Letter to the Editor

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Clarithromycin plus linezolid as a sequential therapy for implantable-cardioverter-defibrillator infection caused by coagulase-negative staphylococci

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Sir,

Success in the treatment of pacemaker infection needs of an appropriate antimicrobial treatment and the removal of the intracardiac device in most cases. When such removal is not feasible or it is difficult, long term or prolonged antibiotic therapy for at least 3 months is recommended[1,2]. Treatment in this clinical scenario may be more difficult and there are few antibiotic combinations that can be administered orally with proven efficacy.

A 68-year-old man was admitted to this hospital because of fever. He had a history of ischemic cardiomyopathy: he suffered a myocardial infarction 26 years before, requiring coronary artery bypass graft surgery. Thereafter his left ventricular ejection fraction was 29% and had a low-apical heart aneurysm and a moderate mitral regurgitation. In 2007 a bicameral implantable cardioverter defibrillator (ICD) was implanted. After the insertion he suffered from a skin infection around the implantation area that was treated with antibiotics with good response.

Five years later he was admitted to our hospital because of fever and chills. On examination, his blood pressure was 105/84 mmHg, he had rhythmic pulse without murmur and neither skin lesions nor lymphadenopathies. His abdomen was normal apart from a left inguinal hernia that was reducible without pain. Results of laboratory tests showed 14,500 white cells per mm^3, C-reactive protein (CRP) was 229 mg/L with normality in the rest of parameters. Blood-cultures were collected growing both *Staphylococcus epidermis* and *Staphylococcus warnerii* (both resistant to oxacillin and sensible to vancomycin with a MIC 1 mg/L). A transthoracic echocardiography was performed, showing a vegetation adhered to the ICP-cable, in the right ventricular tract.

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The patient was transferred to the Cardiac Surgery Unit of our reference hospital being on treatment with daptomycin. ICP was removed and sent for culture but during this procedure the patient suffered from acute heart failure and a new ICD was implanted. The culture of the explanted ICD-pacemaker grew *S. epidermidis* and *S. warnerii* with similar sensitivities than the ones in the blood cultures. The patient completed two more weeks with daptomycin and was thereafter treated with meropenem because infectious complications of the ICU and posterior long-time admission (urinary tract infection due to ESBL-*Escherichia coli* and respiratory tract infection due to *Pseudomonas aeruginosa*). He was later discharged to our hospital to keep in rehabilitation and finish intravenous antibiotics.

The patient deteriorated progressively as a result of this long admission and many complications, suffering from sarcopenia and skin fungus. He started having fevers especially in the afternoons. Blood cultures were taken and another transthoracic echocardiography showed a 15 mm vegetation in the right atrium and an 8 mm vegetation in the ICP-cable in the right ventricle. Blood cultures grew *S. epidermidis* and *S. warnerii* again, with similar sensitivities to antibiotics than the ones in the ICP-cable-culture. The patient was started on intravenous vancomycin 1 g every 12 hours plus rifampicin 600 mg once a day with good response. 6 weeks later the patient was discharged with oral linezolid 600 mg every 12 hours plus oral clarithromycin 500 mg every 12 hours for another 6 weeks. In the follow-up the patient suffered from a UTI caused by ESBL-*Klebsiella pneumoniae* that was successfully treated with intramuscular ertapenem 1 g for 10 days. Apart from that, he was afebrile and stable 24 months later and CRP was <1 mg/L. A control echocardiography showed a residual vegetation over the ICP-cable.

Treatment of ICD infections usually needs of an appropriate antimicrobial treatment and the removal of the intracardiac device but in some cases such removal is not feasible or it is difficult. Some authors have proposed long term or prolonged antibiotic therapy for at least 3 months which is rec-

ommended based in few scientific references[1,2]. We used a 3 months-course with this patient because of the good clinical and analytic evolution.

Linezolid plus clarithromycin are synergic antibiotics that can be used in combination in patients with biofilms-related infections, resistant tuberculosis and non-tuberculous mycobacteria infections but have never been studied in pacemaker or prosthetic-valve endocarditis. Clarithromycin has anti-biofilm properties as demonstrated by *in vitro* studies[3]. Clarithromycin inhibits biofilm formation of gram-positive organisms even when these organisms exhibit *in vitro* resistance. Therefore, this anti-biofilm activity is independent of the antibacterial activity of clarithromycin and this property seems to be specific for clarithromycin and not general to all macrolides.

Clarithromycin also increase linezolid serum concentration as demonstrated by *in vitro* studies with multi-drug resistant *Mycobacterium tuberculosis* isolates[4]. In this study, all patients received linezolid 300 mg every 12 hours and clarithromycin was added as a dosage of 250 mg and 500 mg once daily consecutively. The authors demonstrated a 44% increase in linezolid exposure after co-administration with 500 mg clarithromycin. We used linezolid 600 mg every 12 hours and clarithromycin 500 mg every 12 hours in our patient because it is the recommended dosage. This *in vitro* study highlights the need to revise the dosage when these antibiotics are used together, especially if a prolonged treatment is required.

Linezolid is an oxazolidinone antibiotic with antibacterial activity against gram-positive organisms and it has been associated with inhibition of staphylococcal biofilm growth too[5].

In summary, our clinical success is supported by *in vitro* studies that highlight some optimal properties and synergy of the combination of linezolid and clarithromycin in the treatment of biofilm-related gram-positive infections.

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