

# Ceftolozane/tazobactam and ceftazidime/avibactam for the treatment of complicated intra-abdominal infections

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**Abstract:** Complicated intra-abdominal infections (cIAI) represent a large proportion of all hospital admissions and are a major cause of morbidity and mortality in the intensive care unit. Rising rates of multidrug resistant organisms (MDRO), including extended-spectrum  $\beta$ -lactamase producing Enterobacteriaceae and carbapenem-nonsusceptible *Pseudomonas* spp., for which there are few remaining active antimicrobial agents, pose an increased challenge to clinicians. Patients with frequent exposures to the health care system or multiple recurrent IAIs are at increased risk for MDRO; however, treatment options have traditionally been limited, in some cases necessitating the utilization of last-line agents with unfavorable side-effect profiles. Ceftolozane/tazobactam and ceftazidime/avibactam are two new cephalosporin and  $\beta$ -lactamase inhibitor combinations with recent US Food and Drug Administration approvals for the treatment of cIAI in combination with metronidazole. Ceftolozane/tazobactam has demonstrated excellent in vitro activity against MDR and extensively drug-resistant *Pseudomonas* spp., including carbapenem-nonsusceptible strains, while ceftazidime/avibactam effectively inhibits a broad range of  $\beta$ -lactamases, making it an excellent option for the treatment of carbapenem-resistant Enterobacteriaceae. Both agents were shown to be noninferior to meropenem for treatment of cIAI in Phase III trials; however, reduced responses in patients with renal impairment at baseline highlight the importance of routine serum creatinine monitoring and ongoing dose adjustments. This review highlights in vitro and in vivo data of these two agents and suggests their proper place in cIAI treatment to ensure adequate therapy in our most at-risk patients while sparing unnecessary use in patients without MDRO risk factors.

**Keywords:** resistance, antimicrobials, carbapenamase, *Pseudomonas aeruginosa*, KPC

## Introduction

### IAI and associated pathogens

Complicated intra-abdominal infections (cIAIs) are a common cause of hospital admission, with an estimated 300,000 US patients presenting each year with acute appendicitis alone. They also represent a common cause of morbidity and mortality within the intensive care unit (ICU) and are the number two cause of ICU mortality.<sup>1</sup> Although reported mortality rates are generally low in clinical trials of cIAI patients, potentially owing to the exclusion of patients with high disease severity scores from study enrollment, among patients with APACHE II scores >10, cIAI mortality rates may exceed 30%.<sup>2</sup> These infections are generally characterized as involving the perforation or necrosis of the gastrointestinal (GI) tract viscera, with resulting release of bacteria into the peritoneal and retroperitoneal space and associated abscess formation or peritonitis (Table 1). Uncomplicated IAIs are differentiated from cIAI by

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**Table 1** Complicated IAIs recognized by the FDA for inclusion in clinical trials

Diagnosis	Description
Intra-abdominal abscess	One or more abscess surrounding diseased or perforated viscera, often characterized by nonspecific abdominal pain
Perforation of stomach or intestine	Acute perforation of abdominal viscera associated with diffuse infection of the peritoneum, often characterized by nonspecific abdominal pain
Peritonitis	Diffuse infection of the peritoneum, often characterized by nonspecific abdominal pain
Appendicitis with perforation or periappendiceal abscess	Acute infection of the appendix characterized by colicky abdominal pain, often localized to the right lower quadrant
Cholecystitis with perforation or abscess	Acute infection extending beyond the gallbladder wall, often accompanied by right upper quadrant abdominal pain
Diverticulitis with perforation, peritonitis, or abscess	Acute infection of diverticula (herniation of mucosa or submucosa through the muscularis propria of the colon), most often characterized by left lower quadrant abdominal pain

**Note:** Data from US Food and Drug Administration.<sup>86</sup>

**Abbreviations:** IAI, intra-abdominal infection; FDA, US Food and Drug Administration.

only involving localized inflammation of the GI tract that is confined to a single organ. However, patients with uncomplicated IAIs are at risk of progressing to cIAI with time if inadequately treated.

Adequate treatment of cIAI requires the combination of operative or percutaneous surgical intervention to achieve adequate source control in conjunction with appropriate antimicrobial therapy. Owing to the multitude of organisms normally present in the GI tract, cIAI infections are often polymicrobial, with the most commonly implicated pathogens being aerobic or facultative anaerobic gram-negative bacteria, mainly *Escherichia coli* and other Enterobacteriaceae, derived from the natural gut microbiota. Gram-positive cocci, such as viridans group streptococci, and rarely *Enterococcus* spp., may also contribute to the infectious process. Additionally, anaerobic organisms such as *Bacteroides fragilis* are also frequently present and will require consideration when selecting antimicrobial therapy.<sup>1</sup>

Patients with exposures to the health care system, including patients residing in skilled nursing facilities, patients with hospital-associated intra-abdominal infection (HA-IAI), or patients with tertiary peritonitis present unique challenges, with causative organisms that can differ from the general community population and require empiric therapies with broader spectra of activity. Although the pathogens involved in community-acquired cIAI (CA-IAI) are primarily endogenous flora, patients hospitalized for >48 hours are at increased risk of infection with exogenous hospital-acquired pathogens, including resistant Enterobacteriaceae and *Pseudomonas aeruginosa*.<sup>3</sup> The more resistant microbiologic profiles of these patients may increase their risk for inadequate initial antibiotic therapy, which has been associated with worsened clinical outcomes in this population.<sup>4</sup> However, even when the organisms isolated are similar to those in CA-IAI,

HA-IAI patients may suffer from delayed diagnosis and experience infections of increased severity, with increased need for ICU management and clinical failure rates.<sup>5</sup> Tertiary peritonitis, persistent or recurrent IAI despite previous antibiotic treatment, has also been associated with the presence of nosocomial pathogens, as well as organisms not typically involved in the infectious process of CA-IAI such as *Enterococcus* spp. and *Candida* spp.<sup>6</sup> With these infections carrying a high risk of mortality, over 50% in one study, guideline recommendations support the broadening of antibiotic therapy empirically for these patients to appropriately account for the increased resistance profiles of the pathogens of concern.<sup>7</sup>

## A rising tide of resistance

Over the past decade, the increasing prevalence of bacteria resistant to front-line antimicrobial agents has presented new challenges to clinicians. Once rare, extended-spectrum  $\beta$ -lactamase (ESBL) producers now represent a significant proportion of all Enterobacteriaceae. Data from the Study for Monitoring Antimicrobial Resistance Trends showed an increase in the percentage of ESBL *E. coli* intra-abdominal isolates from 1.7% in 2005 to 7.3% in 2010 ( $P < 0.05$ ), with an even greater increase for *Klebsiella* spp. from 3.2% in 2005 to 13.1% in 2010 ( $P < 0.05$ ).<sup>8</sup> More recently, in a 3-year global surveillance program of hospitalized patients from 2012 to 2014 (INFORM), 15.7% (754/34,062) of all Enterobacteriaceae isolates were molecularly confirmed as ESBL producing, with similar results from 2011 to 2013 in US hospitals alone (12.4% of all Enterobacteriaceae, 1,696/13,692).<sup>9-11</sup> When stratified by infection type, ESBL rates of 10.4% for *E. coli* and 16.3% for *Klebsiella pneumoniae* have been observed for cIAI, consistent with overall prevalence.<sup>12</sup> Similar results were seen by Sader et al,<sup>13</sup> with an overall

