AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

In Vitro Comparison of Ceftolozane-Tazobactam to Traditional Beta-Lactams and Ceftolozane-Tazobactam as an Alternative to Combination Antimicrobial Therapy for *Pseudomonas aeruginosa*

Kellie J. Goodlet,[a]* David P. Nicolau,[b] Michael D. Nailor[a,c]*

Department of Pharmacy, Hartford Hospital, Hartford, Connecticut, USA[a]; Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, Connecticut, USA[b]; University of Connecticut School of Pharmacy, Storrs, Connecticut, USA[c]

ABSTRACT Guidelines for the treatment of sepsis, febrile neutropenia, and hospital-acquired pneumonia caused by *Pseudomonas aeruginosa* include empirical regimens incorporating two antibiotics from different classes with activity against *P. aeruginosa* for select at-risk patients to increase the likelihood that the organism will be susceptible to at least one agent. The activity against *P. aeruginosa* and the rates of cross-resistance of ceftolozane-tazobactam were compared to those of the β-lactam comparators cefepime, ceftazidime, piperacillin-tazobactam, and meropenem alone and cumulatively with ciprofloxacin or tobramycin. Nonurine *P. aeruginosa* isolates were collected from adult inpatients at 44 geographically diverse U.S. hospitals. MICs were determined using reference broth microdilution methods. Of the 1,257 isolates collected, 29% were from patients in intensive care units and 39% were from respiratory sites. The overall rate of susceptibility to ceftolozane-tazobactam was high at 97%, whereas it was 72 to 76% for cefepime, ceftazidime, piperacillin-tazobactam, and meropenem. The rate of nonsusceptibility to all four comparator β-lactams was 11%; of the isolates nonsusceptible to the four comparator β-lactams, 80% remained susceptible to ceftolozane-tazobactam. Among the isolates nonsusceptible to the tested β-lactam comparators, less than half were susceptible to ciprofloxacin. By comparison, approximately 80% of the β-lactam-nonsusceptible isolates were susceptible to tobramycin, for overall cumulative susceptibility rates of 94 to 95%, nearly 10% higher than that of the ciprofloxacin–β-lactam combinations and approaching that of ceftolozane-tazobactam as a single agent. The rates of susceptibility to ceftolozane-tazobactam were consistently high, with little observable cross-resistance. Ceftolozane-tazobactam monotherapy performed at or above the level of commonly utilized combination therapies on the basis of *in vitro* susceptibilities. Ceftolozane-tazobactam should be considered for use in patients at high risk for resistant *P. aeruginosa* infection and as an alternative to empirical combination therapy, especially for patients unable to tolerate aminoglycosides.

KEYWORDS *Pseudomonas aeruginosa*, antimicrobial resistance, ceftolozane-tazobactam, combination treatment, resistance

Received 30 June 2017 **Returned for modification** 10 August 2017 **Accepted** 4 September 2017

Accepted manuscript posted online 18 September 2017

Citation Goodlet KJ, Nicolau DP, Nailor MD. 2017. *In vitro* comparison of ceftolozane-tazobactam to traditional beta-lactams and ceftolozane-tazobactam as an alternative to combination antimicrobial therapy for *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 61:e01350-17. https://doi.org/10.1128/AAC.01350-17.

Address correspondence to Michael D. Nailor, Michael.Nailor@dignityhealth.org.

* Present address: Kellie J. Goodlet, Midwestern University College of Pharmacy, Glendale, Arizona, USA; Michael D. Nailor, St. Joseph's Hospital and Medical Center, Phoenix, Arizona, USA.

Pseudomonas aeruginosa is a notorious cause of nosocomial infection both within the United States and around the world. The CDC's National Healthcare Safety Network lists *P. aeruginosa* as the seventh most common cause of health care-associated infection, accounting for 8% of all reported cases (1), while other surveillance

TABLE 1 Mechanisms of *Pseudomonas aeruginosa* resistance to β-lactam antibiotics

Mechanism of resistance	Example(s)
Enzymatic inactivation via β-lactamase production	Expanded-spectrum β-lactamases (TEM, SHV, CTX-M, PER, VEB, GES, IBC, AmpC) and carbapenemases (KPC, IMP, VIM, SPM, GIM, OXA-40)
Alterations in outer membrane permeability via porin alteration	Decreased production or loss of functional OprD
Active efflux via overproduction of efflux pumps	mexAB-OprM, mexCD-OprJ, mexXY-OprM

data from both U.S. and European centers place it even higher as the third most common isolate causing health care-associated infections in both intensive care unit (ICU) and non-ICU patients (18% and 12% of all isolates, respectively) (2). Within the ICU, *P. aeruginosa* has been implicated in 16% of nosocomial pneumonias, 10% of urinary tract infections, 10% of surgical site infections, and 4% of bloodstream infections (3) and was noted in one European study to be the pathogen responsible for the greatest burden of health care-acquired infections (4).

The mainstay of therapy against *P. aeruginosa* infections involves the administration of an active antibiotic of the β-lactam class; however, the propensity of *P. aeruginosa* to develop resistance to multiple antibiotic agents can pose significant treatment challenges. Resistance to β-lactams may result from a variety of mechanisms (Table 1) that may act alone or in combination to produce a phenotypic profile of resistance (5). Resistance to only a single β-lactam or to the entire class may be conferred depending on the mechanism. Large surveillance studies have demonstrated baseline rates of resistance to traditional β-lactams (e.g., cefepime, ceftazidime, piperacillin-tazobactam, and meropenem) of 15 to 20% or more, regardless of the agent selected (6–8). Additionally, critically ill patients within the ICU are at increased risk of harboring resistant isolates, with these isolates having approximately 10% declines in susceptibility compared to those of isolates from ward patients (2).

Given this risk for resistance, many international guidelines allow or advocate for the empirical use of two agents from different antibiotic classes with activity against *P. aeruginosa* in order to better capture a susceptible result (Table 2) (9–17). In particular, the most recent guidelines for the treatment of ventilator-associated pneumonia (VAP) recommend combination therapy when the local rate of resistance of Gram-negative bacteria to an agent being considered for monotherapy exceeds 10% (9). These combination regimens have traditionally been composed of a β-lactam plus either an aminoglycoside or a fluoroquinolone. This results in expanded anti-*P. aeruginosa* activity, but at the cost of a potential increased risk for adverse effects, including nephrotoxicity and ototoxicity (aminoglycosides) or neuropathies and central nervous system effects (fluoroquinolones).

