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The role of probiotics in nosocomial infections

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ABSTRACT

There is an increasing scientific and commercial interest in the use of beneficial microorganisms, or "probiotics," for the prevention and treatment of disease. The microorganisms most frequently used as probiotic agents are lactic-acid bacteria such as *Lactobacillus rhamnosus* GG (LGG), which has been extensively studied in recent literature. Multiple mechanisms of action have been postulated, including lactose digestion, production of antimicrobial agents, competition for space or nutrients, and immunomodulation. We have reviewed recent studies of probiotics for the treatment and control of infectious diseases. Studies of pediatric diarrhea show substantial evidence of clinical benefits from probiotic therapy in patients with viral gastroenteritis, and data on LGG treatment for Clostridium difficile diarrhea appear promising. However, data to support use of probiotics for prevention of traveler's diarrhea are more limited. New research suggests potential applications in vaccine development and prevention of sexually transmitted diseases. Further studies are needed to take full advantage of this traditional medical approach and to apply it to the infectious diseases of the new millennium.

KEY WORDS: INTENSIVE CARE UNITS; PEDIATRIC; CROSS INFECTION; BACTEREMIA; PNEUMONIA; URINARY TRACT INFECTION; PROBIOTICS

INTRODUCTION

Despite marked improvements in antimicrobial therapy and critical care technology, nosocomial infection remains a significant cause of morbidity and mortality in critically ill patients (Salminen *et al.* 1998; Savaiano *et al*, 1984; DeVrese *et al.* 2001; Kim and Gilliland, 1983). Because the final common pathway of Gram-negative bloodstream infection, ventilator-associated pneumonia, and urinary tract infection (UTI) involves pathogenic enteric organisms, recent interest has emerged in how to suppress the growth of these organisms. Multiple studies have demonstrated that the colonization of the bowel with nonpathogenic commensal bacteria

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(probiotics) competitively inhibits the attachment of these pathogenic organisms (Kolars *et al.* 1984; Allen *et al.* 2003; Guandalini *et al.* 2000). In addition, probiotics have been shown to augment the local gut immunity by enhancing immunoglobulin (Ig)-A–specific responses to enteric pathogens (Shornikova *et al.* 2003; Pant *et al.* 1996). Probiotics also are thought to produce a variety of antimicrobial substances that may interfere with the growth of pathogenic bacteria (Raza *et al.* 1995; Sepp *et al.* 1995; Szajewska *et al.* 2001; Mastretta *et al.* 2002). Finally, probiotics have been shown in numerous animal models to reduce intestinal permeability and decrease the bacterial translocation of pathogenic bacteria (Oberhelman *et al.* 1999; Shornikova *et al.* 1997; Cetina-Sauri and Sierra Basto, 1994).

Moreover, probiotics also have been shown to nonspecifically stimulate the systemic immune system. Probiotic bacteria have been shown in several studies to enhance the phagocytic ability of neutrophils (Ho¨chter *et al.* 1990; Arvola *et al.* 1999). Multiple trials also have demonstrated an improvement in natural killer cell activity following the administration of various probiotic agents (Vanderhoof *et al.* 1999). Probiotic intake also has been shown to modulate production of interleukin-6 and -10, as well as tumor necrosis factor- (Armuzzi *et al.* 2001a). Specific stimulation of the systemic immune system also has been shown using probiotic bacteria as vehicles for vaccines with resultant increases in antigen specific T-cell and immunoglobulin G responses (Cremonini *et al.* 2002; Armuzzi *et al.* 2001b).

As a result of these studies demonstrating stimulation of local and systemic immune defenses and a reduction in bacterial translocation, there has been a rapidly growing interest in the clinical applications of probiotics. A few small clinical trials in intensive care settings have begun looking at the incidence of nosocomial infections with probiotic use and have demonstrated promising results (Siitonen *et al.* 1990). Therefore, the purpose of this study was to evaluate the hypothesis that the administration of probiotics in infants and children admitted to a pediatric intensive care unit setting would reduce the incidence of nosocomial infection, bloodstream infection, pneumonia, tracheobronchitis, and UTI.

