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REVIEW ARTICLE

Probiotics: innocuousness, prevention and risks

Inocuidad, prevención y riesgos de los probióticos

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Abstract

Probiotics have been defined as live microorganisms which, when ingested in adequate numbers, confer health benefits to the host. They are currently consumed without any age restrictions and adverse effects such as sepsis, a marker of the risk of invasion of the bloodstream, are extremely infrequent. However, some health professionals express doubts about probiotics being truly innocuous. This review discusses the incidence of sepsis secondary to probiotics use, mainly lactobacilli and bifidobacteria, evaluated through molecular biology or classic culture techniques, showing that sepsis in large numbers of individuals along decennia is extremely low, of the order of 0,02% en some centers or as low as 1 case/million population in France. These data are important considering the use different species and strains of these microorganisms. Few studies which have reported other adverse effects but many of these have problems with their design that cast doubt about the validity of their results. On the contrary, it has been shown that probiotic microorganisms exert positive stimulatory effects on innate and acquired immunity, with decrease of the manifestations of atopy and eczema. These positive effects are further evidenced by the beneficial effects of many species of probiotics in preventing necrotizing enterocolitis in patients as functionally labile as premature-born babies.

Keywords:
Probiotics,
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lactobacilli,
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Probiotics have been defined by WHO/FAO/UNU as living microorganisms which, when administered in adequate quantities, confer health benefits to the host[1].

In the media, and even in groups of health professionals, there has been speculation about the potential risk that some probiotic could invade the bloodstream and cause episodes of sepsis. This assumption is based mainly on the number of species and strains on the market, the high number of bacteria ingested and their massive consumption without restrictions by healthy and asymptomatic individuals, often without precise knowledge about their state of health, and by subjects of all ages. According to some sources, and without specifying the origin of their information, indeterminate proportions of consumers could be expected to be affected by serious septic episodes caused by these microorganisms. However, a review of the literature reveals that the cases published in the medical literature are scarce, that there are no outbreaks described in the healthy population and that these are widely separated in time and geographically. Published cases that would demonstrate some pathogenic potential mainly affect the elderly, individuals affected by deficiencies of their immune system or who have recently undergone antitumor chemotherapies or the effects of ionizing radiation. Added to this are diabetics or patients with extensive ulcerations of the mucosa of the digestive tract, especially if they have previously been treated with broad-spectrum antibiotics[2]. Cannon *et al.* conducted a Medline search for cases of invasion of the bloodstream by *Lactobacilli* published in English in the medical literature between 1950 and July 2003[3]. Was possible to identify a total of 243 cases (on average 4.6 cases per year), mainly episodes of bacteremia or endocarditis. The species most frequently detected were *L. casei*, in 35.7% of cases and *L. rhamnosus* in 22.9%. There were cases associated with other species of *Lactobacillus* but in lesser numbers, associated mainly with meningitis, peritonitis or abscesses in diverse organs. Mortality reached almost 30%, especially in episodes of polybacterial bacteremia. With this background in mind it is possible to consider bacteremia due to *Lactobacillus* as an index of serious defects in the immunity of those affected[3]. In episodes of bacterial endocarditis in adults, *Lactobacillus* appears as an etiological agent in 0.05 to 0.4% of episodes, reflecting its a limited capacity to adhere to the endothelium of undamaged heart valves, which was confirmed in experimental models[4].

In a study of 280 infants, who received one of three infant formulas containing different probiotics and prebiotics between birth and 4 months of age, there were no negative effects on their growth and development. Of the 28 adverse events detected in these infants none were caused by the invasion of the circulation by the probiotics tested[5].

Another study published in 2002 evaluated in Finland the incidence of bacteremia by *Lactobacillus rhamnosus* GG (ATCC 53103) for 12 years from 1990[6]. In 1999 the annual consumption of products containing this *Lactobacillus* reached 6 liters per person, with a content of approximately 3 x 10^{11} CFU/person/year. Since that year the Laboratory of the Central University Hospital of Helsinki began to save the lactobacilli isolated from blood cultures to apply methods of molecular analysis for their identification. Between 1990 and 2000, 209.497 blood cultures were performed in the laboratory, of which 43 were positive for *Lactobacillus.* This represents 0,021% of all blood cultures and 0,19% of the 23.070 positive cultures. The number of cultures confirmed for *Lactobacillus* by the API method (an culture method of bacteria identification) and the polymerase chain reaction (PCR) were 22 (51,2% of the positive). Of the 46 isolates positive for *Lactobacillus* at the Central University Hospital, 11 (22,9% of the total) were positive for *Lactobacillus rhamnosus GG.* At the national level, the National Register of Infectious Diseases of Finland accumulated 48 positive cases for the whole country between 1995 and 2000. These differences are probably due to differences in the collection and coverage areas of cases[6].