Alternatively, new antibiotic agents with enhanced activity against *P. aeruginosa* may provide a promising substitute for combination therapy. Ceftolozane-tazobactam (Zerbaxa; Merck & Co., Kenilworth, NJ, USA) is a novel cephalosporin–β-lactamase inhibitor engineered to have increased stability against efflux and degradation by multiple classes of β-lactamases. Current FDA approvals for ceftolozane-tazobactam include complicated intra-abdominal infections in combination with metronidazole and complicated urinary tract infections, including pyelonephritis, with clinical trials evaluating its use for bacterial pneumonia currently in progress. Ceftolozane-tazobactam has demonstrated consistently high *in vitro* activity against *P. aeruginosa* in large surveillance studies, with overall rates of susceptibility being >90% (6).

The purpose of this study was to describe the susceptibilities of *P. aeruginosa* isolates to ceftolozane-tazobactam and to compare those to the susceptibilities to traditionally utilized β-lactams alone and the cumulative susceptibilities of each β-lactam used with either ciprofloxacin or tobramycin. Additionally, the rates of cross-resistance among the β-lactam comparators and to ceftolozane-tazobactam were

TABLE 2 International guidelines allowing empirical dual-coverage therapy against *Pseudomonas aeruginosa*[a]

Guideline (reference)	Organization	Yr	Recommendations
Management of adults with hospital-acquired and ventilator-associated pneumonia (9)	IDSA, ATS	2016	For VAP, 2 antibiotics with anti-*P. aeruginosa* activity are recommended if any of the following are present: (i) a risk factor increasing the likelihood of Gram-negative bacterial infection or antimicrobial resistance, (ii) >10% resistance of Gram-negative bacterial isolates on a hospital unit to an agent being considered for monotherapy, (iii) the lack of availability of local antimicrobial susceptibility rates for the ICU, and (iv) an increase in the risk of Gram-negative bacterial infection because of structural lung disease (i.e., bronchiectasis or cystic fibrosis). For HAP, 2 antibiotics with anti-*P. aeruginosa* activity are recommended if any of the following are present: (i) risk factors increasing the likelihood for *P. aeruginosa* or other Gram-negative bacterial infection, and (ii) patients are at high risk for mortality (e.g., need for ventilator support and septic shock).
Guidelines for the management of adult lower respiratory tract infections (10)	ESCMID, ERS	2011	The use of 2 antibiotics with anti-*P. aeruginosa* activity is recommended for CAP patients requiring ICU or immediate care when risk factors for *P. aeruginosa* infection are present.
Use of antimicrobial agents in neutropenic patients with cancer (11)	IDSA	2010	Additional antibiotics with anti-*P. aeruginosa* activity may be added for management of complications (e.g., hypotension and pneumonia) or if antimicrobial resistance is suspected or proven.
Prevention and treatment of cancer-related infections (12)	NCCN	2017	Initial combination therapy should be considered for febrile patients at high risk for *P. aeruginosa* infections. Combination therapy may also be considered in complicated or resistant cases.
European guidelines for empirical antibacterial therapy for febrile neutropenic patients (13)	ECIL	2013	A deescalation treatment approach with the empirical use of 2 antibiotics with anti-*P. aeruginosa* activity may be considered if one of the following criteria are present: (i) known prior colonization or infection with resistant pathogens, (ii) complicated presentation (e.g., severe sepsis, septic shock), (iii) high rates of resistant nonfermenters on the basis of local epidemiology, or (iv) carbapenem use within the past month.
Diagnosis and management of prosthetic joint infection (14)	IDSA	2013	The use of 2 antibiotics with anti-*P. aeruginosa* activity may be considered on the basis of the clinical circumstances of the patient.
Clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults (15)	IDSA	2015	The use of 2 antibiotics with anti-*P. aeruginosa* activity may be considered.
International guidelines for management of sepsis and septic shock (16)	SSC	2016	Supplemental use of an agent with activity against Gram-negative bacteria is recommended for critically ill septic patients at high risk of infection with multidrug-resistant pathogens (including *P. aeruginosa*).
Combination antibiotic therapy for empirical and definitive treatment of Gram-negative bacterial infections (17)	SIDP	2011	The use of 2 antibiotics with anti-*P. aeruginosa* activity is reasonable for empirical treatment of suspected health care-associated infections, particularly when risk factors for multidrug-resistant organisms are present.

[a]Definitions: ATS, American Thoracic Society; CAP, community-acquired pneumonia; ECIL, European Conference on Infections in Leukemia; ERS, European Respiratory Society; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; HAP, hospital-acquired pneumonia; ICU, intensive care unit; IDSA, Infectious Diseases Society of America; NCCN, National Comprehensive Cancer Network; SIDP, Society of Infectious Diseases Pharmacists; SSC, Surviving Sepsis Campaign; VAP, ventilator-associated pneumonia.

assessed. The rates of susceptibility of isolates nonsusceptible to one, two, three, or all four comparator β-lactams to ceftolozane-tazobactam were determined as well.

RESULTS

A total of 1,257 *P. aeruginosa* isolates were evaluated. Approximately 29% of the isolates were obtained from patients residing in an ICU. Over one-third (39%) were isolated from respiratory sources, and 61% were isolated from nonrespiratory sources. Nonrespiratory sources included blood, wounds, and miscellaneous body fluids (e.g., ascites).