MATERIAL AND METHODS

Episode occurring after 48 hours of hospitalization, resulting in a positive blood, CSF, or urine culture.4 Hospital-acquired bloodstream infection: clinical signs of sepsis occurring after 48 hours of life and followed by a positive blood culture drawn after 48 hours of life. If culture was positive for a coagulasenegative Staphylococcus species, an additional positive culture with the same organism was required for confirmation and treatment. Nosocomial pneumonia: development of respiratory distress after 48 hours of hospitalization evidenced by rapid, noisy, or difficult breathing, respiratory rate .60 breaths per minute, chest retractions or grunting, and confirmed with a chest radiograph, a blood culture, or additional blood work. If the chest radiograph was suggestive of pneumonia and the blood culture was negative, clinical signs of sepsis or laboratory tests were required for diagnosis (Duke28 modified definition). Chest radiograph suggestive of pneumonia: presence of nodular or coarse patchy infiltrate, diffuse haziness, or granularity, or lobar or segmental consolidation. Clinical signs of sepsis: presence of lethargy, recurrent apnea, hypothermia (axillary temperature ,37°C) or hyperthermia (.38°C).

Laboratory tests suggestive of sepsis: a leukocyte count out of the reference range (neutropenia ,5000 or neutrophilia .25 000), a ratio of immature to total neutrophilic forms .0.2 or an elevated C-reactive protein. Urinary tract infection: clinical signs of sepsis and a positive urine culture with .104 organisms of a single pathogen obtained by the use of standard sterile technique and urethral catheterization.4 Meningitis: clinical signs of sepsis with a CSF white blood cell count .29/mm3 and neutrophil count .60%, or a positive CSF Gramstain, culture, or polymerase chain reaction for bacterial antigens.4 Feeding intolerance: any of the following: recurring emesis, gastric residuals with 50% or more of the previous feed volume, abdominal distension, or the presence of macroscopic blood in stools. Necrotizing enterocolitis: modification of Bells criteria for stage II29 based clinical and/or radiographic data: (1) pneumatosis or portal vein gas, (2) localized pneumatosis, fixed dilated bowel loops, or pneumoperitoneum AND 2 GI signs/ symptoms and 1 systemic sign/ symptom, or (3) thickened bowel loops AND an abnormal gas pattern AND 2 GI and 2 systemic signs/ symptoms. GI signs: abdominal distension or tenderness, feeding intolerance, erythema of the abdominal wall, and decreased bowel sounds. Systemic signs: lethargy, increased frequency or severity of apnea, temperature instability, new-onset metabolic acidosis, hemodynamic instability, and disseminated intravascular coagulation or thrombocytopenia.

RESULTS AND DISCUSSION

DOCUMENTATION OF THE HEALTH EFFECTS OF PROBIOTICS FOR HUMAN DISEASES AND DISORDERS

Lactose malabsorption. A large number of people, as they age, experience a decline in the level of lactase (bgalactosidase) in the intestinal brush border mucosa.

