REVIEW ARTICLE

Up-to-date clinical and experimental basis for the use of probiotics

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Abstract

Objective: to evaluate the potential of probiotics or biotherapeutic agents for the prevention and/or treatment of selected intestinal infections.

Methods: Medline database was searched for all relevant articles between 1990 and February 1998. Bibliographies of articles were also used. All animal experiments and placebo-controlled human studies were reviewed in order to provide information on the mechanisms of action, potential efficacy, or adverse effects of these biotherapeutic agents.

Results: in the first part of this review, the different mechanisms of action that are effective in the treatment of diarrhea were discussed, and they were well demonstrated in laboratory animals. The most important are: enzymatic induction of disaccharidase activity, trophic effects on the intestinal mucosa, action in blocking bacterial toxins, and also induction of the immunologic response. Therapeutic effects of probiotics in humans, mainly in the gastrointestinal tract, were reported in the second part. Placebo-controlled studies have shown that biotherapeutic agents have been used successfully in the treatment of acute diarrhea in infants, traveler’s diarrhea, antibiotic-associated diarrhea, with or without Clostridium difficile-associated enterocolitis (pseudomembranous colitis), and in immunosuppression-associated diarrhea, including AIDS. Lactobacillus, Bifidobacterium and Saccharomyces boulardii were the most important biotherapeutic agents to be considered.

Conclusions: currently, there is evidence that the administration of selected microorganisms is benefic in the prevention and treatment of certain intestinal infections. According to the literature, Saccharomyces boulardii is the most important probiotic. Possible future indications were discussed, such as the probable synergic effect of many probiotics due to their different and complementary mechanisms of action. The importance of new experimental and clinical studies for the better understanding of actions and the use of probiotics in other clinical situations was emphasized.


Introduction

The microbial communities that inhabit several human surfaces and mucosas, together with the host that lodges them, represent the most complex and least controlled ecosystems ever known. These microbial populations are particularly abundant in the last portions of the digestive...
tract, where they present high population levels (10^{11} viable cells per gram of content) and great variety (400 different species in an only individual). Due to the size, this biomass may be considered as an organ or organism lodged in the human body, where it develops several benefic functions for the host, such as: a) ecological protection; b) immunostimulation; c) nutritional contribution.

Any change in the population equilibrium of this microbial system results in an interference in its functions. Endogenic and exogenic factors, such as the use of antibacterial agents, dietary changes, and stress may perturb the gastrointestinal microbiota, reducing its functions, particularly the protective ones. On the other hand, theoretically, there is no possibility of reinforcing these functions by the gastrointestinal ecosystem modulation. Two experimental or therapeutic ways may be followed aiming at compensating or stimulating these functions: 1) oral administration of live microorganisms (probiotics); 2) ingestion of substrates that stimulate specific groups of the normal microbiota (prebiotics that may be classified as functional foods). A benefic action of the microorganisms ingested or of the stimulators must have been proved previously. Among probiotics, two great microbial groups were particularly studied in experimental and clinical levels, and they are already available commercially: lactic acid bacteria, and yeasts.

Historic

The groups of lactic acid bacteria so far studied were \textit{Lactobacillus}, \textit{Bifidobacterium}, \textit{Streptococcus} and \textit{Enterococcus}, but only the first two present a large quantity of works and more consistent data. The lactobacilli were the first microorganisms whose ingestion in their live form was associated with a benefic effect, when, in the beginning of the century, Metchnikoff\cite{2} suggested the consumption of fermented milk for the modulation of the gastrointestinal microbiota. At the same time, Tissier\cite{3} affirmed that the fecal microbiota of breast-fed human newborns presented more bifidobacteria than those receiving formulae. Although this observation was not confirmed posteriorly, a series of evidence suggested a benefic function of these bacteria in the human gastrointestinal ecosystem. Differently from the lactic acid bacteria, the use of bifidobacteria is relatively recent. The lactic acid bacteria most frequently used as probiotics make part of the species \textit{Lactobacillus acidophilus}, \textit{Lactobacillus casei}, \textit{Bifidobacterium bifidum} and \textit{Bifidobacterium longum}.

