patient attitudes and beliefs that may serve as barriers to the successful integration of probiotics into patient care. With this information, gastroenterologists can develop effective patient-communication strategies that help patients make informed decisions about the use of probiotics.

Box 1. Nontraditional safety-related considerations in the use of probiotics

Unpredictable behavior of naturally occurring microorganisms

Probiotic agents may behave much differently than predicted as a result of unanticipated gene expression in non-native host environments or acquired mutations occurring spontaneously via bacterial DNA-transfer mechanisms. This type of behavior has been observed in bacteria that develop drug resistance through DNA exchange with other bacterial genomes (8). In the case of probiotics, these unexpected behaviors may result in the production of potentially harmful substances within the human gut.

Unpredictable behavior of genetically altered microorganisms

Gene-transfer techniques developed from advances in molecular and genetic technology allow specific genes to be inserted into or removed from an existing microbial genome. The use of this technology can result in the engineering of new bacterial genomes that express a desired set of proteins (14). As in the case of naturally occurring bacteria, genetically modified organisms may manifest the same inherent DNA-exchanging and mutating behaviors. Apparent genetic sequences resulting from bioengineering, sometimes in combination with naturally occurring events, may produce erratic or unexpected behavior. Expression of these genomic products has the potential for even greater deviation from expected results.

Unexpected interactions of bacteria within the specific local environment of the human host

The theory behind probiotics is that these microorganisms affect the ecosystem of the host's organ system in beneficial ways. However, it is important to consider how bacteria may produce unanticipated interactions with the local environment (in relation to both other bacteria and human host cells). One possibility is that a selected probiotic bacterial strain may have one effect when observed *in vitro* but another *in vivo* (47). Another possibility is that the synergistic effect that probiotic bacteria have with other microorganisms in the local environment may produce a negative impact for the host (42). The development of unexpected changes to the microbial ecosystem could result in adverse microbe-host interactions, including the development of a severe host immune response to probiotic bacteria.

Unexpected release of novel bacteria into the (external) environment

Probiotic bacteria are ultimately eliminated from the body by natural mechanisms. In gastrointestinal applications, probiotic microorganisms will be removed in fecal matter. This raises concerns about the possibility of environmental contamination and third-party exposure to bioengineered probiotics (48). Wastewater is a well-documented source of water-supply contamination (49). The introduction of novel bacteria into the environment should be considered, as this may affect other plant and animal ecosystems. Growing public awareness of environmental pollution may prompt concerns that the introduction of new species into an existing human ecosystem can have far-reaching effects on animal and human health.

Acknowledgments

Financial support: This publication was made possible by award R01 HG004877 from the National Human Genome Research Institute, a component of the National Institutes of Health (NIH), and the NIH Roadmap for Medical Research.