**Table 2** Ambler  $\beta$ -lactamase classes

Ambler class	Type	Examples	Inhibited by ceftolozane/tazobactam	Inhibited by ceftazidime/avibactam
Class A	Serine $\beta$ -lactamases	CTX-M-type ESBL TEM-type-ESBL SHV-type ESBL KPC GES	Variable (not carbapenamases)	Yes (including carbapenamases)
Class B	Zinc-dependent metallo- $\beta$ -lactamases	NDM VIM IMP	No	No
Class C	Serine $\beta$ -lactamases	AmpC- $\beta$ -lactamases	Variable	Yes
Class D	Serine $\beta$ -lactamases	OXA-type-ESBL OXA-type-carbapenamases	No	Variable

**Note:** Data from.<sup>20,40,87</sup>

**Abbreviation:** ESBL, extended-spectrum  $\beta$ -lactamase.

rate of 11.1% for cIAI. Such numbers should be interpreted cautiously, as guidelines by the Infectious Diseases Society of America (IDSA) do not recommend routine culturing of the abdomen for CA-IAI except for patients at higher risk of harboring resistant bacteria or in the case of significant resistance of common community isolates to antibiotic regimens in widespread use.<sup>1</sup> Therefore, these data may be more reflective of the prevalence of resistant isolates among those patients already at high risk rather than the general population. Nevertheless, the increases seen in resistant phenotypes of these common cIAI organisms are understandably a cause of concern for clinicians. When looking specifically at the HA-IAI population across 21 US medical centers distributed across 12 states, the most common pathogens isolated were *E. coli* (34%), *K. pneumoniae* (18%), and *P. aeruginosa* (15%), with 8% of all Enterobacteriaceae characterized as multidrug resistant (MDR), standardly defined as nonsusceptibility to  $\geq 1$  antimicrobial agent in  $>3$  antimicrobial classes.<sup>14,15</sup> Additionally, 9% of all *E. coli* and 17% of all *K. pneumoniae* were ESBL producing, and ESBL *K. pneumoniae* were particularly resistant among these patients, with  $<65\%$  of isolates susceptible to carbapenems or amikacin,  $<23\%$  susceptible to cefepime, ceftazidime, or piperacillin/tazobactam, and  $<13\%$  remaining susceptible to fluoroquinolones.<sup>14</sup>

While antibiotics within the carbapenem class have a broad spectrum of antimicrobial activity and have traditionally been considered the agents of first choice for confirmed or suspected infection with ESBL producers, reports of carbapenem nonsusceptibility have also been increasing, representing 2.8% (961/34,062) of all Enterobacteriaceae based on INFORM data.<sup>9,10</sup> Treatment of *P. aeruginosa* is fraught with similar challenges, with 15.7% (310/1,971) of *P. aeruginosa* isolates collected 2011–2012 from 32 US

medical centers characterized as MDR. A similar percentage of all isolates were nonsusceptible to meropenem, a first-line agent for patients with suspected resistant *P. aeruginosa* infections. However, when looking exclusively at the MDR population, the percentage of meropenem-nonsusceptible isolates rose to 64.5%.<sup>16</sup> Concordantly, 11.3% of 155 cIAI *P. aeruginosa* isolates collected in 2012 from 59 US and European medical centers were characterized as extensively drug resistant (XDR), ie, nonsusceptible to  $\geq 1$  agent in all but  $\leq 2$  antimicrobial classes, with overall meropenem nonsusceptibility of  $\geq 16.7\%$ .<sup>13,15</sup>

Carbapenem nonsusceptibility typically occurs by one of two mechanisms: carbapenemase production (KPC, OXA, VIM, IMP, and NDM  $\beta$ -lactamases) or via the hyperproduction of AmpC  $\beta$ -lactamase or ESBL coupled with changes in porin permeability that decrease the ability of the antibiotic to reach its bacterial target.<sup>17</sup> The different  $\beta$ -lactamase enzymes have been organized into four classes, with different implications for drug therapy (Table 2). Effective treatment of carbapenem nonsusceptible bacteria and other MDR organisms requires antibiotic therapies engineered to overcome these resistance mechanisms. Ceftolozane/tazobactam and ceftazidime/avibactam are the first cephalosporin and  $\beta$ -lactamase inhibitor combinations approved by the US Food and Drug Administration (FDA). Like other  $\beta$ -lactam antibiotics, ceftolozane/tazobactam and ceftazidime/avibactam are bactericidal inhibitors of bacterial cell wall synthesis and may have utility for the treatment of cIAI caused by resistant *P. aeruginosa* and Enterobacteriaceae.

## Ceftolozane/tazobactam Background

Ceftolozane/tazobactam (Zerbaxa; Merck & Co., Kenilworth, NJ, USA) was approved by the FDA in December 2014 and has

indications for the treatment of cIAI in combination with metronidazole and for complicated urinary tract infections. The combination contains the novel cephalosporin ceftolozane paired with the established  $\beta$ -lactamase inhibitor tazobactam, and is administered intravenously. Ceftolozane is structurally similar to the third-generation cephalosporin ceftazidime, but with a modified side chain conferring enhanced activity against *P. aeruginosa* via increased resistance to hydrolysis and efflux. Tazobactam, which has decades of use as part of the  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combination piperacillin/tazobactam, restores ceftolozane activity in the presence of most class A and some class C  $\beta$ -lactamases, and was more potent than the  $\beta$ -lactamase inhibitors sulbactam or clavulanate at reducing enzymatic activity by 50% against TEM-1, CTX-M-14, or CTX-M-15.<sup>18–20</sup>

## In vitro activity

### *Escherichia coli* and *Klebsiella pneumoniae*

The combination of ceftolozane/tazobactam is generally highly effective against Enterobacteriaceae commonly associated with cIAI, though with unreliable activity against ESBL producers. In a sample of over 300 US and European isolates of *E. coli* from hospitalized patients with cIAI, 97.7% were inhibited at a ceftolozane/tazobactam MIC of  $\leq 2$  mg/L; however, activity was notably reduced against MDR and ESBL-producing strains (62.5% and 78.9% inhibited, respectively). With respect to  $\beta$ -lactam comparators, 80.3% of isolates were susceptible to levofloxacin, 88.9% to ceftriaxone, 92.1% to cefepime and ceftazidime, 92.7% to piperacillin/tazobactam, and 100% to meropenem, with only meropenem having appreciable activity against MDR *E. coli* (100% versus  $< 40\%$ ). Among *K. pneumoniae* isolated from the same study, while most strains were susceptible (87.3% inhibited at MIC  $\leq 2$  mg/L, with only meropenem having a greater percentage of susceptible isolates among  $\beta$ -lactam comparators at 92.9%), again MDR and ESBL strains exhibited reduced susceptibilities, only 28.6% and 63.6%, respectively. Comparator antibiotics performed poorly as well; only 57.1% of MDR isolates were susceptible to meropenem, and only tigecycline and colistin with susceptibilities  $> 90\%$ .<sup>13</sup> These results are concordant with other in vitro studies, which show excellent activity of ceftolozane/tazobactam against *E. coli* (the most common organism associated with cIAI), though with higher MICs against CTX-M-15  $\beta$ -lactamase producers; however, activity against *K. pneumoniae* in vitro was more variable than *E. coli*, with SHV-5 and CTX-M-15 producing strains demonstrating higher MICs despite the presence of tazobactam.<sup>21–23</sup> It is important to note that

