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Case Report Open Access

Probiotic Related *Lactobacillus rhamnosus* Endocarditis in a Patient with Liver Cirrhosis and Literature Review

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Abstract

Lactobacillus is a commensal in gastrointestinal and genitourinary flora and considered as a friendly bacterium with low pathogenicity. Many species of *Lactobacillus* including *Lactobacillus rhamnosus* are now available as probiotics and their use has widely increased in recent years. *Lactobacillus* has propensity to cause invasive infections such as bacteraemia and endocarditis predominantly in an immune compromised host. We report a case of fatal *Lactobacillus* 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 *Lactobacillus* species.

Keywords: *Lactobacillus rhamnosus;* Immune; Clostridium; Therapy

Introduction

We report a case of fatal *lactobacillus* 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 *lactobacillus* species.

Case Report

A 36-year-old woman presented with three weeks history of lethargy, fever and dyspnoea 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 apnoea syndrome and obesity, BMI 35. Prescribed medications included spironolactone 150 mg daily, frusemide 40 mg daily, thiamine 100 mg daily and trimethoprim/sulfamethoxazole 160+800 mg one tab daily (for secondary prophylaxis of spontaneous bacterial peritonitis).

Past medical history was significant for *Clostridium difficile* colitis seven months prior. 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 and systemic symptoms 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 vegetations or endocarditis. Left ventricular size and volume was normal.

On admission, examination revealed fever (38.5°C), tachypnoea and tachycardia with blood pressure of 130/50 mmHg. Cardiovascular examination revealed collapsing pulse with wide pulse pressure and bilateral splinter haemorrhages on both hands and feet. JVP was raised with pitting pedal oedema up to mid shins, and audible bi-basal fine crepitations on chest auscultation, consistent with biventricular heart failure. There was a grade 3 blowing diastolic murmur heard loudest at left third intercostal space and a pan-systolic murmur at apex radiating towards the axilla, in keeping with aortic regurgitation and mitral regurgitation respectively. Abdomen was distended with moderate ascites. There was no evidence of neurological or musculoskeletal system abnormalities. Trans-oesophageal echocardiogram revealed 3.2 cm vegetation on the aortic valve with possible perforation of the valve leaflet and peri-valvular regurgitation of both aortic and mitral valves. There were oedematous changes of the aortic annulus noted with regurgitant fraction of 65%.

A septic work-up inclusive of blood culture, urine and ascitic fluid culture were obtained prior to initiation of vancomycin 1g twice daily, gentamicin 80 mg thrice daily and benzyl penicillin 1.2 g every four hours as empiric treatment for native valve endocarditis.

On day two of the hospital admission, gram positive bacilli were isolated in anaerobic and aerobic bactec blood culture bottles after 48 hours. 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 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, dose of benzyl penicillin was increased to 1.8 g every 4 hours with synergistic Gentamicin 80 mg bd adjusted for renal function.

Despite directed therapy, the patient's condition deteriorated with multi-organ failure including heart failure, acute kidney injury with severe metabolic acidosis (lactate 18 mmol/L), respiratory failure, hypotension requiring ventilator support, haemodialysis and inotropic support. Blood cultures obtained on day eight cultured *Lactobacillus rhamnosus*, signifying persistent bacteraemia. The patient underwent emergency surgical intervention and aortic valve replacement with

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bio-prosthetic homograft valve due to deteriorating cardiac function on maximum inotropic support. *Lactobacillus rhamnosus* was isolated from operative aortic valve tissue culture after 48 hours of incubation.

Postoperative course was complicated by chest wall haemorrhage as result of coagulopathy from liver cirrhosis (INR 2.4), requiring surgical management to control haemostasis. Despite maximal medical therapy, she continued to decline. In conjunction with the family, a decision was made to withdraw therapy and she 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 reporting cases of *Lactobacillus* endocarditis were retrieved and assessed and the search was limited to the English language. Additional cases were identified from the references of the case reports.