In 1994 the National Institute of Public Health of Finland initiated country wide a similar registration system. In Finlan it is mandatory that all laboratories report the results of blood cultures and cerebrospinal fluid cultures to this instution . From 1995 to 2000 the National Institute of Public Health detected 36.920 positive blood cultures (in a population of approximately 5.3 million inhabitants, 2010) of which 90 were positive for *Lactobacillus*, a rate of 0,24% and an incidence of infection for the period of 2,9 per million inhabitants. Of the positive blood cultures, 39 isolates were confirmed as probiotic *Lactobacillus* (43,3% of the total). During the years of follow-up by the National Institute of Public Health, there has been a tendency the number of positive blood cultures to increase, but the proportion due to *Lactobacillus* has remained unchanged (0,2%, p = 0.7100). There were isolates of other species of lactobacilli without evidence of a pattern that could be considered characteristic[6].

This same group of investigators carried out a retrospective study of blood cultures performed between October 1994 and the end of 2000[7]. After discarding those samples that did not correspond to lactobacilli or which corresponded to other etiologies. 89 cases were included; 25 of these corresponded to *L. rhamnosus*, 9 to *L. fermentum*, 7 to *L. casei*, 2 to *L. gasseri* and 4 to other species. When compared to the standard strain, 11 of the 25 isolates of *L. rhamnosus* were classified as *L.*

rhamnosus GG. In addition to determining the genetic composition of the bacteria isolated, the clinical information of each patient was reviewed. Patients were classified as previously healthy (class 1 McCabe and Jackson classification), patients with minor underlying diseases (class 2, McCabe and Jackson classification), patients with ultimately fatal disease (class 3, McCabe and Jackson), and patients with rapidly fatal disease (in six months, class 4, McCabe and Jackson)[8]. Additionally, a careful record of their etiologies and treatments was made, with special attention to the presence of bacterial endocarditis. In 38% of the cases there was no agreement among the reviewers as regards to how the pathologies were to be classified. All patients had one or more *Lactobacillus* positive blood cultures, one patient had 2 episodes of *Lactobacillus* bacteremia but due to different strains. Patients with *Lactobacillus* bacteremia were divided into 4 groups: 11 patients with bacteremia due to *Lactobacillus casei rhamnosus* GG, 14 with *L. rhamnosus no* GG and 22 affected by other species of *Lactobacillus*. In 42 additional patients the pathogen was not a lactobacillus. 91% of patients in the LGG group were classified in class 3 and 4 of McCabe and Jackson classification and were mainly affected by malignant tumors; most of them had undergone surgery. C-reactive protein was higher in the patients in whom LGG or *L. rhamnosus* was isolated. In 39% of the cases the bacteremia was polymicrobial and in 2% of the patients 2 or more additional lactobacilli were isolated. At the onset of the bacteremia half of the patients were receiving antibiotics and no cases of endocarditis associated with those microorganisms were diagnosed by these microorganisms. In the majority of those affected there were clinical signs of infection: fever, leukocytosis, high levels of C-reactive protein. *L. rhamnosus* caused infections with more intense inflammatory response. In a few cases there were severe septicemic complications. The authors postulated that the detection of lactobacilli in the blood has important clinical significance and prognosis and its treatment must be guided by tests of sensitivity to the antibiotics. This publication emphasizes again that there is little relationship between the consumption of probiotics and adverse effects, taking into account the frequency and magnitude of consumption of these microorganisms and the absence of systematic health controls in the general population. The pathogenesis of opportunistic infections due to *Lactobacillus* is not known but these tend to affect individuals with serious underlying disease. This feature of low pathogenicity has a logical explanation taking into account that probiotic strains have been selected precisely because they lack properties of this type[9]. Analysis of the genome of *Lactobacillus reuteri* ATCC 55730 showed that it carried in its chromosome of a gene encoding a lactamase, and that it also had in its cytoplasm two plasmids that encoded resistance to lincomycin and tetracycline. For this reason *L. reuteri* ATCC 55730 was submitted to a process in which both plasmids were eliminated,,or ignating a new strain of *L. reuteri* which was named *L. reuteri* DSM 17938, which did not include of these plasmids and is devoid of the possibility of transmitting them to other microorganisms[10]. *In vitro* tests confirmed that this new strain maintained the capabilities of the original sand has been widely used worldwide.

