Ceftolozane/tazobactam: a novel antipseudomonal cephalosporin and β-lactamase-inhibitor combination

Mai-Chi Hong1
Donald I Hsu1,2
Mark Bounthavong3,4
1Department of Pharmacy Practice and Administration, Western University of Health Sciences, Pomona, 2Department of Pharmacy, St Joseph Hospital, Orange, 3Department of Pharmacy, Veterans Affairs San Diego Healthcare System, San Diego, 4Department of Pharmacy Practice, University of California, San Diego, CA, USA

Abstract: The management of infections caused by multidrug-resistant Gram-negative bacteria, particularly Pseudomonas aeruginosa, continues to be a significant challenge to clinicians. Ceftolozane/tazobactam is a novel antibacterial and β-lactamase-inhibitor combination that has shown appreciable activity against wild-type Enterobacteriaceae and potent activity against P. aeruginosa. Moreover, ceftolozane/tazobactam has not demonstrated cross-resistance to other antimicrobial classes, particularly those affected by extended-spectrum β-lactamases, AmpC β-lactamase, a loss in porin channels, or the overexpression of efflux pumps in P. aeruginosa. Ceftolozane/tazobactam has completed two Phase II clinical trials in complicated intra-abdominal and complicated urinary tract infections. A Phase III, multicenter, prospective, randomized, open-label study has been initiated to evaluate the safety and efficacy of ceftolozane/tazobactam versus piperacillin/tazobactam for the treatment of ventilator-associated pneumonia. A Medline search of articles from inception to May 2013 and references for selected citations was conducted. Data from abstracts presented at conferences were also appraised. This article reviews the antimicrobial, pharmacokinetic, and pharmacodynamic profile of ceftolozane/tazobactam, and discusses its potential role in therapy.

Keywords: CXA-201, CXA-101, FR264205, Pseudomonas aeruginosa

Introduction
In the past decade, significant attention has been given to research on multidrug-resistant Gram-positive organisms, such as methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci, and associated treatment modalities.1–3 However, infections caused by resistant Gram-negative bacilli continue to cause significant morbidity and mortality without decline.4–6 A report from the Centers for Disease Control and Prevention estimated 1.7 million health care-associated infections in the US in 2002, with approximately 99,000 associated deaths.7 Emergence and spread of drug-resistant Gram-negative bacteria are particularly concerning.8–11 Health care-associated infections caused by resistant Gram-negative bacteria can lead to additional attributable hospital cost and length of stay of 29.3% and 23.8%, respectively, as reported in a single-center study.12

Pseudomonas aeruginosa is a leading nosocomial Gram-negative pathogen well known for its intrinsic as well as extraordinary ability to develop resistance to various antimicrobial agents. It can cause a wide array of infections, due to its multitude of cell-associated (eg, quorum sensing) and secreted virulence factors (eg, type III secretion system).13–17 Infections caused by P. aeruginosa remain a significant challenge to clinicians, given that therapeutic options are limited to a handful of agents in three...
major classes: antipseudomonal β-lactams, antipseudomonal fluoroquinolones, and aminoglycosides. Further complicating the matter is the rapid emergence of antibiotic-resistant strains of *P. aeruginosa*. Data from the 2004 National Nosocomial Infections Surveillance System Report summary showed increasing resistance rates to imipenem, quinolones, and ceftazidime. More specifically, the Centers for Disease Control and Prevention reported the prevalence of resistance to carbapenems, fluoroquinolones, and antipseudomonal extended-spectrum cephalosporins at 16.0%, 29.6%, and 23.3%, respectively, in a collection of strains that caused health care-associated infections. Of greater concern is the spread of multidrug-resistant strains of *P. aeruginosa* due to combinations of resistance mechanisms, including enzymatic degradation, decreased outer-membrane permeability, and efflux pumps, as the observed proportion of strains with resistance to three classes of antimicrobial agents was 10%. Infections caused by such strains are associated with severe outcomes, including increased mortality, increased length of hospital stay, and poorer functional capacity at discharge.