This decline causes lactose to be incompletely absorbed, resulting in flatus, bloating, abdominal cramps, and moderate-to-severe (watery) diarrhea. This results in a severe limitation in consumption of dairy products among the elderly population. There have been several studies that have demonstrated that, during the fermentative process involved in the production of yogurt, lactase is produced, which can exert its influence in the intestinal tract (Savaiano *et al*, 1984; DeVrese *et al*. 2001; Kim and Gilliland, 1983; Kolars *et al*. 1984). The organisms commonly used for the production of yogurt are Lactobacillus bulgaricus and Streptococcus salivarius subsp. thermophilus. Kim and Gilliland (Kim and Gilliland, 1983) found that feeding lactose-intolerant individuals yogurt caused a significant reduction in the level of breath hydrogen compared with that in subjects who were fed milk. The level of hydrogen in the breath is an indication of the extent of lactose metabolism in the large bowel. Kolars *et al*. (Kolars *et al*. 1984) observed that the ingestion of 18 g of lactose in yogurt caused the production of 67% less hydrogen in the breath compared with that produced by a similar dose of lactose delivered in milk. Analysis of aspirates obtained from the duodenum 1 h after the consumption of yogurt showed significant levels of lactase (Kolars *et al*. 1984). These studies indicate that the delivery of lactase to the intestine via the consumption of lactase-producing probiotics is a practical approach for treatment of lactose malabsorption. Acute diarrhea. There are at least 12 studies that have reported the use of probiotics to either treat or prevent acute diarrhea (Allen *et al*. 2003; Guandalini *et al*. 2000; Shornikova *et al*. 2003; Pant *et al*. 1996; Raza *et al*. 1995; Sepp *et al*. 1995; Szajewska *et al*. 2001; Mastretta *et al*. 2002; Oberhelman *et al*. 1999; Shornikova *et al*. 1997; Cetina-Sauri and Sierra Basto, 1994; Ho¨chter *et al*. 1990). The majority of these studies were done with infants or children, the etiologic agent was either rotavirus or unknown, and the probiotic used was Lactobacillus rhamnosus strain GG (Lactobacillus GG) (ATCC 53103) (Guandalini *et al*. 2000; Shornikova *et al*. 2003; Pant *et al*. 1996; Raza *et al*. 1995; Sepp *et al*. 1995; Szajewska *et al*. 2001; Mastretta *et al*. 2002; Oberhelman *et al*. 1999). Other probiotics that have shown positive results for the treatment of acute gastroenteritis include Lactobacillus reuteri and Saccharomyces boulardii (Shornikova *et al*. 1997; Cetina-Sauri and Sierra Basto, 1994; Ho¨chter *et al*. 1990). The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition conducted the most extensive trial using Lactobacillus GG for the treatment of moderate-to-severe diarrhea in children (Guandalini *et al*. 2000). The study included 287 children aged 1–36 months from 10 countries. The patients were randomized to be given either placebo or Lactobacillus GG along with the standard treatment, oral rehydration solution. Patients who received Lactobacillus GG had decreased severity and shorter duration of illness and a shorter hospital stay and were found to have a decreased likelihood of persistent diarrheal illness (Guandalini *et al*. 2000).

A similar study was conducted with 137 children aged 1–36 months who were admitted to the hospital with diarrhea and were randomized to receive placebo or Lactobacillus GG plus oral rehydration solution. Children given Lactobacillus GG had a significantly shorter duration of illness (Shornikova *et al*. 2003). A study of 26 children in Thailand with watery diarrhea showed a significantly shorter duration of symptoms for those who received treatment with Lactobacillus GG (Pant *et al*. 1996). A similar investigation involving 40 children that was conducted in Pakistan found that those who received treatment with Lactobacillus GG were less likely to have persistent diarrhea and had fewer episodes of vomiting, compared with the placebo group (Raza *et al*. 1995). In a preventive study of 81 children aged

Table 1. Medical applications in humans for different classes of probiotics

Medical condition	Class(es) of probiotic	Reference(s)
Lactose maldigestion	LAB and Streptococcus salivarius subsp. Thermophiles	[2–5]
Gastroenteritis Acute diarrhea	LAB, Bifidobacterium species, or Saccharomyces boulardii	[6–17]
Antibiotic-associated diarrhea	LAB or S. boulardii	[18–24]
Traveler's diarrhea	LAB	[25, 26]
Clostridium difficile–induced colitis	LAB	[32–34]
Dental caries	LAB	[35]
Intestinal inflammation in children with cystic fibrosis	LAB	[36]

NOTE. LAB, lactic acid bacteria.