overall susceptibilities and ESBL prevalence and resistance patterns may vary widely by geographic region. In the previous surveillance study of US and European centers, ESBL producers represented 11.1%–12.8% of *E. coli* and 23.8%–27.2% of *K. pneumoniae*, with *E. coli* isolated nearly three times more frequently. Therefore, even with only partial (60%–80%) ESBL activity, overall susceptibility to ceftolozane/tazobactam appears excellent ( $> 95\%$ ).<sup>13</sup> However, this may not be true for all geographic regions. As a comparison, in one US study, ceftolozane/tazobactam was active against 71% of ESBL-producing *K. pneumoniae*, representing 10.6% of all *K. pneumoniae* across 44 hospitals, while in a similar study conducted in Spain this percentage dropped to a dismal 43.8%, with ESBL-producers representing over 15% of all *K. pneumoniae* isolates.<sup>23,24</sup> Given this potential for significant regional variation in ESBL susceptibility profiles, local susceptibility testing is recommended. Overall, ceftolozane/tazobactam demonstrates high in vitro activity against Enterobacteriaceae commonly associated with cIAI; however, its activity is only variable against ESBL producers, potentially limiting the utility of ceftolozane/tazobactam as empiric therapy for patients with significant ESBL risk factors.

### *Pseudomonas aeruginosa*

In contrast, ceftolozane/tazobactam has demonstrated consistently potent activity against *P. aeruginosa* in in vitro studies, including against isolates highly resistant to other  $\beta$ -lactams. In a highly resistant population of *P. aeruginosa* isolates (39.1% MDR, 11.6% sensitive only to colistin) from 31 medical centers across 13 European countries, ceftolozane/tazobactam was the most active agent tested, inhibiting 84.5% of isolates at an MIC of  $\leq 4$  mg/L.<sup>25</sup> In an in vitro assessment of activity of ceftolozane/tazobactam and comparators against *P. aeruginosa* from US and European cIAI inpatients, ceftolozane/tazobactam was the most active  $\beta$ -lactam agent tested, with 4-fold greater activity than ceftazidime, 16-fold greater activity than piperacillin/tazobactam, and up to 2-fold greater activity than meropenem. Overall susceptibility (93.9%) was over 10% higher than other  $\beta$ -lactams, and comparable to amikacin (93.9%–95.7%) and colistin (98.3%). High potency was retained against isolates resistant to other  $\beta$ -lactams, including meropenem, and 53.8% of XDR isolates were inhibited at an MIC of  $\leq 4$  mg/L.<sup>13</sup> These results were consistent with those by Tato et al,<sup>23</sup> where ceftolozane, with or without tazobactam, was again the most potent agent tested against 500 *P. aeruginosa* isolates across a variety of infection types, including cIAI.<sup>23</sup> Ceftolozane/tazobactam was  $\geq 8$ -fold more active than ceftazidime, cefepime, or piperacillin/tazobactam



and  $\geq 2$ -fold more active than meropenem, irrespective of resistance phenotype. In an analysis of 1,044 *P. aeruginosa* non-urine isolates across 40 US hospitals selected to represent clinically important resistance phenotypes (imipenem resistance, ceftazidime resistance, piperacillin/tazobactam resistance, tobramycin resistance, and resistance to three or more drug classes), the activity of ceftolozane/tazobactam again was demonstrated to be 4- to 10-fold higher than that of comparators and was more active than imipenem against MDR.<sup>26</sup> This high degree of activity against *P. aeruginosa* appears to be preserved irrespective of resistance to carbapenems or other  $\beta$ -lactam agents or ICU versus non-ICU, with good activity against MDR and XDR in multiple studies, making ceftolozane/tazobactam a reliable option for the treatment of resistant *P. aeruginosa* infections.<sup>16,24,27–30</sup>

### Anaerobes

While  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations with  $\beta$ -lactams of the penicillin class (eg, amoxicillin/clavulanate, ampicillin/sulbactam, and piperacillin/tazobactam) are highly effective against anaerobic bacteria, ceftolozane has poor intrinsic activity against *Bacteroides* spp., the primary anaerobes of concern in cIAI, and therefore even with the addition of tazobactam, an additional agent with superior anaerobe activity such as metronidazole is recommended for cIAI, where anaerobic organisms are often involved in the infectious process. In assessing in vitro activity against 695 clinical anaerobic isolates, while the combination was very active against *Fusobacterium* spp. and *Prevotella* spp., only variable activity was achieved against *B. fragilis*, and activity was limited against other *Bacteroides* spp.<sup>31</sup> An in vitro analysis of the anaerobic organisms isolated from 35.2% of patients in a Phase III trial of cIAI patients demonstrated similar results.<sup>32</sup>

### Other bacteria

Good activity was achieved against other clinically relevant Enterobacteriaceae, including *Klebsiella oxytoca*, *Proteus mirabilis*, and indole-positive Proteae.<sup>13</sup> Ceftolozane/tazobactam demonstrated excellent activity against a small number of *Serratia* and *Morganella* isolates, as well as good *Enterobacter* spp. activity that however was reduced to only 70% against hyperproducers of AmpC.<sup>23</sup> Ceftolozane/tazobactam had only variable activity against *Acinetobacter* spp. and *Stenotrophomonas* spp.<sup>13</sup> While of greatest interest for its activity against gram-negatives, ceftolozane/tazobactam is also active against *Streptococcus* spp., but with limited activity against *Staphylococcus aureus* ( $MIC_{50} = 32$  mg/L)

and no appreciable in vitro activity against *Enterococcus* spp.<sup>31</sup> However, it should be noted that patients in the Phase III cIAI trial with *S. aureus*, *E. faecalis*, or *E. faecium* isolated who were treated with ceftolozane/tazobactam had high clinical cure rates (100%, 83.8%, and 92%, respectively), supporting guideline assertions that empiric antibiotic regimens with activity against *Enterococcus* spp. are not always necessary for CA-IAI.<sup>1,33</sup>

### Animal studies

Craig et al<sup>34</sup> used a neutropenic murine thigh infection model to compare percent time above minimum inhibitory concentration ( $T > MIC$ ) required for stasis of bacterial growth for ceftolozane against Enterobacteriaceae and four *P. aeruginosa* strains, as well as to determine the optimal ratio of ceftolozane and tazobactam against ESBL-producing Enterobacteriaceae. A 2:1 ratio of ceftolozane/tazobactam was found to be the most potent, with 8- to 16-fold reductions in MIC against ESBL producers versus ceftolozane alone.  $T > MIC$  was confirmed as the PK/PD parameter driving efficacy, with the  $T > MIC$  required for stasis determined to be  $25.2\% \pm 2.8\%$  for non-ESBL and  $31.1\% \pm 4.4\%$  for ESBL isolates, lower than the  $T > MIC$  mean values of 35%–43% observed for other cephalosporins tested and consistent with in vitro data.  $T > MIC$  required for stasis against *P. aeruginosa* was  $24.0\% \pm 3.3\%$ , lower than that observed for ceftazidime (40%), potentially suggesting an increased probability of target attainment for strains near the MIC breakpoint.<sup>34</sup>