Bernardeau *et al*. estimate that during the last century the risk of *Lactobacillus* infections in France has been one case per 10 million inhabitants[11]. An additional publication has discussed the difficulties encountered in analyzing the factors involved in the safety of probiotics. Another publication discussed the difficulties faced in analyzing the factors involved in the safety of probiotics. It is well known that the stimulation of the immune system by these bacteria could be beneficial for those subjects considered healthy even if they have some minor degree of compromise of their immune functions: individuals in situations of stress, the elderly, newborns and pregnant women, who are subject to an increased risk of infections[12]. The administration of probiotics to subjects older than 69 years not only increased the counts of microorganisms considered beneficial in their fecal microbiota, for example the bifidobacteria, but was associated with evidence of activation of their natural immunity[13]. It is not known for how long these improved parameters persist. *Lactobacillus reuteri* estimulates some defensive functions of the enterocytes and colonocytes in mice, even in the presence of a normal resident microbiota[14]. Immunocompromised individuals usually experience beneficial effects when receiving probiotics, including the stimulation of their immune system, but may also experience reactions that could be considered as negative. This would be explained by their lesser capacity to eliminate exogenous bacteria. This underlines the importance of carefully evaluating the health status of the patients as well as the functional capabilities of the probiotics to be used. It must be kept in mind that the most widely used probiotic strains have been marketed for many years and have been under very strict supervision and quality controls without detection of genetic factors associated with possible adverse effects[15]. Adverse effects have not been observed when even using combinations of probiotic species, such as VSL#3. This is a mixture of 4 species of lactobacilli (*L. casei, L. plantarum, L. acidophilus, L. delbruecki subsp. bulgaricus*), 3 species of bifidobacteria (*B. longum, B. breve and B. infantis*) and *Streptococcus salivarius subsp thermophilus* with total counts of 5×10^{11} CFU/g of preparation. There is consensus about the mechanisms through which probiotics induce there effects

work and it is accepted that while some stimulate local immunity and the effectiveness of immune responses, others exert anti-inflammatory or anti-allergic activities or induce and stimulate immune tolerance processes[18,19]. In experimental models of colitis, VSL#3 induced the proliferation of regulatory T lymphocytes that synthesize TGF (Transforming Growth Factor)-beta, which acts as a proliferation and tissue repair factor. Some probiotics strains oalso to induce in the immune system of the digestive tract the proliferation of memory lymphocytes during immune responses. This means that in some way the stimulus represented by probiotics or some factors whose synthesis they generates in the intestinal lumen cross the intestinal barrier to interact with lymphocytes in the lamina propria, including memory T lymphocytes, but without invading the bloodstream. It is important to establish which is the natural mechanism in the organism that reacts to protect it, and which if it fails, could result in episodes of sepsis associated with these agents.

Probiotics improve the defenses of the digestive tract, including its barrier function and immune responses. For this reason, it is logical to argue that its administration should be beneficial for patients whose seriously ill or at risk of becoming so. In these cases, their resident intestinal microbiota is affected by the use of broad-spectrum antibiotics, modifications of their diet, placement of tubes in to digestive tract, changes into in blood pH, arterial irrigation and the presence of anoxia along with alterations of motility and the development of of stress reactions with increases of proinflammatory peptides and catecholamines[19-22]. The synergistic effects of these alterations may lead to conditions that favor the translocation of bacteria from the intestinal lumen, the oral mucosa or the vaginal canal to the bloodstream and increase the risk of a systemic inflammatory response syndrome[25,26]. The preoperative administration of probiotics reduces the risk of infectious complications and the same has been observed after their postoperative administration[15]. However, in critically ill patients an important level of caution must be maintained[27]. A study 298 individuals affected by severe episodes of pancreatitis attempted to investigate the effect of a mixture of four species of *Lactobacillus* and two species of *Bifidobacterium* administered at a rate of 10^{10} CFU/day divided into two doses. Treatment was started within 72 hours of the onset of symptoms and an attempt was made to maintain treatment for 28 days, with a total follow-up of 90 days. The inclusion criteria included concentration of C-reactive protein greater than 150 mg/L. Of the total number of patients, 153 were randomized to receive the probiotic mixture and 145 received a placebo[28]. The primary outcome was the sum of infectious complications including pancreatic necrosis or infected ascites, pneumonia, bacteremia or urinary tract infection. Initially both groups were comparable in their clinical characteristics, the severity of their symptoms and their baseline laboratory parameters. The incidence of infectious complications was similar in both groups: probiotics n = 46 (30%) *versus* controls n = 41 (28%, RR 1.06; CI 95% 0.75 – 1.51). Mortality was 24 patients (16%) in the group that received the probiotics and 9 (6%) in the control group (RR 2.53; 95% CI 1.22-5.25). In addition, there were 9 cases of intestinal ischemia in the group receiving the probiotics (of these 8 died), while none died from this cause in the placebo group ($p < 0.004$). In the most seriously ill individuals, their evolution was complicated by the appearance of multiple organ failure associated with the probiotic treatment, evidenced by urinary increases the intestinal fatty acid binding protein (IFABP), an indicator of ischemic damage of the mucosa. In contrast to these results, in less severe cases the probiotic treatment was associated with decreases in bacterial translocation assessed through the urinary excretion of nitric oxide. In the most severy affected patients with multiple organ failure, bacterial translocation increased when administering probiotics.

