

regimens had more activity compared with the vancomycin-containing regimens ( $p = 0.03$ ). Adding rifampicin or gentamicin to the daptomycin antagonized or delayed the bactericidal effect of daptomycin within the first 24 hours after start of treatment (LaPlante and Woodmansee, 2009). These results were supported by another study in rats showing that the combination of daptomycin with gentamicin was as effective in reducing the density of bacteria in valve vegetations as was daptomycin alone ( $p = 0.83$ ). The combination of daptomycin with rifampicin was less effective than daptomycin alone ( $p < 0.05$ ) (Miró *et al.*, 2009).

## HUMAN STUDIES OF BACTEREMIA AND ENDOCARDITIS

### MRSA bacteremia

An international open-label randomized controlled trial, the largest comparative trial of *S. aureus* bacteremia to date, included 246 (ITT) patients (21–91 years) with bacteremia and right-sided endocarditis due to MSSA or MRSA. Fowler *et al.* (2006) assessed the comparative clinical efficacy of daptomycin (6 mg/kg/day i.v.) vs. “conventional” therapy (initial low-dose gentamicin plus either antistaphylococcal penicillin or vancomycin) for the treatment of MSSA and MRSA bacteremia, including endocarditis. The minimum duration of treatment was determined by the initial diagnosis and lasted 10–42 days. The primary efficacy endpoint in this noninferiority trial was the blinded evaluation of clinical success rate in the two treatment groups, based on the modified ITT and per-protocol populations at the TOC visit 6 weeks after the end of treatment. Noninferiority of daptomycin was demonstrated when the lower limit of 95% CI for the between-group difference in clinical success rates was greater than –20% with 95% CI including 0%. The infecting organism was MRSA in 38% of patients in both treatment groups. Noninferiority of daptomycin was claimed in patients with bacteremia with or without IE. Clinical success rates were 44% vs. 42% for daptomycin vs. standard therapy, respectively, in the modified ITT population and 54% vs. 53%, respectively, in the per-protocol population. Overall survival rates did not differ either: 85% in the daptomycin group vs. 84% in the standard therapy group. No differences were found in the time to clearance of *S. aureus* bacteremia (median time to clearance, 4 and 3 days in patients with MSSA and 8 and 9 days in patients with MRSA). Daptomycin was well tolerated. Although 25% of patients had elevations in CPK, in only three patients did this lead to discontinuation of therapy. A high incidence of renal dysfunction was attributed to the addition of gentamicin for the first 4 days of therapy in the comparator group, who received vancomycin and/or beta-lactam therapy (Fowler *et al.*, 2006).

However, the study of Fowler *et al.* (2006) has a number of important limitations that restrict the interpretation of their findings (Grayson, 2006). First, although this trial was randomized, it was open label with a blinded assessment of the clinical outcome. Thus although bias in assessing treatment efficacy may have been controlled, bias in reporting and acting

on adverse events was not. Second, the study population was rather heterogeneous—a key focus of the study was staphylococcal endocarditis, yet only 29% (53 of 181) of patients who were initially thought to have endocarditis at enrollment were confirmed to have this as a final diagnosis, with a wide variety of nonendocarditis etiologies identified. Although the study aimed to recruit 90 evaluable patients in each treatment arm (to assess a potential treatment difference [ $\Delta$ ] of  $\geq 20\%$ ), only 79 (daptomycin) and 60 (comparator) patients were fully evaluable, and, surprisingly, at least one patient who did not have *S. aureus* bacteremia was included in the assessment of efficacy. Key outcomes of “clinical failure” and “microbiological failure” were not clearly described, and the definitions of complicated endocarditis and bacteremia were perplexing. Finally, about one third (6 of 19) of daptomycin-treated patients who suffered microbiological failure were found to have isolates that had developed resistance to daptomycin ( $\text{MIC} \geq 2 \text{ mg/l}$ ) (see [section 2b](#), Emerging resistance and cross-resistance, and the unnumbered section, Clinical failures in the treatment of bacteremia and endocarditis). Thus clinicians using this agent should be aware that if patients appear to be failing treatment, the emergence of resistance should be carefully assessed.

Several studies retrospectively compared the efficacy of vancomycin and daptomycin in the treatment of MRSA bacteremia. Weston *et al.* (2014) studied 150 patients (100 in the vancomycin arm and 50 in the daptomycin arm). Compared with vancomycin, the use of daptomycin was not significantly associated with treatment failure. These authors did not divide patients based on the vancomycin MIC. Three other studies included only patients infected with an MRSA strain with an MIC for vancomycin of at least 1 mg/l. These studies all reported a better outcome for daptomycin compared with vancomycin (Moore *et al.*, 2012; Murray *et al.*, 2013; Moise *et al.*, 2016). For example, Murray *et al.* (2013) included 170 patients. The rate of clinical failure at 30 days was significantly lower in the daptomycin arm compared with the vancomycin arm (20.0% vs. 48.2%;  $p < 0.001$ ). Both 30-day mortality and persistent bacteremia were significantly lower in the daptomycin group compared with the vancomycin group (3.5% vs. 12.9% [ $p = 0.047$ ] and 18.8% vs. 42.4% [ $p = 0.001$ ], respectively). Logistic regression confirmed the association between vancomycin treatment and increased risk of clinical failure (adjusted OR: 4.5; 95% CI: 2.1–9.8). Falcone *et al.* (2012b) included 106 patients and found a reduced length of hospitalization for the daptomycin-treated group compared with the glycopeptide group, possibly owing to a rapid resolution of the clinical syndrome. In all retrospective studies, many patients treated with daptomycin were previously treated with vancomycin. However, for MRSA, the duration of previous vancomycin treatment did not influence the daptomycin outcome (Culshaw *et al.*, 2015).

### VRE bacteremia

The efficacy of daptomycin with or without concomitant beta-lactams in the treatment of VRE was evaluated in 262 patients. Overall treatment success was 86% ( $n = 225/262$ ),