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Serum Bactericidal Activity Levels Monitor to Guide Intravenous Dalbavancin Chronic Suppressive Therapy of Inoperable Staphylococcal Prosthetic Valve Endocarditis: A Case Report

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Here we describe a case of a methicillin-resistant coagulase-negative staphylococci prosthetic valve endocarditis in a patient considered not eligible for valve replacement due to high perioperative mortality risk and who did not tolerate oral antibiotic treatment. Under these circumstances, intravenous long-term chronic suppressive antibiotic therapy with dalbavancin, scheduling the doses using the serum bactericidal activity titers, proved to be safe and effective.

Keywords. prosthetic valve endocarditis; long-term chronic suppressive antibiotic therapy; serum bactericidal activity; dalbavancin.

Valve replacement and intravenous targeted antibiotics are the cornerstone of therapy of methicillin-resistant coagulase-negative staphylococci prosthetic valve endocarditis (MRCoNS PVE) [1]. However, occasionally patients refuse or are not eligible for valve replacement due to poor clinical conditions, so that long-term chronic suppressive antibiotic therapy (LTCSAT) remains the only viable treatment option. We here report a unique case of intravenous LTCSAT with dalbavancin, a long-acting lipopeptide antibiotic, in a patient who could not receive oral therapy [2].

CASE REPORT

A 78-year-old man presented to the emergency department for fever lasting 1 month. His medical history included benign prostatic hyperplasia, bowel diverticular disease and parkinsonism. Seven months before, he underwent aortic valve and tubular ascending aorta replacement by bioprosthetic devices (MagnaEase n.25 and HemaBridge n.10) due to severe aortic valve regurgitation and ascending aorta aneurysm.

On admission, high-resolution computed tomography revealed a bleb of the ascending aorta posterior wall; additionally, hypodense areas, consistent with ischemic lesions, were detected in the right kidney and spleen. Empiric antibiotic therapy with intravenous (i.v.) piperacillin-tazobactam (4.5 g TID) and i.v. daptomycin (500 mg/d) was started. A transesophageal echocardiogram (TEE) displayed 2 vegetations (maximum diameter 14 × 11 mm) on aortic cusps and a periprosthetic abscess, whereas oxacillin-resistant *Staphylococcus epidermidis* (vancomycin minimal inhibitory concentration [MIC] 1 μg/mL, daptomycin MIC 0.5 μg/mL, rifampicin ≤0.03 μg/mL) and highly penicillin-susceptible *Streptococcus mitis* (MIC 0.006 μg/mL) were isolated from multiple blood cultures. IE was diagnosed, and targeted therapy with ceftriaxone 2 g BID, 10 mg/kg daptomycin, and 600 mg/d rifampicin was started, with prompt clearance of bacteremia, although rifampin was stopped after 2 days for poor tolerance. Poor clinical conditions and high perioperative risk (EuroSCOREII: 39.07%) were considered contraindications for immediate surgery. Thus, after 7 weeks, initial antimicrobial therapy was discontinued, and the patient was discharged after administration of 1500 mg i.v. dalbavancin (DBV). In vitro DBV susceptibility against the *S. epidermidis* isolate was not available, so vancomycin susceptibility has been taken into account as a surrogate marker of DBV activity [3].

As reported in Table 1, DBV therapy was scheduled according to serum bactericidal activity (SBA) titers that were measured according to Leighton et al. [4] and performed immediately before each DBV dose. In particular, after day 42 of therapy, it was decided to administer DBV whenever SBA titers ≤1:8 were detected; these circumstances accounted for SBA titers previously reported as resulting in bacteriological cure in infective endocarditis [5]. DBV concentrations have been assessed using a liquid chromatography–mass spectrometry method [6] at 3 treatment time points: days 63, 112, and 133 (Table 1). Overall, our patient received 5 i.v. doses of 1500 mg of DBV, scheduled as shown in Table 1 (days 1, 7, 42, 112, 189).

