performed better than vancomycin and linezolid. In combination with rifampicin, both dosages of daptomycin were significantly better than the combinations with vancomycin and better than monotherapy. The human-simulated 10 mg/kg dose achieved better cure rates at 11 days compared with the human-simulated 6 mg/kg dose ($p < 0.05$). Resistant strains were found in the human-simulated 6 mg/kg dose group (Garrigós *et al.*, 2010). The increased efficacy of the combination of daptomycin with rifampicin has also been shown in a MRSA-infected knee prosthesis infection model in rabbits (Saleh-Mghir *et al.*, 2011). The beneficial effect of rifampicin added to daptomycin in foreign-body models is in contrast with the results of studies using experimental endocarditis models showing an antagonistic effect (Miró *et al.*, 2009).

The combination of daptomycin with gentamicin in an endocarditis model has been shown to be antagonistic in the treatment of MRSA (LaPlante *et al.*, 2015). In a study of foreign-body infection with *E. faecalis*, which employed various models such as an *in vitro* and a guinea pig model, the addition of gentamicin to daptomycin increased the cure rate from 25% for daptomycin monotherapy to 55% for the combination. Compared with vancomycin, daptomycin was more active, and the addition of gentamicin resulted in a more pronounced increase in cure rate in the daptomycin group (Furustrand Tafin, 2011). The difference in effect between the endocarditis model and the foreign-body model might be due to the infecting microorganism or to the model or type of infection itself.

EXPERIMENTAL OSTEOMYELITIS: COMBINATION THERAPY

Daptomycin and vancomycin were compared alone and in combination with rifampicin in an osteomyelitis model in rabbits over 4 days. Surviving bacteria were counted in bone, bone marrow, and joint fluid. Vancomycin and daptomycin as single therapies were ineffective, but both combinations were significantly more effective than the corresponding monotherapy. Bacterial eradication was achieved more often with the combination of daptomycin and rifampicin compared with the combination of vancomycin and rifampicin. Combination of daptomycin and rifampicin could prevent *S. aureus* from developing resistance. This combination could be a useful alternative for treating MRSA osteomyelitis at an early stage (Lefebvre *et al.*, 2010).

MRSA osteomyelitis in an experimental rat model compared the activity of daptomycin (60 mg/kg) and fosfomycin (40 mg/kg) and their combination. The rats were treated for 4 weeks. Fosfomycin was superior to daptomycin (in doses equal to ~8 mg/kg in humans). Positive bone cultures were found in 9 of 9 animals in the daptomycin group and 1 of 10 in the fosfomycin group. In the combination therapy group, 1 of 9 of the bone cultures was positive for MRSA after the treatment period. No synergistic or antagonistic effect was observed for the combination therapy (Poeppl *et al.*, 2011). However, more recently this study was repeated with lower fosfomycin doses (75 mg/kg) and the same dose of daptomycin. Based on bacterial counts in bones, treatment with daptomycin–fosfomycin was statistically significantly superior to fosfomycin monotherapy, daptomycin monotherapy, and no treatment ($p < 0.003$) (Lingscheid *et al.*, 2015).

CLINICAL DATA ON OSTEOARTICULAR INFECTIONS

A subgroup analysis of patients with osteoarticular infections from the *S. aureus* bacteremia trial (Fowler *et al.*, 2006) was performed. The clinical characteristics and outcomes for patients with osteoarticular infections were described using a *post hoc* analysis of an open-label randomized trial comparing daptomycin with standard therapy (vancomycin or antistaphylococcal penicillin with initial gentamicin) for the treatment of *S. aureus* bacteremia. Osteoarticular infection occurred in 32 of 121 patients (21 on daptomycin and 11 on standard therapy) with complicated *S. aureus* bacteremia (18 septic arthritis, 9 vertebral osteomyelitis, and 7 others). Two patients had osteomyelitis at more than one site. Success rates seen in the two treatment groups were as follows: vertebral osteomyelitis (3 of 5 [60%] daptomycin vs. 0 of 2 [0%] comparator), septic arthritis (7of 11 [64%] vs. 3 of 5 [60%]), sternal osteomyelitis (3 of 3 [100%] vs. 1 of 2 [50%]), and long bone osteomyelitis (0 of 1 [0%] vs. 1 of 1 [100%]). Success rates in both treatment groups improved with surgical therapy. CPK elevations to > 500 IU/l occurred in one patient receiving daptomycin who discontinued therapy, and renal impairment developed in three patients on standard therapy, two of whom discontinued therapy. Two patients treated with daptomycin and one patient on vancomycin had increases in *S. aureus* MICs to daptomycin and vancomycin, respectively. Three patients treated with daptomycin died after completion of therapy, with mortality attributed to multiple comorbid conditions and inadequate débridement of osteoarticular infections in these patients. No deaths were reported in the standard therapy group (Lalani *et al.*, 2008).

A prospective randomized controlled trial has been performed to compare two doses of daptomycin (6 mg/kg and 8 mg/kg) with the comparator (standard care, i.e. vancomycin, teicoplanin, or a semisynthetic penicillin). A group of 75 patients with a prosthetic joint infection undergoing a two-stage revision arthroplasty was studied. After prosthesis removal, patients received 6 weeks of antibiotic treatment followed by a 2- to 6-week antibiotic-free period before implantation of a new prosthesis. TOC was within 1 to 2 weeks after reimplantation. The primary objective was evaluation of CPK levels. Secondary objectives were clinical efficacy and microbiological assessments. Of 73 CPK safety population patients, CPK elevation of > 500 U/l occurred in 4 of 25 (16.0%) patients receiving daptomycin (6 mg/kg), in 5 of 23 (21.7%) patients receiving daptomycin (8 mg/kg), and in 2 of 25 (8.0%) comparator patients. Adverse event rates were similar among daptomycin and comparator groups. Among modified ITT patients at TOC, clinical success rates were 14 of 24 (58.3%) for 6 mg/kg of daptomycin, 14 of 23 (60.9%) for 8 mg/kg of daptomycin, and 8 of 21 (38.1%) for the comparator. Overall microbiological success at TOC was 12 of 24 (50.0%) for 6 mg/kg of daptomycin, 12 of 23 (52.2%) for