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CLINICAL THERAPEUTICS

Real-World Experience with Ceftolozane-Tazobactam for Multidrug-Resistant Gram-Negative Bacterial Infections

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ABSTRACT Our objective was to describe the prescribing practices, clinical characteristics, and outcomes of patients treated with ceftolozane-tazobactam (C/T) for multidrug-resistant (MDR) Gram-negative infections. This was a multicenter, retrospective, cohort study at eight U.S. medical centers (2015 to 2019). Inclusion criteria were age ≥18 years and receipt of C/T (≥72 hours) for suspected or confirmed MDR Gram-negative infection. The primary efficacy outcome, evaluated among patients with MDR *Pseudomonas aeruginosa* infections, was composite clinical failure, namely, 30-day all-cause mortality, 30-day recurrence, and/or failure to resolve or improve infection signs or symptoms after C/T treatment. In total, 259 patients were included, and *P. aeruginosa* was isolated in 236 (91.1%). The MDR and extremely drug-resistant phenotypes were detected in 95.8% and 37.7% of *P. aeruginosa* isolates, respectively. The most common infection source was the respiratory tract (62.9%). High-dose C/T was used in 71.2% of patients with a respiratory tract infection (RTI) overall but in only 39.6% of patients with an RTI who required C/T renal dose adjustment. In the primary efficacy population ($n = 226$), clinical failure and 30-day mortality occurred in 85 (37.6%) and 39 (17.3%) patients, respectively. New C/T MDR *P. aeruginosa* resistance was detected in 3 of 31 patients (9.7%) with follow-up cultures. Hospital-acquired infection and Acute Physiological and Chronic Health Evaluation II (APACHE II) score were independently associated with clinical failure (adjusted odds ratio [aOR], 2.472 and 95% confidence interval [CI], 1.322 to 4.625; and aOR, 1.068 and 95% CI, 1.031 to 1.106, respectively). Twenty-five (9.7%) patients experienced ≥1 adverse effect (9 acute kidney injury, 13 *Clostridioides difficile* infection, 1 hepatotoxicity, 2 encephalopathy, and 2 gastrointestinal intolerance). C/T addresses an unmet medical need in patients with MDR Gram-negative infections.

KEYWORDS ceftolozane-tazobactam, multidrug-resistant *Pseudomonas aeruginosa*

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Pseudomonas aeruginosa is a leading cause of health care-associated infections, particularly among critically ill and immunocompromised patients (1, 2). Treatment of these infections is challenging due to the pathogen's diverse arsenal of virulence factors, intrinsic antimicrobial resistance, and ability to acquire a variety of resistance determinants (3). Furthermore, remaining antibiotics with preserved activity against multidrug-resistant (MDR) strains are limited by unfavorable pharmacokinetics and/or toxicity (4–6). The high morbidity and mortality associated with infections caused by MDR *P. aeruginosa* are due, in part, to the paucity of safe and effective treatment options and attest to the need for new therapeutic strategies (2, 7).

Ceftolozane-tazobactam (C/T) is a combination antibiotic consisting of a novel oxyimino-aminothiazolyl cephalosporin and a well-established beta-lactamase inhibitor (8, 9). It has *in vitro* antipseudomonal activity against isolates with the MDR phenotype (8, 10). It is also active against some extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales*; activity against other problem *Enterobacterales* (i.e., AmpC derepressed and carbapenemase producing) is more limited (11). Labeled indications include complicated intra-abdominal infections (cIAIs), complicated urinary tract infection (cUTIs), and, most recently, hospital-acquired or ventilator-associated bacterial pneumonia (HAP/VAP) (1). The clinical studies leading to the initial approval of C/T included few patients infected with MDR bacteria even though this is the population for whom it can fill an unmet medical need (12–14). Generalizing results from noninferiority studies conducted in patients infected with susceptible pathogens to patients with MDR infections is problematic (15). Those infected with resistant bacteria are typically older, have a higher burden of comorbidities, and are more critically ill (15, 16). These factors influence the effectiveness of antibiotics independent of microbiological activity, and recent history has reminded us that *in vitro* activity does not always reflect direct patient benefits (i.e., delafloxacin for uncomplicated gonorrhea, tigecycline for bacteremia/HAP, ceftobiprole for VAP, and daptomycin for pneumonia) (15, 17–20). In addition, the majority of patients in registry studies were recruited from sites in Eastern Europe where standards of care may differ from those in the United States (12, 13). Published data on the use of C/T for the treatment of MDR infections is slowly accumulating in the form of case reports, case series. and uncontrolled retrospective cohort studies (21–26). We sought to add to these data and describe the prescribing practices, clinical characteristics, microbiology, and outcomes of a large cohort of U.S. patients treated with C/T for confirmed or suspected MDR Gram-negative bacterial infections.