While on LTCSAT, clinical conditions improved, with progressive disappearance of the 2 vegetative lesions on TEE scans (both originally <10 mm in diameter). On day 42 of DBV LTCSAT, a positron-emission tomography/computed tomography (PET/CT) showed a 9-mm leak at the caudal anastomosis of the aortic tube surrounded by an area of focal uptake, suggesting some residual infection. A follow-up PET/CT

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Table 1. Dalbavancin Administration Schedule[a] Based on SBA Titers Against the *S. epidermidis* Blood Isolate

Day of Therapy	i.v. Dalbavancin, mg	SBA Titers	Dalbavancin Serum Concentration, mg/L
Day 1	1500	n.a.	n.a.
Day 7	1500	n.a.	n.a.
Day 42	1500	1:128[b]	n.a.
Day 63	Not administered	1:512	32.8[c]
Day 112	1500	1:8[b]	0.6[c] (410.5[d])
Day 133	Not administered	1:128	17.9[c]
Day 154	Not administered	1:16	n.a
Day 189	1500	1:2[b]	n.a.

Abbreviations: i.v., intravenous; SBA, serum bactericidal activity.

[a]After day 42, it was decided to administer dalbavancin whenever an SBA titer ≤1:8 was detected; these circumstances accounted for through SBA titers previously reported as resulting in bacteriological cure in infective endocarditis [5].

[b]SBA titer before i.v. dalbavancin administration.

[c]Through serum drug concentration.

[d]Peak serum drug concentration (measured 15 minutes after dalbavancin i.v. administration).

performed on day 140 of DBV LTCSAT showed both reduction of the leak lesion (4-mm diameter) and of the focal uptake. No alterations of renal, liver, and hemathopoiesis functions were observed throughout the period of DBV LTCSAT. Currently, the patient is recovered and asymptomatic, and he refuses evaluation for surgery.

DISCUSSION

In our case, the 7-week daptomycin plus ceftriaxone regimen without valve replacement could not be a successful therapy for our inoperable case of MRCoNS PVE. The high risk of recurrence was also suggested by alterations detected at follow-up PET/CT scans. As a matter of fact, this diagnostic tool is not also validated to monitor the clinical course of PVE; however, as some preliminary reports seem to suggest, we hypothesized that it could be of some help to confirm persistence of infection once inflammatory markers and TEE scans became negative [7, 8].

In our case, LTCSAT seemed advisable [9], possibly allowing a progressive clinical improvement with reduction of perioperative mortality risk. To this end, oral options might have been linezolid or fusidic acid plus rifampicin. However, fusidic acid is not available in Italy, rifampicin was not tolerated by the patient, and linezolid has several side effects that contraindicate long-term therapy [10]. In this scenario, an i.v. treatment with DBV, a novel lipoglycopeptide with excellent antistaphylococcal activity and a half-life of approximately 346 hours, seemed an attractive option [2–11]. Even though approved only for therapy of gram-positive acute bacterial skin and skin structure infections [11], in real-life practice DBV has been satisfactorily used also in gram-positive IE treatment [12], and a schedule of 2 i.v. doses of 1500 mg 1 week apart has been recently validated for osteomyelitis treatment, providing plasma and bone tissue exposure above the MIC 99.9 of 0.12 ug/mL for *S. aureus* for 8 weeks [13].

In conclusion, notwithstanding the uncertainty surrounding the appropriate target to redose DBV and the overall lack of clear contemporary data supporting the use of SBA titers as a surrogate for traditional PKPD to guide DBV dosing, an SBA-monitored DBV LTCSAT allowed in our case not only suppression of methicillin-resistant *S. epidermidis* PVE, but also confinement of the infection to a small area adjacent to the anastomosis leak. Further investigations are required to assess the real efficacy of this therapeutic approach to inoperable gram-positive PVEs.

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Author contributions. M.S., C.F., G.T., E.B., R.E., and M.V. participated in patients' clinical management and wrote the draft of the manuscript. A.A. performed dalbavancin plasmatic concentrations, and V.P. assessed serum bactericidal activity titers. All authors have seen and approved the final version of the manuscript.

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