Nonpathogenic yeasts present some characteristics that differentiate them from bacteria. The natural resistance they have to antibiotics has constituted an interesting basis for its application as probiotics. In this point, \textit{Saccharomyces boulardii} was the most widely tested in experimental and clinical assays, showing very important results. This microorganism was initially isolated in Indochinese fruits (lychee). Fruits contaminated with \textit{Saccharomyces boulardii} were used in the local popular medicine for the treatment of diarrhea. The product was introduced in France with the same objective in 1950,\cite{5} and in the present days, it is widely commercialized in European, African, and South American countries.

Types of preparation and ecological impact on the intestinal microbiota

Different probiotics are studied and commercialized in the form of preparations containing one only or a combination of microorganisms. The probiotic should prove viable in the preparation, and should maintain this viability in the gastrointestinal ecosystem, which is an indispensable condition for its action. Probiotics are commercialized in the form of pharmaceutical preparations (capsules or sachets), or naturally (fermented milk or yogurt). In the first case, the lyophilization of the product allows to keep the viability during a long period of storage in room temperature. However, in fermented milk products, refrigeration is indispensable, and the life of microbial cells is extremely reduced.\cite{6} There are no known probiotics capable of getting installed in the gastrointestinal ecosystem after a prolonged ingestion, considering that the local microbiota, either perturbed or not, impedes this colonization. However, several biotherapeutic agents survive during its passage through the bowel, as in the cases of \textit{L. acidophilus}, \textit{Saccharomyces boulardii}, and \textit{Bifidobacterium}.\cite{7,8,9} Survival is not the only important factor for the action of a probiotic. The population levels of biotherapeutic agents should be sufficiently elevated, so that they have an impact on the site where they are expected to develop their function. In microbial ecology, a microorganism is considered to influence the ecosystem where it is installed only when its population is equal or above 10^7 colony-forming units per gram or milliliter of content (CFU/g or CFU/ml).\cite{10} So, the concentration of probiotics in viable cells should be adjusted in the initial preparation taking into consideration the ability of the microorganism to survive without multiplying in the digestive tract and its intestinal dilution effect, so that a minimum of 10^7 CFU/g of intestinal content is achieved. So, the daily intake of a probiotic in an adequate quantity is indispensable for the maintenance of levels artificially elevated of the microorganism in the gastrointestinal ecosystem, which allows it to develop the expected benefic effect.

Mechanisms of action

The possible mechanisms of action suggested to explain the probiotics’ benefic effects are basically the same used by the normal gastrointestinal microbiota to carry out its functions. This is not incoherent with the objective of the use of these biotherapeutic agents, which is to compensate or reinforce the gastrointestinal microbial ecosystem activity.
Ecological protection

Among the mechanisms of ecological protection, we may distinguish two types: a) those that prevent the multiplication of pathogenic targets (antagonism); b) those that inhibit the pathogenic action (toxin modulation).

Antagonism may be explained by the competition for nutrients or for adhesion sites, and also by the production of metabolites and toxic substances. A competition for nutrients has been proposed as one of the mechanisms through which the normal gastrointestinal microbiota can inhibit the growth of Clostridium difficile, but these effects are not correlated to the use of probiotics. Escherichia coli was shown to compete with enteropathogenic Escherichia coli for adhesion in swine’s digestive tract. The Lactobacillus acidophilus also prevents the adhesion of pathogenic microorganisms in cultures of human intestinal cells. The treatment with Saccharomyces boulardii reduces the mortality of young rats infected with Entamoeba histolytica. In vitro, the contact between this protozoan and Saccharomyces boulardii, its membranes, or the supernatant of yeast culture reduces the number of trophozoites capable of adhering to erythrocytes. The production of antimicrobial substances by several probiotics was already shown. These substances can be metabolites, such as organic acids (especially the lactic acid, to which Samonella sp is particularly sensitive), or H2O2 (only at the superior parts of the digestive tract, where the molecular oxygen is still present in a sufficient quantity to permit this production). Bacteriocins, or bacteriocin-like agents are frequently produced in vitro by Lactobacillus sp and Bifidobacterium sp, but it was never possible to prove the action of such compounds in vivo. Saccharomyces boulardii showed an elevated protective ability when used in conventional and gnotoxic mice against Salmonella typhimurium and Shigella flexneri, but the mechanism responsible for this effect involves other factors, which are not characteristic of antagonism.

