comparator cephalosporins). The following adverse events have been reported: hypersensitivity reactions (angioedema, bronchospasm, malaise, possibly culminating in shock, may rarely occur), cutaneous (rash, pruritus, urticaria, erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis), gastrointestinal tract (nausea, vomiting, abdominal pain, diarrhea, pseudomembranous colitis), renal function (slight increases in serum creatinine, acute renal failure in rare cases), liver function (increased plasma levels of transaminases, gamma-glutamyl transferase, lactate dehydrogenase, bilirubin and/or alkaline phosphatase), blood constituents (thrombocytopenia, eosinophilia, and very rarely hemolytic anemia), local reactions (phlebitis, thrombophlebitis and pain at the site of injection), central nervous system (very few cases of convulsions, reversible encephalopathy, impairment of consciousness, abnormal movements, convulsions), cardiovascular system (hemorrhage, ecchymosis, and altered rhythm), respiratory (dyspnea), headache, fever, and taste and/or smell disturbances shortly after injection (Donaubauer and Mayer, 1992; Wiseman and Lamb, 1997).

CEFEPIME–TAZOBACTAM

Specific data are not yet publicly available for cefepime–tazobactam. Manufacturers refer to the same adverse reactions recorded for cefepime and other cephalosporin-class antibiotics. In a small study, Ghafur *et al.* (2012b) evaluated the clinical outcome of patients receiving cefepime–tazobactam. There were no significant side effects in any of the 32 patients assessed for safety.

7. CLINICAL USES OF THE DRUG

7a. Monotherapy for empiric treatment of febrile neutropenic patients

CEFEPIME

Cefepime is one of several recommended options for empiric therapy in patients with neutropenic fever (Averbuch *et al.*, 2013; Freifeld *et al.*, 2011). In a Cochrane meta-analysis of antipseudomonal beta-lactams for initial empirical treatment (21 trials, 3471 participants), all-cause mortality was significantly higher with cefepime as compared with other antibiotics (RR: 1.39; 95% CI: 1.04–1.86) (Paul *et al.,* 2010). The debate on mortality association was described earlier in the chapter. It is important that institutions perform regular surveillance of organisms (and their resistance patterns) involved in neutropenic fever. In the past, emphasis was put on high-dose cefepime (e.g. 6 g/day for adults with normal renal function) and on continuing directed therapy only when cefepime MIC of the infecting organism was low (≤ 2 μg/ml). Studies using PK-PD parameters have shown successful outcomes with cefepime (Rhodes *et al.*, 2015a; Rhodes *et al.*, 2015b; Siedner *et al.*, 2014). Therefore, depending on institutional policy, cefepime remains a suitable option for neutropenic fever.

However, it is uncertain whether in patients with neutropenic fever the risk of developing *Clostridium difficile* infection (CDI) is higher with cefepime compared to other antibiotics. A retrospective study investigated the CDI rate on a hematology/oncology ward before and after 2010, the year in which meropenem was replaced by cefepime as the institutional choice for empiric therapy for neutropenic fever. When comparing defined daily dose of antibiotics per 1000 bed-days, a linear regression model showed a significant increase in the trend of the CDI rate after the switch (Muldoon *et al.*, 2013). This statistical association warrants further investigations with patient-level data.

CEFPIROME

Cefpirome is an option among broad-spectrum beta-lactams for use in the empiric treatment of febrile episodes in neutropenic patients. Its efficacy is comparable to piperacillin–tazobactam. For instance, 208 febrile neutropenic episodes were randomized for treatment using either cefpirome 2 g every 12 hours (105 cases) or piperacillin–tazobactam 4 g every 8 hours (103 cases). Two days after initiation of antibiotics, clinical (fever disappearance) and microbiologic (culture negative) success rates were 62% and 50% for cefpirome vs. 61% and 55% for piperacillin–tazobactam, respectively. At the end of the protocol, the success rate was 59% with cefpirome vs. 50% with piperacillin–tazobactam (Bauduer *et al.*, 2001). In another study, 132 neutropenic patients received an i.v. dose of cefpirome of 2 g every 12 hours. Overall, clinical outcome improved after treatment in 89% of patients. The mean time of fever resolution was 3.1 days (Su *et al.*, 2007).

CEFEPIME–TAZOBACTAM

Data are not available for cefepime–tazobactam.

7b. Serious bacterial infections, including bacteremia and pneumonia

CEFEPIME

In serious infections, cefepime, in a starting dose of 2 g i.v. every 8 hours is recommended in patients with normal renal function. Dose adaptation should be made after clinical stabilization and on availability of the MIC of the infecting organism and cefepime serum trough level. Cefepime is a valuable option for ventilator-associated pneumonia (VAP) (Magnotti *et al.*, 2009) and infections with AmpC-producing Enterobacteriaceae and low MIC (Tamma *et al.*, 2013).

In the case of serious infections due to strains expressing high MICs against cefepime (e.g. *P. aeruginosa* with MIC ≥ 8 μg/ml, *Acinetobacter* spp., or ESBL producers), cefepime therapy might be unable to guarantee a good clinical outcome. A study evaluating cefepime exposures in patients infected with *P. aeruginosa*, included 56 patients with pneumonia (37), skin and skin structure infections (14), and bacteremia (5) (Crandon *et al.,* 2010). Twenty-four (42.9%)