Control and Prevention reported the prevalence of resistance to carbapenems, fluoroquinolones, and antipseudomonal β-lactams, antipseudomonal extended-spectrum cephalosporins, ceftolozane is susceptible to enzymatic degradation by ESBLs and carbapenemases. The addition of amino groups to the 4-position of a 3-amino-2-methylpyrazole cephalosporin improved the minimum inhibitory concentration (MIC) values against AmpC β-lactamases. Additionally, a conformational restriction of the 4-position substituent on the pyrazolium ring of FR264205 decreased the potential for convulsion-inducing effects. The addition of tazobactam sodium, empiric for extended-spectrum cephalosporins, ceftolozane exhibits greater affinity for all essential PBPs (1b, 1c, 2, and 3), in comparison to ceftazidime and imipenem. Tazobactam is a β-lactam sulfone that inhibits most class A β-lactamases and some class C β-lactamases.

**In vitro activity**

Ceftolozane has favorable intrinsic activity against wild-type Enterobacteriaceae, and potent activity against *P. aeruginosa*, with MICs at four- to 16-fold dilutions below the comparative MICs for ceftazidime. However, similar to other extended-spectrum cephalosporins, ceftolozane is susceptible to enzymatic degradation by ESBLs and carbapenemases.

**Mechanism of action**

Ceftolozane/tazobactam is an intravenous cephalosporin combined with a β-lactamase inhibitor in a fixed 2:1 ratio. Similar to other cephalosporins, ceftolozane inhibits cell-wall synthesis via binding of PBPs. More specifically, ceftolozane has demonstrated increased stability to AmpC β-lactamases and is less affected by changes in porin permeability and efflux pumps due to enhanced binding of select penicillin-binding proteins (PBPs).

The addition of tazobactam in a 2:1 ratio broadens its spectrum of activity against β-lactamase-producing Enterobacteriaceae, including those producing extended-spectrum β-lactamases (ESBLs). The primary aim of this review is to provide an overview of this novel cephalosporin and β-lactamase-inhibitor combination, and evaluate its place in therapy.

**Pharmacology**

**Chemical structure**

Ceftolozane (previously referred to as FR264205 or CXA-101) is a novel oxyimino-aminothiazolyl cephalosporin that was developed via the introduction of amino groups to the 4-position of a 3-amino-2-methylpyrazole cephalosporin (Figure 1). The chemical structure of ceftolozane is shown in Figure 1. The addition of amino groups to the 4-position of a 3-amino-2-methylpyrazole cephalosporin broadens its activity to include select ESBL-producing organisms (Figure 2).
degrading enzymes, particularly those exhibiting the ESBL phenotype.\textsuperscript{26}

\textit{P. aeruginosa}

Data from the Program to Assess Ceftolozane/Tazobactam Susceptibility (PACTS) surveillance study have shown greater ceftolozane/tazobactam potency (two- to eightfold) for 973 clinical isolates of \textit{P. aeruginosa} in comparison with ceftazidime and cefepime. At an MIC of $\leq$8 mg/L, ceftolozane/tazobactam inhibited 97.7% of the isolates. Ceftazidime and cefepime inhibited 80.9% and 80.7% of \textit{P. aeruginosa} isolates using the Clinical and Laboratory Standards Institute (CLSI) breakpoint criteria of 8 mg/L.\textsuperscript{29} It should also be noted that ceftolozane/tazobactam retained activity against ceftazidime nonsusceptible strains (88.2% had an MIC of $\leq$8 mg/L), meropenem nonsusceptible strains (89.6% had an MIC of $\leq$8 mg/L), and strains with concomitant ceftazidime and meropenem nonsusceptibility (78.8% at an MIC of $\leq$8 mg/L).\textsuperscript{29} In a study examining the effects of various known resistance mechanisms on ceftolozane/tazobactam, the agent appears to be unaffected by upregulation of efflux pumps or loss of porin channels.\textsuperscript{27} \textit{P. aeruginosa} strains overexpressing multidrug efflux (Mex)-CD–opioid receptor (Opr)-J and MexEF-OprN resulted in a 16-fold increase in MIC to ciprofloxacin. However, overexpression of these efflux pumps, as well as MexAB-OprM, MexCD-OprJ, MexEF-OprN, and MexXY, in \textit{P. aeruginosa} did not appear to affect the MIC of ceftolozane in this study.\textsuperscript{27} Similarly, a 16-fold increase in MIC was observed for imipenem due to membrane impermeability (loss of OprD), while ceftolozane retained its activity against such strains.\textsuperscript{27} Stability of ceftolozane against porin OprD loss was also reported in other studies.\textsuperscript{26,27}