Although some bacteria may also modulate the production of toxins by pathogenic microorganisms, this ability is a remarkable property of Saccharomyces boulardii. Several works showed that this agent is able to reduce the damage resulting from the action of bacterial toxins of Vibrio cholerae (19,20), Escherichia coli, and Clostridium difficile in animal models or in the culture of intestinal cells. Several mechanisms may explain this toxin modulation property of Saccharomyces boulardii, and these hypotheses are not mutually exclusive: a) production of a protein of 12 kilodaltons (kD), without proteolytic activity, which reduces the formation of Ampc by intestinal cells in a setting where cholera toxins or thermolabile Escherichia coli toxins were added; b) production of a protein of 54 kD, which degrades toxin A of Clostridium difficile, as well as its receptor in the in vitro erythrocyte; c) recent data, using a cholera toxin marked with I 1, show that Saccharomyces boulardii presents specific receptors for this toxin on its surface, which could deviate it from its receptors in the enterocytes.

Immunostimulation

The interest in the immune system stimulation ability through probiotics started with the use of fermented viscous extract for the treatment of cancer in the 20s. The stimulating factor was identified as a degradation product for the lactobacilli’s cellular wall. Posteriorly, several experimental works confirmed this stimulating ability, which consists of increasing antibody titers, macrophage activity, number of killer cells, number of T cells, and interferon. The oral treatment of gnotobiotic rats with Saccharomyces boulardii reduced in 10 to 50 times the intestinal production of Candida albicans, probably due to some type of immunostimulation. In immunosuppressed mice (decontamination with antibiotics and injections of prednisolone), the oral administration of Saccharomyces boulardii reduced the frequency of translocation of Candida albicans to mesenteric lymph nodes, liver, and kidney. The treatment with doses inferior to the normal posology of Saccharomyces boulardii in immunosuppressed mice (cyclophosphamide) also protected the animals, as shown by data of: a) bacterial translocation to mesenteric lymph nodes, liver, and spleen; b) histopathology of the intestinal mucosa; c) survival.

Still, in the case of use of Saccharomyces boulardii, an increase in IgA secretion and in immunoglobulin secretory component was observed in rats. The oral administration of Saccharomyces boulardii (1 g/day for 7 days) to 60 volunteers induced an increase in the peripheral blood cells, which suggests the activation of proteins that are typical of the inflammatory response acute phase. There was a significant increase in the number of erythrocytes, hemoglobin, leukocytes, neutrophils, polynuclear cells, phagocytes, complement components, such as C3, C5, and mainly C3d. There was also an increase in the chemotaxis activity of leukocytes, and in the serum anticompound activity. No significant increase in the number of eosinophils, basophils, monocytes, and serum proteins, such as albumin and immunoglobulin, were found. Mitogenic effects or modification in the lymphocyte population were not found either. These alterations were possibly transitory, since 10 of these volunteers, studied 4 weeks after the last administration of Saccharomyces boulardii, returned to basal values. There was no clinical repercussion in any case. The possible explanation for the hemogram variations may be due to the stimulation of the reticulo-endothelial system. After its stimulation, there would be mobilization of cells from hematopoietic organs to circulation. Experiences with mice receiving Saccharomyces boulardii orally showed immunostimulation, represented by an increased expression of the lymphoid component in lamina propria, liver, and spleen. The demonstration that glucan and other extracts of Saccharomyces boulardii are important in the stimulation of the endothelial reticulum reinforces these hypothesis.
The meaning of these observations is not clarified yet, and an increased resistance to infections can be speculated. Another important point to be considered and that deserves more studies concerns the dose/effect ratio.

