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Probiotics: 'Living Drugs'

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Abstract and Introduction

Abstract

The uses, mechanisms of action, and safety of probiotics are discussed.

Probiotics are live microorganisms or microbial mixtures administered to improve the patient's microbial balance, particularly the environment of the gastrointestinal tract and the vagina. The yeast Saccharomyces boulardii and the bacterium Lactobacillus rhamnosus, strain GG, have shown efficacy in clinical trials for the prevention of antimicrobial-associated diarrhea. Other probiotics that have demonstrated at least some promise as prophylaxis for this type of diarrhea are Lactobacillus acidophilus, Bifidobacterium longum, and Enterococcus faecium. The use of S. boulardii as an adjunctive treatment to therapy with metronidazole or vancomycin has been found in controlled studies to decrease further recurrences of Clostridium difficile-associated disease. Other gastrointestinal disorders for which probiotics have been studied include traveler's diarrhea, acute infantile diarrhea, and acute diarrhea in adults. Several Lactobacillus species given in yogurt or in tablet or suppository form have shown clinical efficacy as a treatment for vaginal infections. Lactobacillus strains have also been examined as a treatment for urinary-tract infections. Putative mechanisms of action of probiotics include production of pathogen-inhibitory substances, inhibition of pathogen attachment, inhibition of the action of microbial toxins, stimulation of immunoglobulin A, and trophic effects on intestinal mucosa. The available probiotics are considered nonpathogenic, but even benign microorganisms can be infective when a patient is severely debilitated or immunosuppressed.

Probiotics have demonstrated an ability to prevent and treat some infections. Effective use of probiotics could decrease patients' exposure to antimicrobials. Additional controlled studies are needed to clearly define the safety and efficacy of these agents.

Introduction

The concept of orally taking mixtures of microorganisms for improved health is not new. Yogurt has long been thought to have health benefits. As early as 1908, Metchnikoff, [1] a Nobel laureate, put a scientific spin on the ingestion of microbes in stating that "ingested lactobacilli can displace toxin-producing bacteria, promoting health and prolonging life." Until recently, however, this idea has not received serious attention in the United States and Canada. This lack of medical acceptance has probably been due to the ready availability of antimicrobials but also to a previous lack of sound evidence. Another consideration has been the uneven quality of products on the market.[2]

Continued overuse of antimicrobials is leading to serious problems with antimicrobial resistance. Consequently, there is a need for innovative measures to prevent and treat infectious diseases. The therapeutic use of microorganisms antagonistic to pathogens would have the potential to decrease antimicrobial use. Another impetus for a reevaluation of therapeutic microorganisms has been the favorable results of recent randomized, controlled clinical trials testing newer products.

There is some confusion about the terms applied to microbial preparations used therapeutically. The name used most commonly, including on commercial labels, is "probiotics." A probiotic is generally defined as a live microorganism or microbial mixture administered to "beneficially affect the host animal by improving its microbial balance."[3] These products are taken orally, although there is also interest in intravaginal use to treat vaginal infections. Probiotic doses are usually standardized in terms of the amount of living bacteria per unit of volume. The reader may be most familiar with the many commercial lactobacillus-based probiotic products used orally for diarrhea. "Biotherapeutic agent" has been used to describe a microbe

having specific therapeutic activity against a specific disease.[4,5] An example of effective use of a biotherapeutic agent is the oral administration of Saccharomyces boulardii to treat recurrent Clostridium difficile-associated disease.[6] Another name used is "prebiotic"; this refers to the use of chemicals or nutrients that modify the environment of the gastrointestinal tract to favor proliferation of the beneficial components of the intestinal microflora.[7,8] The prebiotic approach, while promising, has not been thoroughly tested.

This article discusses the uses, mechanisms of action, safety, and selection of probiotics.

