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Failure of combination therapy with daptomycin and synergistic ceftriaxone for enterococcal endocarditis

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Sir,

In their recent evaluation of daptomycin plus ceftriaxone using a simulated endocardial vegetation model, Snyder *et al.*[1] demonstrated *in vitro* synergy against enterococci. We recently treated an 84-year-old male for bioprosthetic valve infective endocarditis (IE) caused by *Enterococcus faecalis* with this regimen, resulting in relapse and death. While the *Enterococcus* was susceptible to ampicillin, vancomycin and daptomycin (MIC=1 mg/L), daptomycin (8 mg/kg intravenously daily) with synergistic ceftriaxone (2 g intravenously every 12 h) was chosen due to a penicillin allergy and barriers to administering vancomycin in an ambulatory setting. The patient appeared cured at the end of treatment, but experienced a relapse of IE 3 days later. Blood cultures were positive for *E. faecalis* with the same susceptibility pattern, except the daptomycin MIC, which had increased 4-fold to 4 mg/L. The patient died after undergoing surgical valve replacement. In this discussion, we offer practical considerations regarding daptomycin and synergistic ceftriaxone for the treatment of enterococcal IE.

Enterococcus is the third most common aetiological cause of IE, responsible for ~10% of cases.[2] Due to the rising prevalence of risk factors such as advanced age and prosthetic heart valves, the incidence of enterococcal IE is increasing.[3] Selecting a bactericidal antimicrobial regimen against enterococci is challenging. Synergistic therapy is required due to intrinsic low-level tolerance to penicillins, while increasing infection rates with strains highly resistant to aminoglycosides and MDR *Enterococcus faecium* further complicate pharmacotherapy decisions.[3] In addition, pragmatic considerations such as local availability of novel alternatives, tolerability of prolonged antibiotic courses and suitability of the regimen for home administration compound the problem. Daptomycin is a welcome addition to the armamentarium for enterococcal IE, especially as it circumvents issues of cross-reactivity, resistance and convenience while having a favourable adverse effect profile. Although its high cost poses a barrier, Snyder *et al.*[1] established that adding ceftriaxone to 6 mg/kg simulations of daptomycin resulted in a degree of activity similar to the 12 mg/kg regimen, suggesting that this combination may be daptomycin sparing. However, before addressing the details of a daptomycin-based regimen, it is important to acknowledge that daptomycin is not approved for the treatment of enterococcal IE, and experience remains limited to case reports. The majority of evidence is summarized by the retrospective, manufacturer-funded Cubicin Outcomes Registry and Experience (CORE) database, which describes 36 patients treated with daptomycin for enterococcal IE, with a cure rate of 78%.[4] In contrast, two separate independent reviews of enterococcal IE case reports noted failure in 5 of 7 and 7 of 10 patients, despite the frequent use of daptomycin with concomitant antibiotics.[5,6] In addition, a recent meta-analysis reported a disconcerting increase in mortality in daptomycin-treated patients with enterococcal bacteraemia.[7] Due to the inconsistency of these outcomes corroborated by our observations, we regard daptomycin as an experimental therapy best reserved for MDR *E. faecium* rather than a significant advancement in the treatment of enterococcal IE in general. Randomized studies evaluating the comparative efficacy of daptomycin, both as monotherapy and combination therapy, are urgently needed to establish its role in the treatment of enterococcal IE.

This case also adds to the growing body of evidence characterizing rapid emergence of daptomycin resistance in *Enterococcus* during treatment.[1,5,8] Previously, the loss of daptomycin susceptibility has been linked to lower doses (4–6 mg/kg),[5] but synergistic therapy that includes ceftriaxone is considered an effective preventative strategy.[1,8] Snyder *et al.*[1] demonstrated that, in an endocardial vegetation simulation model, 6 mg/kg daptomycin plus ceftriaxone for synergy is as effective as 12 mg/kg daptomycin alone in preventing resistance. Surprisingly, we observed a 4-fold MIC increase in our isolate despite the use of 8 mg/kg daptomycin with ceftriaxone. Hence, special consideration should be given to the dose of daptomycin in enterococcal IE. *In vitro* data support the use of 8–12 mg/kg in order to prevent the emergence of resistance in enterococci,[9] while published clinical experience confirms that, for IE, such high doses are considered standard.[4] Based on our experience, doses of 10–12 mg/kg appear most favourable considering daptomycin's post-antimicrobial effect, even as part of combination therapy. Regimens used in IE caused by *Staphylococcus aureus* cannot be used to benchmark doses for enterococci, which have higher MICs. Lastly, we cannot currently rely on employing synergistic ceftriaxone as a cost-saving strategy that permits the use of lower daptomycin doses.