**Trophic effect on intestinal mucosa**

The improvement in the digestion of lactose by human beings is one of the well-known properties of lactic acid bacteria. The good digestibility of lactose in yogurt, for example, was extensively investigated, and three hypotheses were usually proposed: a) stimulation of the intestinal lactase activity; b) reduced intestinal transit time, when compared to milk; c) digestion of lactose in the intestinal light due to the yogurt lactase. Yeasts, as well as other eukaryote and prokaryote cells, present variable quantities of polyamines (spermidine and spermine), which are necessary for cellular division and for the synthesis of DNA and proteins. Rats treated with oral *Saccharomyces boulardii* present elevated spermidine and spermine titters in the intestinal lumen, which would be secreted by *Saccharomyces boulardii* or during its catabolism. Spermidine and spermine would be responsible for the trophic effects on the small bowel mucosa, with increased activity of disaccharidases. DNA content of the mucosa, cellular concentration of polymeric immunoglobulins, IgA secretion, besides the increased IgA secretory component in cells of villosities and crypts. In a study performed in humans, *Saccharomyces boulardii* was administered orally at the dose of 1 g/day for 14 days to seven volunteers. There was an increase in saccharase (82%), lactase (77%), and maltase (75%), which corroborates findings got in animals. These results may have clinical importance, and deserve investigation in the field of diarrheal diseases.

**Clinical assays**

The increased knowledge of corporeal fluids and of water and electrolyte flow in the digestive tract brought a more rational treatment and a great reduction in infant mortality due to acute diarrhea. Oral rehydration therapy using glycol-electrolytic solution, which is recommended by World Health Organization, has proved highly effective for the correction of dehydration associated with acute diarrhea of several etiologies, provided that the patients are able to drink and do not present signs of severe dehydration. Although the oral rehydration solution recommended by World Health Organization is secure and efficacious, it presents important limitations: it does not reduce fecal loss rate, neither shortens the duration of the diarrheal disease. Mothers usually do not comprehend the relationship between diarrhea and dehydration, and their main worry, shared with many health professionals, is to reduce the volume or the frequency of feces, or the duration of the diarrhea. This fact is probably responsible for the uncontrolled use of antidiarrheal drugs and antibiotics, associated or not with the use of oral rehydration solution, to treat diarrhea. The development of an inexpensive, secure, and efficacious drug, stable after a prolonged period of storage, which would be able, together with oral rehydration therapy, to promote a substantial reduction in total fecal loss (through a shorter duration of the diarrheal episode) or in fecal loss rate would represent a great advance, particularly improving the receptivity and the use of oral rehydration therapy by mothers and health professionals. This would also result in a reduced use of inefficacious drugs and antibiotics in the handling of acute diarrhea, as well as in a reduced negative impact on the nutritional status due to shorter episodes. Such changes would represent a great advance in the control of morbidity and mortality due to diarrheal diseases through a more effective treatment.

There is a crescent enthusiasm in the search for a treatment based on current knowledge about the pathophysiology of diarrheal diseases, through which we could interfere by activating and stabilizing the “physiological” intestinal microbiota, or by promoting competition with the pathogenic germ, thus preventing its proliferation. The investigation works that exist in the literature show that, among probiotics, yeasts and the lactobacilli gather the most promising potential characteristics as co-operators in the treatment of diarrheal diseases. *Saccharomyces boulardii* is among the most studied microorganisms with this objective.

Based on the mechanisms of action described in the previous paragraphs - namely microbial antagonism, competition for adhesion site, inhibition of effects or of the production of bacterial toxins, increase in nonspecific anti-infectious defenses (phagocytosis, complement system) and in the disaccharide activity -, some works have been developed showing the existence of some protective effect in the use of lactic acid bacteria and of *Saccharomyces boulardii* in diarrheal diseases.

Saavedra et al., in 1994, published a randomized, double-blind study assessing the protective effect of lactic formulae supplemented with *B. bifidum* and *S. thermophilus* against diarrhea caused by rotavirus in children hospitalized due to chronic diseases. This study showed a lower occurrence of episodes of diarrhea in the supplemented group (6.9%) in relation to the control group (31%). The prevalence of rotavirus was 10.3% in the supplemented group, and 38.5% in the control group. Recent studies have been carried out to evaluate the efficacy of *L. casei*, subspecies GG, in the treatment of acute diarrhea in children. These studies, performed in Finland and Pakistan, have shown that this microorganism is efficacious in reducing the duration of episodes of acute diarrhea. It has also been used successfully in the reduction of traveler’s diarrhea.