RESULTS

Patient characteristics. In total, 259 patients were included. A description of baseline demographic and clinical characteristics is shown in Table 1. Overall, the study cohort represented an elderly population (median age, 62; interquartile range [IQR], 49 to 72 years; ≥65 years, 40.9%) with high prevalences of diabetes mellitus (42.1%) and chronic obstructive pulmonary disease (COPD; 21.6%). The majority of patients (55.2%) had a history of colonization or infection with an MDR pathogen within the past year and 73.7% and 68.3% had a recent (90 day) hospitalization or systemic antibiotic exposure, respectively. Many patients had a high severity of illness at infection onset, with 50.6% residing in the intensive care unit (ICU) and a median (IQR) APACHE II score of 21 (12 to 27).

Infection characteristics. The majority of infections (62.2%) were hospital acquired with the median (IQR) time from admission to infection onset of 5 (1 to 16) days. C/T was most commonly used to treat respiratory tract infections (62.9%), followed by skin and soft tissue (10.9%) and urinary tract (10.0%) infections (Table 2). Blood cultures were positive in eight (3.1%) patients (four with primary bacteremia, three with a respiratory tract infection, and one with a skin infection). A total of 384 isolates were cultured from 259 patients, including *P. aeruginosa* in 236 (91.1%) patients and *Enterobacterales* in 60 (23.2%). Over one-third (35.1%) of cultures were polymicrobial, while 19 (7.3%) patients had negative cultures or cultures were not obtained. All patients

TABLE 1 Demographic and clinical characteristics[a]

Characteristic	Values[b] for: Total cohort ($n = 259$)	Patients with MDR *Pseudomonas aeruginosa* ($n = 226$)
Age (yr)	62 (52–72)	62 (53, 72)
Age ≥65 yr	106 (40.9)	92 (40.7)
Male sex	167 (64.5)	142 (62.8)
Race		
African American	122 (47.1)	116 (51.3)
Caucasian	96 (37.1)	78 (34.5)
Latino	15 (5.8)	11 (4.9)
Other	26 (10.0)	21 (0.3)
BMI	27 (22–32)	26 (22–32)
Obese (BMI, ≥30 kg/m^2)	84 (32.4)	73 (32.3)
Underweight (BMI, <18.5 kg/m^2)	29 (11.2)	26 (11.5)
Estimated CrCl (ml/min)[c]	78 (45–129)	78 (45–128)
CrCl, >50 ml/min	172 (66.4)	149 (65.9)
CrCl, 30–50 ml/min	41 (15.8)	35 (15.5)
CrCl, 15–29 ml/min	21 (8.1)	20 (8.8)
CrCl, <15 ml/min	4 (1.5)	4 (1.8)
Hemodialysis	21 (8.1)	18 (8.0)
Residence prior to admission		
Community	124 (47.9)	104 (46.0)
Skilled nursing facility	83 (32.0)	80 (35.4)
Long-term acute care hospital	4 (1.5)	3 (1.3)
Inpatient rehabilitation facility	8 (3.1)	7 (3.1)
Transferred from outside hospital	40 (15.4)	32 (14.2)
Comorbid conditions		
Diabetes	109 (42.1)	97 (42.9)
Heart Failure	51 (19.7)	46 (20.4)
COPD	56 (21.6)	51 (22.6)
Malignancy	24 (9.3)	22 (9.7)
Liver disease	18 (6.9)	15 (6.6)
Charlson comorbidity index score	3 (2–5)	4 (2–5)
Charlson comorbidity index score, >4	90 (34.7)	82 (36.3)
Immunocompromised	23 (8.9)	18 (8.0)
MDR infection or colonization within 1 yr	143 (55.2)	129 (57.1)
Recent antibiotic exposure (≥24 h within 90 days)	191 (73.7)	173 (76.5)
Recent hospitalization (≥48 h within 90 days)	177 (68.3)	156 (69.0)
Recent surgery (within 30 days)	39 (15.1)	31 (13.7)
ICU at index culture	131 (50.6)	117 (51.8)
SOFA score	5 (2–8)	5 (3–8)
APACHE II score	21 (12–27)	21 (14–28)

