of 4 g piperacillin and 0.5 g tazobactam, the latter is well distributed in many body fluids and tissues. The concentrations in fatty tissue and muscle have been estimated to be 10–13% and 18–30% of the levels in plasma, respectively. Adequate tazobactam concentrations are also reached in normal human bone tissue (Incavo *et al.*, 1994). High concentrations of tazobactam are reached in skin and gastrointestinal mucosa, where concentration of the drug exceeds the levels in plasma after 1 hour (Kinzig *et al.*, 1992). High tazobactam concentrations are also attained in lung tissue and bronchial secretions, but its concentration is lower in the gallbladder wall. High piperacillin levels are usually found in bile, but tazobactam bile concentrations are lower (1.33–42.9 μg/ml). In blister fluid, tazobactam reaches about half of the plasma concentration (Jehl *et al.*, 1994; Sorgel and Kinzig, 1993; Wise *et al.*, 1991). In inflamed soft tissue of patients with diabetic foot infections, adequate levels of both piperacillin and tazobactam were reported (Legat *et al.*, 2005). Among patients with noninflammatory occlusive hydrocephalus who have undergone external ventriculostomy, the AUC ratio of CSF/serum was 0.1 (Nau *et al.*, 1997). Thus the usual doses of tazobactam are probably insufficient to achieve adequate drug concentrations for the treatment of central nervous system infections.

In a phase I trial, the epithelial lining fluid/plasma AUC ratio for ceftolozane was 0.48 compared to 0.26 for piperacillin (Chandorkar *et al.*, 2012). With a plasma/epithelial lining fluid penetration ratio of approximately 50%, a doubling of the currently approved dose regimen is needed to achieve > 90% probability of target attainment for nosocomial pneumonia. Hence for patients with normal renal function 3 g ceftolozane–tazobactam i.v. every 8 hours was used in a clinical study of nosocomial pneumonia.

The binding of avibactam to human plasma proteins is low (5.7–8.2%). Among healthy volunteers, ceftazidime and avibactam penetrate into the bronchial epithelial lining fluid in proportion to the dose, with exposure to both drugs approximately 30% of plasma exposure (Nicolau *et al.*, 2015). Of note, the antimicrobial activity of ceftazidime–avibactam against beta-lactamase-producing Gram-negative pathogens remained unaltered *in vitro* in the presence of pulmonary surfactant at concentrations that antagonized the antimicrobial activity of daptomycin (Dallow *et al.*, 2014).

In phase I studies, the combination meropenem–vaborbactam showed adequate lung penetration, supporting its use in the treatment of lower respiratory tract infections caused by carbapenem-resistant Gram-negative pathogens (Wenzler *et al.*, 2015).

5c. Clinically important pharmacokinetic and pharmacodynamic features

For a detailed discussion about the clinically important pharmacokinetic/pharmacodynamic issues of the beta-lactamase inhibitors, see the relevant chapters of the drugs used in combination with beta-lactams.

The factor that determines the pharmacodynamic activity of both piperacillin and tazobactam is the time above the MIC. Using a Monte Carlo simulation model, piperacillin–tazobactam at a dose of 3.375 g every 6 hours resulted in a robust target attainment rate that exceeded 95% for MICs of ≤ 8 μg/ml (Lodise *et al.*, 2004). Drug administration every 4 hours had a superior pharmacodynamic profile and provided target attainment rates exceeding 95% for MICs of ≤ 16 μg/ml. Similar results were reported using a stochastic model (Ambrose *et al.*, 2003).

Ceftolozane–tazobactam demonstrates linear pharmacokinetics and the pharmacokinetic profile of tazobactam is not affected by the co-administration of ceftolozane (Miller *et al.*, 2012). The pharmacodynamic parameter of significance for the combination of ceftolozane and tazobactam is the percentage of time above the MIC (VanScoy *et al.*, 2013a; VanScoy *et al.*, 2013b). The pharmacokinetic features of ceftolozane–tazobactam have been described in a patient on continuous venovenous hemofiltration (Oliver *et al.*, 2015). A regimen of 1.5 g every 8 hours with an extended infusion rate of 4 hours maintained a free drug concentration above the MIC throughout the dosing interval.

Avibactam exposure generally increases proportionally to dose, and there is no trend for accumulation after multiple doses. Almost all avibactam is excreted largely unchanged in the urine within the first 6 hours after administration. Concomitant ceftazidime administration does not affect the safety and pharmacokinetic profile of avibactam (Merdjan *et al.*, 2015). Similarly, the pharmacokinetic and safety profiles of ceftaroline–avibactam demonstrate that the two drugs can be administered concomitantly (Riccobene *et al.*, 2013). The time above a threshold concentration is the parameter that best predicts the efficacy of avibactam.

Relebactam appears to exhibit a dose-dependent synergistic effect with imipenem until a certain plateau is reached; the relebactam concentration at which this plateau is reached varies, depending on bacterial strain (Mavridou *et al.*, 2015). There appears to be no relationship between peak concentration of relebactam and efficacy; rather, the total daily dose and AUC appear to show the highest correlation with outcomes.

The pharmacokinetic parameters of vaborbactam appear to be similar to those of most beta-lactam antibiotics, including a short half-life and low volume of distribution (Hecker *et al.*, 2015).

5d. Excretion

Some clavulanic acid is excreted in the urine in the active unchanged form. This occurs mainly by glomerular filtration. Tubular secretion plays only a minor, if any, role (Staniforth *et al.*, 1983). Probenecid does not delay the excretion of clavulanic acid. The fraction of an intravenously administered dose which is excreted unchanged in the urine approximates 50%. After oral administration, 18–38% of the dose is excreted unchanged in urine (Jacobs *et al.*, 1985; Nilsson-Ehle *et al.*, 1985). Approximately half of the total dose of clavulanic acid appears to be metabolized in the body. Clavulanic acid is relatively unstable at 37°C, and this may