Evidence-Based Uses of Probiotics

Prevention of Antimicrobial-Associated Diarrhea

Antimicrobial-associated diarrhea is the most common adverse effect of antimicrobial therapy. While common, this diarrhea can be serious and is associated with an increase in hospital stay, a higher risk for other infections, and a threefold increase in mortality.[9-11] Antimicrobial-associated diarrhea is an added burden on health care workers caring for patients and may lead to a significant increase in hospital costs.[12,13] The frequency ranges from 0.05% to 26%, with hospitalized patients having a higher risk.[11] A 22% rate was reported in a Seattle hospital in 1987 [14] and a 15.2% rate in 1994. [13]

The precise causes of antimicrobial-associated diarrhea are not understood. Nevertheless, an antimicrobial-induced perturbation of the balance of the normal intestinal flora is at the heart of the problem. With this perturbation, opportunistic microorganisms may overgrow, resulting in diarrhea. Overgrowth of C. difficile is the most common cause in the hospital setting, accounting for 20-40% of cases of this diarrhea.[15,16] An overgrowth of C. difficile may less frequently present as pseudomembranous colitis, toxic megacolon, or a perforated colon.[17] Other microorganisms have been implicated in antimicrobial-associated diarrhea, but their role is not well substantiated. Another deleterious effect of disturbing the normal protective flora is a possible decrease in the short-chain fatty acids they produce. These fatty acids are important for the nutrition of the enterocyte and for water and electrolyte absorption, and their decrease may result in watery diarrhea.[18,19] Perturbation of the normal flora may also cause a loss of carbohydrate-digesting gut bacteria, with resulting osmotic diarrhea.[20,21] Erythromycin is a special case because this antimicrobial is a motilin agonist that causes diarrhea directly, as well as through suppression of the intestinal flora.[22]

Whatever the etiology, it has long been of interest to attempt to "normalize" microbial activities in the bowel through the oral administration of probiotics. In recent years, clinical studies have lent support to the use of selected probiotic agents for the prevention of antimicrobial-associated diarrhea (Table 1).

S. boulardii, a nonpathogenic yeast that grows optimally at body temperature, has been tested for efficacy in the prevention of antimicrobial-associated diarrhea in a community setting and an institutional setting. This yeast is commercially available as lyophilized cells in capsule form in many countries. It has recently been introduced as a dietary supplement in the United States (Florastor, Biocodex, Inc.). In France, 388 outpatients taking tetracycline or □-lactam antibiotics for a variety of infections received either S. boulardii or placebo. In the placebo group, 17.5% had diarrhea, compared with 4.5% of those in the S. boulardii group.[23] Two studies in hospitalized patients in the United States found reductions in the rate of antimicrobial-associated diarrhea of 57%[24] and 51%[13] compared with placebo. A study in elderly hospitalized patients in England found no protective action of S. boulardii treatment; however, patients were monitored only during the period of antimicrobial administration.[33] Much antimicrobial-associated diarrhea occurs within a few weeks after these drugs are stopped.[34]

Lactobacillus-based probiotics have long been used for antimicrobial-associated diarrhea. Anecdotal evidence indicates that consumption of commercial unpasteurized yogurt is helpful, but this approach has not been carefully tested. Many commercial lactobacillus-based products are sold for the prevention and treatment of diarrhea, but few have been subject to objective clinical evaluation. A product containing Lactobacillus acidophilus and Lactobacillus bulgaricus (Lactinex, BD) showed benefit in one trial [29] but not in another.[35] Many of the presently available commercial probiotics are formulated from dairy strains of lactobacilli, which have not been selected for survival in the human gastrointestinal tract. Recently, a human strain of Lactobacillus rhamnosus, strain GG, was introduced in capsule form in the United States as a dietary supplement (Culturelle, CAG Functional Foods). This strain survives passage in the gastrointestinal tract,[36] adheres to intestinal mucus and epithelial cells,[37] and persists for several weeks after administration ends.[38] L. rhamnosus GG in the form of fermented yogurt was evaluated in 16 volunteers taking erythromycin. The active-yogurt group had two days of diarrhea, compared with eight days in the placebo (sterilized yogurt) group.[39] Two larger, more recent studies in children taking antimicrobials are more convincing (Table 1).[26,27]

Bifidobacteria predominate in the intestinal tract shortly after birth and persist, particularly in breastfed infants, until weaning.[32] They are generally considered to be beneficial and are often included in probiotic products. Bifidobacterium longum in the form of fermented yogurt reduced stool frequency and abdominal discomfort in a crossover study involving 10 volunteers receiving erythromycin, [31] and a B. longum-L. acidophilus yogurt reduced diarrhea in 20 volunteers receiving clindamycin.[32]

The nonpathogenic, lactic acid-producing Enterococcus faecium strain SF68 is commercially available in Switzerland and some other countries but not in the United States. A multicenter, double-blind, placebo-controlled trial investigated the ability of this product to prevent diarrhea in 45 patients receiving antimicrobials. [30] The frequency of diarrhea was 27.2% in the placebo group and 8.7% in the treatment group. Pathogenic strains of E. faecium are feared because of plasmid-coded resistance to many antimicrobials, including, frequently, vancomycin. Absolute safety and the absence of effects on antimicrobial resistance patterns would have to be firmly established before E. faecium SF68 could be recommended for general use.