The rate of susceptibility to ceftolozane-tazobactam was >90% across all locations (ICU or ward) and sources (respiratory or nonrespiratory) (Table 3). Ceftolozane-tazobactam was the most active agent tested against *P. aeruginosa*, with the rates of *in vitro* susceptibility being 20 to 25% higher than those to cefepime, ceftazidime, piperacillin-tazobactam, or meropenem. The trends for susceptibility to ceftolozane-

TABLE 3 Susceptibilities of *P. aeruginosa* isolates to single agents stratified by location and/or source and percentage of nonsusceptible isolates remaining susceptible to ceftolozane-tazobactam[a]

	All patient isolates (n = 1,257)		ICU patient isolates (n = 359, 28.6%)		Non-ICU patient isolates (n = 898, 71.4%)		Respiratory isolates (n = 490, 39.0%)		Nonrespiratory isolates (n = 767, 61.0%)		ICU patient respiratory isolates (n = 156, 12.4%)		ICU patient nonrespiratory isolates (n = 203, 16.1%)		Non-ICU patient respiratory isolates (n = 334, 26.6%)		Non-ICU patient nonrespiratory isolates (n = 564, 44.9%)	
Single agent	% S	Of non-S, % S to C-T	% S	Of non-S, % S to C-T	% S	Of non-S, % S to C-T	% S	Of non-S, % S to C-T	% S	Of non-S, % S to C-T	% S	Of non-S, % S to C-T	% S	Of non-S, % S to C-T	% S	Of non-S, % S to C-T	% S	Of non-S, % S to C-T
Ceftolozane-tazobactam	96.6	NA	95.0	NA	97.2	NA	94.7	NA	97.8	NA	92.3	NA	97.0	NA	95.8	NA	98.0	NA
Cefepime	77.0	87.5	71.6	84.3	79.2	89.3	69.6	83.2	81.7	92.1	59.6	81.0	80.8	89.7	74.3	84.9	82.1	93.1
Ceftazidime	77.0	86.2	68.8	83.9	80.3	87.6	70.0	83.0	81.5	89.4	60.3	80.6	75.4	88.0	74.6	84.7	73.7	90.2
Piperacillin-tazobactam	71.8	90.1	63.0	88.0	75.4	91.4	63.1	87.3	77.4	93.1	50.6	85.7	72.4	91.1	68.9	88.5	79.3	94.0
Meropenem	76.0	90.1	69.9	87.0	78.4	91.8	70.4	85.5	79.5	94.3	59.0	82.8	78.3	93.2	75.7	87.7	80.0	94.7
Tobramycin	91.5	83.2	88.0	76.7	92.9	87.5	90.4	74.5	92.2	90.0	84.0	68.0	91.1	88.9	93.4	81.8	92.6	90.5
Ciprofloxacin	72.3	91.1	71.0	87.5	72.8	92.6	68.0	88.5	75.1	93.2	64.7	83.6	75.9	91.8	69.5	91.2	74.8	93.7

[a]Definitions: C-T, ceftolozane-tazobactam; NA, not applicable; S, susceptible.

tazobactam tended to follow those to the other antibiotics, with ICU isolates being overall less susceptible than non-ICU isolates and respiratory isolates being less susceptible than nonrespiratory isolates. The least susceptible isolates were respiratory isolates from the ICU (92% were susceptible to ceftolozane-tazobactam); however, this decline in susceptibility was less pronounced than that for the β-lactam comparators, with the rates of susceptibility to ceftolozane-tazobactam being 32 to 42% higher for this subgroup.

The rates of susceptibility of *P. aeruginosa* isolates to cefepime, ceftazidime, piperacillin-tazobactam, and meropenem had limited variation and were generally within 10% of each other. Among all *P. aeruginosa* isolates, 24 to 28% were nonsusceptible to any one agent, with the rates of nonsusceptibility being the highest for respiratory isolates in the ICU, at 40 to 49% (Table 3).

Cross-resistance among the β-lactam comparators was common (Table 4). Meropenem was the comparator that was the most likely to be active in the case of resistance to one of the other β-lactams, with a susceptible result being obtained for 39 to 45% of the isolates. Similarly, in the case of meropenem nonsusceptibility, the rates of susceptibility to the other β-lactam comparators ranged from 36 to 44%. By comparison, with cefepime, ceftazidime, or piperacillin-tazobactam nonsusceptibility, the likelihood of activity of one of the other two agents ranged from 15 to 35%. These trends were similar among the subgroups of isolates. In contrast, of the isolates nonsusceptible to one of the other β-lactams, the rates of ceftolozane-tazobactam susceptibility ranged from 86 to 90% overall and from 81 to 86% for respiratory isolates from patients in an ICU. Even in the case of resistance to two, three, or all four β-lactam comparators, the overall rates of ceftolozane-tazobactam susceptibility were ≥80% (Fig. 1). Eleven percent of all isolates and 23% of respiratory isolates from patients in an ICU were resistant to all four β-lactam comparators. Ceftolozane-tazobactam remained active against 80% and 69% of all isolates and respiratory isolates from patients in an ICU with this resistance phenotype, respectively.

With respect to combination therapy, although the overall rates of ciprofloxacin susceptibility were comparable to those for the β-lactams, its activity against those isolates nonsusceptible to the primary β-lactam was significantly reduced (37 to 49% active) (Table 5). Therefore, only 9 to 14% improvements in susceptibility to the β-lactam and ciprofloxacin combination regimens compared to that to the primary β-lactam alone were seen, with these regimens being active against the tested isolates 85 to 88% of the time (Fig. 2). In contrast, tobramycin remained highly active (susceptibility rate, 76 to 80%) against the β-lactam-nonsusceptible isolates, which translated to 14 to 18% gains in susceptibility with tobramycin-containing combinations. The tobramycin-based regimens were active against 94 to 95% of all tested isolates, with the rates of susceptibility to the tobramycin-based regimens consistently being higher than those to the ciprofloxacin-based regimens. These differences were even more pronounced for ICU patient respiratory isolates, with 16 to 25% gains in susceptibility being achieved when ciprofloxacin was added and 28 to 37% gains in susceptibility being achieved when tobramycin was added (Fig. 3). Rates of susceptibility to ceftolozane-tazobactam monotherapy ranged from 92 to 98% across all subgroups of isolates, equaling or surpassing those achieved with the tobramycin-based combination regimens. The gains in susceptibility with the addition of either ciprofloxacin or tobramycin to ceftolozane-tazobactam were negligible (≤3% across all subgroups).

