



Case report

Probiotic related *Lactobacillus rhamnosus* endocarditis in a patient with liver cirrhosisS.S.B. Naqvi^{a,*}, V. Nagendra^{a,b}, A. Hofmeyr^{a,b}^a Infectious Diseases and Microbiology Department, Liverpool Hospital, NSW, Australia^b University of New South Wales, NSW, Australia

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ABSTRACT

Lactobacilli are commensals in the gastrointestinal and genitourinary tracts and considered as having low pathogenicity. Many species including *Lactobacillus rhamnosus* are now available as probiotics and their use has widely increased in recent years. Lactobacilli have the propensity to cause invasive infections such as bacteraemia and endocarditis predominantly in an immunocompromised host. We report a case of fatal *Lactobacillus rhamnosus* endocarditis involving a young patient with a history of complicated cirrhosis and prior *Clostridium difficile* colitis; and present a literature review and discussion of the possible association of systemic infection with 'probiotic' formulations containing lactobacilli.

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Introduction

Lactobacilli have the propensity to cause invasive infections such as meningitis, endometritis, peritonitis, pneumonia, bacteraemia and endocarditis. It has been implicated as a causative agent in 0.05–0.4% of all endocarditis [1]. As these infections tend to occur in immunosuppressed patients [2], the associated mortality ranges from 23 to 29%.

Case report

A 36-year-old woman presented with three weeks history of fever and dyspnea on a background of alcoholic cirrhosis (Child's Pugh Class B) complicated by refractory ascites, spontaneous bacterial peritonitis and grade 1 oesophageal varices. Other active co-morbidities included CPAP dependent obstructive sleep apnea syndrome and obesity. Past medical history was significant for *Clostridium difficile* colitis seven months prior to admission. She was self-medicating with two capsules daily of a commercially available probiotic formulation (containing *Lactobacillus acidophilus* (32 billion CFU organisms), *Lactobacillus rhamnosus* (4 billion CFU organisms), and *Saccharomyces cerevisiae* (4 billion CFU) according to packaging. Two months later, she presented with fever requiring admission to hospital. *Lactobacillus rhamnosus* was isolated from one of two blood cultures. A short course of

parenteral benzyl penicillin was administered, pending investigations to exclude endocarditis. Trans-oesophageal echocardiogram at that time revealed moderate mitral valve regurgitation and mild aortic valve regurgitation but no evidence of valvular vegetation.

On her subsequent admission that was five months after the first admission, examination revealed signs of biventricular heart failure, bilateral splinter hemorrhages and a new diastolic murmur audible at left third intercostal space and also changed intensity of the pre-existing apical pan-systolic murmur radiating towards the axilla. Trans-oesophageal echocardiogram revealed a 3.2 cm vegetation on the aortic valve with possible perforation of a valve leaflet and regurgitation of both aortic and mitral valves.

A septic work-up inclusive of blood cultures was obtained prior to initiation of empiric treatment including vancomycin, benzyl penicillin and gentamicin for native valve endocarditis. Gram positive bacilli were isolated in anaerobic and aerobic BACTEC blood culture bottles after 48 h of incubation. There was a tiny growth of convex, white colonies on chocolate and horse blood agar. Catalase and PYR testing was positive and vancomycin resistance was noted with 5 µg vancomycin disc. *Lactobacillus rhamnosus* was confirmed with Microflex LT MALDI-TOF mass spectrometry (Bruker Daltronics, Bremen, Germany) and 16S ribosomal RNA gene sequencing. The isolate tested sensitive to penicillin with MIC of 0.25 mg/L determined by the Epsilometer test (e-test). Based on the culture results, the dose of benzyl penicillin was increased to 3 million units every 4 h with synergistic gentamicin 80 mg twice daily adjusted for renal function.

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Despite directed therapy, the patient's condition deteriorated with multi-organ failure requiring ventilator support, hemodialysis and inotropic support. The patient underwent emergency surgical intervention and aortic valve replacement with bio-prosthetic homograft valve due to deteriorating cardiac function. *Lactobacillus rhamnosus* was also isolated from operative aortic valve tissue culture. Despite surgical and maximal medical therapy, she continued to decline and died on day 12 of the hospital admission.

Literature review and discussion

A MEDLINE search was performed using the keywords "Lactobacillus endocarditis" and "Probiotics". Papers limited to the English language reporting cases of Lactobacillus endocarditis were retrieved and assessed.

