2 weeks. In injecting drug users receiving the combination regimen, there was a slightly more rapid clinical response (defervescence and normalization of leukocyte count); mean time to clearance of bacteremia was not statistically faster with the combination regimen (2.9 days vs. 3.4 days). In the noninjecting drug users, mean time to clearance of bacteremia occurred after 2.8 days with the combination regimen compared to 4.1 days with nafcillin alone; however, there was a higher frequency of nephrotoxicity with the combination regimen. The addition of gentamicin did not alter morbidity or mortality in either group. The authors suggested that it may be reasonable to initiate combination therapy in patients with *S. aureus* endocarditis, but the aminoglycoside should be stopped after clearance of bacteremia (3–5 days) and that nafcillin alone be continued for a total of 6 weeks (Korzeniowski *et al.*, 1982). In another study, patients with *S. aureus* bacteremia (with or without endocarditis) were treated with nafcillin alone. Patients infected with tolerant organisms remained febrile longer than those infected with nontolerant strains, but they did not require additional antibiotics for cure (Rahal *et al.*, 1986). Injecting drug users with uncomplicated right-sided endocarditis have been treated successfully with a 2-week course of nafcillin plus synergistic doses of tobramycin (Chambers *et al.*, 1988). Cloxacillin at a dose of 2 g every 4 hours, even without gentamicin, has been shown to be effective for this condition provided patients are selected carefully (Ribera *et al.*, 1996).

A growing body of evidence suggests that addition of low-dose aminoglycosides in the treatment of *S. aureus* bacteremia and native valve endocarditis is unnecessary and may cause harm (Ribera *et al.*, 1996; Cosgrove *et al.*, 2009). The safety of synergistic doses of gentamicin added to antistaphylococcal penicillins or vancomycin for treatment of suspected *S. aureus* native valve endocarditis was evaluated in a prospective cohort study. Patients received either standard therapy (antistaphylococcal penicillin or vancomycin) plus gentamicin or daptomycin monotherapy. Renal adverse events occurred in 8 (7%) of daptomycin recipients, 10 (19%) of vancomycin recipients, and 11 (17%) of antistaphylococcal penicillin recipients (Cosgrove *et al.,* 2009). The addition of gentamicin for treatment of native valve endocarditis caused by *S. aureus* is no longer recommended in US or European guidelines; however, the combination of gentamicin with nafcillin or oxacillin plus rifampin is still recommended for prosthetic valve endocarditis (Baddour *et al.*, 2015; Habib *et al.*, 2015). Duration of gentamicin therapy is limited to the initial 2 weeks of therapy. In animal studies, the addition of rifampin was beneficial in sterilization of the foreign prosthetic material infected by *S. aureus* (see Chapter 126, Rifampin).

Nafcillin has been shown to increase killing of MRSA by selecting innate host defense peptides (HDPs) from keratinocytes, neutrophils, and platelets. Furthermore, nafcillin reduced MRSA virulence in a mouse subcutaneous infection model (Sakoulas *et al.,* 2014). This pharmacodynamics interaction with endogenous HDPs is not unique to nafcillin and was observed with other beta-lactam antibiotics against MRSA. Based on *in vitro* studies antistaphylococcal beta-lactams have shown to enhance activity of daptomycin against MRSA. The combination of nafcillin (2 g every 4 hours) and daptomycin (8–10 mg/kg/day) was evaluated for treatment of persistent MRSA bacteremia in six of seven reported cases, one patient received oxacillin and daptomycin. All patients achieved clinical cure and rapid microbiologic clearance. All isolates were daptomycin susceptible initially, but one developed resistance (MIC = 2–4 mg/l) during the therapy (Dhand *et al.*, 2011). However, *in vitro* daptomycin resistant isolate was reduced to susceptible in the presence of nafcillin, which can be explained by synergy demonstrated *in vitro* between the two agents (Leonard *et al.*, 2013b). Similarly, *in vitro* studies have demonstrated synergy between nafcillin and vancomycin; however, this combination has not been evaluated clinically. The combination of flucloxacillin and vancomycin was evaluated in patients with MRSA bacteremia; no significant impact on clinical outcomes was observed with this combination compared to vancomycin monotherapy (see Chapter 7, Isoxazolyl penicillins: oxacillin, cloxacillin, dicloxacillin and flucloxacillin). Adjunctive use of nafcillin to treat MRSA infections requires further evaluation.

7b. *S. aureus* bone and joint infections

Nafcillin is widely used for initial treatment of acute and chronic osteomyelitis caused by *S. aureus* (Kaplan *et al.*, 1982; Gentry and Rodriguez, 1990; Wynn *et al.*, 2005; Osmon *et al.*, 2013; Berbari *et al.*, 2015). A rifamycin–nafcillin combination has been used to treat chronic staphylococcal osteomyelitis, with a trend toward better outcomes; however, the advantages of this combination are not definitive (Norden *et al.*, 1986). In the USA nafcillin or oxacillin is the preferred therapy in combination with rifampicin for the treatment of prosthetic joint infections when hardware is retained or with one-stage exchange if *S. aureus* is susceptible to rifampicin (Osmon *et al.*, 2013).

7c. *S. aureus* CNS infection

Nafcillin has demonstrated good penetration into the CSF (see section 5b, Drug distribution) and has been successfully used for treatment of staphylococcal meningitis (Ruiz and Warner, 1976; Fossieck *et al.*, 1977). If nafcillin is used for this purpose, the parenteral dose should be at least 2 g every 4 hours for adults (Kane *et al.*, 1977; Quintiliani and Cooper, 1988). For the treatment of staphylococcal meningitis, a nafcillin–rifampicin combination was also effective (Gordon *et al.*, 1985).

7d. Coagulase-negative staphylococcus infections

Nafcillin can be used to treat severe hospital-acquired infections caused by these organisms, such as prosthetic valve endocarditis and prosthetic joint infections, provided the strain is