DISCUSSION

Selection of an optimal empirical regimen for the treatment of *P. aeruginosa* infections in the face of an evolving resistance profile remains a continual clinical challenge. A delay of appropriate antibiotic therapy has been associated with detrimental therapeutic outcomes, resulting in prolonged hospital stays and increased mortality (18–20). Thus, ensuring adequate initial therapy should be a high priority. Resistance to β-lactams is commonplace among *P. aeruginosa* isolates, with the rates of nonsusceptibility being 18 to 24% in this study, in line with previously reported data (6,

TABLE 4 Cross-resistance of *P. aeruginosa* isolates to β-lactams and ceftolozane-tazobactam[a]

Isolate and β-lactam	% NS isolates	Of NS isolates, % S to:				
		FEP	CAZ	TZP	MEM	C-T
All patient isolates						
Cefepime	23.0	NA	23.9	20.8	39.4	87.5
Ceftazidime	23.0	23.9	NA	15.2	41.2	86.2
Piperacillin-tazobactam	28.2	35.3	30.8	NA	45.2	90.1
Meropenem	24.0	42.1	43.7	35.8	NA	90.1
ICU patient isolates						
Cefepime	28.4	NA	16.7	13.7	37.3	84.3
Ceftazidime	31.2	24.1	NA	11.6	37.5	83.9
Piperacillin-tazobactam	37.0	33.8	25.6	NA	41.4	88.0
Meropenem	30.1	40.7	35.2	27.8	NA	87.0
Non-ICU patient isolates						
Cefepime	20.8	NA	27.8	24.6	40.6	89.3
Ceftazidime	19.7	23.7	NA	17.5	43.5	87.6
Piperacillin-tazobactam	24.6	36.2	33.9	NA	47.5	91.4
Meropenem	21.6	42.8	48.5	40.2	NA	91.8
Respiratory isolates						
Cefepime	30.4	NA	18.1	16.1	41.6	83.2
Ceftazidime	30.0	17.0	NA	10.9	40.8	83.0
Piperacillin-tazobactam	36.9	30.9	27.6	NA	45.9	87.3
Meropenem	29.6	40.0	40.0	32.4	NA	85.5
Nonrespiratory isolates						
Cefepime	18.3	NA	30.0	25.7	37.1	92.1
Ceftazidime	18.5	31.0	NA	19.7	41.5	89.4
Piperacillin-tazobactam	22.6	39.9	34.1	NA	44.5	93.1
Meropenem	20.5	43.9	47.1	38.9	NA	94.3
ICU patient respiratory isolates						
Cefepime	40.4	NA	17.5	11.1	31.7	81.0
Ceftazidime	39.7	16.1	NA	8.1	32.3	80.6
Piperacillin-tazobactam	49.4	27.3	26.0	NA	32.5	83.6
Meropenem	41.0	32.8	34.4	18.8	NA	85.7
ICU patient nonrespiratory isolates						
Cefepime	19.2	NA	15.4	17.9	46.2	89.7
Ceftazidime	24.6	34.0	NA	16.0	44.0	88.0
Piperacillin-tazobactam	27.6	42.9	25.0	NA	53.6	91.1
Meropenem	21.7	52.3	36.4	40.9	NA	93.2
Non-ICU patient respiratory isolates						
Cefepime	25.7	NA	18.6	19.8	48.8	84.9
Ceftazidime	25.4	17.6	NA	12.9	47.1	84.7
Piperacillin-tazobactam	31.1	33.7	28.8	NA	55.8	88.5
Meropenem	24.3	45.7	44.4	43.2	NA	87.7
Non-ICU patient nonrespiratory isolates						
Cefepime	17.9	NA	35.6	28.7	33.7	93.1
Ceftazidime	16.3	29.3	NA	21.7	40.2	90.2
Piperacillin-tazobactam	20.7	38.5	38.5	NA	40.2	94.0
Meropenem	20.0	40.7	51.3	38.1	NA	94.7

[a]Definitions: CAZ, ceftazidime; C-T, ceftolozane-tazobactam; FEP, cefepime; MEM, meropenem; NA, not applicable; NS, nonsusceptible; TZP, piperacillin-tazobactam; S, susceptible.

7). The β-lactam comparators performed particularly poorly against the ICU patient respiratory isolates, where the rates of susceptibility did not exceed 60%. This was in contrast to the findings for ceftolozane-tazobactam, which demonstrated consistently high levels of activity (>90%) regardless of isolate location or source.

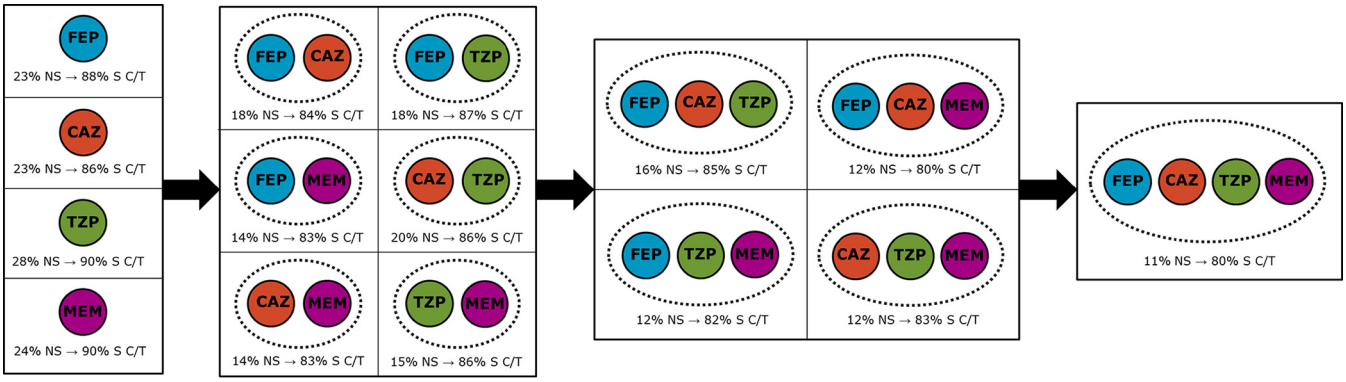

FIG 1 Rates of nonsusceptibility of *P. aeruginosa* isolates to one, two, three, or four β-lactam antibiotics and percentage of nonsusceptible isolates remaining susceptible to ceftolozane-tazobactam. Definitions: CAZ, ceftazidime; C/T, ceftolozane-tazobactam; FEP, cefepime; MEM, meropenem; NS, nonsusceptible; TZP, piperacillin-tazobactam; S, susceptible.