[a]APACHE, Acute Physiological and Chronic Health Evaluation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; ICU, intensive care unit; LTAC, long-term acute care hospital; MDR, multidrug resistant; SOFA, sequential organ failure assessment.
[b]All values represent *n* (%) or median (interquartile range).
[c]Estimated by using the Cockroft Gault equation (46); creatinine measured within 24 h of first dose of ceftolozane-tazobactam.

without a positive culture had a history of MDR or XDR *P. aeruginosa* infection(s). C/T susceptibility testing was performed on 168 (71.2%) *P. aeruginosa* isolates; 88.7% were susceptible. Among MDR ($n = 167$) and XDR ($n = 74$) strains tested, C/T susceptibility rates were 88.6% and 83.8%, respectively. A complete *P. aeruginosa* antibiogram is shown in Supplementary Appendix 1.

Infection management. A summary of infection management is shown in Table 3. Overall, 99.6% of patients received an infectious disease consult. C/T was initiated at a median (IQR) of 84 (18 to 164) hours after the infectious disease consult. Source control (e.g., abscess drainage, wound debridement, and line removal) was pursued in 73.8%

TABLE 2 Infection characteristics

Characteristic[a]	Values[b] for: Total cohort ($n = 259$)	Patients with MDR *Pseudomonas aeruginosa* ($n = 226$)
Hospital-acquired infection	161 (62.2)	142 (62.8)
Hours from admission to culture collection	111 (21–376)	129 (21–384)
Infection source		
Primary bacteremia	4 (1.5)	4 (1.8)
Respiratory	163 (62.9)	149 (65.9)
Ventilator-associated pneumonia	96/163 (58.9)	89/149 (59.7)
Intra-abdominal	18 (6.9)	11 (4.9)
Skin and soft tissue	28 (10.8)	27 (11.9)
Osteoarticular	15 (5.8)	10 (4.4)
Urine	26 (10.0)	21 (9.3)
Prosthetic device	1 (0.4)	1 (0.4)
Intravenous catheter	2 (0.8)	2 (0.9)
Other	1 (0.4)	1 (0.4)
Positive blood cultures	8 (3.1)	8 (3.5)
Enterobacterales		
Klebsiella pneumonia	13 (5.0)	10 (4.4)
Ceftriaxone resistant	10/13 (76.9)	8/10 (80)
K. oxytoca	4 (1.5)	2 (0.9)
Escherichia coli	17 (6.6)	10 (4.4)
Ceftriaxone resistant	11/17 (64.7)	7/10 (70)
Enterobacter spp.	5 (1.9)	4 (1.8)
Proteus mirabilis	14 (5.4)	13 (5.8)
Ceftriaxone resistant	2/14 (14.3)	2/13 (15.4)
Citrobacter spp.	3 (1.2)	3 (1.3)
Serratia marcescens	5 (1.9)	5 (2.2)
Providentia stuarti	13 (5.0)	13 (5.8)
Ceftriaxone resistant	6/13 (46.2)	5/13 (38.5)
Morganella morganii	1 (0.4)	1 (0.4)
Pseudomonas spp.	239 (92.3)	
P. aeruginosa	236 (91.1)	
MDR	226 (87.3)	
XDR	89 (34.4)	89 (39.4)
Acinetobacter spp.	12 (4.6)	10 (4.4)
Stenotrophomonas maltophilia	6 (2.3)	6 (2.7)
Achromobacter xylosoxidans	3 (1.2)	3 (1.3)
Gram-positive	49 (18.9)	42 (18.6)
Polymicrobial infection	91 (35.1)	82 (36.3)
P. aeruginosa C/T MIC (mg/liter) (*n*)	126	125
MIC_{50}	1	1
MIC_{90}	4	8