The activity of ceftolozane/tazobactam against 100 isolates of \textit{P. aeruginosa} (first and last available isolates) from 50 patients with cystic fibrosis was also evaluated.\textsuperscript{28} The MIC\textsubscript{50} and MIC\textsubscript{90} were 0.5 and 2 mg/L, respectively, with 95% of the isolates inhibited at MIC $\leq$ 8 mg/L. Ceftolozane/tazobactam maintained activity against a high distribution of isolates resistant to select antipseudomonal agents tested (ceftazidime, cefepime, imipenem, meropenem, levofloxacin, tobramycin, and piperacillin/tazobactam). In addition, ceftolozane/tazobactam retained some activity for multidrug resistant strains with MIC\textsubscript{50} and MIC\textsubscript{90} of 2 and 16 mg/L, respectively. It also conserved activity against 96% of the last isolates from each patient with MIC $\leq$ 8 mg/L. Cross-resistance from other antipseudomonal agents was not observed.

\textbf{Enterobacteriaceae}

The activity of ceftolozane/tazobactam against selected Gram-negative bacilli is outlined in Tables 1 and 2.\textsuperscript{29,30} Ceftolozane/tazobactam was tested against 1,244 US clinical isolates of \textit{Escherichia coli} in the PACTS surveillance study, with 99.3% of \textit{E. coli} strains inhibited by ceftolozane/tazobactam at the proposed MIC breakpoint of $\leq$8 mg/L. Comparatively, ceftriaxone and ceftazidime inhibited 87.7% and 91.5% of the isolates using the CLSI breakpoint criteria, respectively.\textsuperscript{29} Among the 840 strains of \textit{Klebsiella} spp. tested, 92.1% of strains were inhibited at a ceftolozane/tazobactam MIC of $\leq$8 mg/L. Using the established CLSI breakpoint, 84.4%, 86.2%, and 90.0% of the strains were inhibited by ceftriaxone, ceftazidime, and cefepime, respectively.

\textbf{β-lactamase-producing organisms}

Ceftolozane appears to be minimally affected by primitive β-lactamases, such as TEM-1, TEM-2, SHV-1, and OXA-1.\textsuperscript{27,36} However, its activity against ESBL-producing organisms is reduced. The addition of tazobactam enhanced the activity of ceftolozane against select ESBL-producing organisms in a concentration-dependent manner.\textsuperscript{26} In a checkerboard titration study of ceftolozane and tazobactam versus 57 ESBL-producing Enterobacteriaceae isolates, the addition of tazobactam at a concentration of 8 mg/L restored the MIC of ceftolozane to $\leq$4 and $\leq$8 mg/L in 76% and 93% of the isolates, respectively.\textsuperscript{26} In a larger collection of clinical isolates, data from the PACTS surveillance study suggest that the combination of ceftolozane and tazobactam retains activity against 91.1%, 60.3%, and 100.0% of \textit{E. coli}, \textit{K. pneumoniae}, and \textit{Proteus mirabilis} with the ESBL phenotype at an MIC of 4 mg/L, and 94.6%, 68.0%, and 100% at an MIC of 8 mg/L, respectively.\textsuperscript{29}