REFERENCES

1. Guarner F, Malagelada JR. Gut flora in health and disease. Lancet 2003;361:512–9. [PubMed: 12583961]
2. Quigley EM, Quera R. Small intestinal bacterial overgrowth: roles of antibiotics, prebiotics, and probiotics. Gastroenterology 2006;130(2 Suppl 1):S78–90. [PubMed: 16473077]
3. Food and Agriculture Organization of the United Nations. World Health Organization. Report on Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria. 2001. <ftp://ftp.fao.org/es/ esn/food/probio_report_en.pdf>Accessed 7 February 2008
4. Szajewska H, Mrukowicz J. Meta-analysis: non-pathogenic yeast *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhoea. Aliment Pharmacol Ther 2005;22:365–72. [PubMed: 16128673]
5. Pillai A, Nelson R. Probiotics for treatment of *Clostridium difficile*-associated colitis in adults. Cochrane Database Syst Rev [online] 23 January 2008;CD004611 (doi: 10.1002/14651858.CD004611.pub2).
6. Santosa S, Farnworth E, Jones PJ. Probiotics and their potential health claims. Nutr Rev 2006;64:265–74. [PubMed: 16808112]
7. Zuccotti GV, Meneghin F, Raimondi C, et al. Probiotics in clinical practice: an overview. J Int Med Res 2008;36(Suppl 1):1A–53A. [PubMed: 18230261]
8. Boyle R, Robins-Browne RM, Tang MLK. Probiotic use in clinical practice: what are the risks? Am J Clin Nutr 2006;83:1256–64. [PubMed: 16762934]
9. Jonkers D, StockbrÜgger R. Probiotics in gastrointestinal and liver diseases. Aliment Pharmacol Ther 2007;26(Suppl 2):133–48. [PubMed: 18081657]
10. Sartor RB. Probiotic therapy of intestinal inflammation and infections. Curr Opin Gastroenterol 2005;21:44–50. [PubMed: 15687884]
11. Fedorak R, Madsen KL. Probiotics and prebiotics in gastrointestinal disorders. Curr Opin Gastroenterol 2004;20:146–55. [PubMed: 15703637]
12. Fedorak R, Penner R, Madsen KL. Probiotics in the treatment of gastrointestinal disorders. US Gastroenterol Rev 2006;1:1–7.
13. O'Hara A, Shanahan F. Mechanism of action of probiotics in intestinal disease. Sci World J 2007;7:31–46.
14. Saier MH Jr, Mansour NM. Probiotics and prebiotics in human health. J Mol Microbiol Biotechnol 2005;10:22–5. [PubMed: 16491023]
15. Meier R, Steuerwald M. Place of probiotics. Curr Opin Crit Care 2005;11:318–25. [PubMed: 16015109]
16. Quattropani C, Ausfeld B, Straumann A, et al. Complementary alternative medicine in patients with inflammatory bowel disease: use and attitudes. Scand J Gastroenterol 2003;38:277–82. [PubMed: 12737442]
17. Besselink MG, van Santvoort HC, Buskens E, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet 2008;371:651–9. [PubMed: 18279948]
18. Singhi S. Probiotics in the critically ill: handle with care! Pediatr Crit Care Med 2007;8:499–501. [PubMed: 17873787]
19. Honeycutt TC, El Khashab M, Wardrop RM 3rd. Probiotic administration and the incidence of nosocomial infection in pediatric intensive care: a randomized placebo-controlled trial. Pediatr Crit Care Med 2007;8:452–8. [PubMed: 17693918]

