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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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None to declare

CONFLICT OF INTEREST

Authors declare no have conflict of interest.

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