



Letter to the Editor

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Infective endocarditis on prosthetic valve due to vancomycin-resistant *Enterococcus faecium* with VanA/VanB genotype

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Sir,

Vancomycin-resistant *Enterococcus faecium* (VREF) is one of the 12 bacteria that were part of the first list of priority pathogens developed by the World Health Organization (WHO) in 2017 [1]. In our center we have witnessed an alarming increase in recent years of its isolation in relevant clinical samples, such as blood cultures. In fact, in 2022 vancomycin resistance was reported in 29.2% of the 24 *E. faecium* bacteremias in our hospital, while in 2023 this figure increased to 61.7%.

The genus *Enterococcus* has intrinsic and different levels of resistance to several families of antibiotics such as aminoglycosides, cephalosporins and lincosamides [2]. In addition, it can acquire resistance to other antibiotics such as vancomycin, with the two main vancomycin resistance phenotypes being VanA (high-level resistance to vancomycin and teicoplanin) and VanB (variable resistance to vancomycin) [2].

VREF infection poses a therapeutic challenge, with recommendations currently based on observational studies and case series without solid evidence. For the treatment of VREF bacteremia, high doses of daptomycin (10–12 mg/kg/day) have been shown to decrease mortality in 2 cohort studies compared to lower doses [3, 4]. Furthermore, according to in vitro data, the combination of daptomycin with different beta-lactams would have synergistic and bactericidal activity and would decrease the occurrence of resistance in VREF [5–7].

For all these reasons, we believe it is of interest to share the case of an infective endocarditis on prosthetic valve due to VREF with adequate therapeutic response after the combined administration of daptomycin and ampicillin.

The patient is 73 years old, with a history of arterial hypertension, chronic obstructive pulmonary disease and chronic renal disease in a hemodialysis program due to arteriovenous

fistula. He was admitted in October 2022, one month after the implantation by conventional surgery of an aortic biological prosthesis, due to a febrile syndrome of 24 hours of evolution of probable respiratory origin. Blood cultures were taken in the emergency room and after 14 hours of incubation were positive, showing gram-positive cocci in pairs and short chains. It was decided to perform a short incubation subculture (4 hours) and at the same time multiplex PCR (Filmarray Biofire®) which revealed that we were dealing with an infection by *E. faecium* vanA/vanB (this technique is not able to differentiate between both genotypes). Subsequently, from the sod grown on chocolate agar, identification and susceptibility study was performed by VITEK®2 (BioMerieux), with the minimum inhibitory concentration (MIC) of vancomycin >32 mg/L and teicoplanin >12 mg/L. Both MICs were confirmed by E-test being >256 mg/L and 32 mg/L respectively. The susceptibility study was interpreted according to the EUCAST cut-off points version 2021, both being high-level resistances. Daptomycin was also tested by E-test in Mueller–Hinton enriched with 50 mg/L calcium. The MIC was 0.5 mg/L, it was susceptible according to the ECOFF cut-off point (<4 mg/L), since there are no clinical cut-off points according to EUCAST. In addition, resistance to ampicillin was observed with MIC >32 mg/L by microdilution in VITEK®2 broth. It should be taken into account that 90% of *Enterococcus faecium* strains are resistant to ampicillin due to changes in PBP5 that confer low affinity for beta-lactams.

These resistances were confirmed by another molecular biology technique (Eazyplex®VRE, Amplex), so it is a strain of EFRV carrying the *vanA/vanB* genes, the first and only one detected with this genotype in our environment.

Empirical antibiotherapy with ceftriaxone, initiated in the emergency department, was supplemented with linezolid. Blood cultures were repeated after 48 hours and were positive, so on the third day of admission and in view of the suspicion of infective endocarditis on a biological prosthetic valve, antibiotherapy was modified to intravenous daptomycin 8 mg/kg/48 hours post-dialysis + ampicillin 1 g intravenous every 12

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hours. Pharmacokinetic monitoring was performed, obtaining trough plasma concentrations of 42.98 mg/L. In studies performed using Monte Carlo model simulations in hemodialysis patients and even in vivo, trough levels above 24.3 mg/L have been associated with elevated blood CPK levels [8,9]. Therefore, the dosage was adjusted to 6 mg/kg/48 hours after each hemodialysis session and the new dosing regimen was confirmed with pharmacokinetic monitoring, with a trough plasma concentration of 14.39 mg/L and an $AUC_{24h}/CMI = 1.049$ (>666) indicative of a high probability of therapeutic success.

