Development of daptomycin resistance during therapy in a patient with methicillin-resistant Staphylococcus aureus endocarditis: A case report

Desarrollo de resistencia a daptomicina durante el tratamiento de un paciente con endocarditis por Staphylococcus aureus resistente a meticilina

A 69-year-old woman was sent to the emergency room by her cardiologist after a gastrointestinal bleeding episode. She had a history of allergy to amoxicillin-clavulanic acid (rash), type 2 diabetes, hypertension, hypothyroidism, peptic ulcer disease and iron-deficiency anemia. She had a mechanical prosthetic mitral valve placed four years before due to rheumatic mitral stenosis. At that time a tricuspid anuloplasty had been performed. She had atrial fibrillation and severe pulmonary hypertension and was receiving oral anticoagulation, all of which lead to a NYHA class II–III congestive heart failure (CHF) with multiple hospital admissions due to decompensated CHF. Hematocrit was stable and an upper gastrointestinal endoscopy did not show bleeding, ruling out acute gastrointestinal bleed. Elevated creatinine was observed (1.97 mg/dL); acute renal failure was considered to be pre-renal, associated to diuretics. On day 5 after hospitalization she presented fever and a painful hematoma around a previous peripheral intravenous line. Blood cultures were obtained and levofloxacin therapy was started. Blood cultures became positive in less than 24 h, gram-positive cocci in clusters were observed and identified as Staphylococcus aureus by MALDI-TOF mass spectrometry. Antimicrobial therapy was switched to daptomycin 9 mg/kg q48 h because her creatinine was rising and her estimated creatinine clearance at that time was 33 mL/min. MIC testing was conducted by VITEK® and confirmed by Microscan® and E-test Biomerieux®. The isolate was resistant to meticillin, erythromycin, levofloxacin and tobramycin, and susceptible to trimethoprim-sulfamethoxazole, clindamycin, vancomycin (MIC < 0.5 mg/L), and daptomycin (MIC = 0.25 mg/L). She became febrile in less than 48 h and blood cultures were serially obtained. As part of the initial workup a tranesophageal echocardiogram (TEE), which was negative for endocarditis, and an angio-CT scan were performed, disclosing intramural hematoma without venous thrombosis and several pulmonary nodules consistent with septic emboli. Blood culture from day 11 was positive, so linezolid (600 mg BID iv) was added to daptomycin on day 13. Blood cultures from day 13 continued to be positive for MRSA with the same susceptibility profile as the previous isolates except for daptomycin (MIC of 2 mg/L) and vancomycin (MIC of 1 mg/L). This was confirmed by E-test®. Antimicrobial therapy was switched to teicoplanin (8 mg/kg) plus intravenous fosfomycin (4 g TID). On day 15 a repeat TEE showed a 7.5 mm-long filiform vegetation attached to the auricular side of the prosthetic mitral valve. Thickening of mitro-aortic junction was found too. Cardio surgery consultation was performed but the patient was not considered a surgical candidate given her baseline dyspnea and severe pulmonary hypertension despite a non-disfunctioning prosthetic valve. She remained febrile during the whole hospitalization but having dyspea on minimal physical activity. On day 25 she had a cardiac arrest and died.

Genetic relatedness between the isolates was confirmed by pulsed-field gel electrophoresis (PFGE) with Smal digestion using the protocol described by Pérez-Vázquez et al. Sequencing of genes reported to be involved in decreased susceptibility to daptomycin (walkA, rpoB, agrA and mprF) showed a G2476A mutation (numbering refers to Genbank entry HM140976) in the mprF gene of the resistant isolate, but not in the susceptible isolate. MLST analysis showed that the S. aureus isolates from days 5 and 13 belonged to ST125. This mutation would translate into a leucine to phenylalanine change in position 826 of the protein sequence (L826F), close...
to the C-terminus. The \textit{walk} and \textit{agrA} genes had no mutations and were identical in the susceptible and resistant isolates.

**Discussion**

We report a case of treatment failure associated with the development of daptomycin nonsusceptibility during therapy with daptomycin in a patient with acute infective endocarditis due to methicillin-resistant \textit{S. aureus}. Treatment options for bacteraemia and endocarditis caused by methicillin-resistant \textit{S. aureus} (MRSA) are limited. The standard therapy is vancomycin but has been associated with suboptimal outcomes in some cases. Daptomycin is a cyclic lipopeptide antibiotic that has bactericidal activity against a broad spectrum of gram-positive bacteria and an important agent in treating invasive \textit{S. aureus} infections.

The incidence of daptomycin resistance in clinical isolates is low and the mechanisms of resistance in \textit{S. aureus} appear to be quite diverse. One of the genes most commonly found to be involved in resistance is the multiphage resistance factor gene (\textit{mprF}).

The \textit{mprF} gene codes for a l-lysyl-phosphatidyglycerol (L-PG) synthase that transfers lysine residues to phosphatidyglycerol and translocates the resulting lysyl-phosphatidylglycerol to the outer membrane leaflet.\(^1\) Mutants lacking \textit{mprF} activity show increased susceptibility to cationic antimicrobial peptides, while mutants associated to daptomycin resistance show increased synthesis or enhanced translocation of lysyl-phosphatidylglycerol.\(^2\) The resistance has been mapped to the C-terminal portion of \textit{mprF}, and the L826F mutation has been shown to be causally related to the resistance phenotype in a daptomycin-resistant MRSA clinical isolate.\(^3\)

There are some reports of development of daptomycin resistance in \textit{S. aureus} during treatment with daptomycin in patients with endocarditis, and in most cases vancomycin therapy had been used before switching to daptomycin.\(^4,5\) The emergence of daptomycin resistance in the absence of vancomycin exposure is uncommon.\(^6-8\) In our case, daptomycin was the primary therapy, the resistant isolate emerged after 7 days and had a point mutation in \textit{mprF}. Daptomycin was dosed at 9 mg/kg, but given the impaired renal function of the patient the administration interval was adjusted to 48 h as recommended, resulting in suboptimal dosing during at least 48 h when creatinine clearance increased above the adjustment threshold. Some authors have suggested that a suboptimal dose-regimen may contribute to the emergence of daptomycin resistance.\(^7,9\) Two observational studies including patients with impaired renal function receiving daptomycin for MRSA bloodstream infections showed favorable clinical success rates, in spite that a significant proportion of patients received less than 6 mg/kg. In these cohorts daptomycin non-susceptible strains emerged in 2/38 and 2/106 patients respectively, all between days 5–7 of daptomycin therapy. Two patients were on hemodialysis and two had mild to moderate renal failure with daptomycin being dosed at 4 mg/kg/24 h and 8 mg/kg. No information about the mechanisms of resistance was provided.\(^10,11\) Use of higher dose daptomycin regimens, up to 10–12 mg/kg can forestall the emergence of resistance.\(^12,14\) This case report underlines the importance of dose interval adjustment in patients with moderately impaired renal function.

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**References**


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