Treatment of C. Difficile-Associated Diarrhea and Colitis

C. difficile is the most common cause of antimicrobial- associated diarrhea. Along with simple diarrhea, there is the potential for progression to colitis, pseudomembranous colitis, and even toxic megacolon and death. C. difficile-associated disease is almost always initiated by antimicrobial therapy, but, once established, it may recur in the absence of these drugs. Recurrent C. difficile-associated disease is a debilitating and frustrating infection that puts the physician in the position of prescribing an antimicrobial (metronidazole or vancomycin) for an antimicrobial-induced problem. C. difficile becomes established only in a colon in which the microflora is perturbed. There is strong interest in the potential for probiotics to restore the microbial balance and hence the ability to block C. difficile proliferation.

The ability of S. boulardii to prevent recurrence of C. difficile-related disease when used as an adjunct to a standard anti-C. difficile antimicrobial regimen has been studied. Patients (n = 124) with documented, symptomatic C. difficile-associated disease received a standard course of metronidazole or vancomycin together with four weeks of yeast treatment (0.5 g twice a day).[6] A multivariate analysis showed that the yeast-drug group had a significantly lower relative risk of recurrence (0.43; 95% confidence interval, 0.20-0.97) than the placebo-drug group. The most significant benefit of adjunctive treatment with S. boulardii was seen in patients with recurrent disease.

In a double-blind, multicenter trial in 168 patients, S. boulardii plus a 10-day regimen of vancomycin 2 g/ day reduced the rate of recurrence of C. difficile-associated disease to 16.7%, versus 50% for the placebo group (p = 0.05).[40] No serious adverse reactions resulted from the S. boulardii treatment.

These studies offer examples of a probiotic having a beneficial impact on the course of a serious, life-threatening infection. Successful treatment of recurrent C. difficile-related disease with this yeast would decrease the exposure of patients to vancomycin or metronidazole and help minimize the emergence of resistance to these life saving drugs.

L. rhamnosus GG has been tested in patients with recurrent C. difficile-associated disease, but the reported studies have involved small numbers of patients and no placebo group.[41,42] A controlled clinical trial is warranted to test the efficacy of L. rhamnosus GG against C. difficile. While studies indicate that selected probiotics may be useful in the treatment of recurrent C. difficile-related disease, there is little evidence to support prophylactic use. A controlled study to define the efficacy of probiotics in prevention would be long and expensive.

Prevention of Traveler's Diarrhea

The risk of traveler's diarrhea increases when a person who is at equilibrium with a microbial environment and diet is exposed to unfamiliar microorganisms. In contrast to antimicrobial- associated diarrhea and C. difficile-related disease, traveler's diarrhea is caused by the introduction, through food or water, of pathogenic bacteria that overwhelm the protective effects of the normal intestinal flora. Theoretically, prophylactic ingestion of probiotics that inhibit pathogens, block pathogen-adhesion sites, or otherwise increase the gut's resistance to pathogen colonization could decrease the risk of traveler's diarrhea. This approach could also reduce the need for people traveling to developing countries to rely on prophylactic antimicrobials and bismuth salts.

To date, the reported benefits of using prophylactic probiotics for traveler's diarrhea have been modest. L. rhamnosus GG was evaluated in 756 Finns who went to two resorts in Turkey.[43] Compared with placebo, the probiotic was associated with a reduced frequency of traveler's diarrhea for one resort destination (23.9% for L. rhamnosus GG versus 39.5% for placebo) (p = 0.04) but not the other. A study involving 225 Americans traveling from the New York City area to developing countries found that those given L. rhamnosus GG had a 3.9% rate of diarrhea per day, compared with 7.4% in the placebo group (p = 0.05).[44] Two studies in which the products tested contained Lactobacillus species other than L. rhamnosus GG found no protection compared with placebo,[45,46] indicating the importance of product selection. A large, controlled trial of S. boulardii was conducted in travelers from Austria.[47] Among those compliant with the protocol (n = 1016), the rates of diarrhea were 39.1% in the placebo group and 28.7% in the group receiving 1 g of the lyophilized yeast per day (p = 0.02).