The choice of ceftriaxone as a synergistic agent and its dosing also warrant scrutiny. Snyder *et al.*[1] concluded that 2 g of ceftriaxone intravenously daily provides synergy by enhancing daptomycin binding to the cell wall through alteration in surface charge. However, this mechanism was only observed against *E. faecium*, and while synergy was demonstrated against *E. faecalis*, it did not appear to occur via enhanced binding.[1] In contrast, one study testing synergy of various agents with daptomycin noted no synergy with the addition of ceftriaxone,[10] while another *in vitro* report showed that synergy with ceftriaxone was not consistent across different enterococcal strains.[11] Furthermore, a synergy study of ceftaroline against *E. faecalis* only demonstrated daptomycin synergy in the presence of 5 mg/L ceftaroline and not 1 mg/L,[9] which suggests that higher doses of cephalosporins may be beneficial. Disappointingly, our case resulted in treatment failure despite the use of high-dose ceftriaxone. Reproducible results with further insight into the mechanism of ceftriaxone synergy against *E. faecalis*, along with better characterization of the dose–effect relationship, would be helpful. In the meantime, agents that have been shown to be clinically effective, along with higher doses of cephalosporins, may be preferred for synergistic therapy with daptomycin until more data become available.

Considering the scarcity of effective therapy against enterococci and the need to preserve the utility of new agents, the findings of Snyder *et al*.[1] offer a promising potential therapy for enterococcal IE. However, until more positive clinical evidence is available, the combination of daptomycin and ceftriaxone remains hypothesis-generating, and many unanswered questions regarding daptomycin-based therapies for this infection remain.

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Transparency declarations

None to declare.

References

1 Snyder AH, Werth BJ, Barber KE *et al*. 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; **69**: 2148–54.

2 Murdoch DR, Corey GR, Hoen B *et al*. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis—Prospective Cohort Study. *Arch Intern Med* 2009; **169**: 463–73.

3 Munita JM, Cesar AA, Murray BE. Enterococcal endocarditis: can we win the war? *Curr Infect Dis Rep* 2012; **14**: 339–49.

4 Dohmen PM, Guleri A, Capone A *et al*. Daptomycin for the treatment of infective endocarditis: results from a European registry. *J Antimicrob Chemother* 2013; **68**: 936–42.

5 Cantón R, Ruiz-Garbajosa P, Chaves R *et al*. A potential role for daptomycin in enterococcal infections: what is the evidence? *J Antimicrob Chemother* 2010; **65**: 1126–36.

6 Segreti JA, Crank CW, Finney MS. Daptomycin for the treatment of Gram-positive bacteremia and infective endocarditis: a retrospective case series of 31 patients. *Pharmacotherapy* 2006; **26**: 347–52.

7 Balli EP, Venetis CA, Miyakis S. Linezolid versus daptomycin for treatment of vancomycin-resistant enterococcal bacteremia. *Antimicrob Agents Chemother* 2014; **58**: 734–8.

8 Sakoulas G, Nonejuie P, Nizet V *et al*. Treatment of high-level gentamicin-resistant *Enterococcus faecalis* endocarditis with daptomycin plus ceftaroline. *Antimicrob Agents Chemother* 2013; **57**: 4042–5.

9 Cha R, Grucz RG Jr, Rybak MJ. Daptomycin dose-effect relationship against resistant gram-positive organisms. *Antimicrob Agents Chemother* 2003; **47**: 1598–603.

10 Rand KH, Houck H. Daptomycin synergy with rifampicin and ampicillin against vancomycin-resistant enterococci. *J Antimicrob Chemother* 2004; **53**: 530–2.

11 Snydman DR, McDermott LA, Jacobus NB. Evaluation of *in vitro* interaction of daptomycin with gentamicin or β-lactam antibiotics against *Staphylococcus aureus* and enterococci by FIC index and timed-kill curves. *J Chemother* 2005; **17**: 614–21.