Guidici (1985) (51), using *Saccharomyces boulardii* in outpatient children presenting diarrhea without dehydration, presented results of spontaneous cure in 91% of the patients in 4 days. Some studies tested the effectiveness of *Saccharomyces boulardii* in inpatients with acute diarrhea...
and dehydration, and showed promising results. So, in a controlled study using a sample of 10 patients per group, Chapoy concluded that there is a superiority in the group treated with Saccharomyces boulardii, which presented significant differences for the reduction in the number of dejections (P<0.01), alteration in stool consistency (P<0.05), and reduced intestinal transit (P<0.05). Materana, with a double-blind, randomized study, using Saccharomyces boulardii or placebo in 120 patients, showed a significant difference in the reduction of the number of defections after 3 days, both in the bacterial diarrhea (2.36±1.52 against 3.95±2.4, respectively; P<0.008) as in the viral one (2.55±2.24 against 4.56±3.30, respectively; P<0.03). Acevedo et al presented positive results based on hospitalization time, decreased water loss, reduction in the number of defections/day, among other factors when Saccharomyces boulardii was used in children presenting acute diarrhea. A work published by Cetina-Sauri & Basto showed significant results (P<0.01) in a double-blind, randomized study, with a sample of 130 patients, where the group receiving Saccharomyces boulardii had a cure of 84.6% (55/65), while the placebo group presented efficacy of 40% (26/65), when reduction in the number of defections, and the consistency of stools at 48 and 96 hours were considered as cure criteria. Due to the lack of uniformity in the methodology employed, it would be recommended that additional studies were performed in order to confirm the beneficial effect of this probiotic, using the double-blind, randomized methodology, with samples of patients that are sufficient to evidence statistically significant and clinically relevant differences, measuring the efficacy through metabolic balance studies, where objective and reproducible variables can be tested, such as the fecal loss rate and the duration of the diarrheal episode.

Up to 30% of the patients that were treated with antibiotics may have diarrhea of variable gravity, but only one-third is associated with the presence of Clostridium difficile. What several theories about the causes of diarrhea associated with antibiotics - such as the overgrowth of Clostridium difficile, denudation of receptors or toxin adsorption sites, caused by the disappearance of the normal microbiota, the decrease in the short-chain fatty acids, due to the disappearance of bacteria responsible for the metabolism of complex carbohydrates, or the lack of competition for nutrients, caused by changes in the normal microbiota - have in common is the impact of antibiotics on the normal microbiota of the colon. So, several therapeutic trials have been made with probiotic agents, mainly aiming at preventing diarrhea associated with antibiotics.

Different preparations of lactobacilli were used in the prevention of diarrhea associated with antibiotics. In one of these studies, 79 inpatients using ampicillin received a mixture of L. acidophilus and L. bulgaris, or placebo. The incidence of diarrhea was of 0/36 and 6/43 patients in the treated group and in the placebo group, respectively, but this type of mixture did now show efficacious in a similar study. Other studies using B. longum, Enterococcus faecium, L. casei GG, and mixture of B. longum and L. acidophilus presented interpretation difficulties, either because the number of patients or the time of treatment was too small, or because subjective and clinically little important symptoms were assessed, or still because the studies presented marginal results.

