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MAJOR ARTICLE

Higher MICs (>2 mg/L) Predict 30-Day Mortality in Patients With Lower Respiratory Tract Infections Caused by Multidrug- and Extensively Drug-Resistant *Pseudomonas aeruginosa* Treated With Ceftolozane/Tazobactam

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Background. Ceftolozane/tazobactam (C/T) efficacy and safety in ventilator-associated pneumonia (VAP) is being evaluated at a double dose by several trials. This dosing is based on a pharmacokinetic (PK) model that demonstrated that 3 g q8h achieved ≥90% probability of target attainment (50% fT > minimal inhibitory concentration [MIC]) in plasma and epithelial lining fluid against C/T-susceptible *P. aeruginosa*. The aim of this study was to evaluate the efficacy of different C/T doses in patients with lower respiratory infection (LRI) due to MDR- or XDR-*P. aeruginosa* considering the C/T MIC.

Methods. This was a multicenter retrospective study of 90 patients with LRI caused by resistant *P. aeruginosa* who received a standard or high dose (HDo) of C/T. Univariable and multivariable analyses were performed to identify independent predictors of 30-day mortality.

Results. The median age (interquartile range) was 65 (51–74) years. Sixty-three (70%) patients had pneumonia, and 27 (30%) had tracheobronchitis. Thirty-three (36.7%) were ventilator-associated respiratory infections. The median C/T MIC (range) was 2 (0.5–4) mg/L. Fifty-four (60%) patients received HDo. Thirty-day mortality was 27.8% (25/90). Mortality was significantly lower in patients with *P. aeruginosa* strains with MIC ≤2 mg/L and receiving HDo compared with the groups with the same or higher MIC and dosage (16.2% vs 35.8%; $P = .041$). Multivariate analysis identified septic shock ($P < .001$), C/T MIC >2 mg/L ($P = .045$), and increasing Charlson Comorbidity Index ($P = .019$) as independent predictors of mortality.

Conclusions. The effectiveness of C/T in *P. aeruginosa* LRI was associated with an MIC ≤2 mg/L, and the lowest mortality was observed when HDo was administered for strains with C/T MIC ≤2 mg/L. HDo was not statistically associated with a better outcome.

Keywords. ceftolozane/tazobactam; multidrug-resistant; pneumonia; *Pseudomonas aeruginosa*; tracheobronchitis.

Multidrug-resistant (MDR) and extensively drug-resistant (XDR) *P. aeruginosa* are frequently associated with severe health care–related infections and high mortality rates [1–4]. Until recently, therapeutic options for β-lactam-resistant *P. aeruginosa* were limited to potentially nephrotoxic agents like colistin or aminoglycosides [5–7]. Nevertheless, the development of ceftolozane-tazobactam (C/T) offers a new option for infections caused by many of these resistant strains.

Ceftolozane is a third-generation cephalosporin with improved activity against derepressed AmpC ß-lactamase-producing *P. aeruginosa*, and its effectiveness is not affected by efflux pump expression or deletion of the membrane protein OprD [8]. Tazobactam is a ß-lactamase inhibitor that improves ceftolozane activity against extended-spectrum ß-lactamase-producing *Enterobacteriaceae* and some anaerobes. Currently, C/T is indicated for the treatment of complicated

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intra-abdominal infections (cIAIs) and urinary tract infections (cUTIs) at a dose of 1.5 g q8h [9, 10]. However, the frequency and severity of MDR- and XDR-*P. aeruginosa* pneumonia have led physicians to off-label use of C/T with preliminary good results [11–17], although to date there is no consensus about the proper dose considering the C/T minimal inhibitory concentration (MIC) for the infecting strain.

