of MRSA and vancomycin-intermediate-resistant *S. aureus* (VISA) (Domaracki *et al.,* 2000; Werth *et al.,* 2013; Dilworth *et al.,* 2014). Of note, synergy between vancomycin and oxacillin has not been demonstrated with methicillin-susceptible *S. aureus* (MSSA) isolates (Joukhadar *et al.,* 2010). One potential mechanism of synergy is a phenomenon termed the "seesaw effect," in which a reduced susceptibility to vancomycin is accompanied by an enhanced susceptibility to oxacillin as a result of decreased transcription of the *mec*A gene (Ortwine *et al.,* 2013). However, data evaluating the clinical significance of this *in vitro* synergy are limited. A pilot study of 60 patients with MRSA bacteremia randomized to receive vancomycin monotherapy or combination therapy with vancomycin plus flucloxacillin i.v. (2 g every 6 hours) failed to show a statistically significant difference in duration of bacteremia, mortality or relapsed infection (Davis *et al.,* 2016).

Synergy between daptomycin and oxacillin has also been described. In an *in vitro* study of 18 clinical isolates of MRSA, time-kill studies demonstrated synergistic killing using concentrations of daptomycin that were one half the MIC and oxacillin concentrations of 32 mcg/ml. Synergy was also demonstrated in 61% of isolates with daptomycin concentrations at one fourth the MIC. For all isolates in this study, oxacillin MICs were ≥ 96 mcg/ml and daptomycin MICs were ≤ 1 mcg/ml. Yang *et al.* (2010) did not observe loss of *mec*A gene transcription as was previously described with the combination of vancomycin and beta-lactams, suggesting the mechanism of synergy is different for glycopeptides and lipopeptides. Animal studies have demonstrated improved cure rates in foreign-body infections with MRSA and MSSA using daptomycin plus cloxacillin as compared to daptomycin alone (Garrigos *et al.* 2012; El Haj *et al.,* 2014). Combination therapy with daptomycin and nafcillin has been evaluated in a small number of patients with MRSA bacteremia (see Chapter 8, Nafcillin).

5d. Excretion

Isoxazolyl penicillins are mainly excreted in the urine. After oral administration of cloxacillin, about 30% of the dose is excreted in this way (Stewart, 1965); a higher percentage of the dose is recoverable when it is administered i.m. Compared with cloxacillin, oral oxacillin is excreted to a lesser extent via the kidney, partly because of its poorer absorption and partly because more oxacillin is cleared by other mechanisms. Larger amounts of dicloxacillin and flucloxacillin are excreted in urine after oral administration because the absorption of these drugs is better than that of cloxacillin (Sutherland *et al*., 1970).

Antibacterially active metabolites of the isoxazolyl penicillins exist in serum and are excreted in urine (Thijssen and Mattie, 1976). Under normal conditions serum levels of these metabolites are low, representing only 9% of the total antibiotic serum concentration. In patients with markedly impaired renal function, metabolites may represent up to 50% of the total serum level. In healthy subjects, 10–23% of these penicillins excreted in urine are in the form of metabolites; higher percentages occur with oxacillin and lowest with flucloxacillin. As only small amounts of active metabolites are formed from the isoxazolyl penicillins, and these have similar activity to the parent drugs, they have no clinical significance.

Isoxazolyl penicillins are excreted by both glomerular filtration and tubular secretion. Probenecid can delay their excretion by partly blocking renal tubular secretion. Nauta *et al*. (1974) showed that the volume of distribution of cloxacillin in anephric patients was not significantly affected by probenecid, but it reduced cloxacillin elimination. This indicates that probenecid does not limit the access of penicillins to tissues, but it diminishes the extrarenal elimination of the penicillin via the liver. Isoxazolyl penicillins are eliminated by the biliary tract to some extent; this is more marked with oxacillin than with cloxacillin.

All the isoxazolyl penicillins are inactivated to some degree in the body, probably in the liver. Oxacillin is more rapidly destroyed in the body than the others, and therefore has little tendency to accumulate in patients with renal failure (Bulger *et al*., 1964).

5e. Drug interactions

Isoxazolyl penicillins have relatively few drug interactions, and none is considered predictable. There are occasional reports of interaction between oxacillin and methotrexate, with the former reducing the clearance of methotrexate and in one case leading to significant methotrexate toxicity (Titier *et al*., 2002). This interaction does not occur with flucloxacillin (Herrick *et al*., 1996). One case of reduced phenytoin levels resulting in status epilepticus has been attributed to oral oxacillin (Fincham *et al*., 1976). Dicloxacillin, cloxacillin, and flucloxacillin appear to reduce the effects of warfarin and prolong prothrombin times (Krstenansky *et al*., 1987; Mailloux *et al*., 1996; Choi *et al*., 2011; Khalili *et al.,* 2012). This has also been described with nafcillin (see Chapter 8, *Nafcillin*).

6. ADVERSE REACTIONS AND TOXICITY

6a. Hypersensitivity reactions

These drugs are generally contraindicated in penicillin-allergic patients, because they may evoke all the hypersensitivity reactions caused by penicillin G. Instances of patients who developed allergic reactions to cloxacillin but tolerated other beta-lactams have been reported (Dominguez-Ortega *et al*., 2006).

6b. Gastrointestinal side effects

Oral administration of isoxazolyl penicillins may cause nausea and diarrhea, which only occasionally necessitates cessation of treatment. Antibiotic-associated colitis due to *Clostridium difficile* can be caused by these drugs; toxin-producing *C. difficile* was isolated from the feces of one child who developed watery diarrhea with i.v. oxacillin therapy, and from another