lactamase producers and 17 vancomycin-resistant *Enterococcus faecalis*, ceftobiprole MIC values ranged from < 0.015 to 4 μg/ml, with MIC_{90} 1 μg/ml against 93 clinical isolates (Arias *et al.*, 2007). All beta-lactamase producers and vancomycin-resistant isolates were inhibited by ceftobiprole concentrations of ≤ 1 and ≤ 4 μg/ml , respectively, at the standard inoculum concentration (Arias *et al.*, 2007). Ceftobiprole exhibited synergism with aminoglycosides against selected isolates (Arias *et al.*, 2007).

Ceftobiprole generally has poor activity against *E. faecium*, with MIC_{90} 32 μg/ml (Deshpande and Jones, 2003; Green *et al.*, 2014; Hebeisen *et al.*, 2001; Jones *et al.*, 2002). Time-kill studies note that the activity of ceftobiprole with gentamicin is slightly enhanced (no synergy) or indifferent against staphylococci; this combination shows early synergy (4–8 hours), and indifference or synergy at 24 hours (no antagonism) for enterococci (Deshpande and Jones, 2003). Ceftobiprole and daptomycin have also demonstrated synergy in time-kill studies (Barber *et al.*, 2014; Werth *et al.*, 2015). Against six vancomycin resistant enterococci, ceftobiprole and ampicillin independently demonstrated synergy with daptomycin but not among the same strains (Werth *et al.*, 2015). Ceftobiprole plus daptomycin was the most potent combination against 20 MRSA isolates with varying vancomycin MICs compared to ceftobiprole and gentamicin, vancomycin, or rifampicin (Barber *et al.*, 2014).

The activity of ceftobiprole was compared to high-inoculum ($10^{6.4}$ to $10^{7.2}$ colony forming units (CFUs]) and low-inoculum ($10^{4.5}$ to $10^{5.7}$ CFUs) infections using a neutropenic mouse thigh model with four strains of *S. aureus* and two strains of *S. pneumoniae* (Lee *et al.*, 2013). For the *S. aureus* strains, the mean inoculum effect index (defined as the difference between high inoculum and low inoculum for static doses) for ceftobiprole was 2.9 (range: 1.7–4.6), which was the lowest among any of the agents tested (daptomycin, linezolid, and vancomycin) (Lee *et al.*, 2013). The indexes for ceftobiprole against the two *S. pneumoniae* strains were 1.3 and 3.3, which were similar to the other agents tested (Lee *et al.*, 2013).

GRAM-NEGATIVE ORGANISMS

Ceftobiprole demonstrates antibacterial activity against Enterobacteriaceae and resembles that of cefepime more closely than that of ceftazidime (Jones, 2007). As with cefepime, ceftobiprole activity was decreased among isolates of Gram-negative bacilli producing ESBLs and other class A, B, and D cephalosporinases (Green *et al.*, 2014; Hebeisen *et al.*, 2001; Pillar *et al.*, 2008; Queenan *et al.*, 2007; Rouse *et al.*, 2006).

Ceftobiprole demonstrates antibacterial activity against most Enterobacteriaceae lacking ESBLs (Green *et al.*, 2014; Hebeisen *et al.*, 2001; Issa *et al.*, 2004; Table 33.2). In a large study of clinical isolates, ceftobiprole inhibited 83.4% of 17,480 Enterobacteriaceae isolates at an MIC of ≤ 0.25 μg/ml (EUCAST definition of susceptible breakpoint) (Green *et al.*, 2014) It has comparable activity to cefepime and ceftriaxone against ESBL-negative *K. pneumoniae* (MIC_{90} ≤ 0.125 μg/ml for ceftobiprole and cefepime and 0.25 μg/ml for ceftriaxone) and ESBL-negative *Enterobacter cloacae* (≤ 0.125 μg/ml for all three compounds) (Issa *et al.*, 2004). These findings were confirmed in studies of ESBL-negative *K. pneumoniae, E. coli*, and *P. mirabilis* strains in which ceftobiprole $MIC_{50/90}$ values were 0.03–0.06 and 0.06–0.12 μg/ml, respectively, which were similar to the activities exhibited by cefepime and ceftriaxone (Green *et al.*, 2014; Issa *et al.*, 2004; Pillar *et al.*, 2008). In contrast, and as with other cephalosporins, *in vitro* activity of ceftobiprole against ESBL-positive strains of *E. coli*, *K. pneumoniae*, and *P. mirabilis* (MIC_{90} > 32 μg/ml) was notably diminished (Green *et al.*, 2014; Hebeisen *et al.*, 2001). However, there are some ESBL-positive strains with ceftobiprole MICs as low as ≤ 0.03 μg/ml (Hebeisen *et al.*, 2001), presumably because of preferential hydrolytic activity of certain ESBLs for certain cephalosporins.