Recently, a population pharmacokinetic (PK) model demonstrated that doubling the current Food and Drug Administration (FDA) and European Medicines Agency (EMA)–approved dose to 3 g q8h in patients with normal renal function increases the probability of target attainment (PTA) in the epithelial lining fluid (ELF) for *P. aeruginosa* with MICs of up to 8 mg/L, although for susceptible strains (MIC ≤ 4 mg/L), the regular dosage (1.5 g q8h) still had a 90% PTA for a 50% *f*T > MIC and virtually a 100% PTA for 1-log kill target (32.2% *f*T > MIC) [18]. The efficacy and safety of high-dose C/T are being assessed in a trial on subjects with ventilator-associated pneumonia (VAP; ClinicalTrials.gov Identifier: NCT02070757). In the meantime, we conducted a retrospective multicenter study to evaluate the efficacy of different C/T doses in a cohort of patients with lower respiratory infection (LRI) due to MDR- or XDR-*P. aeruginosa* considering the C/T MIC.

METHODS

Study Design

This is a retrospective, observational study of all consecutive patients with a diagnosis of LRI (pneumonia or purulent tracheobronchitis) due to MDR- or XDR-*P. aeruginosa* who received treatment with C/T between 2016 and 2018. The study was conducted at 13 hospitals in 4 countries (United States, n = 6; Spain, n = 5; France, n = 1; United Kingdom, n = 1). To be eligible, patients had to have resistant *P. aeruginosa* isolation from at least 1 of the following samples: sputum, pleural fluid, tracheobronchial aspirate, bronchoalveolar lavage, or blood culture. Some of them have been previously published [12–14, 16, 17, 19]. The following data were recorded: age, sex, comorbidities (diabetes, chronic obstructive pulmonary disease, asthma, heart disease, peripheral vascular disease, cerebrovascular disease, chronic hepatocellular disease, chronic kidney disease, hematologic and solid malignancy, cystic fibrosis), solid organ or bone marrow transplant, severity of underlying disease calculated by the Charlson Comorbidity Index (CCI), ventilator-associated infection, presence of septic shock and bacteremia, glomerular filtration, renal replacement therapy requirement, previous active antibiotherapy, days from LRI diagnosis to start of C/T, dose and duration of therapy, and concomitant active antibiotic therapy. Patients' epidemiological and clinical data were collected from the electronic medical records of each participant hospital. Patients with any of the following criteria were excluded: (a) duration of therapy shorter than 72 hours, (b) nonavailability of MIC, or (c) documented resistance to C/T. Each investigator obtained approval from the ethics committee of the corresponding institution.

Microbiological Data

The identification of *P. aeruginosa* was performed according to the standard criteria of each center. *P. aeruginosa* was classified as MDR or XDR, as previously defined [20]. C/T susceptibility was determined by e-test [21]. The strain was classified as susceptible if the C/T MIC was ≤4 mg/L, according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Definitions

All eligible patients met the clinical diagnosis of pneumonia or tracheobronchitis, as defined by the Centers for Disease Control and Prevention/National Healthcare Safety Network. Thereby, pneumonia was identified by using a combination of imaging; clinical and laboratory criteria consisting of new and persistent infiltrate; consolidation or cavitation on chest imaging; at least 2 of the following: fever (>38.0°C), leukopenia (≤4000 white blood cell count [WBC]/mm^3), or leukocytosis (>12 000 WBC/mm^3); for adults >70 years old, altered mental status with no other recognized cause; at least 3 of the following: new onset of purulent sputum or change in character of sputum, increased respiratory secretions, increased suctioning requirements, new-onset or worsening cough, dyspnea, tachypnea, rales or bronchial breath sounds, or worsening gas exchange (eg, O2 desaturation, increased oxygen requirements, or increased ventilator demand); and isolation of *P. aeruginosa* in at least 1 sample: sputum, tracheal aspirate, broncoalveolar aspiration or bronchoalveolar lavage, pleural fluid, or blood culture. Tracheobronchial infection must include at least 1 of the following criteria: patient had no clinical or radiographic evidence of pneumonia and patient had at least 2 of the following signs or symptoms with no other recognized cause: fever (>38.0°C), cough, new or increased sputum production, rhonchi, wheezing; and at least 1 positive culture for *P. aeruginosa* obtained by deep tracheal aspirate or bronchoscopy on respiratory secretions [22]. Impaired renal function was defined as an estimated creatinine clearance (CrCl) ≤50 mL/min in those patients without renal replacement therapy requirement. The standard dose was considered when C/T was administered at the FDA/EMA-approved dosage for cIAI and cUTI: 1.5 g q8h for patients with a CrCl >50 mL/min; 750 mg q8h for patients with a CrCl of 30–50 mL/min; 375 mg q8h for patients with a CrCl of 15–29 mL/min; and a single loading dose of 750 mg followed by a 150-mg maintenance dose q8h for patients with end-stage renal disease or on intermittent hemodialysis. SDo for patients on continuous renal replacement therapy (CRRT) was 1.5 g q8h [23, 24]. High-dose was defined as the administration of double (or more) the FDA/EMA-approved dose for C/T. These means a patient with a CrCl of 30–50 mL/min who received 750 mg q8h would be included in the SDo group, whereas another patient with the same CrCl who received 1.5 g q8h would be included in the HDo

