with CPS type Ia (76.2%, 16/21) as compared with all other CPS types (p <0.0001).

Seventy-nine per cent of the strains (320/401) were phenotypically resistant to tetracycline (MIC >8 mg/L). Among these strains, *tet*(M), *tet*(O) and tet(L) accounted for 93.75% (300/320), 5% (16/300), and 0.3% (1/320), respectively, and the search for *tet*(M), *tet*(O) *tet*(K) and *tet*(L) gave negative results for three strains (not shown). Interestingly, 14 strains that were phenotypically susceptible to tetracycline (MIC <8 mg/L) were *tet*(M)-positive.

In conclusion, this study provides the clinical and microbiological characteristics of GBS strains isolated from adult invasive infections in France. From these data, we show that: (i) GBS invasive infections in adults are more frequent among people ≥65 years of age, as described in other European and US surveys [1–6]; (ii) CPS types Ia, III and V accounted for 72% of all strains, a distribution similar to those observed in other countries [1–6]; (iii) resistance to erythromycin increased from 2007, reaching 35.24% in 2010, and was strongly associated with CPS type V; and (iv) the *mef* genotype was associated with CPS type Ia GBS. Continued surveillance of invasive GBS disease in adults and genetic characterization of isolated strains are necessary, as this might impact on strategies related to antibiotic use and vaccine design.

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## Transparency Declaration

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# *Lactobacillus rhamnosus* administration causes sepsis in a cardiosurgical patient—is the time right to revise probiotic safety guidelines?

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## Abstract

A 24-year-old female patient developed sepsis resulting from preoperative administration of probiotics following an aortic valve replacement. Blood cultures revealed the causative agent to be the probiotic *Lactobacillus rhamnosus*, which has recently been implicated as an emerging aetiology of infection in those taking probiotics. In the past few years, probiotic use in hospitals has increased greatly. However, there is growing global evidence that the use of probiotics in patients with organ failure, immunocompromised status and dysfunctional gut barrier mechanisms can cause infections. This and other reports show the importance of establishing generally recognized safety guidelines.

**Keywords:** Adverse events, aortic valve replacement, endocarditis, *Lactobacillus*, perioperative care, probiotics, safety, sepsis

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Probiotics, according to the WHO/FAO, are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Most have 'generally recognized as safe' status, meaning that they are regarded as food-grade microorganisms with no imposed health risk for consumers. Some are members of the human flora, being found in the mouth, gastrointestinal tract and female genital tract. Because of their safety and the possible health benefits, there has been an increase in their use worldwide. Despite these levels of safety, there are many documented cases of various *Lactobacillus* strains resulting in human infections [1–6]. Currently, there are no universally accepted guidelines for the administration of probiotics in patients with organ failure, immunocompromised status and dysfunctional gut barrier mechanisms.

A 24-year-old female patient, following an aortic valve replacement for a congenital bicuspid aortic valve, presented in August 2009 with relapsing remitting fevers. Previous medical history was significant for a percutaneous aortic valvuloplasty for the treatment of aortic valve stenosis when she was 11 years old. As infectious endocarditis was suspected clinically in April 2009, having in mind the medical history, she was treated on an outpatient basis with empirical antibiotics. In August of the same year, she was hospitalized with circulatory insufficiency of NYHA class II, owing to significant aortic valve insufficiency and a previous infectious episode. After completion of antimicrobial therapy, she underwent aortic valve replacement surgery in August. Perioperative antimicrobial prophylaxis was administered, and supplementation with a probiotic preparation containing three *Lactobacillus rhamnosus* strains continued for a total period of 6 weeks during antibiotic therapy, until admission to the cardiac surgery department.

During surgery, a 10-mm post-inflammatory perforation of the valvular cusp was recognized. The affected valve was excised, and a mechanical ATS 20-mm valve was implanted. Cultures from the excised valve yielded negative results. However, on the first day postoperatively, the patient presented with high fever and other SIRS parameters. Blood samples were collected for microbiological examination, and empirical antimicrobial therapy was started. Two blood cultures yielded *L. rhamnosus*, and the strains were collected for further analysis. Following the diagnosis of *L. rhamnosus* sepsis, the patient was treated promptly and recovered fully. She was discharged from the hospital in good general health.

Analysis was performed with API 50CHL (bioMerieux, Marcy l'Etoile, France), and cultures were sent to a probiotic reference laboratory for molecular testing. By the use of pulsed-field gel electrophoresis, the two blood isolates of *L. rhamnosus* (named hereafter 10330/1 and 10330/2) from the cardiosurgical patient were compared with eight other *L. rhamnosus* strains (including five strains from three probiotic drugs and three strains from human physiological flora) [7]. The results, including the strain designations, are shown in Fig. 1. Genotyping of the strains confirmed that strains 10330/1 and 10330/2 had identical pulsed-field gel electrophoresis profiles to those of the *L. rhamnosus* strains contained in the probiotic drug given to the patient, and were therefore the causative agents.

