

and ATCC 700788 VISA strain (vancomycin MIC 8 mg/l) was studied in a rabbit model of infective endocarditis (IE). Time-kill experiments had demonstrated that daptomycin was bactericidal *in vitro* against these two strains. The effect of daptomycin (6 mg/kg/day) was compared with the activities of a high-dose vancomycin regimen (1 g i.v. every 6 hours), the recommended dosage of vancomycin regimen (1 g i.v. every 12 hours) for 48 hours, and no treatment (control). Daptomycin was significantly more effective than the vancomycin recommended dose in reducing the density of bacteria in the vegetations for the MRSA strains (0 [interquartile range, 0–1.5] vs. 2 [interquartile range, 0–5.6] log CFU/g vegetation; $p = 0.02$) and VISA strains (2 [interquartile range, 0–2] vs. 6.6 [interquartile range, 2.0–6.9] log CFU/g vegetation; $p < 0.01$) studied. In addition, daptomycin sterilized more MRSA vegetations than the vancomycin recommended dose (13 of 18 [72%] vs. 7 of 20 [35%]; $p = 0.02$) and sterilized more VISA vegetations than either vancomycin regimen (12 of 19 [63%] vs. 4 of 20 [20%]; $p < 0.01$). No statistically significant difference between the high-dose vancomycin and the vancomycin recommended dose for MRSA treatment was noted. These results support the use of daptomycin for the treatment of aortic valve endocarditis caused by VISA and MRSA (Marco *et al.*, 2008).

The superiority of daptomycin over vancomycin as described for VISA and MRSA has also been shown for methicillin-resistant and glycopeptide-intermediate-susceptible *S. epidermidis*. An experimental rabbit endocarditis model with methicillin-resistant and glycopeptide-intermediate-susceptible *S. epidermidis* was used to compare daptomycin (doses of 6 mg/kg and 10 mg/kg) vs. vancomycin (1 g every 12 hours). Both doses of daptomycin sterilized more vegetations than vancomycin (9 of 15 [60%] and 11 of 15 [73%] vs. 3 of 16 [19%]; $p = 0.02$ and $p = 0.002$, respectively) (García-de-la-Mària *et al.*, 2010). However, in a study in rabbits using human-equivalent daptomycin doses of 6 mg/kg and 10 mg/kg, the higher dose was found to be more efficacious in eradicating *S. aureus*, with an MIC of 2 mg/l from endocardial vegetations compared with the 6 mg/kg dose. By using the high dose, a 3 log₁₀ kill was found, whereas there was no kill in the 6 mg/kg group (Chambers *et al.*, 2009).

In a rabbit endocarditis model, both of the fifth-generation cephalosporins ceftobiprole and ceftaroline were compared with daptomycin and were both found to be more efficacious than daptomycin. Residual organisms in vegetations were significantly fewer in ceftobiprole-treated animals than in the comparator groups, of which daptomycin was one ($p < 0.05$) (Tattevin *et al.*, 2010). Ceftaroline was also superior to daptomycin in terms of sterilization of the vegetations (Jacqueline *et al.*, 2011).

EXPERIMENTAL ENDOCARDITIS: COMBINATION THERAPY

Various combinations with daptomycin have been evaluated by using *in vitro* endocarditis models. One of the combinations is daptomycin with trimethoprim-sulfamethoxazole. The activity of high-dose daptomycin plus trimethoprim-

sulfamethoxazole de-escalated to high-dose daptomycin or trimethoprim-sulfamethoxazole was evaluated against four clinically daptomycin-nonsusceptible (MRSA) isolates in an *in vitro* pharmacokinetic/pharmacodynamic model of simulated endocardial vegetations. Simulated regimens included high-dose daptomycin at 10 mg/kg/day for 14 days, trimethoprim-sulfamethoxazole at 160/800 mg every 12 hours for 14 days, high-dose daptomycin plus trimethoprim-sulfamethoxazole for 14 days, and the combination for 7 days de-escalated to high-dose daptomycin for 7 days and de-escalated to trimethoprim-sulfamethoxazole for 7 days. Differences in CFU/g (at 168 and 336 hours) were evaluated. A ≥ 8 log₁₀ CFU/g decrease was observed with high-dose daptomycin plus trimethoprim-sulfamethoxazole against all strains (at 48 to 144 hours), which was maintained with de-escalation to high-dose daptomycin or trimethoprim-sulfamethoxazole at 336 hours. The combination for 14 days and the combination for 7 days de-escalated to high-dose daptomycin or trimethoprim-sulfamethoxazole were significantly better than daptomycin monotherapy ($p < 0.05$) and trimethoprim-sulfamethoxazole monotherapy ($p < 0.05$) at 168 and 336 hours. However, superiority of combination therapy including daptomycin over daptomycin monotherapy for the treatment of daptomycin-nonsusceptible microorganisms can be expected. Combination therapy followed by de-escalation offers a novel bactericidal therapeutic alternative for high-inoculum, serious MRSA infections (Steed *et al.*, 2012).

Another interesting combination is daptomycin combined with beta-lactams, such as ceftriaxone or oxacillin. In an experimental infectious endocarditis model with simulated endocardial vegetations, daptomycin was combined with ceftriaxone against VRE. Daptomycin (6 and 12 mg/kg/day) with and without 2 g of ceftriaxone every 24 hours was evaluated. Daptomycin (6 mg/kg) with ceftriaxone and daptomycin (12 mg/kg) alone and in combination with ceftriaxone displayed significantly more activity than daptomycin (6 mg/kg) alone from 48 to 96 hours ($p \leq 0.005$). The addition of ceftriaxone significantly enhanced the activity of daptomycin (6 mg/kg) against both strains and improved the activity of daptomycin (12 mg/kg) against one of the two strains at 96 hours. Daptomycin (12 mg/kg) plus ceftriaxone displayed no appreciable activity against one strain with a daptomycin MIC of 32 mg/l (Hall Snyder *et al.*, 2014). The combination of daptomycin with oxacillin improved the activity as compared with daptomycin monotherapy (doses equal to human doses of 6 mg/kg) as well (Yang *et al.*, 2010). More data, especially clinical, are needed to conclude whether this combination is beneficial. The combination of daptomycin plus ceftaroline also resulted in enhanced killing over monotherapy of one of the drugs in an *in vitro* endocarditis model with simulated endocardial vegetations (Werth *et al.*, 2014a).

An antagonistic effect between daptomycin and rifampicin and gentamicin has been shown. In one study, an experimental infectious endocarditis model with simulated endocardial vegetations was used to evaluate the use of daptomycin and vancomycin in combination with rifampicin or gentamicin in the treatment of MRSA. The daptomycin-containing