In an immunocompetent murine thigh infection model,  $T > MIC$  was approximated for ceftolozane with or without tazobactam at a dose equivalent to 1,000 mg Q8H as 1 hour infusions against 16 clinical gram-negative isolates: six *P. aeruginosa* (piperacillin/tazobactam MIC range 8–64 mg/L), four *E. coli* (two ESBL-producing), and four *K. pneumoniae* isolates (three ESBL-producing). Piperacillin/tazobactam was used as a comparator and administered to simulate a human dose of 4.5 g Q6H as 30-minute infusions. With or without tazobactam, a predicted ceftolozane  $T > MIC$  of  $\geq 37.5\%$  resulted in log unit decreases of 1–3 for non-ESBL organisms, with reductions in colony-forming units versus piperacillin/tazobactam for nine of the isolates at a similar  $T > MIC$ . Greater than or equal to 1-log-unit decreases in bacterial density were achieved for 4/6 *P. aeruginosa* isolates using ceftolozane versus no isolates using human-simulated doses of piperacillin/tazobactam. The addition of tazobactam enhanced ceftolozane activity against all ESBL producers with the exception of one *K. pneumoniae* isolate.<sup>35</sup>

## Phase II studies

Lucasti et al<sup>36</sup> conducted a prospective, double-blind, randomized, active-controlled, Phase II trial from June 2010 to March 2011 across 35 sites in five countries. Hospitalized patients aged 18–90 years with cIAI were recruited and randomized 2:1, stratified by infection site, to treatment with ceftolozane/tazobactam 1.5 g Q8H (as 1 g ceftolozane and 0.5 g tazobactam) with or without added metronidazole, or meropenem 1 g Q8H for 4–7 days of therapy. The most common diagnosis in this patient population was appendiceal perforation or periappendiceal abscess, followed by cholecystitis and diverticular disease. More patients in the ceftolozane/tazobactam group had an APACHE II score of  $\geq 10$  than in the meropenem group (25.0% and 14.3%, respectively); however, in the meropenem group, the number of patients with prior antibiotic treatment failure was higher (23.1% and 11.0%). The primary outcome was clinical cure at the test-of-cure (TOC) visit 7–14 days after the last dose of study drug in the microbiologically modified intention-to-treat (micro-ITT) population (all patients randomized who received at least one dose of study drug with evidence of IAI and an associated pathogen isolated at baseline) and in the microbiologically evaluable (ME) population (all protocol-compliant patients who received the study drug, did not have a missing or indeterminate clinical outcome response at the TOC visit, had no confounding factors that interfered with outcome assessments, and had an intra-abdominal pathogen isolated at baseline that was susceptible to the study drug received). Secondary outcomes included microbiological response and safety.

Eighty-two patients received ceftolozane/tazobactam, with 90.2% receiving concomitant metronidazole, while 39 patients received meropenem. Clinical cure was achieved in 83.6% (95% CI: 71.9%–91.8%) of micro-ITT patients in the ceftolozane/tazobactam group versus 96% (95% CI: 79.6%–99.9%) in the meropenem group (–12.4% difference; 95% CI: –34.9% to 11.1%). In the ME population, clinical cure rates of 88.7% and 95.8% were achieved in the ceftolozane/tazobactam and meropenem groups, respectively (–7.1% difference; 95% CI: –30.7% to 16.9%). Clinical failure was reported more often numerically in the ceftolozane/tazobactam group, six patients compared to one patient in the meropenem group. The most commonly isolated pathogen at baseline was *E. coli*, present in 41/61 (67.2%) and 19/25 (76.0%) patients in the ceftolozane/tazobactam and meropenem groups, respectively. Polymicrobial infections were present in 39.3% of ceftolozane/tazobactam patients and 36.0% of meropenem patients in the micro-ITT population.

Successful microbiological eradication was common, with all *E. coli*, *Streptococcus* spp., *K. pneumoniae*, and *P. aeruginosa* isolates collected at baseline susceptible to both ceftolozane/tazobactam and meropenem. Success against *E. coli* infection occurred in 89.5% (34/38) of ceftolozane/tazobactam patients and 94.7% (18/19) of meropenem patients. Adverse event rates were similar between the groups (~50%) and were predominantly GI in nature. The most common laboratory abnormalities were increases in liver function tests.

## Phase III studies

ASPECT-cIAI (Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam in Complicated Intra-abdominal Infections) was the Phase III trial that led to the FDA approval of ceftolozane/tazobactam for cIAI.<sup>33</sup> Data were pooled from two multicenter (196 sites), prospective, randomized, double-blind, active-controlled trials conducted December 2011 to September 2013. Hospitalized patients aged 18 years and older with clinical evidence of cIAI were enrolled and randomized 1:1 to receive ceftolozane/tazobactam 1.5 g Q8H plus metronidazole 500 mg Q8H (487 patients) or meropenem 1 g Q8H (506 patients) for 4–10 days. Treatment durations of up to 14 days were permitted for patients with multiple abscesses, nonappendiceal diffuse peritonitis, failure of prior antimicrobial therapy, or hospital-acquired infection. For patients with moderate renal impairment (CrCl 30 to  $\leq 50$  mL/min; 5.9% of all patients), reduced doses of ceftolozane/tazobactam 750 mg Q8H and meropenem 1 g Q12H were used. Patients with severe renal impairment (CrCl  $< 30$  mL/min) were excluded. The primary outcome was clinical cure rate in the micro-ITT population at TOC visit 24–32 days from the start of therapy, with clinical cure defined as the complete resolution or significant improvement in signs and symptoms with no additional intervention or antimicrobial therapy required. Secondary outcomes included clinical cure in the ME population, microbiological outcomes, and safety. The most common cIAI diagnoses were appendiceal perforation or abscess and cholecystitis. The majority of patients had one or more abscesses present and local or diffuse peritonitis. Approximately 87% of all patients had an APACHE II score of 10 or less.

The micro-ITT population included 806 patients, with 83.0% in the ceftolozane/tazobactam group meeting the definition of clinical cure at the TOC visit compared to 87.3% in the meropenem group (–4.2% weighted difference; 95% CI: –8.91 to 0.54), meeting the predefined criteria for noninferiority. Noninferiority was also achieved in the ME population (94.2% compared to 94.7% for ceftolozane/tazobactam and

meropenem, respectively;  $-1.0\%$  weighted difference;  $95\%$  CI:  $-4.52$  to  $2.59$ ). Of concern, for the  $6\%$  of ceftolozane/tazobactam patients with renal impairment at baseline, clinical cure rates in the micro-ITT population dropped below  $50\%$ , a more marked reduction in efficacy than in the meropenem group, where  $69.2\%$  achieved clinical cure. In the ME population, the cure rate did not differ between the two groups; however, only 18 total patients were evaluated.

The most commonly isolated pathogens in the micro-ITT group were *E. coli* ( $65.1\%$ ), *K. pneumoniae* ( $9.4\%$ ), and *P. aeruginosa* ( $8.9\%$ ). Over half of all patients had a polymicrobial infection. For patients with ESBL-producing Enterobacteriaceae isolated ( $7.2\%$ ), clinical cure rates were  $95.8\%$  ( $23/24$ ) and  $88.5\%$  ( $23/26$ ) in the ceftolozane/tazobactam plus metronidazole and meropenem groups, respectively, and  $100\%$  ( $13/13$ ) and  $72.7\%$  ( $8/11$ ) in patients with CTX-M-14/15 ESBL producers. Adverse events were similar in both groups, most commonly nausea and diarrhea. One patient in each treatment arm experienced a serious adverse effect attributed to study drug, both *Clostridium difficile* infections.