While ceftolozane is also susceptible to hydrolysis by the AmpC enzyme, the efficiency of hydrolysis may be dependent on the genus of the organism. In a checkerboard titration study of ceftolozane and tazobactam against 20 AmpC hyperproducing isolates, the MIC of ceftolozane was restored to $\leq$8 mg/L.
in 95% of the isolates at a tazobactam concentration of 8 mg/L.26 However, it should be noted that seven (35%) of the strains exhibited lower MICs to ceftolozane at baseline (MIC 1–2 mg/L) without the addition of tazobactam. This finding is consistent with a previous study that described the relative stability of ceftolozane to some AmpC enzymes, with fourfold-greater activity in comparison to ceftazidime.25,28

The activity of ceftolozane is compromised in the presence of carbapenemases, such as metallo-β-lactamases and K. pneumoniae carbapenemases. The addition of tazobactam does not appear to enhance the activity of ceftolozane against carbapenemase-producing organisms.26,27

**Pharmacokinetics**

Ceftolozane is parenterally administered and exhibits linear pharmacokinetics after single doses of 500/250 mg, 1,000/500 mg, and 2,000/1,000 mg, and multiple doses of 1,000/500 mg every 8 hours and 1,500/750 mg every 12 hours of ceftolozane/tazobactam.31,40 In healthy adults, the maximum plasma concentration (Cₘₐₓ) and plasma half-life (t½) for ceftolozane/tazobactam 1,000/500 mg and 2,000/1000 mg infused over 60 minutes given every 8 hours were 74.4 mg/L, 3.12 hours, and 117 mg/L, 2.67 hours, respectively.40,41 Accumulation of ceftolozane after multiple dosing was negligible.31,40,42 Ceftolozane is eliminated unchanged primarily through the urine (>90%).31,40,42 Pharmacokinetic parameters such as clearance, Cₘₐₓ, area under the curve (AUC), steady-state volume, and Cₘₐₓ are similar when tazobactam is coadministered with ceftolozane compared to ceftolozane alone.40 Minimal increases in AUC and t½ were observed in patients with mild renal impairment (creatinine clearance 60–89 mL/minute). In patients with moderate renal impairment (creatinine clearance 30–59 mL/minute), the observed increases in AUC and t½ were 2.6- and 2.1-fold for ceftolozane, and 2.0- and 1.6-fold for tazobactam, respectively.

As such, no dosage adjustment is required in patients with mild renal impairment. However, patients with moderate renal impairment may require a 50% dose reduction.43 The data describing the pharmacokinetic profile of ceftolozane/tazobactam in patients with severe renal insufficiency and hemodialysis have been submitted for presentation at a conference at the time of writing.

Ceftolozane/tazobactam exhibits rapid tissue distribution, including excellent lung penetration, and low protein

**Table 1** Comparative activity of ceftolozane/tazobactam against selected U.S. clinical Gram-negative bacilli

<table>
<thead>
<tr>
<th>Organism</th>
<th>Ceftolozane/ tazobactam</th>
<th>Ceftazidime</th>
<th>Cefepime</th>
<th>Meropenem</th>
<th>Piperacillin/ tazobactam</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>1/4</td>
<td>2/&gt;32</td>
<td>4/16</td>
<td>0.5/8</td>
<td>8/&gt;64</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>0.25/0.5</td>
<td>0.12/2</td>
<td>≤0.5/4</td>
<td>≤0.06</td>
<td>2/8</td>
</tr>
<tr>
<td><em>Klebsiella spp.</em></td>
<td>0.25/2</td>
<td>0.12/32</td>
<td>≤0.5/8</td>
<td>≤0.06</td>
<td>4/&gt;64</td>
</tr>
<tr>
<td><em>Enterobacter spp.</em></td>
<td>0.25/8</td>
<td>0.25/32</td>
<td>≤0.5/2</td>
<td>≤0.06</td>
<td>2/6</td>
</tr>
<tr>
<td><em>Serratia spp.</em></td>
<td>0.5/1</td>
<td>0.12/0.5</td>
<td>≤0.5/0.5</td>
<td>≤0.06</td>
<td>2/4</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>0.5/0.5</td>
<td>0.06/0.06</td>
<td>≤0.5/0.5</td>
<td>≤0.06</td>
<td>0.5/1</td>
</tr>
<tr>
<td><em>Citrobacter spp.</em></td>
<td>0.25/8</td>
<td>0.25/32</td>
<td>≤0.5/1</td>
<td>≤0.06</td>
<td>2/6</td>
</tr>
</tbody>
</table>