group. The antibiotic dosage was selected at the discretion of the attending physician. Combination therapy was considered when another active antipseudomonal drug (aminoglycoside, colistimethate or quinolone) was given intravenously and simultaneously with C/T. Adverse events were defined as any untoward effect starting during the course of treatment that could be attributable to C/T. Clinical success was defined as resolution of clinical signs and symptoms of infection, absence of recurrence, and 30-day survival from the beginning of C/T therapy. Thirty-day mortality was considered when the patient died within 30 days after C/T onset.

Statistical Analysis

The primary outcome was 30-day mortality. The Student *t* test was used to compare continuous variables. The chi-square test or Fisher exact test was used to compare categorical variables. Univariable and multivariable logistic regression models were constructed to identify risk factors associated with mortality. All variables that showed significance in the univariate analysis (<.10) were included in a stepwise backward multivariate logistic regression analysis. Data were analyzed using Statistical Package for the Social Sciences (SPSS) software (version 23.0). All analyses were 2-tailed, and a *P* value <.05 was considered statistically significant.

RESULTS

Cohort Description

Of the 123 patients with LRI due to resistant *P. aeruginosa* who received treatment with C/T, 90 (73.2%) patients were eligible for the study. The flowchart of the inclusion process is shown in Figure 1. Sixty-five (72.2%) were male, and the median age (interquartile range [IQR]) was 65 (51–74) years. The main comorbidities were chronic lung disease (43.3%), vascular disease (28.9%), and diabetes (16.7%). Eight (8.9%) patients were solid organ transplant recipients (5 lung transplant). Six (6.7%) patients had cystic fibrosis. The median CCI (IQR) was 5 (2–6). The respiratory infection was pneumonia in 63 (70%) patients, of whom 4 had bacteremia and 3 empyema, and purulent tracheobronchitis in the remaining 27 (30%). In 33 (36.7%) patients, the infection was ventilator-associated and 31 (34.4%) presented with septic shock. Twenty-five (27.8%) subjects had impaired renal function, and 11 (12.2%) required CRRT.

Microbiology and Treatment

Sixty-nine (76.7%) isolates of *P. aeruginosa* were XDR. The median C/T MIC (range) was 2 (0.5–4) mg/L. The distribution for C/T MICs is shown in Figure 2. Thirty-six (40%) patients received SDo of C/T, and 54 (60%) received HDo according to the definition described in the "Methods" section. Thirty-seven out of 68 (54.4%) patients with an MIC ≤2 mg/L for *P. aeurginosa* received HDo, whereas 17 out of 22 (77.2%) patients with an MIC >2 mg/L received HDo (*P* = .080). In the SDo group, 77.7% (28/36) of patients had pneumonia, and in the HDo group 64.8% (35/54; *P* = .243). The median duration of therapy (IQR) was 14 (10–16) days. Sixty (40%) patients received concomitant intravenous and/or nebulized active antibiotics, which were intravenous colistimethate, aminoglycosides, or fluoroquinolones in 36 (40%) and nebulized colistimethate or aminoglycosides in