In the empirical setting, many institutions employ a workhorse β-lactam, such as cefepime or meropenem, to be utilized in cases where *P. aeruginosa* infection is suspected. However, these data demonstrate that ≥20% of patients with *P. aeruginosa* infection have an isolate that is resistant and missed by this initial empirical regimen. Resistance to one β-lactam does not always confer resistance to the entire class, and these study data suggest that in approximately 50% of cases an alternative β-lactam will have activity. This discordance in β-lactam susceptibility profiles is primarily due to alterations in membrane permeability or efflux pumps with different affinities for the various β-lactams. For example, overexpression of the multidrug efflux pump mexXY-OprM was previously associated with an increase in the incidence of *P. aeruginosa* strains with a cefepime-resistant, ceftazidime-susceptible phenotype at one institution (21). Therefore, in cases where susceptibilities are known, if an isolate is reported to be susceptible to an alternative β-lactam, it is reasonable to switch therapy to that agent. However, prior to the reporting of susceptibilities or when a sample for culture is unobtainable, the decision of how to manage clinically failing patients is less clear. The use of rapid diagnostic tests to more quickly and accurately detect resistance is a promising future strategy for identifying patients who may benefit from ceftolozane-tazobactam therapy; however, the various technologies are still being developed.

These data indicate that switching to an alternative β-lactam in the absence of susceptibilities is expected to be effective only 20 to 40% of the time due to high rates of cross-resistance. In contrast, ceftolozane-tazobactam would be expected to have activity against approximately 90% of strains resistant to the primary β-lactam, making it a far more reliable therapeutic option. Additionally, in this study *P. aeruginosa* was nonsusceptible to all four β-lactams 11% of the time; however, 80% of these isolates remained ceftolozane-tazobactam susceptible. These data demonstrate that ceftolozane-tazobactam is a viable therapeutic option for the treatment of infections caused by β-lactam-resistant isolates; however, verification of susceptibility using an FDA-cleared test should still be performed when feasible. Additionally, little is known at this time about the potential for the emergence of resistance while on ceftolozane-tazobactam therapy. Although molecular characterization of the mechanisms of β-lactam resistance was not performed in this study, certain mutations in AmpC resulting in overexpression and structural modification have been shown to confer high-level resistance to ceftolozane, even in the presence of tazobactam (22, 23). As with all antibiotics, clinicians should aim to treat patients for the shortest duration necessary in order to ameliorate the potential for the propagation of resistant isolates.

The use of combination therapy is a commonly employed strategy when infection with a resistant *P. aeruginosa* strain is suspected. Although synergistic interactions between antimicrobials play an important role in some infections (e.g., ampicillin and ceftriaxone for enterococcal endocarditis), clinical studies with *P. aeruginosa* have failed

TABLE 5 Susceptibility of *P. aeruginosa* isolates to β-lactams alone and in combination with ciprofloxacin or tobramycin compared to susceptibility to ceftolozane-tazobactam monotherapy[a]

Isolate and β-lactam	% S isolates	Of BL NS isolates, % CIP S	% S to BL-CIP	Of BL NS isolates, % TOB S	% S to BL-TOB	% C-T S
All patient isolates						
Cefepime	77.0	39.8	86.2	78.2	95.0	96.6
Ceftazidime	77.0	45.7	87.5	78.9	95.1	
Piperacillin-tazobactam	71.8	49.2	85.7	80.2	94.4	
Meropenem	76.0	37.4	85.0	76.2	94.3	
ICU patient isolates						
Cefepime	71.6	44.1	84.1	69.6	91.4	95.0
Ceftazidime	68.8	49.1	84.1	74.1	91.9	
Piperacillin-tazobactam	63.0	51.1	81.9	75.2	90.8	
Meropenem	69.9	38.9	81.6	69.4	90.8	
Non-ICU patient isolates						
Cefepime	79.2	37.4	87.0	82.9	96.4	97.2
Ceftazidime	80.3	43.5	88.9	81.9	96.4	
Piperacillin-tazobactam	75.4	48.0	87.2	83.3	95.9	
Meropenem	78.4	36.6	86.3	79.9	95.7	
Respiratory isolates						
Cefepime	69.6	41.6	82.7	81.2	94.7	94.7
Ceftazidime	70.0	45.6	81.6	81.6	92.4	
Piperacillin-tazobactam	63.1	50.3	81.6	82.9	93.7	
Meropenem	70.4	37.2	81.4	74.5	92.4	
Nonrespiratory isolates						
Cefepime	81.7	37.9	88.7	75.0	95.4	97.8
Ceftazidime	81.5	45.8	90.0	76.1	95.6	
Piperacillin-tazobactam	77.4	48.0	88.3	77.5	94.9	
Meropenem	79.5	37.6	87.2	77.7	95.4	
ICU patient respiratory isolates						
Cefepime	59.6	47.6	78.8	74.6	89.7	92.3
Ceftazidime	60.3	51.6	80.8	77.4	91.0	
Piperacillin-tazobactam	50.6	50.6	75.6	75.3	87.8	
Meropenem	59.0	39.1	75.0	67.2	86.5	
ICU patient nonrespiratory isolates						
Cefepime	80.8	38.5	88.2	61.5	92.6	97.0
Ceftazidime	75.4	46.0	86.7	70.0	92.6	
Piperacillin-tazobactam	72.4	51.8	86.7	75.0	93.1	
Meropenem	78.3	38.6	86.7	72.7	94.1	
Non-ICU patient respiratory isolates						
Cefepime	74.3	37.2	83.8	86.0	96.4	95.8
Ceftazidime	74.6	41.2	85.0	84.7	96.1	
Piperacillin-tazobactam	68.9	50.0	84.4	88.5	96.4	
Meropenem	75.7	35.8	84.4	80.2	95.2	
Non-ICU patient nonrespiratory isolates						
Cefepime	82.1	37.6	88.8	80.2	96.5	98.0
Ceftazidime	83.7	45.7	91.1	79.3	96.6	
Piperacillin-tazobactam	79.3	46.2	88.8	78.6	95.6	
Meropenem	80.0	37.2	87.4	79.6	95.9	