Lactobacillus, a gastrointestinal and genitourinary flora commensal, can cause invasive infections such as meningitis, endometritis, peritonitis, pneumonia, bacteraemia and endocarditis. It has been implicated as a causative agent in 0.05-0.4% of all endocarditis [1]. Griffith et al reviewed two cases of lactobacillus endocarditis as well as 39 cases from the literature and found there was a lower (39%) rate of response to medical therapy alone, and the mortality rate of 27%. The possible reasons proposed were unreliable antimicrobial susceptibility studies and lack of standardized therapy [3,4]. Similarly, Cannon et al reviewed 241 cases of clinical infection with lactobacilli. Of these cases, 73 patients had endocarditis. A majority had underlying structural heart disease (63%), or dental condition (47%) [2]. The most common species identified in these clinical cases were *L. casei*, followed by *L. rhamnosus* and *L. plantarum*.

From the literature, there have been only 11 reported cases of adult endocarditis associated with *L. rhamnosus* and of these, two have been linked to probiotic use [5,6]. The first case of endocarditis due to *L. rhamnosus* associated with self-medication with freeze-dried probiotic preparation in a 67 year-old-man with pre-existing history of mitral valve prolapse and was reported by Mackay et al. in 1999 [5]. He was treated with medical therapy alone (synergistic gentamicin and ampicillin) with clinical success. Another case of *L. rhamnosus* aortic valve endocarditis was associated with excessive yogurt ingestion, and in this case the patient received medical therapy for 6 weeks, followed by surgery for aortic valve replacement [6]. There has not been any reported case of probiotic associated lactobacillus endocarditis in Australia. To our knowledge, our case represents the first adult case of probiotic related *L. rhamnosus* endocarditis in Australia.

Our patient had recurrent *L. rhamnosus* bacteremia, which was possibly inadequately treated and investigated on her first presentation. She had multiple possible risk factors for *Lactobacillus* bacteremia and endocarditis including advanced cirrhosis and abnormal portal circulation, previous colitis, pre-existing bivalvular structural abnormality and concomitant probiotic use. The bacteremia in our patient may have originated from the probiotic formulation through bacterial translocation. Our patient consumed two capsules of probiotics for 7 months for recurrent *Clostridium difficile* associated colitis that would have contributed to her developing blood stream infection and endocarditis. Although we are not able to confirm the association by typing the probiotic strain and the clinical strain, we postulate that she had invasive infection as result of prolonged probiotic use.

The treatment of severe lactobacillus infection can be challenging. In the literature, treatment recommendations for invasive infections from Lactobacillus species are mainly based on series of case reports and expert opinions owing to the rarity of the infections. Many strains of Lactobacillus including *L. rhamnosus* are intrinsically resistant to vancomycin; resistance to ciprofloxacin,

tetracycline, meropenem, metronidazole and sulphonamides has been reported, with some isolates exhibiting intermediate resistance to linezolid [7]. The commonly recommended treatment for infective endocarditis is synergistic therapy with intravenous penicillin G (or ampicillin) and an aminoglycoside [2,3,8,9].

In the recent years, probiotic use has increased worldwide for the treatment of infantile and adult diarrhea, antimicrobial associated diarrhea and candidal vaginitis [10]. Lactobacilli are recognized as relatively safer organisms with low virulence potential. However, the probiotic strains have been linked to invasive clinical infections. Gut translocation and systemic dissemination of organisms may be the underlying pathogenesis for invasive infections in immunocompromised patients [11,12].

This case highlights that the presence of lactobacillus in blood culture should not be routinely considered as a contaminant and careful evaluation of patient clinical status is recommended. When determined to be cause of either bacteremia or endocarditis, it should be treated aggressively. With the isolation of lactobacillus, linkages to diet and probiotic consumption should be sought. More importantly, it highlights that immunosuppressed patients should be cautious before consuming probiotics, containing live or lyophilized organism.

To date, there is insufficient standardization of safety and administration protocols for probiotics. Probiotics are often regulated as dietary supplements rather than as pharmaceuticals or biological products. Thus, there is usually no requirement to demonstrate safety before marketing probiotics. In the United States, although dietary supplements do not generally require premarket review and approval by FDA, those that are marketed specifically for the treatment or prevention of a disease are classified as biological products and do need review and approval by FDA. Similarly, in Australia, those probiotics marketed for specific health benefits require premarket review by the Therapeutic Goods Administration (TGA) and are usually regulated as complementary medicines. However, there are no FDA or TGA requirements about adding specific labelling warnings on probiotics' packaging. We feel that the responsibility to inform consumers about the potential risks of probiotics for certain categories of individuals with impaired health status should be considered an integral part of the food or pharmaceutical industry. This responsibility should be concomitant with the establishment of new safety standards in this area. Therefore, patients who are immunosuppressed and/or have pre-existing heart disease should avoid probiotic preparations. Warnings on the package should be considered.

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Ethical approval

The authors declare that the ethical approval was not required for this case report as no patient information has been used.

Conflict of interest

The authors declare that they have no competing interests.

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