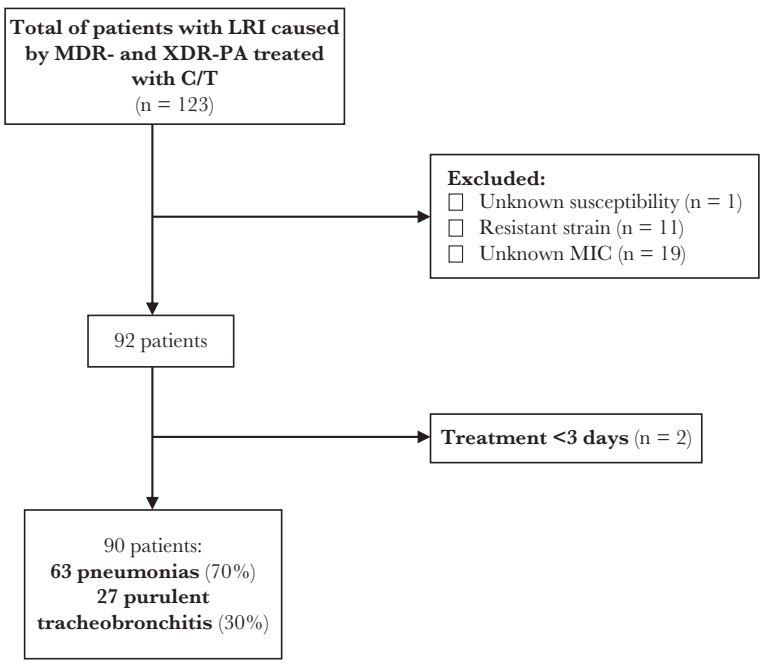

Figure 1. Flowchart of patients' inclusion criteria. Abbreviations: C/T, ceftolozane/tazobactam; LRI, lower respiratory infection; MDR, multidrug-resistant; MIC, minimal inhibitory concentration; XDR-PA, extensively drug-resistant P. aeruginosa.

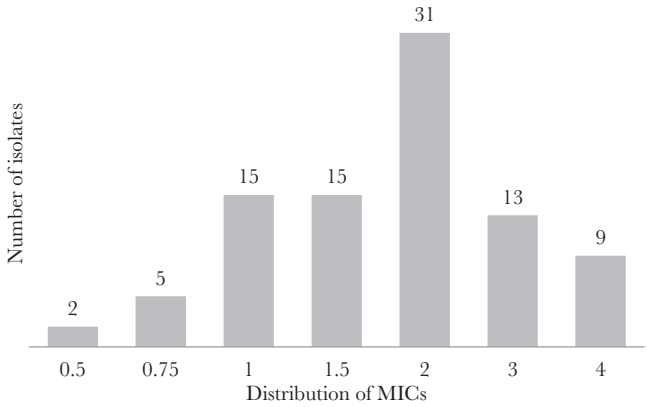

Figure 2. Ceftolozane/tazobactam minimal inhibitory concentration distribution for *Pseudomonas aeruginosa*. Abbreviation: MIC, minimal inhibitory concentration.

30 (33.3%). Follow-up samples to document eradication were obtained in 67 cases.