The third blood culture control, on the fourth day of admission, was still positive but on the sixth day the first blood cultures were negative. Two transthoracic echocardiograms (TTE) and one transesophageal echocardiogram (TEE) were performed, and the cardiac prosthesis was described as well positioned and normal functioning. Finally, a cardiac computed axial tomography (CAT) scan was performed, identifying soft tissue density surrounding the prosthetic ring, compatible with infective endocarditis. The intravenous antibiotic combination was maintained for 6 weeks, the first 4 during hospitalization and the last 2 on an outpatient basis through the Home Hospitalization Unit and the dialysis center.

The patient presented an adequate clinical and analytical evolution, with a control TTE at 2 months and 6 months after discharge, with no findings suggesting persistence or relapse of the infectious process. At the time of writing this document, there has been no relapse of the infection a year and a half after hospital discharge.

We report the successful treatment of infective endocarditis on prosthetic valve due to VREF with 6 weeks of combined intravenous treatment with daptomycin and ampicillin. In fact, the grade I recommendation of the current European guidelines on the treatment of infective endocarditis, for infections caused by VREF, is based on the antibiotic bitherapy used in our patient [10]. However, the recommendation has a level of evidence C, based on expert opinion or retrospective studies. For this reason, we believe it is particularly interesting to share our experience.

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CONFLICT OF INTEREST

Authors declare no have conflict of interest.

REFERENCES

- Organización Mundial de la Salud. 2017. Comunicado de prensa 27 de febrero de 2017. <https://www.who.int/es/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed> (accessed 15 May 2024).
- Gold HS. Vancomycin-resistant enterococci: mechanisms and clinical observations. *Clin Infect Dis*. 2001 Jul 15;33(2):210-9. doi: 10.1086/321815.
- Britt NS, Potter EM, Patel N, Steed ME. Comparative Effectiveness and Safety of Standard-, Medium-, and High-Dose Daptomycin Strategies for the Treatment of Vancomycin-Resistant Enterococcal Bacteremia Among Veterans Affairs Patients. *Clin Infect Dis*. 2017 Mar 1;64(5):605-613. doi: 10.1093/cid/ciw815.
- Chuang YC, Lin HY, Chen PY, Lin CY, Wang JT, Chen YC, et al. Effect of Daptomycin Dose on the Outcome of Vancomycin-Resistant, Daptomycin-Susceptible *Enterococcus faecium* Bacteremia. *Clin Infect Dis*. 2017 Apr 15;64(8):1026-1034. doi: 10.1093/cid/cix024.
- Geriak M, Haddad F, Rizvi K, Rose W, Kullar R, LaPlante K, et al. Clinical Data on Daptomycin plus Ceftaroline versus Standard of Care Monotherapy in the Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia. *Antimicrob Agents Chemother*. 2019 Apr 25;63(5):e02483-18. doi: 10.1128/AAC.02483-18..
- Smith JR, Barber KE, Raut A, Aboutaleb M, Sakoulas G, Rybak MJ. β -Lactam combinations with daptomycin provide synergy against vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*. *J Antimicrob Chemother*. 2015;70(6):1738-43. doi: 10.1093/jac/dkv007.
- Hall Snyder A, Werth BJ, Barber KE, Sakoulas G, Rybak MJ. Evaluation of the novel combination of daptomycin plus ceftriaxone against vancomycin-resistant enterococci in an in vitro pharmacokinetic/pharmacodynamic simulated endocardial vegetation model. *J Antimicrob Chemother*. 2014 Aug;69(8):2148-54. doi: 10.1093/jac/dku113. .
- Patel N, Cardone K, Grabe DW, Meola S, Hoy C, Manley H, et al. Use of pharmacokinetic and pharmacodynamic principles to determine optimal administration of daptomycin in patients receiving standardized thrice-weekly hemodialysis. *Antimicrob Agents Chemother*. 2011 Apr;55(4):1677-83. doi: 10.1128/AAC.01224-10.
- Bhavnani SM, Rubino CM, Ambrose PG, Drusano GL. Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. *Clin Infect Dis*. 2010 Jun 15;50(12):1568-74. doi: 10.1086/652767.
- Delgado V, Ajmone Marsan N, de Waha S, Bonaros N, Brida M, Burri H, et al; ESC Scientific Document Group. 2023 ESC Guidelines for the management of endocarditis. *Eur Heart J*. 2023 Oct 14;44(39):3948-4042. doi: 10.1093/eurheartj/ehad193.