A subgroup analysis was performed looking specifically at the micro-ITT patients with cIAI involving *P. aeruginosa* (72 patients).<sup>37</sup> *P. aeruginosa* infection was found to occur more frequently in North American patients ( $17.6\%$ ) than European patients ( $7.9\%$ ), and seen most commonly in colonic ( $14.4\%$ ) or appendiceal ( $11.2\%$ ) infections. All but two patients ( $97.2\%$ ) presented from the community. In the ME population, the clinical cure rate was  $100\%$  ( $26/26$ ) for ceftolozane/tazobactam with *P. aeruginosa* isolates and  $93.1\%$  ( $27/29$ ) for meropenem. A clinical cure was achieved in all ten ME patients with an AmpC producer, and all three patients in the meropenem group with a MDR strain. In an in vitro analysis of the isolates, ceftolozane/tazobactam was the most potent antibiotic tested based on  $MIC_{90}$  values, 2-fold more active than meropenem, 32-fold more active than piperacillin/tazobactam, and 8-fold more active than cefepime, aztreonam, or gentamicin.

The ASPECT trial results have been questioned by some authors, who note the  $95\%$  confidence interval for clinical cure only narrowly crosses 0 for the micro-ITT population, and the greater than expected treatment success rates ( $83\%$  and  $87\%$  for ceftolozane/tazobactam and meropenem respectively) compared to the  $75\%$  treatment success rates expected a priori. The authors hypothesize that this relatively healthy cohort (based on APACHE II scores) may have biased the results toward ceftolozane/tazobactam meeting the statistical noninferiority thresholds.<sup>38</sup> It is unlikely we will ever know

the answer to such a question. Despite this limitation, it is unlikely the study trial design was biased prior to enrollment as the trial did enroll patients according to FDA guidance for new drug approvals for cIAI. It is also not surprising that a clinical trial involving 196 study centers had some deviation from the pretrial estimates. Furthermore, based on the acquisition cost of the medication compared with other agents/combinations recommended for cIAI, it is likely to only be used for patients with confirmed or at highest risk for *P. aeruginosa* infections, for which ceftolozane/tazobactam performed numerically higher than meropenem.

## Ceftazidime/avibactam Background

Ceftazidime/avibactam (Avycaz [Allergan, Inc., Irvine, CA, USA]) was approved by the FDA in February 2015 for the treatment of cIAI in combination with metronidazole and complicated urinary tract infections. The combination contains the well-established third-generation cephalosporin ceftazidime paired with the novel non- $\beta$ -lactam  $\beta$ -lactamase inhibitor avibactam. Ceftazidime has activity against many clinically relevant gram-negative bacilli, including *P. aeruginosa*; however, it is readily hydrolyzed by a variety of  $\beta$ -lactamases, which limits its efficacy against MDR organisms. Avibactam lacks clinically significant antibacterial activity; however, it inhibits a broad spectrum of  $\beta$ -lactamases, with high affinity for class A, C, and some D enzymes (Table 2), restoring the in vitro activity of ceftazidime.<sup>39,40</sup> Ceftazidime/avibactam is available only as an intravenous formulation.

## In vitro activity

### *Escherichia coli* and *Klebsiella pneumoniae*

Ceftazidime/avibactam has been shown to be highly active against Enterobacteriaceae in in vitro studies, inhibiting a broad spectrum of  $\beta$ -lactamases. Among 4,381 ICU and 14,483 non-ICU Enterobacteriaceae collected from 71 US medical centers from 2012 to 2013,  $99.8\%$  of all ICU isolates and  $100\%$  of non-ICU isolates were susceptible ( $MIC \leq 8$  mg/L), including  $99.3\%$  of MDR strains,  $96.5\%$  of XDR strains, and  $98\%$  of meropenem nonsusceptible strains. In comparison, meropenem was effective against  $75.1\%/85.4\%$  of MDR and  $8.1\%/27.1\%$  of XDR ICU and non-ICU isolates.<sup>41</sup> This high activity is retained despite ceftazidime resistance.<sup>11,42-46</sup>

Carbapenem nonsusceptible Enterobacteriaceae have been examined specifically in several studies. Ceftazidime/avibactam was more effective than any other  $\beta$ -lactam

tested against meropenem nonsusceptible isolates, with 83.5% susceptible compared to <13% for ceftazidime alone, cefepime, aztreonam, piperacillin/tazobactam, and imipenem.<sup>9</sup> Ceftazidime/avibactam was 100% effective against 77 isolates from the German National Reference Laboratory.<sup>46</sup> Among an international collection of 177 gram-negative bacilli producing a variety of carbapenamases, ceftazidime/avibactam was active (93% susceptible) against all but metallo- $\beta$ -lactamase producers, with the most active comparators being colistin (88%), tigecycline (79%), and fosfomicin (78%).<sup>47</sup> Similar results were observed against 609 non-class-B carbapenemase-producing Enterobacteriaceae; susceptibility rates were higher using ceftazidime/avibactam (98.7% susceptible) versus any other tested agent, including tigecycline (91.5%) and colistin (81.0%).<sup>9,10</sup> Ceftazidime/avibactam was also active against Enterobacteriaceae with carbapenem nonsusceptibility not mediated by carbapenemase production.<sup>48,49</sup> Ceftazidime/avibactam has demonstrated consistent activity against a wide variety of internationally diverse isolates of carbapenem-nonsusceptible Enterobacteriaceae.

Higher ceftazidime/avibactam MICs have been observed for KPC-3 producing *K. pneumoniae* versus KPC-2 variants, though these elevated MICs were still below breakpoint values.<sup>50</sup> Ceftazidime/avibactam was not active in vitro against metallo- $\beta$ -lactamases, with 96.6% resistant based on MIC interpretation breakpoints.<sup>9,10</sup> Avibactam also failed to inhibit certain KPC-2  $\beta$ -lactamase variants with amino acid substitutions at its binding site; however thus far these mutants have remained susceptible to ceftazidime and are therefore of limited clinical significance.<sup>51</sup>

### *Pseudomonas aeruginosa*

Ceftazidime/avibactam is active against the majority of *P. aeruginosa* isolates, including some MDR strains. Of 3,902 *P. aeruginosa* isolates across 75 US medical centers, 96.9% were susceptible to ceftazidime/avibactam, higher than the rates seen for ceftazidime alone, piperacillin/tazobactam, or meropenem (83.8%, 78.5%, and 81.9%, respectively).<sup>52</sup> In general, activity against MDR has been observed to be around 80%, and 73.7% of XDR isolates remained susceptible to ceftazidime/avibactam in one study.<sup>41</sup> In a study of cIAI patients across 57 US hospitals from 2012 to 2014, ceftazidime/avibactam was the most active  $\beta$ -lactam tested against *P. aeruginosa* (97.1% susceptible), second only to amikacin (99.0% susceptible), with retained activity against meropenem nonsusceptible strains (88.6% susceptible).<sup>53</sup> In a similar study of 1,743 *P. aeruginosa* isolates across 69 US medical

centers collected from a variety of infection sites, ceftazidime/avibactam again demonstrated the highest percentage of susceptible isolates versus comparator  $\beta$ -lactams across all nine census regions, with 91.5%–100% susceptible, second only to colistin (98.0%–100% susceptible).<sup>54</sup> Of note, none of the above studies included ceftolozane/tazobactam.