Prevention of Acute Infantile Diarrhea

Impoverished children in developing countries may have seven or more diarrheal episodes per child per year.[48] Persistent diarrhea, with a high risk of death, occurs in 3-10% of cases.[49] The problem as a whole is best addressed by improving

sanitation and nutrition, but an inexpensive and effective probiotic would have value also. Oberhelman et al.[50] studied the effectiveness of a daily L. rhamnosus GG-containing supplement in preventing acute diarrhea in undernourished Peruvian children. The 204 subjects were treated for 15 months. A modest protective effect was found (5.21 episodes of diarrhea per child per year for L. rhamnosus GG versus 6.02 for placebo). The effect was largely confined to non-breast-fed children (4.69 episodes per child per year for L. rhamnosus GG versus 5.86 for placebo), particularly non-breast-fed 18- to 29-month-old children (4.77 versus 6.32 episodes per child per year) (p = 0.006). The causes of diarrhea were similar in both groups and involved mostly bacteria and parasites. In developed countries, rotavirus is the most common cause of acute diarrhea in children.

Saavedra et al.[51] studied the efficacy of an infant formula supplemented with Bifidobacterium bifidum and Streptococcus thermophilus versus the unsupplemented formula in preventing diarrhea in a hospitalized infant population in the Baltimore, Maryland, area. Over a 17-month period, 31% of infants given the control formula developed diarrhea, while only 7% given the supplemented formula did so. The supplement sharply reduced rotaviral shedding (39% of controls versus 10% of experimentals).

Treatment of Acute Diarrhea

Several probiotic preparations have been shown to be of significant benefit as an adjunct to oral rehydration for acute diarrhea (Table 2). L. rhamnosus GG has been found to reduce the number of days of diarrhea in studies conducted in Thailand,[54] Russia,[55] Pakistan,[53] and Finland [52] and in a multicenter trial in Europe.[56] The most consistent benefit was observed in patients with rotaviral diarrhea.

Another Lactobacillus species that has been recently studied is L. reuteri. This species is a common inhabitant of the gastrointestinal tract and is associated with breast milk. An antimicrobial carbohydrate (reuterin) has been found to be produced in vitro by L. reuteri [63] ; it is available commercially as a probiotic in the United States (Primadophilus Reuteri, Nature's Way, and Probiotica, McNeil Consumer Healthcare) and in several other countries. Two studies found efficacy similar to that reported for L. rhamnosus GG in childhood diarrhea associated with rotavirus (Table 2).[57,58] Trials to compare L. rhamnosus GG and L. reuteri have not been reported but would be of great interest.

S. boulardii, too, has been found to speed up recovery from acute diarrhea both in adults 60 and in infants.[59]

Saint-Marc et al.[61] reported that AIDS-associated diarrhea resolved in 10 of 18 patients given S. boulardii, compared with 1 of 11 patients given placebo. A high (3-g/day) dosage of the yeast was employed for one week. Using a similar protocol, Elmer et al.[64] found no resolution within one week, but 7 of 11 patients responded in weeks 2 to 4. Further evaluation of S. boulardii and other probiotics in AIDS-related diarrhea appears warranted.

Adults (n = 78) with acute diarrhea reported less diarrhea after seven days of treatment with E. faecium SF68 than after placebo treatment (0.6% versus 8.7%) (p = 0.01).[30] A study in Bangladesh in patients infected with Vibrio cholera or enterotoxigenic Escherichia coli found no difference in diarrhea resolution time between E. faecium SF68 treatment and placebo; however, the treatment time was only three days.[62]

Vaginal Infections

While many studies of probiotics for vaginal infections have been reported, most lack a rigorous design. McGroarty [65] and Reid et al.[66] have reviewed the literature; more recent studies were critically discussed by Sobel.[67] Although bacterial vaginosis (BV) and candidal vulvovaginitis are common, few randomized, double-blind, placebo-controlled trials have evaluated the efficacy of probiotics for these infections. The availability of inexpensive oral antimicrobial regimens (metronidazole 2 g once dose for BV and fluconazole 150 mg once for candidal vaginitis) has somewhat diminished the incentive for such studies. Nevertheless, an effective probiotic that could prevent vaginitis or help break the cycle of recurrence would be extremely helpful. For example, a probiotic could be taken whenever women take antimicrobials in order to decrease the risk of candidal vulvovaginitis associated with antimicrobial perturbations of the protective vaginal microflora. Similarly, there could be an important role for probiotics in decreasing the frequency of recurrence (80% risk within nine months) associated with BV.[67] Lactobacilli are normally present in the vagina, and those strains producing hydrogen peroxide and other inhibitory substances are widely assumed to offer protection against the overgrowth of pathogens. Most probiotic preparations for vaginal use include one or more Lactobacillus species.