Outcomes and Adverse Events

The overall 30-day mortality rate was 27.8% (25/90), 33% (21/63) in pneumonia and 14.8% (4/27) in tracheobronchitis. Clinical success was reached in 56.7% of patients (51/90). Factors associated with 30-day mortality in the univariate analysis included a high CCI ($P = .029$), septic shock ($P < .001$), and an MIC ≤2 mg/L ($P = .033$). A trend toward higher mortality was observed in patients with pneumonia ($P = .072$), ventilator-associated LRI ($P = .061$), and CRRT ($P = .066$). Renal failure, bacteremia, use of intravenous combination therapy, C/T administered within the first 48 hours of the infection diagnosis, and time to initiation of C/T or HDo were not significantly associated with 30-day mortality. For the analysis of the interaction between the MIC and C/T doses, we created a new combined variable using dichotomized MIC (≤ or >2 mg/L) and C/T dose (SDo or HDo) to describe the outcome (Table 1). Interestingly, mortality was significantly lower in those patients receiving HDo and having *P. aeruginosa* with a C/T MIC ≤2 mg/L than in the rest of the groups (6 out of 37, 16.2%, vs 19 out of 53, 35.8%; $P = .041$) and progressively increased from 29% (9 out of 31) in the MIC ≤2 mg/L and SDo group to 41.2% (7 out of 17) in the MIC >2 mg/L and HDo group, and to 60% (3 out of 5) in the MIC >2 mg/L and SDo group (Table 1). Mortality trend according to C/T dosing and MIC is shown in Figure 3. The best multivariable model predicting 30-day mortality is shown in Table 2. Factors independently associated with mortality were septic shock ($P < .001$), C/T MIC >2 mg/L ($P = .045$), and increasing CCI ($P = .037$).

Four episodes of adverse reactions were attributable to C/T: leukopenia, encephalopathy plus myoclonus, renal failure, and hepatitis.

DISCUSSION

To our knowledge, this is the largest cohort study evaluating the outcome of patients with LRI due to MDR- and XDR-*P. aeruginosa* treated with C/T. The overall 30-day mortality rate was 27.8% (25/90), and 33% (21/63) for patients with pneumonia. These figures were lower than the 40%–50% previously reported in patients with pneumonia due to resistant and nonresistant *P. aeruginosa* treated with other antibiotics [1–4]. In recent retrospective studies of patients with resistant *P. aeruginosa* infections who received C/T, 30- and 90-day mortality rates for LRI ranged between 11% (2/18) and 33% (2/6) [14, 15, 17] and 21% (3/14) [13], respectively. Despite the small size, retrospective nature, and potential indication bias in these studies, the low mortality rate is noteworthy, particularly in a cohort like ours, characterized by a median age of 65 years, a median CCI of 5, and the presence of septic shock in 34% of the cases.

C/T current approved dosage is 1.5 g q8h, and a population pharmacokinetic model indicated that this exposure had a ≥90% probability of attaining a 50% fT > MIC target in plasma and ELF against *P. aeruginosa* with an MIC of up to 4 mg/L (EUCAST breakpoint) [18]. However, SDo was far from achieving the 50% fT > MIC ELF target for strains with MICs of up to 8 mg/L (59% PTA), which only could be approached with HDo (87.7% PTA). Even if in Europe, a strain with an MIC of 8 mg/L would be considered resistant, and hence the use of C/T strongly discouraged. Clinicians may still consider it more reliable to resort to high-dose C/T when treating patients with pneumonia due to C/T-susceptible *P. aeruginosa* because in about 25% of cases the MIC may be higher than 2 mg/L, and therefore anywhere within a double dilution of the actually measured 3–4 mg/L MIC value. Although there are no clinical data supporting the use of higher doses of C/T considering the MIC value [11–17], 2 studies showed a relationship between clinical failure and a higher MIC [13, 17].