Varying percentages of susceptibility have been reported for ceftazidime-resistant isolates, as low as ~80% in some studies, while others reported highly potent activity, with up to 94% susceptible.<sup>41,55–57</sup> These differences may likely be attributed to differing *P. aeruginosa* resistance mechanisms, with the addition of avibactam effectively reversing AmpC-mediated ceftazidime resistance and some ESBLs, but not efflux-mediated resistance or OXA-type-ESBL.<sup>58</sup> Among a sample of 54 clinical *P. aeruginosa* isolates with a variety of  $\beta$ -lactam resistance mechanisms, 18.5% were also resistant to ceftazidime/avibactam.<sup>55</sup> In another small study, up to 40% resistance was seen for MDR *P. aeruginosa*.<sup>59</sup> Among *P. aeruginosa* isolates nonsusceptible to ceftazidime, cefepime, piperacillin/tazobactam, and meropenem, 67.4% of isolates were inhibited at an MIC of  $\leq 8$  mg/L.<sup>43</sup>

Head-to-head comparisons of ceftolozane/tazobactam and ceftazidime/avibactam are lacking; however, in one study, ceftolozane/tazobactam demonstrated statistically lower median MIC values than ceftazidime/avibactam (1 mg/L compared to 4 mg/L, respectively;  $P < 0.0001$ ) against 38 meropenem-nonsusceptible *P. aeruginosa* isolates (20 bloodstream, 18 respiratory tract), as well as a significantly lower percentage of isolates (13% compared to 47%) that exhibited MIC values at or above the designated breakpoints ( $P = 0.003$ ). While overall both drugs were active against >90% of the tested isolates, including 80% of the isolates resistant to piperacillin/tazobactam, ceftazidime, and cefepime, ceftolozane/tazobactam clearly demonstrated enhanced in vitro activity over ceftazidime/avibactam against this resistant subpopulation.<sup>60</sup> For MDR *P. aeruginosa*, ceftolozane/tazobactam should, therefore, be considered the preferred choice owing to its enhanced stability over ceftazidime against multiple *P. aeruginosa* resistance mechanisms as well as sparing the enhanced  $\beta$ -lactamase inhibition offered by ceftazidime/avibactam for those infections with resistant Enterobacteriaceae where ceftazidime/avibactam demonstrates a broader spectrum of activity.

### Anaerobes

Ceftazidime/avibactam activity against anaerobic bacteria is similar to that of ceftolozane/tazobactam, in that only variable activity was achieved against *B. fragilis*, with poor activity



against other members of the *B. fragilis* group.<sup>61</sup> With the addition of avibactam, the antibiotic resistance rate among 316 anaerobic bacteria was lowered to 15.2% from 37.7% with ceftazidime alone, still unacceptably high for most cIAI infections and necessitating the use of metronidazole.<sup>62</sup>

#### Other bacteria

Avibactam did not enhance the activity of ceftazidime against *Acinetobacter* spp. with or without OXA-type-carbapenamase.<sup>12,58,63,64</sup> Its activity against gram-positive organisms is as expected for ceftazidime alone, with good activity against  $\beta$ -hemolytic streptococci ( $MIC_{90}=0.5$  mg/L) but poor activity against *S. aureus* ( $MIC_{90}\geq 32$  mg/L).<sup>65</sup> Clinically appreciable activity is not expected against *Enterococcus* spp.; however, as with ceftolozane/tazobactam, >70% of cIAI patients with *Enterococcus* spp. isolated had favorable responses on ceftazidime/avibactam therapy in its major Phase III trial.<sup>66</sup>

#### Animal studies

Several animal studies have been conducted to test ceftazidime/avibactam efficacy. In the studies evaluating ceftazidime/avibactam activity against Enterobacteriaceae, ceftazidime/avibactam demonstrated consistent activity against clinical isolates with MICs of  $\leq 16$  mg/L with a T > MIC of  $\geq 62\%$ , including against ceftazidime and carbapenem nonsusceptible strains, and appeared to be a more potent inhibitor than piperacillin/tazobactam.<sup>67,68</sup>

Crandon et al<sup>69</sup> used a murine thigh infection model in both immunocompromised and immunocompetent murine hosts to compare the efficacy of a human-simulated ceftazidime dose of 2 g Q8H as a 2-hour infusion with and without avibactam 500 mg Q8H against 27 clinical *P. aeruginosa* isolates with ceftazidime MICs ranging from 8 to 128 mg/L. The ceftazidime/avibactam combination demonstrated enhanced reduction of bacterial density, with a decrease of  $\geq 0.5$  log unit in 22/27 isolates versus 10/27 isolates for ceftazidime alone in the neutropenic model. Of the 15 isolates tested in the immunocompetent model, ceftazidime/avibactam achieved  $\geq 0.3$  log unit reductions in all isolates versus 10/15 for ceftazidime.<sup>69</sup>

#### Phase II studies

In a randomized, double-blind, active-controlled, Phase II trial by Lucasti et al,<sup>70</sup> 203 hospitalized patients with confirmed cIAI requiring surgical intervention and antibiotic therapy were randomized 1:1 to ceftazidime/avibactam 2.5 g Q8H (as 2 g ceftazidime and 500 mg avibactam) plus

metronidazole 500 mg Q8H or meropenem 1 g Q8H and placebo for 5–14 days of treatment. The primary end point was favorable clinical response 2 weeks after the last study dose of antibiotic in the ME population. The most common infection sites were the appendix (48.5%/46.1%), stomach or duodenum (28.7%/22.5%), and colon (11.9%/5.9%). Patients were excluded if they had an APACHE II score >25. After a median treatment duration of ~6 days, 91.2% (62/68) and 93.4% (71/76) of patients in the ceftazidime/avibactam and meropenem groups, respectively, achieved the primary end point (–2.2% observed difference; 95% CI: –20.4% to 12.2%). *E. coli* was the most commonly isolated pathogen from the site of infection, with all isolates testing susceptible to both ceftazidime/avibactam and meropenem. Of all other gram-negative isolates, six had a ceftazidime/avibactam MIC >8 mg/L: three *Klebsiella* spp., two *P. aeruginosa*, and one *Acinetobacter baumannii*. Of these, two were also nonsusceptible to meropenem. However, all ME patients in either treatment group with *Klebsiella* spp. or *P. aeruginosa* isolated demonstrated a favorable microbiological response. After pooling the Phase II data for complicated urinary tract infection and cIAI, a higher percentage of patients with ESBL Enterobacteriaceae isolates who received treatment with ceftazidime/avibactam achieved a favorable clinical response, 85.7% compared to 80.0% for those receiving carbapenem therapy.<sup>71</sup>

#### Phase III studies

In an international study by Mazuski et al,<sup>66</sup> two identical, prospective, randomized, double-blind, active comparator trials were conducted across 136 centers in 30 countries. The study was designed as a noninferiority trial with a –12.5% margin, lower than the –10% margin recommended by the FDA. Over 1,000 patients aged 18–90 years with cIAI requiring surgical intervention or percutaneous drainage were recruited between March 2012 and April 2014. As in the Phase III trial for ceftolozane/tazobactam, more than 80% of patients in this study had an APACHE II score <10. The most common primary diagnoses were appendiceal perforation or periappendiceal abscess (–42%), acute gastric or duodenal perforation, and cholecystitis. Patients were assigned 1:1 using block randomization to receive ceftazidime/avibactam 2.5 g Q8H as a 2-hour infusion plus metronidazole 500 mg Q8H over 1 hour or meropenem 1 g Q8H as a 30-minute infusion. Treatment could be stopped after a minimum of 5 days if the patient showed clinical improvement, or continued for a maximum of 14 days. The primary end point was clinical cure 28–35 days after randomization