The *L. rhamnosus* doses used as supportive therapy during and after antibiotic therapy in this patient were those specified in the probiotic product information; that is, recommended doses of $1 \times 10^{10}$ CFU twice daily (extra-strength formulation, 3-mL ampoule containing powder for making a *per os* suspension) or $2 \times 10^{9}$ CFU three times daily (normal formulation, ampoule containing powder for making a *per os* suspension). The product contains three strains of *L. rhamnosus* (40% *L. rhamnosus* Pen, 40% *L. rhamnosus* E/N, and 20% *L. rhamnosus* Oxy). Indications for use include: post-antibiotic enterocolitis with special indication for supportive therapy for pseudomembraneous colitis; as treatment for relapsing pseudomembraneous colitis; prevention of travellers' diarrhoea; and as supportive therapy during and after antibiotic therapy. The only contraindication is hypersensitivity to cow's milk protein. There are no special warnings or precautions related to the use of the drug. The strains are resistant to many antibiotics (with no MIC values listed).

Our patient was given *L. rhamnosus* to prevent antibiotic-associated gastrointestinal complications, such as diarrhoea and gastroenteritis. There are many emerging cases of adverse events resulting from the administration of probiotics, especially in hospitalized patients; these include mild treatable conditions such as bowel distension, and more

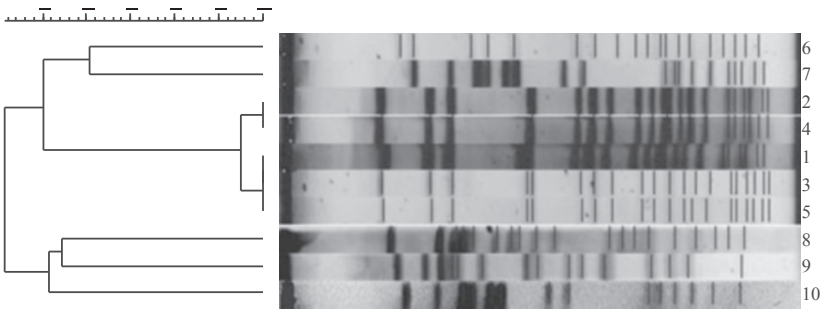


**FIG. 1.** Typing profiles of lactobacilli obtained with *Sgs*I. Electrophoretic parameters: initial pulse, 1 s; final pulse, 25 s; voltage, 5.5 V/cm; run time, 24 h (Molecular Analyst software). 1, *Lactobacillus rhamnosus* strain 10330/1 from patient; 2, *L. rhamnosus* strain 10330/2 from patient; 3, *L. rhamnosus* Pen from drug 1; 4, *L. rhamnosus* E/N from drug 1; 5, *L. rhamnosus* Oxy from drug 1; 6, *L. rhamnosus* GG from drug 2; 7, *L. rhamnosus* KL53A from drug 3; 8, 9 and 10, human physiological flora strains.

severe conditions such as sensitization to allergens, bacteraemia, fungaemia, sepsis and even death [1–8]. Patients with organ failure, severely immunocompromised patients and patients with dysfunctional gut barrier mechanisms seem to be at risk for adverse events related to probiotic use [1–9].

This report identifies the first known case of sepsis in a female aortic heart valve recipient caused by probiotic *L. rhamnosus*. This infection was most likely caused by bacterial translocation through a weakened intestinal barrier, possibly linked with ischaemia resulting from the patient's heart failure. Normally, a healthy immunocompetent host would trap and kill translocated bacteria in the mesenteric lymph nodes. However, this mechanism was probably defective in this patient, because of mesenteric ischaemia resulting from heart failure impairing the gut barrier mechanism. Previous authors have confirmed that impaired intestinal barrier function may result from splanchnic ischaemia, and that the majority of infections in humans result from mucosal transmission [8,9].

In conclusion, this report highlights the potential adverse effects of administering probiotics, such as *Lactobacillus*, to patients who are presenting with organ dysfunction or failure. Although probiotics have been shown to be of benefit for the majority of patients on treatment, the risks may outweigh the benefits in those predisposed to adverse events, such as the immunosuppressed. To date, there is insufficient standardization of safety and administration protocols for probiotics. We also feel that the responsibility to inform consumers about the potential risks of probiotics for certain categories of individuals with impaired health status should be an integral part of the food or pharmaceutical industry. This responsibility should be concomitant with the establishment of new safety standards in this area. A revision of probiotic status and warnings given with the treatment may be required in order to encompass the potential for harm.

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## Transparency Declaration

Potential conflicts of interest are as follows. P. B. Heczko is the President and P. Kochan is a member of the Board of Directors of the Polish Society for Probiotics and Prebiotics; both are non-profit positions. P. Kochan is the American Society for Microbiology Ambassador to Central and Eastern Europe.

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