[a]MDR, multidrug resistant; XDR, extensively drug resistant.
[b]All values represent *n* (%) or median (interquartile range).

of patients with infections potentially amendable to source control ($n = 80$). The median time from culture collection to C/T initiation was 87 (51 to 139) hours. Among patients with a positive culture ($n = 250$), 86 (34.4%) received *in vitro*-active antibiotic therapy prior to C/T, most commonly with an aminoglycoside ($n = 31$, 12.4%). The median time to active antibiotic therapy was 50 (7 to 94) hours. High-dose C/T was used in 165 (63.7%) patients, including 116 (71.2%) with a respiratory tract infection. The C/T dose was renally adjusted in 79 (30.5%) patients. Among patients with a respiratory tract infection who had their dose adjusted for impaired kidney function ($n = 48$), only 19 (39.6%) received renally adjusted high-dose C/T, while the remainder were potentially underdosed. Combination IV antibiotic therapy was used in 64 (24.7%) patients, most commonly with an aminoglycoside (18.1%). Among patients with a respiratory

TABLE 3 Treatment information

Parameter[b]	Values[a] for: Total cohort ($n = 259$)	Patients with MDR *Pseudomonas aeruginosa* ($n = 226$)
Infectious disease consult	258 (99.6)	226 (100.0)
Surgical consult	62 (23.9)	51 (22.6)
Source control in patients with infection amendable to source control	59/80 (73.8)	47/63 (74.6)
Active antibiotic(s) before C/T	86 (34.4)[c]	72 (31.9)
Time to active antibiotic(s) (h)	50 (0–94)[c]	54 (0–94)
Active antibiotic(s) within 48 h	123 (49.2)[c]	104 (46.0)
Time to C/T (h)	85 (49–139)	84 (51–127)
C/T within 48 h	63 (24.3)	51 (22.6)
C/T dose		
High dose (3 g every 8 h)	165 (63.7)	143 (63.3)
Respiratory source	116/163 (71.2)	105/149 (70.5)
Standard dose (1.5 g every 8 h)	94 (36.3)	83 (36.7)
Renal dose adjustment	79 (30.5)	69 (30.5)
C/T IV combination therapy	64 (24.7)	58 (25.7)
Aminoglycoside	47 (18.1)	45 (19.9)
Colistin-polymyxin B	11 (4.2)	10 (4.4)
Fluoroquinolone	10 (3.9)	6 (2.7)
Inhaled antibiotic therapy in patients with a respiratory tract infection[d]	48/163 (29.4)	44/149 (29.5)
C/T duration (days)	10 (6–15)	10 (6–15)

[a]All values represent number (%) or median (interquartile range).
[b]C/T, ceftolozane-tazobactam; MDR, multidrug-resistant.
[c]Evaluated in patients with a positive culture only, $n = 250$.
[d]Inhaled tobramycin or colistin.

tract infection, 48 (29.4%) received adjuvant therapy with inhalation tobramycin or colistin. The median (IQR) duration of C/T was 10 (6 to 15) days.