To investigate these questions, we analyzed 90 patients treated with C/T. The main finding was the association of an increasing MIC with mortality. A relative 82% increase in mortality per each point of increment in MIC was noted after adjusting for the most relevant prognostic factors (septic shock and CCI) (Table 2). We also noted what seems to be an influence of dosage on mortality, as is shown in Figure 3 by the rather parallel disposition of the SDo and HDo lines. However, the 12%–20% greater 30-day mortality between patients receiving SDo and HDo observed across the entire MIC range did not reach statistical significance. Indeed, the lowest mortality rate was observed in those patients receiving HDo when the C/T MIC was ≤2 mg/L (16%), supporting the recommendation of HDo for patients with *P. aeruginosa* LRI. On the other hand, even using HDo, the mortality rate when the C/T MIC was >2 mg/L was high (Figure 3). These results agree with a recent study in which the authors evaluated the outcome of *P. aeruginosa* bacteremia treated with cefepime and observed that the use of a high dose (2 g q8h) did not improve the outcome when the MIC was >2 mg/L [25]. We cannot provide a definitive explanation of the

Table 1. Univariate Analysis of Factors Associated With 30-Day Mortality in the 90 Patients With MDR- and XDR-*Pseudomonas aeruginosa* Lower Respiratory Tract Infection

Variable	Survivors (n = 65)	Nonsurvivors (n = 25)	*P* Value	OR (95% CI)
Male sex	48 (73.8)	17 (68)	.579	1.3 (0.5–3.6)
Age (SD), y	61 (18.8)	63 (13.5)	.626	1 (0.9–1)
Comorbidities				
Diabetes	11 (16.9)	4 (16)	1	0.9 (0.9–3.2)
Chronic renal failure	11 (16.9)	2 (8)	.503	0.4 (0.1–2.1)
Vascular disease	17 (26.2)	9 (36)	.356	1.6 (0.6–4.3)
Cirrhosis	3 (4.6)	1 (4)	1	0.9 (0.1–8.7)
Asthma/COPD	28 (43.1)	11 (44)	.937	1 (0.4–2.6)
Cystic fibrosis	6 (9.2)	0	.181	-
Solid cancer	9 (13.8)	4 (16)	.749	1.2 (0.3–4.3)
Hematological cancer	3 (4.6)	1 (4)	1	0.9 (0.9–8.7)
Solid organ transplant recipient	6 (9.2)	2 (8)	1	0.9 (0.2–4.5)
Charlson index score (SD)	4.2 (2.6)	5.56 (2.8)	.029	1.2 (1–1.4)
Pneumonia	42 (64.6)	21 (84)	.072	2.9 (0.9–9.4)
Ventilator-associated infection	20 (30.8)	13 (52)	.061	2.4 (0.9–6.3)
Bacteremia	3 (4.6)	1 (4)	.899	0.9 (0.9–8.7)
Septic shock	15 (23.1)	16 (64)	<.001	5.9 (2.2–16.1)
Glomerular filtration ≤50 mL/min	19 (29.2)	6 (24)	.620	0.8 (0.3–2.2)
CRRT	5 (7.7)	6 (24)	.066	3.8 (1–13.8)
XDR	48 (73.8)	21 (84)	.308	1.9 (0.6–6.2)
MIC ≤ 2 mg/L	53 (81.5)	15 (60)	.033	0.3 (0.1–0.9)
MIC (SD), mg/L	1.8 (0.9)	2.4 (1.1)	.019	1.8 (1.1–3)
HDo	41 (63.1)	13 (52)	.349	0.6 (0.3–1.6)
C/T MIC and dose interaction				
MIC ≤ 2 mg/L + HDo	31 (47.7)	6 (24)	.041	0.3 (0.1–0.9)
MIC ≤ 2 mg/L + SDo	22 (33.8)	9 (36)	.847	1.1 (0.4–2.9)
MIC > 2 mg/L + HDo	10 (15.4)	7 (28)	.229	2.1 (0.7–6.4)
MIC > 2 mg/L + SDo	2 (3.1)	3 (12)	.129	4.3 (0.7–27.4)
C/T within 48 h (55 out of 78)[a]	32 (58.2)	13 (56.5)	1	0.9 (0.4–2.5)
Previous active antibiotherapy (33 out of 78)[b]	11 (47.8)	8 (80)	.131	1.8 (0.8–2.2)
Mean time to C/T (SD), d[a]	3.6 (5.7)	3.7 (5.8)	.971	1 (0.9–1.1)
Mean duration of C/T (SD), d	14 (5.8)	12.8 (5.8)	.363	0.9 (0.8–1)
Concomitant intravenous treatment	23 (35.4)	13 (52)	.150	2 (0.8–5)
Adverse reactions	3 (4.6)	1 (4)	1	1.2 (0.1–11.7)