in the micro-ITT population. The modified intention-to-treat (mITT) and CE populations were also assessed. Secondary end points included clinical response within 24 hours of last infusion and at late follow-up 42–49 days postrandomization, microbiological response, efficacy against ceftazidime-resistant pathogens, and adverse effects. For the primary end point, noninferiority was achieved across all primary analysis populations (micro-ITT, mITT, and CE). For the micro-ITT population, clinical cure was achieved in 81.6% and 85.1% of patients in the ceftazidime/avibactam and meropenem groups, respectively (–3.5% observed difference; 95% CI: –8.64 to 1.58). Similar efficacy rates were observed against ceftazidime-nonsusceptible isolates (present in 13.5% of patients), comparable to that of meropenem (83.0% and 85.9%, respectively), with the primary mechanism of ceftazidime resistance being ESBL production (80%). Of all isolated gram-negative pathogens, nine were nonsusceptible to ceftazidime/avibactam and eight were nonsusceptible to meropenem. No differences were found in adverse effects. In the subgroup of patients with moderate renal impairment (8% of all subjects), although not powered to detect a difference, the results appeared to heavily favor meropenem (micro-ITT –29.1% difference; 95% CI: –50.05 to –5.36) to an even greater extent than in the ceftolozane/tazobactam Phase III trial. A reduced ceftazidime/avibactam dose of 1.25 g Q12H was used in this population, 33% lower than current manufacturer recommendations.<sup>72</sup>

A second Phase III trial (REPRISE) by Carmeli et al<sup>73</sup> was conducted internationally across 16 countries and enrolled 333 patients aged 18–90 years with complicated urinary tract infection or cIAI specifically caused by ceftazidime-resistant Enterobacteriaceae or *P. aeruginosa*. Patients were randomized 1:1 to receive open-label ceftazidime/avibactam 2.5 g Q8H as a 2-hour infusion or best available therapy (96% carbapenem monotherapy) for 5–21 days of treatment. Of the 154 patients receiving ceftazidime/avibactam, only 11 had cIAI. The primary outcome was clinical response at TOC visit 7–10 days after the last infusion of study therapy in the micro-ITT population. Safety was evaluated as a secondary outcome. The proportions of patients achieving the primary outcome of clinical cure were similar (both 91%). Thirty-one percent of patients in the ceftazidime/avibactam group and 39% of patients in the best available therapy group experienced an adverse effect (most mild or moderate), predominantly GI in nature.

## Impaired renal function

Both ceftolozane/tazobactam and ceftazidime/avibactam undergo a high degree of renal elimination. Ceftolozane

is eliminated near-exclusively in urine, with tazobactam undergoing mostly renal elimination and some metabolism. Similarly, ceftazidime is eliminated almost solely by the kidneys. Avibactam is eliminated in the urine unchanged; however, excretion of avibactam decreases to a lesser proportion in patients with renal impairment than ceftazidime.<sup>72</sup> Both ceftazidime and avibactam are dialyzable, and are recommended to be administered after hemodialysis (HD) on HD days.<sup>72,74</sup> In two Phase I, open-label, single-dose studies by Wooley et al,<sup>75</sup> patients with stable mild or moderate impairment were administered the same recommended ceftolozane/tazobactam dose as patients with normal renal function, while patients with severe renal function or receiving HD were administered doses of 750 mg (pre- and posthemodialysis for dialysis patients). The increase in drug exposure with the mild impairment group was not deemed significant, and while the moderate and severe impairment groups did experience 2- to 4-fold increases in drug exposure, the doses were well tolerated with the most common side effect being headache.

Patients with reduced renal function often comprise a small subset of patients in Phase III clinical trials and there is a paucity of clinical data verifying optimal doses for these patients with almost all drugs. Both ceftolozane/tazobactam and ceftazidime/avibactam carry FDA warnings regarding decreased efficacy in patients with baseline creatinine clearance of 30–50 mL/min after lower clinical cure rates were observed for these patients in Phase III trials.<sup>72,74</sup> However, the ceftazidime/avibactam daily dose that was used in the trial was 33% lower than the current manufacturer recommendations (Table 3).

Several possible explanations exist with regard to the decreased efficacy observed in the renally impaired in clinical trials. The first possible explanation is that patients given renally adjusted doses had acute kidney injury secondary to intravascular depletion at the time of study enrollment. Given serum creatinine measurements to estimate creatinine clearance lag behind in situations of changing creatinine clearance rates, patients could have been underdosed initially before the serum creatinine normalized. Another possible explanation is the patients were inherently more at risk for poor outcomes, which was not detected in multivariate analysis. Either one of these theories is supported by the fact that meropenem success rates also declined in the clinical trials in patients with reduced renal function, from 88% to 69% in the ceftolozane/tazobactam trial, albeit not as much as the numerical difference observed with ceftolozane/tazobactam.<sup>33</sup> However, it is possible that the numerical differences observed in these subgroups are the result of

**Table 3** Renal dose adjustments per manufacturer recommendations

CrCl (mL/min)	Ceftolozane/tazobactam <sup>a,b</sup>	CrCl (mL/min)	Ceftazidime/avibactam <sup>a,c</sup>
>50	1.5 g Q8H	>50	2.5 g Q8H
30–50	750 mg Q8H	31–50	1.25 g Q8H
15–29	375 mg Q8H	16–30	0.94 g Q12H
ESRD on HD <sup>d</sup>	750 mg ×1 then 150 mg Q8H	6–15 <sup>d</sup>	0.94 g Q24H
		≤5 <sup>d</sup>	0.94 g Q48H

**Notes:** <sup>a</sup>Total dose of cephalosporin and β-lactamase inhibitor. <sup>b</sup>All doses infused over 1 hour. <sup>c</sup>All doses infused over 2 hours. <sup>d</sup>Administer dose following completion of dialysis on dialysis days. Data from.<sup>72,74</sup>

**Abbreviations:** CrCl, creatinine clearance per Cockcroft–Gault formula; ESRD, end-stage renal disease; HD, hemodialysis.

the variability inherent to examination of subpopulations. In a registry trial for daptomycin, lower numerical differences were observed in renally impaired patients prompting a warning in the package insert for the drug. However, in a study examining real-world use of the agent, no difference was observed compared to vancomycin in patients with reduced renal function with a larger sample size than what was seen in the registry trial.<sup>76</sup> The reduced efficacy seen in the renally impaired for ceftolozane/tazobactam and ceftazidime/avibactam suggests that further study is warranted, but it should not cause undue concern when these agents are likely being used when other options are not available.

The tolerability of ceftolozane/tazobactam doses up to 4.5 g and ceftazidime/avibactam doses of up to 4 g has been established in Phase I trials, and some clinicians have thus advocated for higher doses for infections such as pneumonia, where drug tissue concentrations are lower than in IAIs.<sup>77–79</sup> Given the safety of these agents (and the long-term safety from this class of drugs) in patients whose serum creatinine might underestimate their true renal function, such as acute renal insufficiency from initial intravascular volume depletion, providers should err on the side of administering the unadjusted renal dose or the full dose for normal renal function until a more accurate assessment of renal function is available.

