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Endocarditis due to vancomycin-resistant *Enterococcus raffinosus* successfully treated with linezolid: case report and review of literature

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ABSTRACT

Enterococcus raffinosus is scarcely found in clinical samples and even less frequently as etiologic agent of endocarditis. We are herein presenting one case of mitral prosthetic-valve endocarditis in a 77-y-o male due to a vancomycin-resistant *Enterococcus raffinosus* isolate, successfully treated with 6 weeks of linezolid, and a two-year follow up.

Key words: endocarditis, vancomycin resistance, *Enterococcus raffinosus,* linezolid

RESUMEN

Endocarditis por *Enterococcus raffinosus* resistente a vancomicina exitosamente tratada con linezolid: caso clínico y revisión de la literatura. *Enterococcus raffinosus* es una especie poco frecuente en materiales clínicos y menos aún como agente etiológico de endocarditis. En este trabajo se presenta un caso de endocarditis de válvula mitral protésica en un paciente de 77 años debida a *Enterococcus raffinosus* resistente a vancomicina y que fue exitosamente tratada con linezolid durante 6 semanas, con un seguimiento de 2 años.

Palabras clave: endocarditis, resistencia a vancomicina, *Enterococcus raffinosus*, linezolid

Vancomycin-resistant enterococci (VRE) were isolated for the first time in Argentina in 1996 (11). Afterwards, they increased in number, especially as colonizers. They mainly had the *vanA* genotype and belonged to the *Enterococcus faecium* species. However, a few isolates of VanB *E. faecium*, VanA and VanB *Enterococcus faecalis*,VanA *Enterococcus avium,* VanA *Enterococcus gallinarum* and VanA *Enterococcus raffinosus* have also been found in Argentina (6, 10). This latter species has scarcely been found in clinical samples and even less frequently as etiologic agent of endocarditis (8).

We are herein presenting a case of mitral prosthetic-valve endocarditis in a 77-y-o male due to a vancomycin-resistant isolate of *E. raffinosus,* successfully treated with 6 weeks of linezolid (LZD).

Case report. A 77-year-old man with bioprosthetic mitral valve replacement due to severe valve insufficiency and a recent history of cured viridans group streptococcal endocarditis, was admitted to hospital with a febrile episode. Five blood cultures were taken, all of which were positive for *E. raffinosus,* which was identified according to the scheme proposed by Teixeira *et al.* (13). Vancomycin resistance was rapidly recognized by a 6-mm zone in a disk diffusion test with a 30 µg disk of vancomycin. It was later confirmed by Etest (MIC = 1,024 µg/ml) and characterized as due to the *vanA* genotype by a specific PCR performed at our reference center. As expected for a VanA isolate, the MIC of teicoplanin was 32 µg/ml.

The prosthetic valve endocarditis diagnosis was confirmed by the appearance of a new murmur, the observation of a moderate to severe valve prolapse and light insufficiency of the mitral valve by transesophagic ultrasonography. Two peripheral periprosthetic jets, probably caused by periprosthetic leaks, were also observed.

Treatment began with intravenous LZD (600 mg every 12 hours) for four weeks followed by oral LZD (600 mg every 12 h) for two weeks. The isolate was susceptible to this drug (MIC = 2 µg/ml) by the macrobroth dilution method but was resistant to quinupristin-dalfopristin by the disk diffusion test. It was also resistant to penicillin (32 µg/ml), streptomycin (>1,024 µg/ml), gentamicin (>1,024 µg/ml), and rifampin (>32 µg/ml) by the Etest (AB-Biodisk, Solna, Sweden). During this treatment, the patient underwent another valve replacement. The infectious

Table 1. Characteristics of patients with infective enterococcal endocarditis treated with linezolid.

Patient N°, age/sex[1] [reference]	Preexisting medical condition	Organism[2]	Site of infection	Dose of linezolid	Duration of treatment [3]	Outcome	Previous antibiotic treatment[4]
1, 34 yr/F [3]	Hemodyalisis Congenital cyanotic heart disease	VR *E. faecium*	Native tricuspid and aortic valves	600 mg/12 h	3 d, i.v. 6 w, p.o.	Cure	Chloramphenicol and Q&D
2, ND/ND [5]	None	VS *E. faecium*	Pulmonic valve	600 mg/12 h	21 d ND [5]	Death during multiple therapy (probably therapy failure)	No
3, ND/ND [5]	Diabetes, hemodyalisis, recent abdominal aortic repair	VR *Enterococcus* sp.	Not reported	600 mg/12 h	6 w ND	Cure	Alatrofloxacin and VAN
4, 78 yr/M [12]	Diabetes, coronary artery bypass, aortic valve replacement	VS *E. faecalis*	Prosthetic aortic valve	600 mg/12 h	7 w ND	Cure	AMP + GEN
5, 4 mo/M [1]	Prematurity, tracheostomy, atrial septal defect, indwelling central venous catheter	VR *E. faecium*	Native tricuspid valve	15 mg/kg every 8 h 15 mg/kg every 8 h	7 w, i.v. 2 w, p.o.	Cure	VAN
6, 64 yr/M [9]	Coronary artery disease, hypothyroidism, hypertension, chronic renal failure	VR *E. faecalis*	Native pulmonic valve	600 mg/12 h	6 w, i.v.	Non- evaluable (1 w. after completion treatment, the patient died due to another cause)	VAN + GEN
7, 79 yr/F [15]	Prosthetic mitral valve	VR *E. faecalis*	Prosthetic mitral valve	600 mg/12 h 600 mg/12 h	2 w, i.v + GEN 12 w, p.o.	Cure	VAN + GEN Q&D + GEN DOX
8, 37 yr/F [14]	Hemodyalisis, four failed allografts. Bilateral subclavian subcutaneous hemodyalisis ports	VR *E. faecalis*	Native aortic and mitral valves	600 mg/12 h	9 d, i.v.	Failure	No Cure with PEN + STR
9, 64 yr/M [2]	HIV, Hep C, cadaveric renal transplant, perinephric hematoma infected with VR *E. faecium*	VR *E. faecium*	Native mitral valve	600 mg/12 h	6 w, p.o.	Cure	Q&D + AMS Q&D + DOX
10, 40 yr/M [16]	Hemodyalisis, previous group B streptococcal endocarditis	VS *E. faecalis*	Native tricuspid, aortic and mitral valves	600 mg/12 h	3 w, i.v.	Failure	AMP+GEN and LEV. Cure with AMP + STR and surgery
11, 77 yr/M [this study]	Bioprosthetic mitral valve replacement	VR *E. raffinosus*	Prosthetic mitral valve	600 mg/12 h 600 mg/12 h	4 w, i.v. 2 w, p.o.	Cure	No