Abbreviations: C/T, ceftolozane/tazobactam; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; HDo, pharmacokinetics-based dose; MDR, multidrug-resistant; MIC, minimal inhibitory concentration; OR, odds ratio; SDo, standard dose; XDR, extensively drug-resistant.

[a]Within the first 48 hours after *P.aeruginosa* was isolated. This information was available in 78 cases.

[b]Information available in 78 cases. The 45 cases where C/T was the initial antibiotic were also excluded.

relationship between increasing MIC and mortality. In the neutropenic mouse infection model, the MIC value does not affect the microbiological response when the appropriate %*f*T > MIC is attained [26]. Obviously, an increase in MIC will diminish the magnitude of any PK-PD parameter, including the *f*T > MIC. However, for MICs ≤1 mg/L, a 100% PTA in ELF for the 50% *f*T > MIC target is expected with SDo, and we still found a 23% greater mortality in patients infected with these strains when treated with SDo vs HDo. The majority of animal models have demonstrated that *f*T > MIC values of ≥60%–70% for cephalosporins, ≥50% for penicillins, and ≥40% for carbapenems provide maximal bactericidal effect [27]. However, some clinical studies have indicated that a 100% *f*T > MIC for ceftazidime and cefepime, or even a 95% 4.3*T > MIC for cefepime, is necessary for optimal response in patients with infections due to gram-negative bacilli [28, 29]. In the neutropenic mouse infection model, *P. aeruginosa* T > MIC targets for C/T in plasma are lower than for other cephalosporins and similar to those for carbapenems (about 40% *f*T > MIC for maximal bactericidal activity) [26, 30]. However, even for carbapenenems, more stringent PK-PD targets have been associated with improved clinical or microbiological response in febrile neutropenic patients with bacteremia (>75% T > MIC) and patients with LRI (fC_{min}/MIC > 5) [31, 32]. Aditionally, MICs > 2 mg/L may reflect the presence of first-step (low-level) resistance mechanisms (such as AmpC overexpression) that could favor the emergence of high-level (clinical) resistance (such as mutations leading to the structural modification of AmpC) leading to treatment failure