[a]Definitions: BL, β-lactam; CIP, ciprofloxacin; C-T, ceftolozane-tazobactam; NS, nonsusceptible; S, susceptible; TOB, tobramycin.

to demonstrate superior outcomes with combination therapy over active monotherapy. Therefore, the primary purpose of dual therapy against *P. aeruginosa* is to increase the probability of having at least one active agent and enhance initial adequate therapy (17). In applying the most recent Infectious Diseases Society of America (IDSA) guidelines for the treatment of VAP, dual therapy with two agents active against Gram-

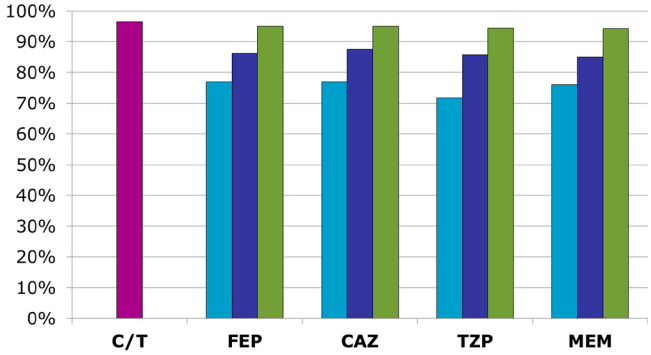

FIG 2 Percent susceptibility of all *P. aeruginosa* isolates ($n = 1,257$) to ceftolozane-tazobactam (pink bar) compared to that to β-lactams alone (light-blue bars) or in combination with ciprofloxacin (dark-blue bars) or tobramycin (green bars). Definitions: CAZ, ceftazidime; C/T, ceftolozane-tazobactam; FEP, cefepime; MEM, meropenem; TZP, piperacillin-tazobactam.

negative bacteria is recommended when the ICU-level incidence-weighted resistance rates of Gram-negative bacteria exceed 10% (9). Although *P. aeruginosa* represents approximately 20% of VAP isolates, enteric Gram-negative bacteria, such as *Klebsiella pneumoniae* and *Escherichia coli*, are collectively more common causes of VAP (20 to 40%) (24, 25) and, within the United States, where the rates of bacterial extended-spectrum β-lactamase production are low, are often more susceptible than *P. aeruginosa* isolates to the comparator β-lactams examined in this study. However, not all facilities have the capacity to calculate a pooled rate of Gram-negative bacterial resistance to each potential empirical antibiotic choice. Therefore, use of the rate of susceptibility of *P. aeruginosa* as a conservative proxy value for the rate of susceptibility of Gram-negative bacteria overall is a common, guideline-endorsed strategy.

The low rates of susceptibility to the comparator β-lactams observed in this study would warrant initial combination therapy; however, a concerning finding of this study was that even when representative combination regimens were utilized, the rates of susceptibility were still below or barely exceeded the threshold of 90% for the ICU patient respiratory isolates. Ciprofloxacin-based combinations performed particularly poorly, with the rates of susceptibility of this resistant subgroup being only 75 to 81%. This observed inferiority of fluoroquinolone-based combinations compared to aminoglycoside-based regimens is in line with previous data, with β-lactam–fluoroquinolone cross-resistance being more common than β-lactam–aminoglycoside cross-resistance (26, 27). This is a limitation of standard antibiograms, which do not account for cross-resistance and may cause clinicians to overestimate the effectiveness of dual therapy. Combination antibiograms, which report *in vitro* suscep-

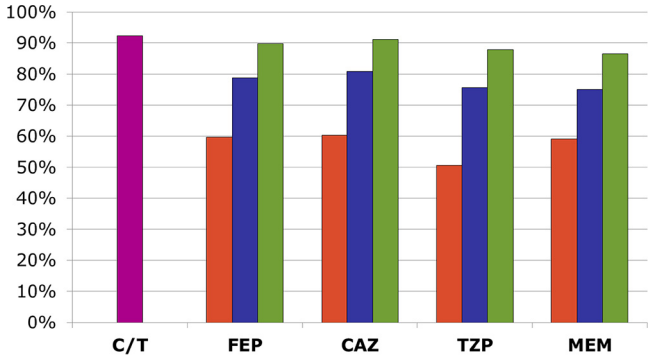

FIG 3 Percent susceptibility of ICU patient respiratory *P. aeruginosa* isolates ($n = 156$) to ceftolozane-tazobactam (pink bar) compared to that to β-lactams alone (orange bars) or in combination with ciprofloxacin (blue bars) or tobramycin (green bars). Definitions: CAZ, ceftazidime; C/T, ceftolozane-tazobactam; FEP, cefepime; MEM, meropenem; TZP, piperacillin-tazobactam.

tibilities to the select antibiotic combinations, may be of enhanced utility when dual therapy is being considered by providing a more accurate picture of the expected benefit (27). Although these data imply that tobramycin-based combination regimens should be preferred, it must be considered that patients with β-lactam-resistant, tobramycin-susceptible isolates would essentially be treated only with an aminoglycoside, at least until the final reporting of susceptibilities. The IDSA guidelines for the treatment of hospital-acquired pneumonia and VAP specifically recommend against aminoglycoside monotherapy, citing meta-analysis data demonstrating lower clinical response rates with aminoglycoside-containing regimens than with aminoglycoside-free regimens (56% versus 68%; relative risk, 0.82; 95% confidence interval, 0.71 to 0.95), though without a corresponding increase in mortality (9). In contrast, ceftolozane-tazobactam susceptibilities were sufficient to allow empirical monotherapy; in addition, ceftolozane-tazobactam had a more favorable side effect profile than either the aminoglycosides or fluoroquinolones. Robust clinical data assessing the efficacy of ceftolozane-tazobactam for the treatment of nosocomial pneumonia are still needed; however, early data from a retrospective study are promising (28). Currently, a phase 3 randomized controlled trial (ClinicalTrials.gov registration number NCT02070757) of ceftolozane-tazobactam versus meropenem is in the recruitment phase and should help to further define ceftolozane-tazobactam's efficacy for this indication.