Outcomes. Patient outcomes are displayed in Table 4. Overall, composite clinical failure and 30-day mortality occurred in 85 (37.6%) and 39 (17.3%) patients in the primary efficacy population (MDR *P. aeruginosa* infections), respectively. Among patients originally admitted from home ($n = 104$), 36.5% and 7.7% required new nursing home placement or inpatient rehabilitation following discharge, respectively. By source, the highest rates of clinical failure and 30-day mortality were recorded in patients with a respiratory tract infection (45.0% and 24.2%), while the lowest rates were in patients with a urinary tract infection (9.5% and 4.8%). Outcomes were similar in patients with MDR *P. aeruginosa* infections confirmed to be C/T susceptible (Table 4). On bivariate analysis, additional variables associated with higher clinical failure included (Supplementary Appendix 2 and 3) the following: older age, CrCl of $\leq$30 ml/min or on hemodialysis, chronic obstructive pulmonary disease, hospital-acquired infection, respiratory tract infection, ICU at infection onset, sequential organ failure assessment (SOFA) score, APACHE II score, and C/T renal dose adjustment. The impact of renal dose adjustment on clinical failure was most pronounced in patients with a respiratory tract infection (OR, 3.409; 95% CI, 1.627 to 7.142). Early active antibiotic therapy, early C/T, high-dose C/T, and combination antibiotic therapy did not impact clinical failure rates in the overall efficacy population or among patients with an MDR *P. aeruginosa* respiratory tract infection (Supplementary Appendix 2 and 3). The final multivariable logistic regression models for clinical failure in the primary efficacy population and in patients with MDR *P. aeruginosa* infections confirmed to be susceptible to C/T are shown in Table 5. Hospital-acquired infection and higher APACHE II score were the independent predictors of clinical failure in both models, while CrCl of $<$30 ml/min or receipt of hemodialysis remained an explanatory variable in the primary efficacy population, and older age was an additional independent predictor in the subgroup analysis restricted to patients with C/T-susceptible MDR *P. aeruginosa* infections.

TABLE 4 Effectiveness outcomes[a]

Parameter	Values[b] for patients with: MDR *Pseudomonas aeruginosa* (*n* = 226)	C/T-susceptible MDR *Pseudomonas aeruginosa* (*n* = 148)
Discharge disposition		
Home	51 (22.6)	31 (20.9)
Skilled nursing facility/LTAC	107 (47.3)	73 (49.3)
Inpatient rehabilitation facility	16 (7.1)	9 (6.1)
Hospice	13 (5.8)	10 (6.8)
In-hospital mortality	39 (17.3)	25 (16.9)
Discharge disposition among patients admitted from home (*n*)	104	57
Home	38 (36.5)[c]	20 (35.1)[d]
Skilled nursing facility/LTAC	38 (36.5)[c]	24 (42.1)[d]
Inpatient rehabilitation facility	8 (7.7)[c]	2 (3.5)[d]
Hospice	4 (3.8)[c]	3 (5.3)[d]
In-hospital mortality	16 (15.4)[c]	8 (14.0)[d]
Composite clinical failure	85 (37.6)	61 (41.2)
30-day mortality	39 (17.3)	28 (18.9)
30-day recurrence	31 (13.7)	18 (12.2)
Worsen or failure to improve while on C/T	49 (21.7)	39 (26.4)
Development of C/T resistance	3 (6.8)[e]	3 (9.7)[f]
Length of stay (days)	27 (15–51)	25 (14–54)

[a]All values represent number (%) or median (interquartile range).
[b]ALT, alanine aminotransferase; AST, aspartate aminotransferase; C/T, ceftolozane-tazobactam; LTAC, long-term acute care; MDR, multidrug resistant.
[c]*n* = 104, patients admitted from home only.
[d]*n* = 57, patients admitted from home only.
[e]*n* = 44, evaluated in patients with follow-up cultures.
[f]*n* = 31, evaluated in patients with follow-up cultures.