**Notes:** MIC breakpoint for ceftolozane/tazobactam has not been established. Data from Sader et al.29

**Abbreviations:** MIC, minimum inhibitory concentration.

**Table 2** Comparative activity of ceftolozane/tazobactam against selected European clinical Gram-negative bacilli

<table>
<thead>
<tr>
<th>Organism</th>
<th>Ceftolozane/ tazobactam</th>
<th>Ceftazidime</th>
<th>Cefepime</th>
<th>Meropenem</th>
<th>Piperacillin/ tazobactam</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>1/4</td>
<td>2/&gt;32</td>
<td>4/16</td>
<td>0.5/8</td>
<td>8/&gt;64</td>
</tr>
<tr>
<td><em>Escherichia coli</em> (non-ESBL)</td>
<td>0.25/0.25</td>
<td>0.12/0.25</td>
<td>≤0.5/0.5</td>
<td>≤0.06</td>
<td>2/8</td>
</tr>
<tr>
<td><em>Escherichia coli</em> (ESBL)</td>
<td>0.5/4</td>
<td>0.16/&gt;32</td>
<td>&gt;16/&gt;16</td>
<td>≤0.06</td>
<td>8/&gt;64</td>
</tr>
<tr>
<td><em>Klebsiella spp.</em> (non-ESBL)</td>
<td>0.25/0.5</td>
<td>0.12/0.5</td>
<td>≤0.5/0.5</td>
<td>≤0.06</td>
<td>2/8</td>
</tr>
<tr>
<td><em>Klebsiella spp.</em> (ESBL)</td>
<td>2/&gt;32</td>
<td>32/&gt;32</td>
<td>≤0.5/4</td>
<td>≤0.06</td>
<td>4/6</td>
</tr>
<tr>
<td><em>Enterobacter spp.</em></td>
<td>0.25/4</td>
<td>0.25/&gt;32</td>
<td>≤0.5/4</td>
<td>≤0.06</td>
<td>4/6</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>0.5/1</td>
<td>0.06/0.25</td>
<td>0.5/0.5</td>
<td>≤0.06</td>
<td>≤0.5/1</td>
</tr>
<tr>
<td><em>Citrobacter spp.</em></td>
<td>0.25/8</td>
<td>0.25/32</td>
<td>≤0.5/1</td>
<td>≤0.06</td>
<td>2/6</td>
</tr>
</tbody>
</table>

**Notes:** MIC breakpoint for ceftolozane/tazobactam has not been established. Data from Sader et al.29

**Abbreviations:** MIC, minimum inhibitory concentration; ESBL, extended-spectrum β-lactamase.
binding.31,41,44 The probability of achieving 40% time of unbound drug above the MIC of the organism (T > MIC) in plasma and epithelial lining fluid was observed in >90% of the simulated ventilator-associated pneumonia (VAP) population for important Gram-negative pathogens, such as P. aeruginosa, E. coli, and K. pneumoniae.41,44

