Table 8.2. Minimum inhibitory concentration (MIC) distributions for nafcillin among key species

Species	Reference	MIC (μg/ml)						
		0.125	0.25	0.5	1	2	4	8
Clostridium difficile	Wiedemann and Grimm (1996)			1			10	4
Staphylococcus aureus	Wiedemann and Grimm (1996)		2	15	18			
Staphylococcus aureus (penicillin-susceptible)	Barber and Waterworth (1964)	1	21	18				
Staphylococcus aureus (methicillin-susceptible)	Barber and Waterworth (1964)	3	41	68	3			
Staphylococcus epidermidis	Wiedemann and Grimm (1996)		23	81	34	24	5	

variety of other beta-lactams. MICs were determined by broth microdilution against 1238 MSSA isolates from US hospitals (Kang *et al.*, 2015).

2b. Emerging resistance and cross-resistance

In common with isoxazolyl penicillins, strains of *S. aureus* harboring the *mecA* gene encoding PBP2a are resistant to nafcillin as well as methicillin. Nafcillin susceptibility is also reduced in the setting of altered penicillin-binding proteins in *Streptococcus pneumoniae*, which confer reduced susceptibility or resistance to penicillin G, other penicillins, and cephalosporins. In regard to both, nafcillin resistance can be inferred from resistance to methicillin or oxacillin or the presence of *mecA* in *S. aureus* and coagulase-negative staphylococci, and by the presence of penicillin resistance in *S. pneumoniae*. Presumably, a situation analogous to that of *S. pneumoniae* applies to the viridans group of streptococci.

For a broader discussion about emerging resistance among staphylococcal strains to beta-lactam agents see Chapter 6, Methicillin, and Chapter 7, Isoxazolyl penicillins: oxacillin, cloxacillin, dicloxacillin and flucloxacillin, section 2a, Antimicrobial activity.

2c. *In vitro* assessment of synergy

Synergy between antistaphylococcal penicillins and aminoglycosides is readily demonstrated *in vitro* (Watanakunakorn and Glotzbecker, 1977; Eliopoulos and Moellering, 1996). A synergistic combination of nafcillin plus gentamicin had a superior therapeutic effect, compared with nafcillin alone in experimental animals (Fantin and Carbon, 1992). Furthermore, increased bactericidal activity can be shown between antistaphylococcal penicillins and gentamicin when these agents are co-administered to patients with *S. aureus* bacteremia (Licht, 1979).

Historically, the aminoglycosides have been the most commonly used agents in combination with antistaphylococcal penicillins to treat *S. aureus* infections. Synergy in an *in vitro* pharmacokinetics/pharmacodynamics (PK/PD) model was explored between vancomycin and nafcillin against *S. aureus,* including 25 heterogeneous vancomycin-intermediate *S. aureus* (hVISA), 2 methicillin-resistant *S. aureus* (MRSA), and 2 methicillin-susceptible *S. aureus* (MSSA strains). Potential for synergy was assessed by time kill at 0.5 times MIC in triplicate. The addition of nafcillin to vancomycin showed synergy in 92% of hVISA strains in time-kill analysis. Five hVISA strains were selected for the PK/PD model with a vancomycin MIC of 2 mg/l, while nafcillin MICs ranged from 4 to 256 mg/l. Strong enhancement in bacterial killing and organism burden at 72 hours was observed with the combination relative to either drug alone, despite nafcillin drug concentrations being below the MIC for most of the dosing interval. Similarly, the same enhanced killing was observed against MRSA and MSSA; however, the magnitude of the effect was much less for MSSA due to strong activity of nafcillin alone against MSSA (Leonard, 2012). The exact mechanism of synergy between nafcillin and vancomycin has not been elucidated. Because there are structural and mechanistic similarities between vancomycin and telavancin, Leonard *et al* (2013a) used the same model to examine synergy between telavancin (10 mg/kg/day) and nafcillin (2 g every 4 hours) against 30 strains of *S. aureus* (10 hVISA, 10 MRSA, 10 MSSA). In the time-kill studies, 70% of strains displayed synergy with nafcillin combined with telavancin; however, when methicillin-resistant strains (MRSA, hVISA) were separated from MSSA, the proportion of the strains demonstrating synergy was higher, 80% versus 50%. In the PK/PD model, the activity of the combination was superior to the individual drugs alone (Leonard *et al.*, 2013a).

Synergy between nafcillin and daptomycin was observed in 55% of 20 vancomycin-intermediate-resistant *S. aureus* (VISA) isolates tested by time kill at 0.5 times MIC in triplicate (Leonard *et al.*, 2013b). In the PK/PD model no benefit of this combination was seen in isolates with low daptomycin MIC (0.5 mg/l). However, for the isolates with daptomycin MICs of 1–2 mg/l, combination therapy was superior to either agent alone, this effect was more pronounced as the daptomycin MIC increased (highest with MIC of 2 mg/l) and the dose of daptomycin increased (highest with 10 mg/kg/day) (Leonard *et al.*, 2013b). In addition, the combination of nafcillin and daptomycin may significantly enhance the antibacterial activity of daptomycin against daptomycin nonsusceptible MRSA isolates (Steed *et al.*, 2010; Mehta *et al.,* 2012) and prevent the selection of daptomycin-resistant strains (Mehta *et al.,* 2012; see section 7a, *S. aureus* bacteremia and endocarditis).