Follow-up cultures were available for 31 (20.9%) patients with MDR *P. aeruginosa* infections that were susceptible to C/T at baseline. Follow-up cultures were obtained more frequently in patients who experienced clinical failure than those who did not (29.5% versus 14.9%, $P = 0.032$). The development of new C/T resistance among MDR *P. aeruginosa* isolates was documented in 3 patients (9.7%) at 3, 7, and 8 days after C/T initiation. Two patients had VAP (one with bilateral necrotizing infection) and were treated with high-dose C/T. The third patient to develop resistance had necrotizing fasciitis and was treated with standard-dose C/T. No patients among this group received combination therapy. Two of the three patients had worsening signs and symptoms of infection at the time resistance was documented. Resistance was detected

TABLE 5 Multivariable logistic regression models for clinical failure[a]

Variable according to:	Adjusted odds ratio (95% CI)	*P* value
Primary efficacy population (MDR *Pseudomonas aeruginosa* infection) (*n* = 226)[b]		
Hospital-acquired infection	2.472 (1.322–4.625)	0.005
APACHE II score[c]	1.068 (1.031–1.106)	<0.001
CrCl, <30 ml/min or receipt of hemodialysis	1.954 (0.945–4.040)	0.071
Patients with C/T susceptible MDR *P. aeruginosa* infections (*n* = 148)[d]		
Hospital-acquired infection	2.650 (1.212–5.795)	0.015
APACHE II score[c]	1.064 (1.016–1.114)	0.009
Age[e]	1.028 (1.001–1.056)	0.040

[a]APACHE, Acute Physiological and Chronic Health Evaluation; CI, confidence interval; COPD, chronic obstructive pulmonary diseases; CrCl, creatinine clearance; C/T, ceftolozane-tazobactam; ICU, intensive care unit; MDRO, multidrug-resistant organism; SOFA, sequential organ failure assessment.
[b]Variables considered for model entry were age, CrCl of <30 ml/min or receipt of hemodialysis, COPD, Charlson comorbidity index, infection source, monomicrobial infection, APACHE II score, SOFA score, ICU at infection onset, hospital-acquired infection, and C/T renal dose adjustment.
[c]Per one unit increase in score.
[d]Variables considered for model entry were age, CrCl of <30 ml/min or receipt of hemodialysis, COPD, infection source, infection or colonization with an MDRO within 1 year, APACHE II score, SOFA score, ICU at infection onset, hospital-acquired infection, and C/T renal dose adjustment.
[e]Per 1-yr increase in age.

TABLE 6 Safety outcomes for total cohort[a]

Outcome	No. (%)
Acute kidney injury[b]	9 (3.8)
Clostridioides difficile infection	13 (5.0)
Hepatotoxicity	1 (0.4)
Central nervous system side effects (encephalopathy)	2 (0.8)
Gastrointestinal adverse effects	2 (0.8)

[a]$n = 259$.
[b]$n = 238$, patients receiving hemodialysis excluded.

by disk diffusion in two patients and by Etest in one patient (initial C/T MIC, 3 mg/liter; day 3 MIC, 128 mg/liter).

With regard to safety, a total of 27 adverse events occurred in 25 patients (9.7%) (Table 6). Nine patients developed acute kidney injury (AKI) while receiving C/T; all of these patients were receiving concomitant nephrotoxic agents around the time of the event. In particular, 7 (12.7%) patients who received C/T combination therapy with an aminoglycoside or a polymyxin experienced AKI compared to 2 (1.0%) who did not receive either of these antibiotic classes ($P < 0.001$). Thirteen patients (5.0%) developed *Clostridioides difficile*-associated diarrhea (two received C/T combination therapy and eight received high-dose C/T). Two patients experienced possible C/T-associated encephalopathy (decreased mentation and confirmed by electroencephalogram). One of these patients received high-dose C/T (CrCl, 65 ml/min) and the other received standard-dose C/T adjusted for hemodialysis. Both patients had other contributing factors. Hepatotoxicity occurred in one patient and gastrointestinal (GI) intolerance (nausea and vomiting diarrhea) occurred in two.