Pharmacodynamics

The bactericidal potential of ceftolozane was characterized by evaluating the in vitro killing kinetics of P. aeruginosa strain PA01. A greater than 3-log reduction in bacterial load was observed after 8 hours at 1 × MIC (0.5 mg/L).33 In comparison to ceftazidime, ceftolozane initiated killing at two- to fourfold-lower multiples of MIC. Similarly, with the addition of tazobactam to ceftolozane, concentration-independent rapid bactericidal activity was observed against four isogenic strains of E. coli (wild type, β-lactamase-producing AmpC, CMY10, and ESBL CTX-M 15 strains), with 99.9% kill within 8 hours.45 In vivo infection models in neutropenic mice also revealed bactericidal activity against most organisms (four non-ESBL-producing E. coli and K. pneumonia strains, and four P. aeruginosa strains), with greater than 2-log reduction in bacterial load at 24 hours.46 The addition of tazobactam enhances the killing potential of ceftolozane against various β-lactamase-producing organisms. However, this observation is dependent on the dosing schedule of tazobactam. Bacterial reduction of greater than 2-log10 colony-forming units at 24 hours was observed when tazobactam was administered every 6 or every 8 hours. Administration of tazobactam every 12 or 24 hours resulted in much less bacterial killing (<2-log reduction) at 24 hours in comparison to administration every 6 or 8 hours.47

Similar to other cephalosporins, the pharmacodynamic parameter predicting bacteriological efficacy is the T > MIC of the organism. Ceftolozane/tazobactam concentrations remain above MIC approximately 40%–50% of the time between dosage administrations, similar to other cephalosporins.32 However, the percentage of T > MIC required for ceftolozane against Enterobacteriaceae and P. aeruginosa in an infected murine thigh model is much less than observed with other cephalosporins.46 The mean (±standard deviation) percentages of T > MIC required for stasis and 1-log kill of wild-type Enterobacteriaceae, Enterobacteriaceae-producing ESBLs, and P. aeruginosa were 26.3 ± 2.1 and 31.6 ± 1.6; 31.1 ± 4.9 and 34.8 ± 4.4; and 24.0 ± 3.3 and 31.5 ± 3.9, respectively.46

The probability of pharmacokinetic and pharmacodynamic target attainment was determined using Monte Carlo modeling. The simulated target attainment revealed that 50% T > MIC of 8 mg/L was achieved in 90% of the subjects with a 1,500 mg dose infused over 60 minutes, every 8 hours. Based on observed MIC distribution of select organisms in the 2008 surveillance data, a high probability of target attainment was observed for E. coli (MIC90 = 0.25), K. pneumoniae (MIC90 = 2), and P. aeruginosa (MIC90 = 2). Thus, ceftolozane/tazobactam demonstrated a high probability of target attainment using 50% T > MIC, supporting a proposed breakpoint of 8 mg/L.48

Resistance

Ceftolozane is predominantly active against Gram-negative bacteria. Takeda et al reported a lower frequency of spontaneous resistance of P. aeruginosa to ceftolozane compared to ceftazidime at concentrations of 4 ×, 8 ×, and 16 × MIC, as well as compared to imipenem and ciprofloxacin at 4 × MIC.27 More specifically, after five serial passages, a fourfold reduction in susceptibility was observed for ceftolozane. Comparatively, 32-, 16-, and 16-fold reductions in susceptibility were observed for ceftazidime, imipenem, and ciprofloxacin, respectively.44 The most significant mechanism is the production of β-lactamases with hydrolysis of ceftolozane. While ceftolozane has demonstrated stability against AmpC β-lactamases,28 the addition of tazobactam is necessary to improve its stability and activity against organisms producing ESBLs.29 However, significant hydrolysis is observed in organisms producing carbapenemases (metallo-β-lactamase and K. pneumoniae carbapenemase), despite the combination of ceftolozane and tazobactam.26

Ceftolozane/tazobactam has demonstrated minimal cross-resistance with other antimicrobials, as well as maintained susceptibility in some organisms that exhibit resistance to other antipseudomonal agents.49 More specifically, ceftolozane/tazobactam is unaffected by upregulation of efflux pumps or loss of porin channels that may affect selected antipseudomonal β-lactams, fluoroquinolones, and aminoglycosides.27 Overexpression of MexAB-OprM, MexCD-OprJ, MexEF-OprN, or MexXY in clinical isolates of P. aeruginosa did not increase the MIC of ceftolozane.27 Similarly, ceftolozane maintained its activity against imipenem-resistant clinical isolates of P. aeruginosa demonstrating loss of OprD.27