Although this study's results suggest a significant potential role for ceftolozane-tazobactam within empirical and definitive therapy regimens, it should be noted that local resistance rates are key to determining the utility of ceftolozane-tazobactam for a specific institution. For example, at an institution where the rates of *P. aeruginosa* susceptibility to cefepime, ceftazidime, and piperacillin-tazobactam approach or exceed 90%, including within the ICU, empirical therapy with ceftolozane-tazobactam would be rarely indicated in the absence of patient-specific risk factors indicating a high probability of multidrug-resistant *P. aeruginosa* infection and the use of ceftolozane-tazobactam should not be routine. However, in regions where resistant *P. aeruginosa* is endemic, such as southern and southeastern Europe (8), the use of ceftolozane-tazobactam as empirical therapy for at-risk patients may be a promising strategy. With the increased utilization of hospital order sets, members of hospitals' antimicrobial stewardship committees and pharmacy and therapeutics committees are encouraged to utilize antibiogram results in building disease-specific order sets to help direct clinicians to the most appropriate antibiotic on the basis of local resistance trends and risk factors.

Whether these high levels of susceptibility to ceftolozane-tazobactam can be maintained over time remains to be seen. As noted above, resistance already exists among *P. aeruginosa* isolates, albeit at very low levels. Active and ongoing antimicrobial stewardship efforts, including dose optimization and prompt deescalation to alternative antibiotics as susceptibilities become available, will likely be required to preserve the activity of ceftolozane-tazobactam in the future.

Conclusions. The rates of *P. aeruginosa* resistance to commonly utilized antibiotics can be substantial, and the risk appears to be the highest for the most critically ill patients. Ceftolozane-tazobactam demonstrated significantly enhanced activity against *P. aeruginosa* compared to the other β-lactams, with its potency against ICU isolates being maintained and cross-resistance being limited. Additionally, ceftolozane-tazobactam monotherapy may provide a safe and effective alternative to combination antimicrobial therapy. Although clinical data are needed to substantiate these results, ceftolozane-tazobactam appears to be a highly active option for the treatment of documented or suspected *P. aeruginosa* infections.

MATERIALS AND METHODS

Between June 2013 and September 2014, 1,257 nonduplicate, nonurine isolates of *P. aeruginosa* were obtained from adult inpatients in 44 geographically diverse hospitals. The isolates were processed at the Center for Anti-Infective Research and Development (Hartford Hospital, Hartford, Connecticut) and transferred onto Trypticase soy agar plates (5% blood) for MIC determination. The β-lactam comparators investigated were cefepime, ceftazidime, piperacillin-tazobactam, and meropenem. Ciprofloxacin and

tobramycin were additionally assessed. MICs for ceftolozane-tazobactam and comparator antimicrobials were determined with CLSI broth microdilution methods and interpreted according to 2017 CLSI breakpoints. An isolate was classified as susceptible to a combination regimen if it was susceptible to one or both antibiotics. Ceftolozane-tazobactam was provided courtesy of Cubist Pharmaceuticals (Lexington, MA); other antibiotics were purchased from Sigma (St. Louis, MO). Additional laboratory methods are further described in detail in a previous publication (29).

ACKNOWLEDGMENTS

This work was supported by Cubist Pharmaceuticals (Lexington, MA) for collection of the original surveillance data. No additional funds were provided for the current analysis.

The funders had no role in study design, data collection and interpretation, or the decision to submit the work for publication.

During 2016 and 2017, K. J. Goodlet received grant support from Merck. D. P. Nicolau has received research grants and is on the speakers' bureau of Cubist Pharmaceuticals. M. D. Nailor has received grant support or honorarium from Merck and Astellas.

