Sir,

In their recent evaluation of daptomycin plus ceftaroline 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 ceftaroline (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 ceftaroline 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 welcomed 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 ceftaroline 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 10 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 with drugs such as ceftaroline is considered an effective preventative strategy.1 Synergistic therapy with ceftriaxone was not consistent across different enterococcal strains.9 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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**References**

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**Successful use of ceftaroline for the treatment of MRSA meningitis secondary to an infectious complication of lumbar spine surgery**

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Sir,

MRSA meningitis is uncommon; however, it has a relatively high mortality rate. Treating MRSA meningitis is challenging because of limited available antimicrobial agents. We present a case of MRSA meningitis successfully treated with ceftaroline, a newer cephalosporin that has activity against MRSA.

A middle-aged woman was admitted with confusion for several days and a seizure episode. Her medical history included migrane headache, depression and chronic back pain. Three months prior to her presentation she underwent lumbar spine surgery, which was complicated with MRSA post-operative wound infection and treated with 2 weeks of oral antibiotics (trimethoprim/sulfamethoxazole). She was transferred to our neurosurgical ICU as a CT image of her head showed a small intracranial haemorrhage. On arrival she was incoherent, unable to provide a history and complaining of frontal headache and left ankle pain. She was febrile and had tachycardia with left ankle swelling and redness. Laboratory work revealed a white blood cell count of 20 × 10^9/L with a significantly elevated sedimentation rate and C-reactive protein. She was started on intravenous vancomycin and cindamycin for left ankle cellulitis. Admission blood cultures showed MRSA in all bottles. It was susceptible to vancomycin with an MIC of 1 mg/L. Her mental status deteriorated with increased lethargy requiring intubation for respiratory support. The patient continued to be febrile despite reduction of her white blood cell count to normal. MRI of the left ankle was negative for osteomyelitis while MRI of the lumbar spine showed epidural fluid collection at L3 with no evidence of bone involvement. A CT-guided fluid aspirate from the L3 site grew MRSA with a vancomycin MIC of 2 mg/L. Repeat blood cultures remained negative, but the patient continued to have fever and persistent confusion. CSF analysis