In literature, there are three double-blind, randomized studies aiming at verifying the preventive effect of the use of Saccharomyces boulardii in patients receiving antibiotics. The first study was carried out in 1976, in France, considering 25 medical centers, with a total of 388 patients above 15 years of age receiving tetracycline or β-lactam antibiotic due to infection of the superior respiratory tract. Of the 199 patients treated with Saccharomyces boulardii (100 mg, twice a day, orally), only nine (4.5%) developed diarrhea when compared to patients receiving placebo (33/189; 17.5%). The other study also showed its efficacy in the prevention of diarrhea in inpatients. In this study, the Saccharomyces boulardii was introduced 48 hours after the beginning of antibiotic therapy, and maintained for 2 weeks after its suspension. The yeast was administered at the dose of 500 mg, twice a day, orally. Of the 180 patients that completed the study, 14 out of 64 (21.8%) of the placebo group presented diarrhea, compared to 11 out of 116 (9.5%; P=0.038) in the group receiving Saccharomyces boulardii. In the third study, which was also multicentric, Saccharomyces boulardii was tested in 193 hospitalized patients with ages equal or superior to 18 years receiving at least one β-lactam antibiotic or in association with other antibiotics. The probiotic was administered orally at the dose of 500 mg, twice a day, initiated at the most 3 days after the beginning of antibiotic therapy, and continued for up to 2 days after its suspension. Patients were followed up for 7 weeks. Of the 97 patients that received the Saccharomyces boulardii, 7 (7.2%) presented diarrhea, compared to 14 out of the 96 (14.6%; P=0.02) in the control group. The efficacy of Saccharomyces boulardii associated with antibiotics in preventing diarrhea was important. In this same work, when using a multivariate analysis for the control of risk factors, a relative risk of 0.29 (95%) was found in patients receiving Saccharomyces boulardii, with a confidence interval of 0.08-0.98. The result of these works indicate the protective effect of Saccharomyces boulardii in the presence of associated diarrhea, mainly β-lactam antibiotics. Side effects related to the use of Saccharomyces boulardii were not observed in these studies.

Diarrhea in patients infected with HIV constitutes a serious complication of this disease, being frequently of difficult control due to its multifactorial cause. Blehaut et al. (1992) presented a controlled, double-blind work, with 35 AIDS adult patients presenting chronic diarrhea for more than 24 days. The Saccharomyces boulardii was used at the dose of 1.5 g, twice a day, during 1 week. The etiologies for the diarrhea cases were Cryptosporidium (17%), Candida (14%), Kaposi sarcoma (8%), atypical
Saccharomyces boulardii (8%), cytomegalovirus (8%), Mycobacterium (6%), and unknown cause (39%). At the end of the clinical assay, 10 out of 18 patients that had received Saccharomyces boulardii cured the diarrhea, while only 1 out of 17 patients got cured in the placebo group (P<0.001).

The effect of Saccharomyces boulardii in the prevention of traveler’s diarrhea was evaluated in a double-blind study by Kollarith et al.,73 with its administration to adults that had traveled to several regions of the world. The 1,231 travelers were divided in three groups: placebo, Saccharomyces boulardii at the daily dose of 150 mg, and a third group that received the probiotic at a daily dose of 500 mg. The incidence of diarrhea was 42.6%, 33.6%, and 31.8%, respectively (P<0.002). The results in preventing diarrhea were better depending on the geographic region to which they traveled, as to Africa, for example (58%: P<0.01); this effect may be due to the variation in the etiologic agent. Another important point to be considered is the adhesion to treatment.

Patients fed through nasoenteral probe presented a higher risk for developing diarrhea. The cause is related mainly to the alteration in the intestinal microbiota, with bacterial overgrowth at the small bowel, which may interfere with the digestion of carbohydrates and with the deconjugation of bile salts. Another causal factor for diarrhea is related to the diet osmolality, administration speed, drugs, and underlying disease. Two randomized, double-blind studies74,75 using Saccharomyces boulardii were performed with adult patients receiving nasogastric and enteral feeding. The first one74 had 40 patients under intensive care and receiving continuous nasoenteral feeding. Twenty patients receiving Saccharomyces boulardii (500 mg/l of solution) presented 34 days of diarrhea (8.7%) during 389 days of observation. In the placebo group, there were 63 days of diarrhea (16.9%) during the 373 days of observation (P<0.001). The second study75 was performed in 20 patients seriously burned who received nasogastric feeding. These patients were randomized to receive Saccharomyces boulardii (2 g/day) or placebo during 8 to 28 days of feeding. The number of patients receiving Saccharomyces boulardii who presented at least 1 day of diarrhea, as well as the duration of this symptom, were significantly lower when compared to the group receiving placebo (P<0.001). Other studies with a higher number of patients are recommended to the confirmation of the use of Saccharomyces boulardii in preventing diarrhea in patients receiving enteral feeding.