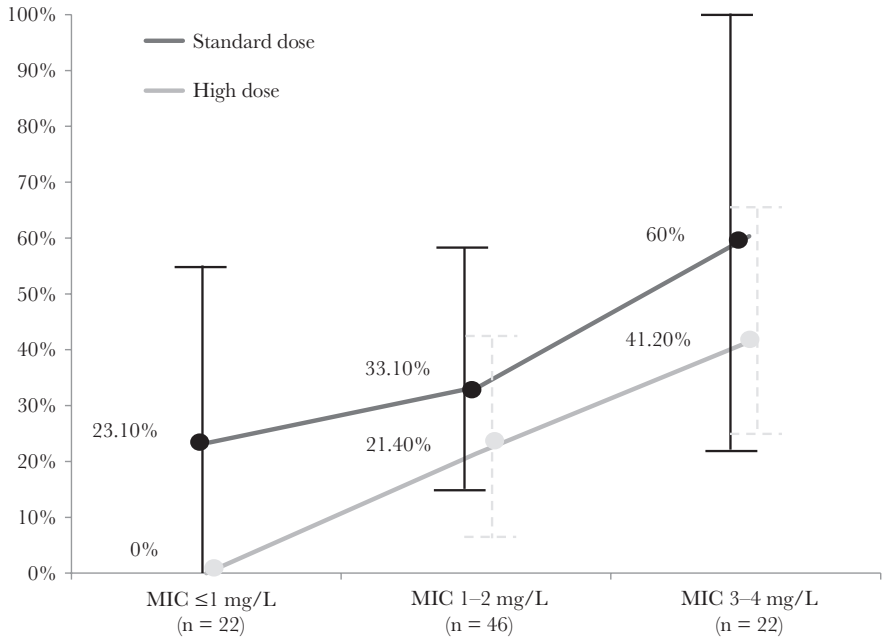

Figure 3. Thirty-day mortality rates according to ceftolozane/tazobactam dosing and minimal inhibitory concentration. Abbreviation: MIC, minimal inhibitory concentration.

[33]. In any case, we encourage the use of HDo in all patients with MDR-*P. aeruginosa*, as well as additional actions when MIC >2 mg/L. In the latter circumstance, administration of C/T as an extended or continuous infusion and/or in combination with other active agents may be worth considering [34].

On the other hand, selection of C/T-resistant mutants was evaluated in a hollow-fiber infection model that exposed 2 strains of *P. aeruginosa* with C/T MICs of 0.5 and 4 mg/L to a range of C/T doses [35]. No resistant mutant was selected for the low-MIC strains, but only the 3 g q8h simulated dosage avoided the emergence of resistance from the strain with an MIC of 4 mg/L. This hollow-fiber model simulated the plasma concentrations but not the concentration achieved in the ELF, respiratory secretions, cerebrospinal fluid, or abscesses. This may explain why in the clinical setting the HDo may not be enough to prevent resistance.

It is of note that neither in our series nor in others was combination of C/T with other antibiotics associated with an improved outcome or prevention of resistance emergence. However, the most common companion drugs were aminoglycosides or colistin, which are frequently underdosed and may have low diffusion to some tissues. It is necessary to prospectively evaluate the effect of combining C/T with correctly dosed aminoglycosides, colistin, or even meropenem in severe infections with a high bacterial inoculum [36–38].

Our study has some limitations. First, its retrospective nature and the relatively small size of the cohort preclude a generalization of the results; however, this is the largest cohort of LRI due to resistant *P. aeruginosa* treated with C/T. Second, the C/T dose was not standardized but was decided by each physician; therefore, neither the reason for receiving SDo or HDo nor the dose adjustment in case of renal failure was well defined. Nevertheless, this variability allowed us to analyze the impact of different regimens. Third, we did not assess clinical failure due to the inherent difficulties for evaluating it retrospectively and chose 30-day mortality as the most objective evaluable outcome. Finally, subsequent strains of *P. aeruginosa* isolated after starting C/T were not available; hence, documentation of persistence (microbiological failure) and emergence of resistance could not be assessed.

Table 2. Multivariate Analysis of Factors Associated With 30-Day Mortality in the 90 Patients With MDR- and XDR-*Pseudomonas aeruginosa* Lower Respiratory Tract Infections

	OR	95% CI	*P* Value
Septic shock	7.96	2.59–24.54	<.0001
C/T MIC > 2 mg/L	3.33	1.02–10.86	.045
Charlson index score	1.27	1.04–1.55	.019

Abbreviations: C/T, ceftolozane/tazobactam; CI, confidence interval; MDR, multidrug-resistant; MIC, minimal inhibitory concentration; OR, odds ratio; XDR, extensively drug-resistant.

In conclusion, this study indicates that C/T is a valuable option for treating LRI caused by resistant *P. aeruginosa*. However, the effectiveness was associated with lower MICs and to a lesser extent with higher dosage; hence, the lowest mortality (16%) was observed when the HDo was administered for treating strains with MIC ≤2 mg/L. A randomized controlled trial is required to confirm these findings. For higher MICs (up to 4 mg/L), further actions aimed at improving prognosis, such as the administration of C/T as an extended or continuous

infusion or in combination with other active antibiotics, also deserve clinical testing.

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