[1]M: male, F: female, [2]VR: vancomycin-susceptible, VS: vancomycin-resistant, [3]i.v.: intravenous, p.o.: oral.
[4]AMP: ampicillin, AMS: ampicillin-sulbactam, VAN: vancomycin, GEN: gentamicin, STR: streptomycin, Q&D: quinupristin-dalfopristin, PEN: penicillin, LEV: levofloxacin, DOX: doxycycline.
[5]ND: non determined.

process involved the valve annulus at the site of attachment with extension to adjacent structures. The valve was removed with extensive debridement and resection of the annular tissue. Replacement with a mechanical prosthetic valve was performed prior to reconstruction of the destroyed annulus. The patient had an uneventful recovery within a two-year follow-up. Cultures of the replaced valve tissue were negative.

Treatment of enterococcal endocarditis simultaneously resistant to vancomycin, penicillin and aminoglycosides is really a major challenge. Despite its already known bacteriostatic effect, LZD was chosen in this case for lack of better options. In fact, LZD also behaved as bacteriostatic agent in this isolate as shown in the corresponding time-killing curve (data not shown).

There has been limited experience in the use of LZD to treat infective endocarditis due to enterococci. Tsigrelis *et al.* described one case of endocarditis due to vancomycin-resistant (VR) *E. faecalis* in a 37-y-o female patient that had failed to respond to LZD therapy administered during nine days by intravenous route (case 8, Table 1). She had no predisposing heart condition but had undergone prolonged hemodyalisis, four failed allografts, multiple failed arteriovenous grafts and fistulas, and the placement of bilateral subclavian subcutaneous hemodyalisis ports. Finally, she was successfully treated with penicillin plus streptomycin (14). These authors had reviewed all VR *E. faecalis* endocarditis that fulfilled the modified Duke criteria for definite or possible infective endocarditis. Only two out of six patients had been treated with LZD. One of them, a 79-y-o woman was cured after two weeks of intravenous treatment with 600 mg/12 h LZD plus 80 mg/12 h gentamicin (case 7, Table 1) (15). The other, a 64-y-o man with pulmonic valve endocarditis, died one week after completion of LZD therapy (case 6, Table 1). No pathogen was isolated from blood cultures and no evidence of acute myocardial infarction or gastrointestinal bleeding was recorded. As no autopsy was performed, the outcome could not be evaluated (9).

In Table1, in addition to the three previously commented cases, we included other seven enterococcal endocarditis episodes that were treated with LZD: four endocarditis due to *E. faecium*, one of them susceptible to VAN (VS), one case due to an unidentified VR *Enterococcus* sp. and two cases due to VS *E. faecalis*.

Babcock *et al*. and Archuleta *et al.* reported the cure with LZD of two patients with endocarditis by VR *E. faecium* and severe preexisting medical conditions: hemodyalisis plus congenital heart disease in the first case, and HIV, hepatitis C plus renal transplantation in the second (2, 3).

Chien *et al*. partially described several patients infected with VRE. Among them, there was one patient who died due to VS *E. faecium* endocarditis after 21 days of therapy with LZD, and another case of endocarditis due to an unidentified VR *Enterococcus* sp. that was cured with a 7-week treatment with the same antibiotic (5).

Ang *et al*. reported the cure of a pediatric patient with a VR *E. faecium* endocarditis with 15 mg/kg/8 h LZD (1).

One of the two cases of VS *E. faecalis* endocarditis located in a prosthetic aortic valve and treated with LZD, was successfully cured with 7 weeks of antibiotic treatment. The other case, involving native tricuspid, aortic and mitral valves, failed after three weeks of intravenous therapy (12, 16).

The whole experience with these eleven patients (Table 1) is similar to that published by Birmingham *et al*. related to cases of VR *E. faecium* endocarditis recorded from compassionate treatments with LZD: 10 clinical cures, 2 clinical failures and one indeterminate case; 7 microbiological cures, and 4 microbiological failures (4).

Falagas *et al*. reviewed the efficacy of LZD in infective endocarditis due to multidrug-resistant gram-positive cocci and found approximately the same results: of 33 evaluable patients (25% of them with prosthetic valve), 21 (63.6%) were cured after LZD administration; in 66.7% of cases it was administered alone. Most cases were staphylococcal endocarditis, but the outcome of the subgroup of 8 patients with VRE was not significantly different from the whole (cure = 75%, improvement = 12.5%, failure = 12.5%) (7).

We described one case of mitral prosthetic-valve endocarditis in a 77-y-o male cured with 6 weeks of LZD. To the best of our knowledge, this is the first report of a case of prosthetic endocarditis due to a VR *E. raffinosus* isolate successfully treated with LZD, with a two-year follow-up. We will have to wait for other similar reports to define the best therapeutic scheme (dose, intervals, administration route and treatment duration).

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