1–36 months who were hospitalized for illnesses other than diarrhea, symptoms of hospital-acquired rotavirus gastroenteritis were prevented by administration of Lactobacillus GG (Szajewska *et al.* 2001). In another prevention study conducted in Peru, 204 children aged 6–24 months who were undernourished were randomized to receive placebo or Lactobacillus GG. There was a significant decrease in the rate of incidence of diarrhea among the children who received Lactobacillus GG who were not being breast-fed (Oberhelman *et al.* 1999). In one study, Lactobacillus reuteri was shown to shorten the duration of diarrhea in children (Shornikova *et al.* 1997). In a clinical trial involving 130 children, S. boulardii was found to be effective for the treatment of acute diarrhea in children (Cetina-Sauri and Sierra Basto, 1994), and, in another study of 92 adults, a similar finding was reported (Ho¨chter *et al.* 1990).

Probiotic Use and Safety Probiotics are widely considered to be safe for human oral and vaginal use and there is a long history of the use of fermented milk products with minimal recorded reported side effects. The number of probiotic products available on the world market is estimated to be over 2000 (Shornikova *et al.* 2003), but the industry remains largely unregulated and unstandardized—making comparative studies difficult. To begin filling this void, scientists have formalized groups such as the International Scientific Association for Probiotics and Prebiotics (ISAPP), a nonprofit founded in 2002 to raise the scientific credibility of the field by working with experts and conducting meetings on high quality research. By providing an objective, science-based voice, ISAPP hopes to benefit the end users of these products by helping them make informed choices (Pant *et al.* 1996). ISAPP has endorsed the guidelines set by the World Health Organization (WHO) and the United Nations Food and Agriculture Organization (FAO) for evaluation of probiotics—governing, strain designation, efficacy/effectiveness and safety (Kim and Gilliland, 1983; Raza *et al.* 1995). For example, new strains and products should be proven safe in human studies amend those bearing some limitations, (such as use of S. boulardii [S. cerevisiae]) in patients with a leaky gut or other risks) should be clearly labeled (Sepp *et al.* 1995). In the United States, probiotics are currently classified as —dietary supplements, (not —drugs) and as such, the Food and Drug Administration (FDA) only requires premarket notification, with no demonstrations of safety and efficacy required (Szajewska *et al.* 2001). Due to their overall safety, guidelines for use of probiotics in the hospital are generally lacking, although some caution is advised for use in certain disease states (e.g., severe colitis, bowel leaks, neutropenia) where the potential exists for the probiotic to enter the blood or peritoneum (Mastretta *et al.* 2002). Likewise, special care should be taken by healthcare personnel who handle both probiotic capsules and venous catheters in order to avoid transfer to the bloodstream (Szajewska *et al.* 2001). Of more recent interest and concern are safety considerations relating to transferable genetic elements that may confer antibiotic resistance from the probiotic to pathogenic strains, or even to the commensal flora (Oberhelman *et al.* 1999).

In a mouse model have demonstrated a possible role for these agents in the prevention or treatment of graft-versus-host disease in transplant recipients (ksanen *et al.* 1990).

Table 2. Present and future clinical applications of probiotics, by level of evidence of efficacy

Applications with strong evidence
Gastroenteritis
Acu
Antibiotic associated
Applications with substantial evidence of efficacy
Allergic reactions, specifically atopic dermatitis
Applications that have shown promise
Childhood respiratory infection
Dental caries
Nasal pathogens
Relapsing Clostridium difficile-induced
Gastroenteritis (prevention)
Inflammatory bowel disease
Potential future applications
Rheumatoid arthritis
Irritable bowel syndrome
Cancer (prevention)
Ethanol-induced liver disease
Diabetes
Graft-versus-host disease

FUTURE DIRECTIONS

The following are some of the future possibilities for these biological products in the field of infectious diseases.The use of LAB as live vectors for oral immunization appears to be an exciting approach, on the basis of their safety, ability to persist within the indigenous flora, adjuvant properties, and low intrinsic immunogenicity. Medaglini *et al.* [38] have recently developed a genetic system for the expression of heterologous antigens from human papillomavirus and HIV type 1 (HIV-1) in the surface of the human commensal Streptococcus gordoonii and L. casei. Local and systemic immune responses were detected in BALB/c mice and Cynomolgus monkeys after vaginal colonization with the aforementioned

recombinant strains. Both macrophage activation and IL-12/g-IFN pathway stimulation are promising areas of research with regard to resistance to intracellular pathogens by enhancement of mucosal and systemic immunity (Malchow *et al.* 1997; Guslandi *et al.* 2000). More experimental and clinical studies are needed to clarify the role of probiotics as immunomodulators, not only in infectious diseases of the GI tract, but also for inflammatory and allergic conditions.