The complications of the use of Saccharomyces boulardii have been investigated mainly in animal models. In mice, the administration of Saccharomyces boulardii for 70 days in drinking water, at the concentration of 5%, did not lead to translocation from the gastrointestinal tract to other organs.76 In immunosuppressed animal models (prednisolone and decontamination through antibiotics), Saccharomyces boulardii was found in low concentration at the mesenteric lymph nodes, and was not detected in the liver, spleen, or kidneys.26 In studies using conventional mice immunosuppressed with cyclophosphamide and receiving variable doses of Saccharomyces boulardii orally (0.1 mg, 1.0 mg, and 10 mg) for 7 days, translocation of the yeast in low concentrations was found in some animals, independently of the dose and mainly to the mesenteric lymph nodes. Translocation to the liver and spleen rarely occurred, but in animals where there was translocation of the Saccharomyces boulardii, a significant level of bacterial translocation was found. In this study, a protection against bacterial translocation to the liver was found in animals that had received Saccharomyces boulardii at the dose of 0.1 mg.29 Along 40 years of use, thousands of treatment using Saccharomyces boulardii in men were developed, and seven cases have been published in which the microorganism was found in the patient’s blood.77-82 Some factors were present in these patients, such as precarious general conditions, probable lesion of the intestinal mucosa due to malnutrition, chronic diarrhea, intestinal ischemia, use of broad-spectrum antibiotics, which alters the intestinal microbiota, and high doses of the probiotic. Among these cases, three occurred in children: one with severe burn (55%), with infection at the urinary tract caused by E. faecium; another infant 1 year old with protracted diarrhea, severe malnutrition, and bronchopneumonia; and another infant 20 months old with short-bowel syndrome, recent history of septicemia, which had received Saccharomyces boulardii during 11 months.79 Among the four adults, one patient had undergone colectomy, and presented recent history of septic shock; two were HIV-positive, immunosuppressed with central venous catheters; one developed fungemia after recovery from a cardiac arrest and ischemia of the intestinal mucosa.77 All patients recovered after antimycotic treatment. There are no reports of resistance by Saccharomyces boulardii to antimycotic agents. These data of the literature indicate safety for the oral use of Saccharomyces boulardii. Care should be taken with seriously sick patients, mainly the immunosuppressed ones.

Conclusions and perspectives

Experimental and clinical works using probiotics show a possibility of application of these biotherapeutic agents to compensate an expected reduction (prevention) or an installed reduction (treatment) of the gastrointestinal microbiota functions. Data available in the literature do not suggest a possibility of stimulation of ecological defenses above the basal levels, similarly to the stimulation of immunologic defenses with the use of vaccines. There are some aspects about probiotics that require complementary elucidation, and this situation sometimes leads many researches to adopt extreme positions in relation to these products. However, we should remember that we can not expect probiotics to show functional characteristics that are
not seen in other therapeutic agents (no contraindication, no secondary effect, total efficiency, etc.).

Probiotics represent an important alternative to conventional antimicrobials, to which many pathogenic microorganisms may develop resistance. In relation to their protective potential, each probiotic has simultaneous multiple mechanisms of action, such as: antagonism against pathogenic microorganisms, trophic effect on mucosas, immunostimulation of the host, and/or inhibition of the production or action of bacterial toxins. This represents a great difference and advantage in relation to chemotherapeutic agents, making the development of resistance due to punctual mutations caused by pathogenic agents difficult. Another advantage of the probiotics when compared to conventional antimicrobials is the absence of a malign impact on the gastrointestinal ecosystem.

Lactic acid bacteria and Saccharomyces boulardii were particularly studied, but most clinical works with probiotics will represent a strategy even more efficient to use of lactobacilli requires more well-controlled, broad evidence of benefic actions, which should be reinforced by new well-controlled assays. Works with other probiotics, such as L. casei GG, L. acidophilus, and B. longum, suggest possible applications in different types of diarrhea, but the use of lactobacilli requires more well-controlled, broad studies.

Two great problems require further investigations for the better use - thus performance - of probiotics: more accurate knowledge about both the mechanisms of action of this biotherapeutic agents, and the rules that regulate the population equilibrium in the microbial ecosystem in which they should act. With the obtainment of more detailed information concerning these two problems, the use of probiotics will represent a strategy even more efficient to the treatment of these infections, considering the more and more frequent resistance of pathogenic microorganisms to antibiotics.

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