BV is associated with an overgrowth of Gardnerella vaginalis and anaerobes and, usually, a reduction in vaginal lactobacilli. The pH of vaginal secretions becomes alkaline, which is not favorable for growth of protective lactobacilli. Treatment with metronidazole or clindamycin is effective but can be associated with adverse effects, and recurrences are common. According to Sobel [67] and Reid and Heinemann,[68] women with chronic or recurrent BV associated with diminished vaginal lactobacilli would be prime candidates for biotherapy. Hillier et al.[69] found a relationship between the presence of hydrogen peroxide-

producing lacto-bacilli and a reduced risk of BV in pregnant women. Controlled studies to examine probiotic efficacy for BV have been few, however. Neri et al.[70] reported favorable effects of intravaginal administration of yogurt to 34 women with BV, but a placebo (pasteurized) yogurt was not tested. Ingestion of yogurt enriched with a hydrogen peroxide-producing strain of L. acidophilus was compared with ingestion of pasteurized yogurt for prophylaxis of recurrent candidal vaginitis and recurrent BV by Shalev et al.[71] At one month, 25% of the women in the treatment group (n = 21) had an episode of BV, compared with 50% of the controls (n = 19) (p = 0.04). Attrition in this study was high; only 7 of 46 patients starting the study completed the six-month protocol.

In a well-controlled study, Parent et al.[72] tested the efficacy of a vaginal tablet containing a hydrogen peroxide-producing strain of L. acidophilus and 0.03 mg of estriol in 32 patients with BV. The patients received one or two tablets per day for six days or an identical placebo. Two weeks after the start of therapy, the cure rate in the treatment group was 77%, versus 25% in the placebo group ($p < 0.05$). The lactobacillus strain used was shown to colonize the vagina. Another well-designed study used a hydrogen peroxide-producing strain of L. acidophilus in suppository form to treat women with BV.[73] At the end of the six-day treatment regimen, 16 of 28 treated women had normal wet-mount smears, compared with 0 of the 29 placebo recipients. The treated women also had reduced counts of Bacteroides species but unchanged counts of G. vaginalis and Mobiluncus species compared with the placebo recipients. Most patients had a recurrence of BV after their next menstruation, indicating the need for longer treatment.

Chronic infections and frequent recurrence are also features of candidal vulvovaginitis, and there has long been empirical, self-prescribed use of yogurt and a myriad of commercial probiotic products. As in the case of BV, there have been few well-controlled efficacy studies of probiotics for candidiasis. The limited information available is promising, however.

In theory, lactobacillus strains that have in vitro inhibitory activity against Candida species, that can adhere to vaginal epithelial tissues, and that can be instilled directly into the vagina in a suppository dosage form would be effective. However, oral use of lactobacilli has resulted in recovery of the same strain in the vagina, [71,74] presumably because of the proximity of the anal and vaginal orifices. In a study by Hilton et al.,[74] patients consumed either no yogurt or a hydrogen peroxide-producing strain of L. acidophilus for six months before being crossed over the opposite treatment for another six months. The number of candidal vaginal infections per patient was 2.54 during the six months for the no-yogurt group and 0.38 per patient during the six months for the yogurt group ($p = 0.001$). Only 13 of the 33 patients completed the 12-month study, however. In a later study, the same group treated women with recurrent candidal vulvovaginitis with suppositories containing L. rhamnosus GG.[75] Subjective improvement was reported in this open-label study. On the other hand, Shalev et al.[71] could not find an effect of yogurt containing hydrogen peroxide-producing L. acidophilus compared with pasteurized yogurt; a reduced percentage of women with Candida species-positive cultures was observed in both groups. Perhaps nonviable yogurt cultures have an anticandidal effect. For example, probiotic effects have been noted in immunodeficient mice given heat-killed lactobacilli.[76] S. boulardii has been found to inhibit Candida albicans in germ-free mice,[77] but studies in humans have not been reported.

