and treatment success for patients taking concomitant beta-lactams was 86% (n = 105/122). Logistic regression identified treatment failure to be associated with sepsis (OR: 3.42; p = 0.009) and an elevated daptomycin MIC (3–4 μg/ml) (OR: 3.23; p = 0.013) (Moise *et al.*, 2015). The lower efficacy with an MIC of 3–4 mg/l was confirmed later (Shukla *et al.*, 2016). No significant increase in clinical failure was seen among patients with elevated daptomycin MIC who received concomitant beta-lactam therapy (clinical success, 88% vs. 79% for MIC ≤ 2 vs. 3–4 μg/ml, respectively; p = 0.417) (Moise *et al.*, 2015). Daptomycin was effective in a case of VRE bacteremia. The efficacy is lower in cases with MICs of 3–4 mg/l, but this decrease in efficacy might be compensated for with the concomitant use of beta-lactam therapy.

Three systematic reviews with meta-analyses have been performed to compare daptomycin with linezolid in the treatment of VRE bacteremia (Whang *et al.*, 2013; Balli *et al.*, 2014; Chuang *et al.*, 2014). The entry criteria for the studies differed, but all three meta-analyses suggested a survival benefit of linezolid over daptomycin. In addition, significant methodological limitations to the underlying literature have been identified in these studies. The limitations of prior studies included variable case definitions, limited sample size, heterogeneous patient populations, wide variation in outcome measures, insufficient daptomycin dosing, and documented but unadjusted treatment selection bias (McKinnell and Arias, 2015). A relatively large retrospective study (N = 644) has also been performed comparing daptomycin (6 mg/kg) and linezolid, but it reported opposite results (Britt *et al.*, 2015). Linezolid was associated with a significantly higher risk of treatment failure compared with daptomycin (RR: 1.37; 95% CI: 1.13–1.67; p = 0.001). After adjusting for confounding factors in Poisson regression, the relationship between linezolid use and treatment failure persisted (adjusted RR: 1.15; 95% CI: 1.02–1.30; p = 0.026). Linezolid was also associated with higher 30-day mortality (42.9% vs. 33.5%; RR: 1.17; 95% CI: 1.04–1.32; p = 0.014) and microbiological failure rates (RR: 1.10; 95% CI: 1.02–1.18; p = 0.011). Although this study has been performed on patients treated only with daptomycin or linezolid—not those who received sequential treatment—there might be some bias between the treatment groups. The cohort of patients treated with linezolid may actually have been sicker than patients treated with daptomycin (McKinnell and Arias, 2015). The linezolid cohort had more patients in intensive care (84% vs. 71%; p < 0.001), higher median Acute Physiology and Chronic Health Evaluation II score (16 vs. 14; p = 0.005), and more mechanical ventilation (22% vs. 11%; p < 0.001). Therefore, a definite conclusion for the comparison between daptomycin and linezolid cannot be drawn.

Infective endocarditis

Although daptomycin can be used to treat right-sided IE caused by MSSA and MRSA, the clinical trial included limited data from patients with left-sided IE; outcomes in these patients were poor. Daptomycin has not been studied in patients with prosthetic valve endocarditis (Package Insert, 2007).

Data from the EU-CORE registry were collected for patients with IE who had received at least one dose of daptomycin between January 2006 and April 2012, across 18 countries in Europe (12), Latin America (5), and Asia (1). Of 6075 patients included in the EU-CORE registry, 610 were diagnosed with IE as primary infection; 149 (24.4%) had right-sided IE, 414 (67.9%) had left-sided IE, and 47 (7.7%) had both right- and left-sided IE. Overall clinical success was achieved in 80.0% of patients (right-sided IE, 88.6%; left-sided IE, 76.6%; and both right- and left-sided IE, 82.9%). Success rates for MRSA infections were 90.9%, 71.7%, and 66.6% in patients with right-sided IE, left-sided IE, and both right- and left-sided IE, respectively. The overall sustained clinical success rate in patients followed for up to 2 years was 86.7% (right-sided IE, 93.5%; left-sided IE, 88.3%; and both right- and left-sided IE, 77.8%) (Guleri *et al.*, 2015). The clinical success rates found by Kullar *et al.* (2013) were comparable in a much smaller study using a median daptomycin dose of 9.8 mg/kg.

Two studies in patients with endocarditis compared daptomycin with standard care, and the results were in disagreement. Among patients with left-sided IE due to *S. aureus*, coagulase-negative staphylococci, or *E. faecalis*, daptomycin (cohort A) was compared with standard-of-care antibiotics (cohort B). One of the outcomes was the time to clearance of bacteremia. There were 29 and 149 patients included in cohort A and cohort B, respectively. Baseline comorbidities did not differ between the two cohorts, except for a significantly higher prevalence of diabetes and previous episodes of IE among patients treated with daptomycin. The median daptomycin dose was 9.2 mg/kg of body weight per day. Median time to clearance of MRSA bacteremia was 1.0 day, irrespective of daptomycin dose, representing a significantly faster bacteremia clearance compared with standard of care (1.0 vs. 5.0 days; p < 0.01) (Carugati *et al.*, 2013). The other study compared daptomycin vs. ampicillin/ceftriaxone vs. conventional antibiotic regimens (ampicillin or vancomycin ± gentamicin) for enterococcal endocarditis in a limited number of patients and reported that patients taking daptomycin had longer duration of bacteremia (6 vs. 1 day; p < 0.01) (Cerón *et al.*, 2014).

Adding ceftaroline to daptomycin, as has been suggested in *in vitro* studies (Barber *et al.*, 2015; Smith *et al.*, 2015), has been shown to be beneficial in a an 81-year-old medically complex patient with persistent bacteremia due to daptomycin-nonsusceptible VISA native mitral valve endocarditis who was not an operative candidate (Baxi *et al.*, 2015).

CLINICAL FAILURES IN THE TREATMENT OF BACTEREMIA AND ENDOCARDITIS

Daptomycin susceptibility may decrease during treatment of persistent infections. In the bacteremia clinical trial (Fowler *et al.*, 2006), 7 of 120 daptomycin-treated patients (6 of whom had clinical failure) experienced increases in the daptomycin MIC while on therapy. Of the 53 vancomycin-treated patients, 9 had microbiological failure, 4 of whom experienced increases in vancomycin MIC. In 10 *S. aureus* isolates