20. Lata J, Novotny I, Príbramska V, et al. The effect of probiotics on gut flora, level of endotoxin and Child-Pugh score in cirrhotic patients: results of a double-blind randomized study. Eur J Gastroenterol Hepatol 2007;19:1111–3. [PubMed: 17998837]
21. Malaguarnera M, Greco F, Barone G, et al. Bifidobacterium longum with fructo-oligosaccharide (FOS) treatment in minimal hepatic encephalopathy: a randomized, double-blind, placebo-controlled study. Dig Dis Sci 2007;52:3259–65. [PubMed: 17393330]
22. Rolfe VE, Fortun PJ, Hawkey CJ, et al. Probiotics for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev [online]. October 18;2006 CD004826 (doi: 10.1002/14651858.CD004826.pub2)
23. Guslandi M, Mezzi G, Sorghi M, et al. Saccharomyces boulardii in maintenance treatment of Crohn's disease. Dig Dis Sci 2000;45:1462–4. [PubMed: 10961730]
24. Plein K, Hotz J. Therapeutic effects of *Saccharomyces boulardii* on mild residual symptoms in a stable phase of Crohn's disease with special respect to chronic diarrhea: a pilot study. Z Gastroenterol 1993;31:129–34. [PubMed: 8465554]
25. Kruis W, Fric P, Pokrotnieks J, et al. Maintaining remission of ulcerative colitis with the probiotic *Escherichia coli* Nissle 1917 is as effective as with standard mesalazine. Gut 2004;53:1617–23. [PubMed: 15479682]
26. Cui HH, Chen CL, Wang JD, et al. Effects of probiotic on intestinal mucosa of patients with ulcerative colitis. World J Gastroenterol 2004;10:1521–5. [PubMed: 15133865]
27. Verdú EF, Bercȍk P, Bergonzelli GE, et al. Lactobacillus paracasei normalizes muscle hypercontractility in a murine model of postinfective gut dysfunction. Gastroenterology 2004;127:826–37. [PubMed: 15362038]
28. O'Mahony L, McCarthy J, Kelly P, et al. *Lactobacillus* and *bifidobacterium* in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. Gastroenterology 2005;128:541–51. [PubMed: 15765388]
29. Bittner AC, Croffut RM, Stranahan MC. Prescript-assist probiotic-prebiotic treatment for irritable bowel syndrome: a methodologically oriented, 2-week, randomized, placebo-controlled, double-blind clinical study. Clin Ther 2005;27:755–61. [PubMed: 16117982]
30. Guyonnet D, Chassany O, Ducrotte P, et al. Effect of a fermented milk containing *Bifidobacterium animalis* DN-173 010 on the health-related quality of life and symptoms in irritable bowel syndrome in adults in primary care: a multicentre, randomized, double-blind, controlled trial. Aliment Pharmacol Ther 2007;26:475–86. [PubMed: 17635382]
31. Gionchetti P, Lammers KM, Rizzello F, et al. VSL#3: an analysis of basic and clinical contributions in probiotic therapeutics. Gastroenterol Clin N Am 2005;34:499–513.
32. Frank DN, St Amand AL, Feldman RA, et al. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci USA 2007;104:13780–5. [PubMed: 17699621]
33. Frank DN, Pace NR. Gastrointestinal microbiology enters the metagenomics era. Curr Opin Gastroenterol 2008;24:4–10. [PubMed: 18043225]
34. Jia W, Li H, Zhao L, et al. Gut microbiota: a potential new territory for drug targeting. Nat Rev Drug Discov 2008;7:123–9. [PubMed: 18239669]
35. Snydman DR. The safety of probiotics. Clin Infect Dis 2008;46(Suppl 2):S104–11. [PubMed: 18181712]discussion S144-51
36. Eisenberg DM, Kessler RC, Van Rompay MI, et al. Perceptions about complementary therapies relative to conventional therapies among adults who use both: results from a national survey. Ann Intern Med 2001;135:344–51. [PubMed: 11529698]
37. Koretz RL, Rotblatt M. Complementary and alternative medicine in gastroenterology: the good, the bad, and the ugly. Clin Gastroenterol Hepatol 2004;2:957–67. [PubMed: 15551247]
38. Fugh-Berman A, Ernst E. Herb-drug interactions: review and assessment of report reliability. Br J Clin Pharmacol 2001;52:587–95. [PubMed: 11736868]
39. Hu Z, Yang X, Ho PC, et al. Herb-drug interactions: a literature review. Drugs 2005;65:1239–82. [PubMed: 15916450]
40. Eisenberg DM. Advising patients who seek alternative medical therapies. Ann Intern Med 1997;127:61–9. [PubMed: 9214254]

41. Pappas S, Perlman A. Complementary and alternative medicine. The importance of doctor-patient communication. Med Clin North Am 2002;86:1–10. [PubMed: 11795082]

42. Paton AW, Morona R, Paton JC. Designer probiotics for prevention of enteric infections. Nat Rev Microbiol 2006;4:193–200. [PubMed: 16462752]

43. Palling J. Strategies for helping patients understand risks. BMJ 2003;327:745–8. [PubMed: 14512489]

44. Edwards A, Elwyn G, Mulley A. Explaining risks: turning numerical data into meaningful pictures. BMJ 2002;324:827–30. [PubMed: 11934777]

45. Thomson R, Edwards A, Grey J. Risk communication in the clinical consultation. Clin Med 2005;5:465–9. [PubMed: 16268328]

46. Wade N. Patient dies during a trial of gene therapy. New York Times September 29;1999 :A24.

47. Walker, R.; Buckley, M. Probiotic microbes: the scientific basis. American Academy of Microbiology; Washington, DC: 2006.

48. Steidler L. Genetically engineered probiotics. Best Pract Res Clin Gastroenterol 2003;17:861–76. [PubMed: 14507594]

49. Messner M, Shaw S, Regli S, et al. An approach for developing a national estimate of waterborne disease due to drinking water and a national estimate model application. J Water Health 2006;4(Suppl 2):201–40. [PubMed: 16895092]