4.0 mg/kg for cSSSI (mean, 4.5 ± 1.0 mg/kg; range, 2.3–12 mg/kg) and 4.0 mg/kg for uSSSI (mean, 4.2 ± 0.8 mg/kg; range, 2.1–9 mg/kg); the dose was significantly higher in cSSSI ($p < 0.001$, median test). Median daptomycin treatment duration was 12 days and was longer for cSSSI than for uSSSI (14 vs. 10 days; $p = 0.002$) (Owens *et al.*, 2007).

7b. Staphylococcal bacteremia and endocarditis

CATHETER-RELATED BLOODSTREAM INFECTION

Catheter-related bloodstream infections are a major health problem. *In vitro* studies indicated that daptomycin (combinations) could be a good option in the treatment and prevention of these infections. Daptomycin was one of the antibiotics that resulted in a significant reduction in the viability of *S. aureus* biofilm formed over a 24-hour incubation period (Hogan *et al.*, 2016). The combination of daptomycin (5 mg/ml) plus ethanol and daptomycin (5 mg/ml) plus clarithromycin (5 mg/ml) prevented regrowth at 24 hours after removal for the catheter lock (Parra *et al.*, 2015). These results might support the use of daptomycin as antimicrobial lock therapy.

Animal studies supported this finding. Three different lock solutions were compared in an *S. aureus*–infected i.v. catheter model implanted in New Zealand white rabbits. The solutions with daptomycin (5 mg/ml), daptomycin (50 mg/ml), and vancomycin (10 mg/ml) were compared by determining the minimum biofilm eradication concentration. Daptomycin showed greater *in vitro* activity than vancomycin against biofilm bacteria. (Minimum biofilm eradication concentrations of vancomycin and daptomycin for MSSA were > 2000 mg/l and 7 mg/l, respectively; for MRSA, they were > 2000 mg/l and 15 mg/l, respectively.) Daptomycin (5 mg/ml) achieved significant reductions relative to vancomycin (10 mg/ml) in $\log_{10}$ CFUs recovered from catheter tips for both strains ($p < 0.05$). Only daptomycin (50 mg/ml) achieved negative catheter-tip cultures (up to 75% in MSSA and 85% in MRSA; $p < 0.05$), showing the greatest median $\log_{10}$ CFU reduction compared with controls (6.07 in MSSA and 6.59 in MRSA; $p < 0.05$) (Meije *et al.*, 2014). A study in rats using a central venous catheter biofilm model compared daptomycin lock therapy combined with systemic therapy to that of vancomycin. A methicillin-resistant *S. epidermidis*–infected central venous catheter was treated for 3 days with daptomycin or vancomycin lock therapy (18 hours at 5 mg/ml) with systemic dosing (40 mg/kg/day of daptomycin or 100 mg/kg/day of vancomycin). The regimens were equally effective 1 week post-therapy in maintaining cleared central venous catheters (90% [$n = 10$] vs. 100% [$n = 8$]). However, the lactated Ringer's formulation was superior to that of saline in sustaining the bacterial clearance of treated central venous catheters (83% vs. 50%) (Van Praagh, 2011).

Two retrospective studies evaluated the use of daptomycin lock therapy in combination with systemic administration. In one study 13 patients with long-term catheter-related bloodstream infections were evaluated. The primary endpoint used in this study was failure to cure the episode of long-term catheter-related bloodstream infection. Cure was defined as fever disappearance, negative blood cultures within 1 month after the end of treatment, and catheter salvage. Daptomycin lock therapy (5 mg/ml) was administered for a mean of 14 days (interquartilic range 10–14). I.v. daptomycin was administered in nine patients for a mean of 10 days (interquartilic range 5–11). Clinical cure and blood culture sterilization occurred in 11 of 13 patients (85%). Two patients had fever during treatment, and catheters were removed. Median length of followup in patients with therapeutic success was 67 days (interquartilic range 14–88) (Del Pozo *et al.*, 2012). The other evaluation included eight patients. The primary outcome was catheter maintenance, after clinical success and microbiological eradication. Eight patients who had failed previous standard therapy (7 vancomycin, 1 cefazolin) were included in the study. Daptomycin, given intravenously and as lock therapy, was successful in six of eight cases. The mean time to negative blood cultures was 2 days (range 1–6). In two cases neither clinical nor microbiological response was documented, and the catheter was removed (Tatarelli *et al.*, 2015). Although both studies included limited numbers of patients, they support the potential of daptomycin when used as catheter lock therapy.

EXPERIMENTAL ENDOCARDITIS

Daptomycin has been tested in rats with experimental endocarditis against an ampicillin- and vancomycin-susceptible *E. faecalis* strain, vancomycin-resistant (VanA type) mutant of the strain, and an ampicillin- and vancomycin-resistant (VanB type) *E. faecium* strain. Rats with catheter-induced aortic vegetations were treated with dosages simulating i.v. kinetics in humans of daptomycin (6 mg/kg every 24 hours), amoxicillin (2 g every 6 hours), vancomycin (1 g every 12 hours), or teicoplanin (12 mg/kg every 12 hours). Treatment was started 16 hours postinoculation and continued for 2 days. MICs of daptomycin were 1, 1, and 2 mg/l, respectively, for the three strains. In time-kill studies, daptomycin showed rapid (within 2 hours) bactericidal activity against all strains. Daptomycin was highly bound to rat serum proteins (89%). In the presence of 50% rat serum, simulating free concentrations, daptomycin killing was maintained but delayed (6–24 hours). *In vivo*, daptomycin treatment resulted in 10 of 12 (83%), 9 of 11 (82%), and 11 of 12 (91%) culture-negative vegetations in rats infected with the three strains, respectively ($p < 0.001$ compared with controls). Daptomycin efficacy was similar to that of amoxicillin and vancomycin for susceptible isolates. Daptomycin, however, was significantly ($p < 0.05$) more effective than teicoplanin against the glycopeptide-susceptible strain and superior to all comparators against resistant isolates. These results support the use of the newly proposed daptomycin dose of 6 mg/kg every 24 hours for the treatment of enterococcal infections in humans (Vouillamoz *et al.*, 2006).

The *in vitro* and *in vivo* efficacies of daptomycin against one MRSA clinical isolate with vancomycin MIC of 2 mg/l