CONCLUSIONS

The current and proposed uses of probiotics cover a wide range of diseases and ailments. An attempt has been made to classify the quality of evidence that supports these various applications (Nase *et al.* 2001). These classifications are based on existing studies, most of which are cited in this article, and not on an exhaustive review of the entire literature on probiotics. The broad classifications include (table 2) applications with proven benefits, applications with substantial evidence that require additional support, promising applications that need substantial additional evidence, and proposed future applications. Proven benefits of probiotics include the treatment of acute and antibiotic associated diarrhea; applications with substantial evidence include the prevention of atopic eczema and traveler's diarrhea; promising applications include the prevention of respiratory infections in children, prevention of dental caries, elimination of nasal pathogen carriage, prevention of relapsing C. difficile– induced gastroenteritis, and treatment of inflammatory bowel disease; and proposed future applications include the treatment of rheumatoid arthritis, treatment of irritable bowel syndrome, cancer prevention, prevention of ethanol-induced liver disease, treatment of diabetes, and prevention or treatment of graft versus-host disease.

The mechanisms of action of probiotics are strain specific but can be summarized mainly in three areas: changes of gut ecology, modulation of gut mucosal barrier and regulation of the immune response through interaction with gut-associated immune system (Savaiano *et al*, 1984). Several studies regarding the supplementation of probiotics in nosocomial infections have been conducted mainly in adult population. Among pediatric studies major findings have been observed in treatment of acute gastroenteritis, primarily caused by Rotavirus (DeVrese *et al.* 2001; Kim and Gilliland), and in the prevention of antibiotic associated diarrhea (AAD) (Kolars *et al.* 1984). Supplementation with probiotics has proven useful even in the treatment of Clostridium difficile disease (CDD), the most common pathogen involved in AAD (1983Allen *et al.* 2003). Data from meta-analysis and cochrane review on the prevention of necrotizing enterocolitis (NEC) show an overall benefit of probiotic supplementation (Guslandi *et al.* 2000). The limitations of the above cited studies are mainly related to heterogeneity in terms of strain, dosage and duration of treatment and the lack of studies on extremely low birth weight preterm infants. Data on nosocomial pneumonia and ventilatorassociated pneumonia in neonatal and pediatric age is scanty. In a large randomized, double-blind placebo controlled study, Hojsak *et al* demonstrated that supplementation with Lactobacillus GG significantly decreased the risk of nosocomial respiratory tract infections (Shornikova *et al.* 1997). On the other hand, the data from adult studies have been conflicting, with a tendency towards the demonstration of probiotic efficacy in reducing the incidence of ventilatorassociated pneumonia (Pant *et al.* 1996). Meticillin-resistant Staphylococcus aureus is a multidrug-resistant nosocomial pathogen; a recent review of literature (Raza *et al.* 1995) showed that many probiotic strains inhibit MRSA growth in vitro. Furthermore, this review describes that there is little published clinical data on the use of probiotics in prophylaxis or treatment of MRSA-mediated infections (Nase *et al.* 2001).

The use of probiotics in medical practice is rapidly increasing, as are studies that demonstrate the efficacy of probiotics. A note of caution should be applied: negative findings are being reported, as would be expected as more studies are being performed and as more applications are being sought for the use of probiotics. Overall, probiotics appear to be here to stay as part of the physician's armamentarium for the prevention and treatment of disease; however, more evidence-based research is required to firmly establish medical areas of use and areas in which probiotics are not applicable.

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