This study has been widely criticized in the literature for the defects in its design: affected, the most serious patients were incorporated directly into the group that received the probiotics, prejudging possible positive effects. This accumulated in the group that received the probiotics to the most severe cases and introduced bias in the distribution of fatal cases with respect to the control group. Second, the evolution of acute pancreatitis is unpredictable and therefore it is difficult to judge who will follow a more severe course or a more benign evolution. Additionally, the evolution towards any of these courses occurs in a few hours. On the other hand, many of those who died already showed evidences of multiple organ failure when they were incorporated into the protocol and probably would have died, regardless of the administration of the probiotics. Despite these negative aspects of the protocol design it was observed that the administration of probiotics decreased bacterial translocation to the bloodstream. This study, probably the best known of those showing negative effects of any probiotics, has been repeatedly cited in the literature despite doubts about the validity of its conclusions.

The literature review also reveals that there are even less frequent episodes of sepsis with invasion of the bloodstream by bifidobacteria. One of the first studies was published in 1978 in the United States and covered a period of 7 years during which 91,493 blood cultures were performed in adults thes about 9,000 isolates were anaerobic bacteria[29]. Out of this total, 10 cultures were positive for bifidobacteria isolated from 9 pregnant

patients affected by gynecological pathologies, adult patients with gastrointestinal tract or autoimmune pathologies. In 4 other patients, 7 blood cultures were positive for lactobacilli and *Eubacterium* was detected 8 times in as many patients. In all cases, the patients' defensive mechanisms were seriously affected, in addition to suffering surgical conditions with considerable deterioration of their nutritional status. The recovery rate for all three microorganisms was 1:3500 blood cultures and for bifidobacteria this figure was approximately 1 in 8000 cultures. The episodes of sepsis due to *Bifidobacterium* described in the medical literature are few, they are isolated cases and in the pediatric patients they preferentially affect preterm infants with very low birth weight (generally less than 1,500 grams), with infections of the periumbilical skin, necrotizing enterocolitis (NEC) with advanced degrees of evolution (Bell stage > 2), congenital malformations and intravenous lines for parenteral feeding. Some cases received probiotics as a preventive measure against the possibility of NEC or sepsis[30-35]. In cases of preschool or school age children and in adults in whom invasion to the bloodstream by *Bifidobacterium* was detected, some were affected by tumors or haf been subjected to antitumor therapies.

It is evident that the factor that would facilitate the entry of probiotic bacteria into the bloodstream is mainly the failure of the mucosal barrier function of the epithelium of the digestive tract. The anatomical substrate of this barrier are the tight junction in the of the enterocytes, a complex structure that regulates the transit of molecules from the lumen of the intestine to the lamina propria of the mucosa and inversely, from the intercellular space of through the enterocytes, into the lumen. To this must be added the immaturity of the mucin layer, the decreased production of molecules with antibacterial abilities, intestinal motility defects, insufficient secretion of digestive enzymes and of other protective factors[36,37]. Faced with this lower quality of the local nd systemic and defenses, in view of the practically unrestricted use of probiotics both in the general population and in preterm infants to prevent NEC, it is striking that the frequency of *Bifidobacterium* sepsis remains so low that these episodes become almost anecdotal phenomena. At this point it is important to note that probiotics have been selected precisely because they are devoid of factors that would allow them to develop pathogenic capacities, including the invasion of the circulation. Furthermore most of them are of human origen.

However, as with all medical treatments, an adequate level of caution and vigilance in administering probiotics to labile individuals is necessary because conditions at birth, age, and the possible effects of medical or surgical treatments are important in this respect. It is also important to mention that in preterm infants, despite the evidence of a certain level of risk, the administration of probiotics decreases the risk of NEC and decreases its mortality[38,39].

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

The author is representative in Chile of the Nestle Nutrition Institute and Medical Director, Nestlé de Chile.

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