a broader spectrum of activity. It is also active against resistant Gram-positive pathogens such as MRSA and VRE.

Despite the fact that daptomycin is only effective against Gram-positive microorganisms, the drug has been evaluated in combinations with other antibiotics for Gram-negative pathogens. Several studies indicate enhanced activity of colistin when combined with daptomycin for *Acinetobacter baumannii* (Phee *et al.*, 2013; Galani *et al.*, 2014; Córdoba *et al.*, 2015; Yang *et al.*, 2015). Another study showed some synergistic effect when daptomycin was added to aztreonam or ceftazidime (LaPlante and Sakoulas, 2009).

## AEROBIC GRAM-POSITIVE COCCI

Table 45.1 shows susceptibility data against aerobic Gram-positive bacteria from relatively recent, larger surveillance studies conducted in different parts of the world. Susceptibility data against anaerobic Gram-positive bacteria and unusual species are shown in Table 45.2. The tables include only those studies that have used Clinical and Laboratory Standards Institute (previously National Committee for Clinical Laboratory Standards; USA) methods or European Committee on Antimicrobial Susceptibility Testing (EUCAST) methods. EUCAST breakpoints and epidemiological cut-offs, if determined, are also listed in Table 45.1 and Table 45.2 (EUCAST, 2016).

Data from large surveillance studies in the USA show that between 2001 and 2003, all staphylococci isolates were inhibited at ≤ 1 mg/l (equal to the EUCAST and Clinical and Laboratory Standards Institute breakpoints) (Anastasiou *et al.*, 2008). In other reports (data from 2002–2006) from the USA and Canada, isolates from all staphylococcal species with nonsusceptible minimum inhibitory concentration (MIC) values (i.e. 2 mg/l) were rarely found (Pfaller *et al.*, 2007; Castanheira *et al.*, 2008). Surveillance data from the SENTRY Program platform 2005 (Europe, Turkey, and Israel) showed that all *S. aureus* strains were susceptible, and only one coagulase-negative strain (0.1%) showed an elevated daptomycin MIC of 4 mg/l (Sader *et al.*, 2007). In the Asia-Pacific region SENTRY program (2003–2004), daptomycin $MIC_{90}$ (0.5–1 mg/l), when tested against staphylococci, was twofold more potent than vancomycin (Biedenbach *et al.*, 2007). In a recent SENTRY report the distributions were similar (Sader *et al.*, 2014), although recently some strains with MICs have been reported (Sader *et al.*, 2015). In Greek hospitals, the $MIC_{50}$ and $MIC_{90}$ were comparable in 2008–2012 to earlier years and did not increase for methicillin-susceptible *Staphylococcus aureus* (MSSA), MRSA, methicillin-susceptible coagulase-negative staphylococcus, methicillin-resistant coagulase-negative staphylococcus, vancomycin-sensitive enterococci, and VRE (Papadimitriou-Olivgeris *et al.*, 2015).

The MIC for daptomycin (MIC range, 0.03–2 mg/l) against MSSA obtained between 1999 and 2006 was two to four times lower than for vancomycin and two to eight times lower than for linezolid (Hair and Keam, 2007). The new lipoglycopeptide dalbavancin is more potent than daptomycin. *S. aureus* daptomycin MIC distributions from 2006 compared with those of previous years did not show a "MIC creep" (Castanheira *et al.*, 2008).

The MIC range (≤ 0.06–2) for daptomycin against MRSA strains was similar to that for methicillin-susceptible isolates (Table 45.1). Anastasiou *et al.* (2008) reported on daptomycin susceptibility for 318 MRSA isolates from North America. All isolates were inhibited at ≤ 1 mg/l daptomycin. Community-acquired MRSA with known virulence factors ($n = 50$) and hospital-acquired multidrug-resistant *S. aureus* ($n = 268$) collected between 2001 and 2003 were equally susceptible (Table 45.1) (Anastasiou *et al.*, 2008). Tsuji *et al.* (2007) studied 200 isolates of community-acquired MRSA (SCCmec type IV) and 50 hospital-acquired MRSA isolates (HA-MRSA; SCC*mec* type II) of clinical origin obtained from infected patients at the Detroit Medical Center, Michigan. Daptomycin was four times more potent than vancomycin and levofloxacin, eight times more potent than linezolid, and of comparable potency with trimethoprim–sulfamethoxazole and clindamycin (Tsuji *et al.*, 2007). In an *in vitro* study that determined the activity of daptomycin against MRSA associated with endocarditis ($n = 37$) and bone and joint infections ($n = 31$), two MRSA isolates associated with bone and joint infections were found to be nonsusceptible to daptomycin (MIC 2 mg/l, minimal bactericidal concentration [MBC] 2 and 16 mg/l, respectively) (Rouse *et al.*, 2007).

*S. aureus* strains that are intermediately susceptible to glycopeptides, intermediately susceptible to vancomycin (vancomycin-intermediate *S.* aureus [VISA]), heterogeneously intermediately susceptible to glycopeptides, or heterogeneously intermediately susceptible to vancomycin (hVISA) constitute a growing clinical problem. Susceptibilities to hVISA strains are variable. Some authors report MICs in the susceptible range (Diederen *et al.*, 2006; Chin *et al.*, 2007; Samra *et al.*, 2007). Daptomycin MICs ranged from 0.125–1 mg/l against 50 hVISA/VISA strains, and MBCs were equal to MICs (Chin *et al.*, 2007). Thirty-two VISA strains from Israel had an MIC for daptomycin of ≤ 0.5 mg/l (Samra *et al.*, 2007). One of three VISA strains was not killed by daptomycin (MBC = 8 mg/l) (Fuchs *et al.*, 2002).

Daptomycin also retains activity against the few *S. aureus* strains that are resistant to vancomycin (VRSA; MIC > 8 mg/l). Daptomycin was active *in vitro* (MIC 0.125–0.5 mg/l) against the VRSA strains $VRSA_{MI}$ 2002, $VRSA_{MI}$ 2005, $VRSA_{PA}$ = Hershey, and $VRSA_{NY}$ and displayed good killing activity (MBC = MIC except for $VRSA_{MI}$ 2002). Similarly, linezolid and quinupristin–dalfopristin demonstrated some activity (MIC 0.25–2 mg/l) (Leuthner *et al.*, 2006; Chin *et al.*, 2007).

Daptomycin possesses good *in vitro* activity against *Streptococcus* spp., with an MIC range of 0.03–2 mg/l (Biedenbach *et al.*, 2007; Jones *et al.*, 2007; Pfaller *et al.*, 2007; Castanheira *et al.*, 2008). Beta-hemolytic streptococci ($MIC_{90}$ 0.5–1 mg/l) have lower MICs than viridans streptococci ($MIC_{90}$ 0.5–1 mg/l). Although streptococcal susceptibility to daptomycin is favorable compared with most antibiotics that are active against Gram-positive bacteria, one should keep in mind that penicillin (see Chapter 3, Benzylpenicillin [Penicillin G])