Lactobacillus is a commensal in gastrointestinal and genitourinary flora, invasive infections such as meningitis, endometritis, peritonitis, pneumonia, bacteraemia and endocarditis have been reported. 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 23-29% [2,3]. 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 in his cohort the mortality rate was 27%. The possible reasons proposed were unreliable antimicrobial susceptibility studies and lack of standardised therapy including use of sub-optimal antibiotics without activity against lactobacilli [3,4]. Similarly, Cannon et al. reviewed 241 cases of clinical infection with *lactobacillus*. Of these cases, 73 patients had endocarditis. Majority had underlying structural heart disease (63%), or dental condition or recent dental procedure (47%) [2]. Clinical infections have also been linked to invasive procedures such as endoscopy and colonoscopy [2,5]. *Lactobacillus* has a propensity to bind collagen and fibrinogen, aggregate platelets and produce glycosidases and protease enzymes, which may contribute to colonisation of vascular endothelial surfaces [6,7]. 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 [8,9]. 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 [8]. 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 [9]. 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* bacteraemia, which was possibly inadequately treated and investigated on her first presentation. She had multiple possible risk factors for *Lactobacillus* bacteraemia and endocarditis including advanced cirrhosis and abnormal portal circulation, previous colitis and concomitant probiotic use. The bacteraemia in our patient may have originated from the probiotic formulation through bacterial translocation. Also, pre-existing bi-valvular structural abnormality in the form of mitral and aortic regurgitation further increased the risk of seeding of *L. rhamnosus* on the valves, leading to establishment of infective endocarditis. Our patient consumed two capsules of probiotics for 7 months for recurrent *Clostridium difficle* associated colitis (CDAD). Furthermore, her underlying immunosuppressed state due to advanced alcoholic cirrhosis and structural heart diseases would have contributed to her developing blood stream infection and severe sepsis. 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 [10]. Other antibiotics that have *in vitro* activity against *Lactobacillus* species include erythromycin and clindamycin but due to their bacteriostatic activity, they are not recommended in endocarditis. Therefore the commonly recommended treatment for infective endocarditis is synergistic therapy with intravenous penicillin G (or ampicillin) and an aminoglycoside [2,3,11,12].

In the recent years, probiotic use has increased worldwide for the treatment of infantile and adult diarrhoea, antibiotic associated diarrhoea and candidal vaginitis [13]. Lactobacilli are recognized as relatively safer organisms with low virulence potential. However the probiotic strains have been linked to invasive clinical infections such bacteraemia, endocarditis, septic arthritis and hepatic abscess. Gut translocation and systemic dissemination of organisms may be the underlying pathogenesis for invasive infections in immunocompromised patients [6,9,14,15].

There is insufficient evidence and conflicting reports in the literature in regards to the perceived beneficial effect of probiotics for the treatment and prevention of recurrent *Clostridium difficle* associated diarrhoea CDAD. A Finnish [16] and American [17] study of children with respiratory infections reported some beneficial effect of *L. rhamnosus*. The stool frequency improved and stool consistency was increased in those who received concurrent *L. rhamnosus* with an antibiotic. However, other studies have refuted this and no clinical benefit was observed in 38 patients who received *L. acidophilus* and *L. bulgaricus* [18]. A systematic review of 20 randomized trials (3818 patients) reported probiotic use lead to a 66% reduction in prevention of CDAD [19]. Furthermore, another meta-analysis of nine trials by D'Souza et al. showed that probiotic agents may be useful in preventing antibiotic associated diarrhoea, but has little role in the treatment of diarrhoea [20]. Differences in antibiotics given, variation in probiotics and organisms tested, lack of a control or placebo group, and small numbers of patients reduce the ability to interpret some of these clinical studies.

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 bacteraemia 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 probiotic or other dietary supplements, which may contain live or lyophilised 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, purity, or potency before marketing probiotics. In Europe, those dietary supplements intended for use by infants and young children do have specific compositional legal requirements [21]. In the United States, although dietary supplements do not generally require premarket review and approval by the Food and Drug Administration, 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 the Food and Drug Administration. Similarly, in Australia, those probiotics marketed for specific health benefits require premarket review by the Therapeutic Goods Administration and are usually regulated as complementary medicines. However, there are no FDA or TGA regulations or 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. A revision of probiotic status and warnings given with the treatment may be required in order to encompass the potential for harm.

Therefore, patients who are immunosuppressed or have pre-existing heart disease should avoid probiotic preparations. Warnings on the package should be considered.

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