Clinical trials

A Phase II clinical trial evaluating the safety and efficacy of ceftolozane/tazobactam in the setting of complicated
Infection and Drug Resistance downloaded from https://www.dovepress.com/ by 54.70.40.11 on 28-Jul-2019
For personal use only.
Powered by TCPDF (www.tcpdf.org)

Hong et al

Adverse effects

The safety of ceftolozane/tazobactam has been evaluated in Phase I and II studies, which found the drug to be generally well tolerated. In 64 healthy volunteers who received single and multiple ascending infusions of ceftolozane/tazobactam, no serious adverse events requiring discontinuation of drug therapy or deaths were observed. The most common adverse event was peripheral infu

Discussion

The increasing prevalence of multidrug-resistant Gram-negative pathogens presents significant challenges to clinicians. The Antimicrobial Availability Task Force of the Infectious Diseases Society of America released a report titled “Bad Bugs, No Drugs: As Antibiotic R&D Stagnates, a Public Health Crisis Brews” to address the lack of antibi

mortality, particularly in strains demonstrating cross-resistance to the handful of agents with
clinical utility against *P. aeruginosa*. Currently, several β-lactam/β-lactamase-inhibitor combinations are in clinical development (ceftazidime/avibactam, ceftaroline/avibactam, and imipenem/cilastatin).

Ceftolozane/tazobactam is a novel antibacterial and β-lactamase-inhibitor combination consisting of ceftolozane, a novel antipseudomonal cephalosporin, and tazobactam, a well-established β-lactamase inhibitor. It has demonstrated potent bactericidal activity against select Gram-negative isolates, mainly wild-type Enterobacteriaceae and *P. aeruginosa*. The addition of tazobactam has enhanced the spectrum of ceftolozane to Enterobacteriaceae-producing select ESBLs. Moreover, ceftolozane/tazobactam has not demonstrated cross-resistance to other antimicrobial classes, particularly those affected by ESBLs, AmpC β-lactamase, a loss in porin channels, or the overexpression of efflux pumps in *P. aeruginosa*.

It is in this context that the utility of ceftolozane/tazobactam appears particularly attractive. The selection of antimicrobial agents in infectious settings where *P. aeruginosa* may be a likely pathogen requires careful review of the institution-specific antimicrobial susceptibility profile, an antibiogram. Specifically, in institutions lacking antipseudomonal agents with reliable susceptibility, a combination of agents (including agents with narrow therapeutic indices and high risk of toxicity) may be needed. Ceftolozane/tazobactam carries the potential to be a first-line agent in this setting, given its in vitro/in vivo data and favorable adverse-effects profile. In contrast, in institutions with favorable antipseudomonal susceptibility profiles, ceftolozane/tazobactam nonetheless requires serious consideration for addition to the formulary, for the management of challenging cases caused by strains with resistant phenotypes. However, given its early stage of development, the role of ceftolozane/tazobactam will be determined by the results of Phase III clinical data.

**Acknowledgments**

We would like to thank Philip Tam, PhD for building the chemical structures of ceftolozane and tazobactam. Chemical structures were developed using BKChem software (http://bkchem.zirael.org). We would also like to thank John Mohr, PharmD for provision of data.

**Disclosure**

The authors report no conflicts of interest in this work. Donald Hsu is a speaker for Astellas, Inc, Optimer Pharmaceuticals, and Merck Inc. The views expressed in this article are solely those of the authors and do not necessarily reflect the views of the Western University of Health Sciences, St Joseph Hospital Orange, Veterans Affairs San Diego Healthcare System, nor University of California San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences.

**References**