Ceftobiprole has similar activity as cefepime against non-derepressed AmpC isolates of *E. cloacae* and *Citrobacter* spp. (Hebeisen *et al.*, 2001; Issa *et al.*, 2004; Pillar *et al.*, 2008). For AmpC-overexpressing Gram-negative bacilli, ceftobiprole, like cefepime, generally has lower MICs than other cephalosporins, such as ceftazidime and ceftriaxone (Pillar *et al.*, 2008; Queenan *et al.*, 2007). Cefepime tends to be more potent than ceftobiprole against derepressed AmpC-positive isolates (Hebeisen *et al.*, 2001; Pillar *et al.*, 2008). $MIC_{50/90}$ against derepressed AmpC-positive *E. cloacae* were 8 and > 32 μg/ml, respectively, for ceftobiprole; 4 and 16 μg/ml, respectively, for cefepime; > 32 and > 32 μg/ml, respectively, for ceftazidime; and > 64 and > 64 μg/ml, respectively, for ceftriaxone (Pillar *et al.*, 2008).

Ceftobiprole is also generally active against nonfermenting Gram-negative bacteria, such as *P. aeruginosa* and *A. baumannii*. Among 3434 *P. aeruginosa* isolates, ceftobiprole potency ($MIC_{50/90}$ = 2 and >8 μg/ml, respectively; 64.6% susceptible according to the EUCAST non-species-specific susceptibility breakpoint of 4 μg/ml) was similar to that of cefepime ($MIC_{50/90}$ = 4 and 16 μg/ml, respectively; 78.6% susceptible) and ceftazidime ($MIC_{50/90}$ = 2 and >16 μg/ml, respectively; 75.4% susceptible) (Green *et al.*, 2014). However, ceftobiprole and cefepime are less potent against ceftazidime-non-susceptible *P. aeruginosa* strains than against ceftazidime-susceptible strains (Farrell *et al.*, 2014a; Hebeisen *et al.*, 2001; Pillar *et al.*, 2008). Against 491 ceftazidime-susceptible strains, ceftobiprole MICs ranged from 0.03 to > 32 μg/ml, with MIC_{90} 8 μg/ml; against 130 ceftazidime-non-susceptible strains, MICs ranged from 0.25 to > 32 μg/ml, with MIC_{90} > 32 μg/ml (Pillar *et al.*, 2008). From a large collection of clinical isolates obtained between 2005 and 2010 and tested against 2588 ceftazidime-susceptible *P. aeruginosa* strains, ceftobiprole ($MIC_{50/90}$ = 2 and 8 μg/ml, respectively; range: ≤ 0.06 to >8 μg/ml) demonstrated significantly more potent activity than against 846 ceftazidime-non-susceptible strains ($MIC_{50/90}$ = > 8 μg/ml; range: 0.12 to > 8 μg/ml (Farrell *et al.*, 2014a).

In a recent study of 1146 *Acinetobacter* spp. isolates, ceftobiprole showed poor activity ($MIC_{50/90}$ > 8 and > 8 μg/ml,