Probiotic treatment of candidal vulvovaginitis holds promise, but more data from well-designed trials of defined products are needed for an objective assessment.

Urinary-Tract Infections

The ready availability of effective antimicrobials (e.g., trimethoprim-sulfamethoxazole) has limited the attention paid to probiotics for urinary-tract infections (UTIs). Nevertheless, an effective probiotic would have applicability in recurrent and chronic UTI and potentially decrease the risk of antimicrobial resistance. Most urinary-tract pathogens originate in the intestines.[78] The close proximity of the urethra to the vagina allows potential probiotic transfer from vaginal application. However, highly adherent strains of probiotic microorganisms would seem to be of paramount importance for use in UTIs. With probiotic treatment of intestinal disease, adhesion is not necessary for therapeutic activity, provided that daily administration is maintained. Daily vaginal administration does not wash treatment microorganisms over the bladder or urethra, so it would be important for those few probiotic microbes that do access the infected surfaces of the urinary tract to remain there. Other desirable features of a probiotic microbe for UTIs would be the same as for gastrointestinal use, namely, stimulation of a local immune response, production of pathogen-inhibitory compounds, and inhibition of pathogens or their actions.

Well-controlled investigations of probiotics for treating UTIs are few, but studies of microbial strains selected for desirable attributes suggest some promise. Reid and coworkers have been the most active researchers in selecting strains of lactobacilli for UTIs.[78-81] They reported that intravaginal insertion of preparations containing specially selected lactobacillus strains reduced the frequency of recurrent UTIs in a group of highrisk women,[81-83] as did a preparation that stimulated the restoration of endogenous vaginal lactobacilli.[82] Reid et al.[83] evaluated lactobacillus-containing vaginal suppositories for efficacy in preventing UTI recurrence after antimicrobial treatment. The recurrence rate in patients receiving active suppositories was 21% (3/14), compared with 47% (8/17) in patients receiving placebo; the difference was not significant. A placebo-controlled study in 47 patients in Norway did not find a therapeutic effect of twice-weekly applications of a Lactobacillus casei var. rhamnosus-containing vaginal suppository product in cystitis-prone women.[84] Periurethral lactobacilli were not found more frequently in the treated women, which opens the question of the appropriateness of this lactobacillus strain with respect to its ability to adhere to

urogenital cells.

More work is needed to determine the efficacy of probiotics for UTIs. Frequent, long-term vaginal application of a probiotic may not be practical. It would be highly desirable to establish that oral use of a probiotic had a favorable influence on the rate of recurrence of UTIs.

Mechanisms of Action of Probiotics

A common belief about how probiotics work (and one used in marketing these products) is that ingestion improves the "balance" of the intestinal and vaginal microflora so that pathogen growth is restricted. Recent studies indicate that this concept is simplistic and that probiotics probably work by multiple mechanisms. Furthermore, each agent may have unique actions.

Colonization resistance is the ability of the normal microbial flora to resist the establishment of pathogens. Perturbation by antimicrobials and other agents may diminish colonization resistance. An objective of probiotic therapy is to restore colonization resistance until the normal flora becomes reestablished. More specific mechanisms of action have been identified for individual probiotics (Table 3). The ability of a probiotic to inhibit pathogen adhesion or to stimulate a local immunoglobulin A-mediated immune response would be highly desirable, because these properties would provide a broad spectrum of antipathogen activity. However, pathogen antagonism in vitro may not necessarily occur in vivo.

Safety of Probiotics

The available probiotic microorganisms are considered nonpathogenic, but even benign microorganisms can be infective when a patient is severely debilitated or immunosuppressed. For example, lactobacilli are present in dairy products and are part of the normal flora, yet cases of lactobacillemia have been reported in patients with severe underlying conditions.[96,97] To date, there have been only isolated reports linking probiotics with adverse effects. A case of a liver abscess was associated with L. rhamnosus in a 74-year-old diabetic,[98] and cases of fungemia involving S. boulardii have been reported. [99-101] All patients responded to standard antimicrobial therapy. S. boulardii has been used, without complications, to treat chronic diarrhea in AIDS patients,[61,64] and L. reuteri has been safely given to HIV-infected patients.[102] There is a theoretical risk of transfer of antimicrobial resistance from the probiotic to other microorganisms with which it might come in contact, but this has not yet been observed during therapy.