REFERENCES

1. Sievert DM, Ricks P, Edwards JR, Schneider A, Patel J, Srinivasan A, Kallen A, Limbago B, Fridkin S. 2013. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009-2010. Infect Control Hosp Epidemiol 34:1–14. https://doi.org/10.1086/668770.
2. Sader HS, Farrell DJ, Flamm RK, Jones RN. 2014. Antimicrobial susceptibility of gram-negative organisms isolated from patients hospitalized in intensive care units in United States and European hospitals (2009–2011). Diagn Microbiol Infect Dis 78:443–448. https://doi.org/10.1016/j.diagmicrobio.2013.11.025.
3. Richards MJ, Edwards JR, Culver DH, Gaynes RP. 2000. Nosocomial infections in combined medical-surgical intensive care units in the United States. Infect Control Hosp Epidemiol 21:510–515. https://doi.org/10.1086/501795.
4. Lambert ML, Suetens C, Savey A, Palomar M, Hiesmayr M, Morales I, Agodi A, Frank U, Mertens K, Schumacher M, Wolkewitz M. 2011. Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study. Lancet Infect Dis 11:30–38. https://doi.org/10.1016/S1473-3099(10)70258-9.
5. Lister PD, Wolter DJ, Hanson ND. 2009. Antibacterial-resistant *Pseudomonas aeruginosa*: clinical impact and complex regulation of chromosomally encoded resistance mechanisms. Clin Microbiol Rev 22:582–610. https://doi.org/10.1128/CMR.00040-09.
6. Farrell DJ, Flamm RK, Sader HS, Jones RN. 2013. Antimicrobial activity of ceftolozane-tazobactam tested against *Enterobacteriaceae* and *Pseudomonas aeruginosa* with various resistance patterns isolated in U.S. hospitals (2011-2012). Antimicrob Agents Chemother 57:6305–6310. https://doi.org/10.1128/AAC.01802-13.
7. Morrow BJ, Pillar CM, Deane J, Sahm DF, Lynch AS, Flamm RK, Peterson J, Davies TA. 2013. Activities of carbapenem and comparator agents against contemporary US *Pseudomonas aeruginosa* isolates from the CAPITAL surveillance program. Diagn Microbiol Infect Dis 75:412–416. https://doi.org/10.1016/j.diagmicrobio.2012.12.012.
8. European Centre for Disease Prevention and Control. 2017. Antimicrobial resistance surveillance in Europe 2015. Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). European Centre for Disease Prevention and Control, Stockholm, Sweden.
9. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, Napolitano LM, O'Grady NP, Bartlett JG, Carratalà J, El Solh AA, Ewig S, Fey PD, File TM, Jr, Restrepo MI, Roberts JA, Waterer GW, Cruse P, Knight SL, Brozek JL. 2016. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 63:e61–e111. https://doi.org/10.1093/cid/ciw353.
10. Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, Ortqvist A, Schaberg T, Torres A, van der Heijden G, Read R, Verheij TJ. 2011. Guidelines for the management of adult lower respiratory tract infections. Clin Microbiol Infect 17:E1–E59. https://doi.org/10.1111/j.1469-0691.2011.03672.x.
11. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR. 2011. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 52:427–431. https://doi.org/10.1093/cid/ciq147.
12. Baden LR, Swaminathan S, Angarone M, Blouin G, Casper C, Cooper B, Dubberke ER, Engemann AM, Freifeld AG, Greene JN, Gregg K, Hakim H, Ito JI, Lustberg ME, Montoya JG, Rolston K, Satyanarayana G, Schulz L, Segal B, Seo SK, Shoham S, Taplitz R, Tupal J, Wilson JW. NCCN clinical practice guidelines in oncology: prevention and treatment of cancer-related infections, version 2.2017. National Comprehensive Cancer Network, Washington, PA.
13. Averbuch D, Orasch C, Cordonnier C, Livermore DM, Mikulska M, Viscoli C, Gyssens IC, Kern WV, Klyasova G, Marchetti O, Engelhard D, Akova M. 2013. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. Haematologica 98:1826–1835. https://doi.org/10.3324/haematol.2013.091025.
14. Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, Rao N, Hanssen A, Wilson WR. 2013. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 56:e1–e25. https://doi.org/10.1093/cid/cis803.
15. Berbari EF, Kanj SS, Kowalski TJ, Darouiche RO, Widmer AF, Schmitt SK, Hendershot EF, Holtom PD, Huddleston PM, III, Petermann GW, Osmon DR, Infectious Diseases Society of America. 2015. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. Clin Infect Dis 61:e26–e46. https://doi.org/10.1093/cid/civ482.
16. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, et al. 2017. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med 45:486–552. https://doi.org/10.1097/CCM.0000000000002255.
17. Boyd N, Nailor MD. 2011. Combination antibiotic therapy for empiric and definitive treatment of gram-negative infections: insights from the Society of Infectious Diseases Pharmacists. Pharmacotherapy 31:1073–1084. https://doi.org/10.1592/phco.31.11.1073.
18. Chamot E, Boffi El Amari E, Van Delden C. 2003. Effectiveness of combination antimicrobial therapy for *Pseudomonas aeruginosa* bacteremia. Antimicrob Agents Chemother 47:2756–2764. https://doi.org/10.1128/AAC.47.9.2756-2764.2003.
19. Dupont H, Mentec H, Sollet JP, Bleichner G. 2001. Impact of appropriateness of initial antibiotic therapy on the outcome of ventilator-associated pneumonia. Intensive Care Med 27:355–362. https://doi.org/10.1007/s001340000640.

20. Kollef KE, Schramm GE, Wills AR, Reichley RM, Micek ST, Kollef MH. 2008. Predictors of 30-day mortality and hospital costs in patients with ventilator-associated pneumonia attributed to potentially antibiotic-resistant gram-negative bacteria. Chest 134:281–287. https://doi.org/10.1378/chest.08-1116.
21. Laohavaleeson S, Lolans K, Quinn JP, Kuti JL, Nicolau DP. 2008. Expression of the MexXY-OprM efflux system in *Pseudomonas aeruginosa* with discordant cefepime/ceftazidime susceptibility profiles. Infect Drug Resist 1:51–55.
22. Cabot G, Bruchmann S, Mulet X, Zamorano L, Moyà B, Juan C, Haussler S, Oliver A. 2014. *Pseudomonas aeruginosa* ceftolozane-tazobactam resistance development requires multiple mutations leading to overexpression and structural modification of AmpC. Antimicrob Agents Chemother 58:3091–3099. https://doi.org/10.1128/AAC.02462-13.
23. Berrazeg M, Jeannot K, Ntsogo Enguéné VY, Broutin I, Loeffert S, Fournier D, Plésiat P. 2015. Mutations in β-lactamase AmpC increase resistance of *Pseudomonas aeruginosa* isolates to antipseudomonal cephalosporins. 2015. Antimicrob Agents Chemother 59:6248–6255. https://doi.org/10.1128/AAC.00825-15.
24. Weiner LM, Webb AK, Limbago B, Dudeck MA, Patel J, Kallen AJ, Edwards JR, Sievert DM. 2016. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. Infect Control Hosp Epidemiol 37:1288–1301. https://doi.org/10.1017/ice.2016.174.
25. Jones RN. 2010. Microbial etiologies of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. Clin Infect Dis 51:S81–S87. https://doi.org/10.1086/653053.
26. Micek ST, Welch EC, Khan J, Pervez M, Doherty JA, Reichley RM, Kollef MH. 2010. Empiric combination antibiotic therapy is associated with improved outcome against sepsis due to gram-negative bacteria: a retrospective analysis. Antimicrob Agents Chemother 54:1742–1748. https://doi.org/10.1128/AAC.01365-09.
27. Liang B, Wheeler JS, Blanchette LM. 2016. Impact of combination antibiogram and related education on inpatient fluoroquinolone prescribing patterns for patients with health care-associated pneumonia. Ann Pharmacother 50:172–179. https://doi.org/10.1177/1060028015625658.
28. Munita JM, Aitken SL, Miller WR, Perez F, Rosa R, Shimose LA, Lichtenberger PN, Abbo LM, Jain R, Nigo M, Wanger A, Araos R, Tran TT, Adachi J, Rakita R, Shelburne S, Bonomo RA, Arias CA. 14 March 2017. Multicenter evaluation of ceftolozane/tazobactam for serious infections caused by carbapenem-resistant *Pseudomonas aeruginosa*. Clin Infect Dis. https://doi.org/10.1093/cid/cix014.
29. Sutherland CA, Nicolau DP. 2015. Susceptibility profile of ceftolozane/tazobactam and other parenteral antimicrobials against *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* from US hospitals. Clin Ther 37:1564–1571. https://doi.org/10.1016/j.clinthera.2015.05.501.