had not received antibiotics within 48 hours and after wound débridement. The activity of daptomycin (MIC_{90} 0.125–1 mg/l) against anaerobic Gram-positive cocci was similar to that of clindamycin (Goldstein *et al.*, 2006). In an earlier study by Goldstein *et al.* (2003), daptomycin (MIC_{90} 1 mg/l) was twofold more potent than vancomycin against 18 *C. difficile* isolates (Goldstein *et al.*, 2003).

OTHER GRAM-POSITIVE BACTERIA

Daptomycin had decreased activity (MIC < 4 mg/l) against 14 strains of *Actinomyces* spp. and all *Clostridium ramosum, Eubacterium lentum,* and *Lactobacillus plantarum* strains (Goldstein *et al.*, 2005). Daptomycin was twofold more potent against 10 penicillin-resistant *Corynebacterium jeikeium* strains (MIC_{90} 0.25 mg/l) than vancomycin (Goldstein *et al.*, 2003).

MISCELLANEOUS

Some *in vitro* studies indicated that there might be some activity of daptomycin against *Borrelia burgdorferi,* but the data are too diverse to use in clinical practice. In an *in vitro* study using 7- and 15-day-old stationary-phase cultures of *Borrelia burgdorferi*, an additional effect of doxycycline was suggested on biofilm-like structures to the combination of doxycycline and cefuroxime (Feng *et al.*, 2016). Daptomycin alone could not eliminate microcolonies, but the combination with doxycycline or beta-lactams was more effective (Feng *et al.*, 2015). Another study also showed the presence of persister cells in Lyme disease. Daptomycin kills stationary-phase cells but not the persisters. The presence of drug-tolerant persisters can explain the recalcitrance of chronic infections due to antimicrobial therapy (Sharma *et al.*, 2015). This is in contrast with a previous study showing that daptomycin did kill persisters more effectively than regular cells (Feng *et al.*, 2014).

2b. Emerging resistance and cross-resistance

In vitro experiments have demonstrated that bacterial resistance to daptomycin evolves occasionally (see section 5c, Clinically important pharmacokinetic and pharmacodynamic features). A subtle increase in MIC (within susceptible range) over time, also defined as MIC creep, has been described for vancomycin MICs of MRSA (see Chapter 43, Vancomycin). The emergence of resistance to daptomycin was studied using three different methods: high inocula, serial passage in the presence of increasing drug concentrations, and chemical mutagenesis. No spontaneously resistant mutants were obtained for any organism tested ($< 10^{-10}$ for *S. aureus*, $< 10^{-9}$ for *S. epidermidis*, $< 10^{-9}$ for *E. faecalis*, $< 10^{-9}$ for *E. faecium*, and $< 10^{-8}$ for *S. pneumoniae*). However, population analysis demonstrated that bacterial susceptibility to daptomycin is heterogeneous. Stable *S. aureus* mutants were isolated by both serial passage in liquid media and chemical mutagenesis. The daptomycin MICs for these isolates were 8- to 32-fold higher than for the parent strain. *In vivo* data showed that some daptomycin-resistant mutants had lost significant virulence. For other mutants, the degree of *in vitro* resistance was greater than the change in *in vivo* susceptibility (Silverman *et al.*, 2001).

The concentrations of daptomycin required to prevent the selection of resistant *S. aureus* are discussed later in section 5c, Clinically important pharmacokinetic and pharmacodynamic features—especially the mutant selection window (MSW) hypothesis, which has been tested using the pharmacodynamics of daptomycin and vancomycin by Firsov *et al.* (2006).

The impact of bacterial inoculum on the likelihood of emergence of daptomycin resistance has been assessed in detail. Daptomycin is able to kill high inocula of staphylococci and does not require cell division or active metabolism, most likely as a consequence of its direct action on the bacterial membrane (see section 3, Mechanism of action). In a kill-curve study with the MSSA strain ATCC 29213, daptomycin displayed concentration-dependent bactericidal activity against cultures in stationary phase (10^{10} colony forming units [CFUs]/ml)—requiring daptomycin (32 mg/l) to achieve a 3-log reduction. In a study comparing several antibiotics at concentrations of 100 mg/l, daptomycin demonstrated faster bactericidal activity than nafcillin, ciprofloxacin, gentamicin, and vancomycin. In experiments in which bacterial cell growth was halted by chemical treatment, daptomycin (10 mg/l) achieved the bactericidal endpoint (a 3-log reduction) within 2 hours. In contrast, ciprofloxacin (10 mg/l) did not produce bactericidal activity. Daptomycin (2 mg/l) remained bactericidal against cold-arrested *S. aureus*, which was protected from the actions of ciprofloxacin and nafcillin (Mascio *et al.*, 2007). In an *in vitro* 72-hour pharmacodynamic model with simulated endocardial vegetations, the impact of high (9.5 $\log_{10}$ CFU/g) and moderate (5.5 $\log_{10}$ CFU/g) inocula of MSSA and MRSA on the activity of daptomycin was compared with nafcillin, linezolid, vancomycin, and daptomycin, alone and in combination with gentamicin. Human therapeutic dosing regimens were simulated. At a moderate inoculum, daptomycin demonstrated significant ($p < 0.01$) bactericidal (99.9% kill) activity (decrease 3.34 ± 0.8 $\log_{10}$ CFU/g). Bactericidal activity was demonstrated at 4 hours against both MSSA and MRSA. At a high inoculum, daptomycin exhibited bactericidal activity against both MSSA and MRSA by 24 hours (decrease of 5.51–6.31 ± 0.10 $\log_{10}$ CFU/g). The addition of gentamicin increased the rate of 99.9% kill to 8 hours ($p < 0.01$). Overall, high-inoculum *S. aureus* had a significant impact on the activities of nafcillin and vancomycin. In contrast, daptomycin was affected minimally, and linezolid was not affected by inocula (LaPlante and Rybak, 2004).

Epidemiological studies on blood or invasive MRSA isolates have been conducted in two large US institutions. The first study over a 5-year period (2001–2005) using Etest MICs showed that daptomycin MICs increased slightly (but statistically) over time ($p = 0.0386$) (Steinkraus *et al.*, 2007). In the second study, the MICs and MBCs of daptomycin against invasive/blood MRSA isolates obtained during an 8-year period from 1999–2006 were assessed. The MIC_{50} was equal