Successful treatment of methicillin-resistant *Staphylococcus aureus* mitral valve endocarditis with sequential linezolid and telavancin monotherapy following daptomycin failure—authors’ response

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Sir,

We are grateful for the informative comment by Camou1 and would like to take the opportunity to address some of the points.

With regard to our first-line treatment choice, several factors led us to initially use vancomycin as empirical therapy. First, the patient presented as an intravenous drug user without abnormalities on transthoracic two-dimensional echocardiogram, prompting coverage for *methicillin-resistant Staphylococcus aureus* (MRSA) bacteraemia. Though the patient had renal dysfunction, the dosage was adjusted with the help of our clinical pharmacy department to provide adequate AUC/MIC,2 while attempting to minimize exacerbating the patient’s kidney dysfunction. Secondly, vancomycin comes ready to administer in pre-made bags (Baxter, Deerfield, IL, USA). Daptomycin, on the other hand, requires reconstitution using aseptic techniques,3 and, in our experience, requires at least 15 min of undisturbed reconstitution time, which may not be practical in an emergency department. Lastly, our institutional price for 1 g of vancomycin intravenously every 8 h (our most common dose) is $23.09/day, versus $256.29 for 500 mg of daptomycin intravenously every 24 h. For our patient, who might have benefited from a 10 mg/kg dose, the cost of daptomycin would have been $512.58/day. For comparison, our price for 1 g of vancomycin intravenously every 12 h is $186.71.

In response to comments about the lack of therapeutic drug monitoring of vancomycin: given vancomycin’s time-dependent bactericidal activity, interpretation of trough levels before reaching steady state can be misleading. Typically, a trough is drawn during a drug’s steady state to ensure proper therapeutic response (and that administration of the drug is equal to its clearance).4 In a patient with acute kidney injury, such as ours, the patient-specific half-life of the drug increases, and thus the time to steady state does as well. Our patient only received two doses of vancomycin; his initial concentration ([Cp0]=dose (mg)/V) of 17.5 mg/L was well below the toxic level.

Camou is correct to point out that daptomycin is a reasonable alternative to vancomycin in MRSA infections.5 The literature notes, however, that no agent has proven superior to vancomycin5,6 and that even the use of high-dose daptomycin (8–10 mg/kg) requires further study to determine whether improved outcomes occur.5

Should daptomycin replace vancomycin for empirical treatment of MRSA infections? We feel that optimizing the use of vancomycin (utilizing clinical pharmacy can be helpful in this regard) is still the most cost-effective solution. If in the face of factors that predict vancomycin failure, an alternative agent should be sought. Indeed, once blood cultures returned a vancomycin MIC of 2 mg/L (by broth microdilution), we opted for daptomycin.7

Transparency declarations

None to declare.

References


Comment on: Successful therapy of treatment-emergent, non-clonal daptomycin-non-susceptible *Enterococcus faecium* infections

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Sir,

Daptomycin-non-susceptible Enterococcus (DNSE) infections are increasingly being described.1 King et al.2 conclude that until there is a better understanding of the mechanisms of altered daptomycin susceptibility, clinicians should be aware of its uncommon existence.

The genetic basis for in vivo daptomycin resistance in enterococci was recently reported, and mutations in proteins involved in the stress-sensing response of the cell envelope to antibiotics (such as LiaF) and in enzymes that are responsible for phospholipid metabolism in the cell membrane [such as glycerophosphoryl-diester-phosphodiesterase (GdpB) and cardiolipin synthase] are implicated in the development of daptomycin resistance.3,4 Arias et al.3 suggest that the mutations that occur in the LiaF and GdpD proteins may have originated from recombination between adjacent repetitive nucleotide sequences. Acquired resistance among Enterococcus spp. is mediated by transferable transposons or plasmids encoding resistance cassettes.1,5 Thus, a possible mechanism of resistance in DNSE cases could be the co-transfer of resistance.1,5 Many of these elements of resistance appear to have been mobilized from more obscure types of bacteria.5

Enterococci and anaerobes are members of the gastrointestinal tract consortium in humans and most other organisms.6 The dominant members of the colonic flora, anaerobic bacteria, can serve as reservoirs of antibiotic resistance genes, many of which are carried by mobile genetic elements.5 The transport of genetic elements of resistance between enterococci and anaerobes has been described previously.7 Changes in cardiolipin have been implicated in the mechanism of development of daptomycin resistance in enterococci.3,6 A smaller amount of cardiolipin, which plays an important role in the bioenergetics of the cell and changes in phospholipid biosynthesis and the remodelling of membrane phospholipids, has been described in anaerobic bacteria such as clostridia.8

Another mutated gene that was identified by Arias et al.3 in daptomycin-resistant enterococci encodes a putative LacI (lactose-operon-repressor)-family transcriptional repressor that is probably involved in carbohydrate metabolism. Mutations that regulate lac operon expression have been described in anaerobes, including lactobacilli and facultative anaerobic bacteria.9

In addition, the anaerobic microflora provides an important host defence by inhibiting the growth of potentially pathogenic microorganisms.10 Thus, the use of antianaerobic antibiotics in hospitalized patients may increase the risk for the acquisition and overgrowth of a variety of nosocomial and antibiotic-resistant bacteria, including vancomycin-resistant enterococci (VRE).10 In a recent multivariate analysis of risk factors for the isolation of daptomycin-non-susceptible versus daptomycin-susceptible VRE, the use of metronidazole in the past 3 months was a significant risk factor for the development of daptomycin resistance.11 In a recent case–control study at our institution, patients with de novo (no prior exposure to daptomycin) DNSE infection were significantly less likely to have received antianaerobic antibiotics in the prior 3 months compared with patients who developed DNSE infection after exposure to daptomycin (T. Kelesidis, A. Chow, R. Humphries, D. Uslan and D. Pegues, unpublished data).

Lastly, various anaerobes can have daptomycin non-susceptibility.12 However, it remains unknown whether there is gene transfer of daptomycin resistance factors between Enterococcus spp. and anaerobes. The above evidence may suggest a possible role of the interplay between anaerobes and enterococci in the dissemination of daptomycin resistance. Although King et al.2 do not report whether their patients were receiving antianaerobic antibiotics, this information may be important when evaluating cases of DNSE infections. Further studies are needed to confirm this hypothesis.

Transparency declarations
None to declare.

References