On the basis of published findings, the risks of therapy with available probiotics seem small. However, published studies systematically evaluating the safety of probiotics are lacking. The use of probiotics must be carefully considered when these "living drugs" are used therapeutically in patients at high risk for opportunistic infections or when the gastrointestinal tract is badly damaged.

Product Selection in the United States

There are many probiotic products on the market in the United States, but only four commercially available agents have been tested in placebo-controlled, double-blind studies: L. rhamnosus GG (Culturelle, CAG Functional Foods), S. boulardii (Florastor, Biocodex Inc.), L. acidophilus-L. bulgaricus (Lactinex, BD), and L. reuteri (Primadophilus, Nature's Way, and Probiotica, McNeil Consumer Healthcare). This is not to say that other probiotic products might not be effective; there are simply no well-controlled studies. Only those probiotics shown to be efficacious and safe in controlled studies can be recommended.

Conclusion

Probiotics have demonstrated an ability to prevent and treat some infections, particularly those confined to the vagina and the gastrointestinal tract. Effective use of probiotics has the potential to decrease patients' exposure to antimicrobials. Available probiotics appear safe but should probably be avoided in patients at high risk for septicemia.

Tables

Table 1. Placebo-Controlled Trials of Oral Probiotics for Prevention of Antimicrobial-Associated Diarrhea

Probiotic	Ref (s).	No. Subjects	Days of Treatment	% Subjects with Diarrhea	

				Treatment Group	Control Group
S. boulardii	23	388	7	4.5 [a]	17.5
	24	180	28	9.5 [a]	21.8
	25	193	28	7.2 [a]	14.6
L. rhamnosus	26	188	10	8 [a]	26
	27	167	30	5 [a]	16
L. acidophilus-L. bulgaricus (Lactinex)	28	38	10	66	69.5
	29	79	5	0 a	14
E. faecium SF68	30	45	7	8.7 [a]	27.2
B. longum	31	10	3	10 [a]	60
B. longum-L. acidophilus	32	20	21	20 [a]	70

a Significantly different from corresponding value for control group ($p < 0.05$).

Table 2. Placebo-Controlled Trials of Oral Probiotics for Treatment of Acute Diarrhea

Probiotic	Ref (s).	No. Subjects	Days of Treatment	Duration and Frequency of Diarrhea [a]	
				Treatment Group	Control Group
L. rhamnosus GG	52	71 children	5	1.4 days [b]	2.4 days
	53	40 children	2	31% (at day 2)[b]	75% (at day 2)
	54	26 children	2	1.9 days [b,c]	3.3 days
	55	123 children	5	2.7 days [b,d]	3.7 days
	56	287 children	Until diarrhea stopped	2.4 days [b]	3.0 days
L. reuteri	57	66 children	5	1.5 days [b,e]	2.5 days
	58	40 children	5	26% (at day 2)[b]	81% (at day 2)
S. boulardii	59	130 children	4	15% (at day 2)[b]	60% (at day 2)
	60	98 adults	7	4.9% (at day 3)[b]	23.9% (at day 3)
	61	35 adults with HIV	7	44%[b]	94%
E. faecium SF68	30	78 adults	7	0.6%b	8.7%
	62	114 adults with vibriorelated cholera	3	3.3 days	3.3 days
	62	41 adults with enterotoxigenic E. coli	3	2 days	2 days

a Mean number of days of diarrhea during treatment interval or frequency of diarrhea at end of treatment or period indicated.

b Significantly different from corresponding value for control group ($p < 0.05$).

c Benefit seen only in children with nonbloody diarrhea.

d Benefit seen only in children with rotavirus-associated diarrhea.

e Effect seen at highest dose (1 x 10 10 organisms).

Table 3. Potential Mechanisms of Action of Probiotics

Mechanism	Probiotic Microorganism	Observation	Ref(s).
Production of pathogen-inhibitory substances	L. reuteri	In vitro	85
	L. rhamnosus GG	In vitro	86
Inhibition of pathogen attachment	S. boulardii	Human erythrocytes in vitro	87
	L. acidophilus	Piglet mucus in vitro	88
Inhibition of action of microbial toxins	S. boulardii	Rat ileal loops	89-91
Stimulation of immunoglobulin A	S. boulardii	Rat intestine	92
	L. rhamnosus GG	Human serum	93
Trophic effects on intestinal mucosa	S. boulardii	Rat intestine	94,95

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