For patients receiving continuous renal replacement therapy, there are currently no manufacturer dose recommendations; however, 4-hour infusions of ceftolozane/tazobactam 1.5 g Q8H achieved concentrations eight times the susceptibility breakpoint for a critically ill 61-year-old male with an MDR *P. aeruginosa* prosthetic joint infection (ceftolozane/tazobactam MIC = 1.5 mg/L) receiving continuous venovenous hemofiltration for acute kidney injury.<sup>80</sup> Another pharmacokinetic analysis was performed on a 47-year-old critically ill male receiving continuous venovenous hemodialfiltration on 3 g Q8H ceftolozane/tazobactam for MDR *P. aeruginosa* pneumonia, bacteremia, and osteomyelitis. Decreased clearance was observed versus the expected clearance of a patient with normal renal

function, and the study authors concluded that ceftolozane/tazobactam 1.5 g Q8H should be adequate for achieving concentrations above an MIC of 8 mg/L.<sup>81</sup>

## Role in therapy

The 2010 IDSA recommendations for the treatment of cIAI advocate for empiric antibiotic regimens with activity against enteric gram-negative aerobic and facultative bacilli and enteric gram-positive streptococci, with additional coverage of obligate anaerobic bacilli such as *B. fragilis* for distal small bowel, appendiceal, and colon-derived infections, or for infections involving obstruction or paralytic ileus. The selection of therapies active against *Enterococcus* spp. in the setting of CA-IAI does not require routine consideration, even for high-risk patients or infections of high severity (APACHE II > 15 or other clinical feature predicting failure of source control). Treatment with a cephalosporin such as ceftriaxone in combination with metronidazole is a commonly utilized, guideline-appropriate regimen for infections of mild-to-moderate severity, while antibiotic regimens including an agent with activity against *P. aeruginosa* such as cefepime, again in combination with metronidazole, is recommended for infections of high severity or for patients at high risk for infection with resistant isolates. While the fluoroquinolones ciprofloxacin and levofloxacin are listed as potential therapies in the guidelines for both mild/moderate or severe infections, due to increasing resistance rates empiric therapy with these agents is not recommended unless hospital antibiogram data indicate >90% susceptibility of *E. coli*. For HA-IAI infections, regimens with expanded spectra of activity against gram-negative pathogens may be needed. An agent with activity against *P. aeruginosa* is again recommended, with potential consideration for the addition of an MRSA-active agent in patients known to be colonized or with additional risk factors. Enterococci may be of concern for patients with previous cephalosporin exposure, prosthetic intravascular materials, or those who are immunocompromised.<sup>1</sup>

Widespread utilization of ceftolozane/tazobactam or ceftazidime/avibactam as empiric therapy is not

recommended, and it is advised to limit use to the few high-risk patients who may truly require an antibiotic providing an expanded gram-negative spectrum empirically, such as those with recent health care exposures or tertiary peritonitis, in order to avoid the development and spread of resistance that has already been observed with other antibiotic classes. Implementation of validated stewardship interventions such as preauthorization and/or prospective audit and feedback may assist in this goal.<sup>82</sup> Alternatively, the development of a hospital cIAI protocol based on institution-specific risk factors for MDR organisms may provide a tailored approach for guiding clinicians to optimal empiric options.

Testing for susceptibility to ceftolozane/tazobactam or ceftazidime/avibactam should be considered for patients as definitive therapy in the setting of confirmed resistance to other  $\beta$ -lactam agents. For isolates remaining sensitive to carbapenems, ceftolozane/tazobactam or ceftazidime/avibactam may potentially be considered as carbapenem-sparing options for select institutions with increasing reports of carbapenem resistance. Knowledge of community and institutional resistance patterns will be invaluable for aiding in appropriate antimicrobial selection of these new  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations.

*P. aeruginosa* is present in ~10%–15% of cIAI infections and warrants increased consideration empirically in the case of HA-IAI, recurrent infection and tertiary peritonitis, or infectious symptoms that persist despite adequate source control. For institutions with reported rates of >20% resistance to ceftazidime, the only empiric antimicrobial therapies recommended for cIAI per IDSA guidelines are piperacillin/tazobactam or a carbapenem with *P. aeruginosa* activity.<sup>1</sup> However, resistance to one or more of the classically utilized  $\beta$ -lactams for *P. aeruginosa* commonly coincide with cross-resistance to other  $\beta$ -lactam agents, with ceftolozane/tazobactam being the notable exception, with

demonstrated high activity even against isolates resistant to all other  $\beta$ -lactams including the carbapenems.<sup>25</sup> Patients with previous MDR or XDR *P. aeruginosa* infections or patients at higher risk for mortality such as those with tertiary peritonitis may therefore benefit from broad initial coverage with ceftolozane/tazobactam, the most potent option against *P. aeruginosa* currently available.

Carbapenamase and ESBL-producing Enterobacteriaceae are associated with significant costs to the healthcare system, including increased length of hospital stay and higher rates of treatment failure. Significant risk factors associated with community-acquired ESBL-producing Enterobacteriaceae include recent antibiotic use, recent hospitalization, residence in a skilled nursing facility, age  $\geq 65$  years, and, potentially, male sex.<sup>83</sup> Similar risk factors, including prolonged hospitalization, mechanical ventilation, and organ or stem-cell transplantation have been reported for KPC producers.<sup>84</sup> Globally, KPC production is endemic to Greece, Israel, and Italy, with many more countries reporting sporadic hospital-associated outbreaks with associated mortality of up to 66.7%.<sup>85</sup> In the United States, pockets of endemic KPC production exist, including many hospitals within New York and New Jersey, with one academic medical center in New York City reporting a rise in carbapenem-nonsusceptible *K. pneumoniae* from 9% in 2002 to a staggering 38% in 2008.<sup>84</sup> Within such regions of high ESBL and carbapenamase production, ceftazidime/avibactam therapy should be considered for patients with risk factors or as escalation of initial therapy for patients not improving on standard treatments.

As new therapies, the acquisition costs of ceftolozane/tazobactam and ceftazidime/avibactam will be inevitably higher than standard empiric cIAI regimens (Table 4). However, increased drug prices should never be used as justification for inferior therapy, as the costs of increased length of stay and mortality associated with treatment failure are

**Table 4** Acquisition costs for ceftolozane/tazobactam, ceftazidime/avibactam, and comparator agents

Drug	AWP price (USD)	AWP unit	Standard dosing for cIAI	cIAI treatment cost per day (USD)
Novel agents				
Ceftolozane/tazobactam	\$104.48	1.5 g <sup>a</sup>	1.5 g Q8H <sup>a</sup>	\$313.44 <sup>b</sup>
Ceftazidime/avibactam	\$359.10	2.5 g <sup>a</sup>	2.5 g Q8H <sup>a</sup>	\$1,077.30 <sup>b</sup>
Comparator agents				
Ceftriaxone	\$0.34	1 g	1 g Q24H	\$0.34 <sup>b</sup>
Cefepime	\$0.51	2 g	2 g Q8H	\$1.53 <sup>b</sup>
Piperacillin/tazobactam	\$8.31	4.5 g	4.5 g Q6H	\$33.24
Meropenem	\$26.40	1 g	1 g Q8H	\$79.20

**Notes:** <sup>a</sup>Total dose of cephalosporin and  $\beta$ -lactamase inhibitor. <sup>b</sup>Does not include the negligible cost of added metronidazole therapy. Data from Red Book Online.<sup>88</sup>

**Abbreviations:** AWP, average wholesale price; cIAI, complicated intra-abdominal infection; USD, United States dollars.



likely to far outweigh acquisition costs. Prompt de-escalation to more narrow-spectrum antibiotics when susceptibilities are known will also assist in ameliorating increased costs of therapy.

Overall, the development of the new antibiotic combinations ceftolozane/tazobactam and ceftazidime/avibactam provides new hope after the long-lamented dearth of new antimicrobials with activity against gram-negative pathogens. Used judiciously, they promise to be valued additions to the clinician's toolbox of antibiotics effective for the treatment of MDR infections.

## Disclosure

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