DISCUSSION

Registration studies conducted for drug approval give information about the efficacy and safety of a drug under ideal conditions in patient populations that may be very different from those we care for in everyday clinical practice (27). Real-world studies are, therefore, necessary and complementary to ensure that the results seen in registration studies actually translate into benefits for our patients (27). This is particularly relevant for new antibiotics, such as C/T, that are brought to market under the FDA accelerated approval program. Under this program, antibiotics with a novel mechanism of action or structural alteration that confer an expanded spectrum of antimicrobial activity may be granted regulatory approval on the basis of noninferiority to the current standard of care in patients who have other treatment options (i.e., not restricted or required to include resistant isolates) (28, 29). Extrapolating results from noninferiority studies to patients in whom the control intervention would not be effective is difficult (15). In the present study, we, therefore, sought to augment data from these studies by evaluating C/T patterns of use, effectiveness, and adverse effects in routine clinical practice using a cohort of patients from a diverse range of academic and community medical centers across the United States. Patients enrolled in the present study represent a population that has been underrepresented in C/T randomized controlled trials (RCTs). Our patients were older, had multiple comorbidities, and had extensive prior health care and antibiotic exposures, and over 40% of them resided in the ICU at infection onset. *P. aeruginosa* was isolated from over 90% of patients, and the vast majority (95.8%) were MDR strains. Approximately one in four patients received combination antibiotic therapy, which was prohibited in RCTs, and many patients received doses that differed from the current FDA-approved doses.

With regard to the last point, approximately 70% of patients with a respiratory tract infection in our study received high-dose C/T. The FDA approval for the HAP/VAP indication, along with the modified dosing recommendations, came shortly after our study closed. We infer that the use of higher C/T doses was based on pharmacokinetic/pharmacodynamic data published in 2016 suggesting 3 grams every 8 hours may improve the probability of target attainment within epithelial lining fluid (30). The

recommended C/T doses for HAP/VAP are also 2- and 3-fold greater than for the former indications in patients with CrCl of <50 ml/min and those receiving intermittent hemodialysis, respectively. However, the appropriate renally adjusted high-dose C/T was only used in 39.6% of patients with a respiratory tract infection who had their C/T dose renally adjusted. The higher rate of clinical failure observed in patients with renal impairment highlights the importance of dose optimization in this setting.

These observations also call attention to the potential tradeoffs of initial accelerated antibiotic approval based on indications that are not reflective of the medical need the antibiotic is targeted to meet. That is, antipseudomonal drugs are rarely indicated for cUTIs and cIAIs. On the other hand, *P. aeruginosa* is one of the primary pathogens responsible for HAP/VAP, and not surprisingly, respiratory tract infections have been the most common C/T indication in postapproval observational studies to date, including the present study (12, 13, 21, 23–26). The C/T HAP/VAP approval, along with a modified dosing recommendation, came nearly 5 years after initial approval (1).

Although C/T was mostly used for off-label indications in this study, it clearly addressed an unmet need in our patients. As noted previously, the vast majority of patients received C/T to treat *P. aeruginosa* infections, with 95.8% demonstrating the MDR phenotype. All patients without a positive culture also had a history of MDR or XDR *P. aeruginosa* infections. In agreement with previous surveillance data (8, 11), C/T was active against 88.7% of these highly resistant *P. aeruginosa* isolates. The only agent with greater *in vitro* activity was amikacin, which is not recommended for monotherapy in respiratory tract infections due to inferior clinical outcome versus beta-lactams, which is likely related to poor pulmonary penetration and diminished antibacterial activity in the acidic pneumonic airways (6, 31, 32). Aminoglycosides are also challenging to use in elderly patients, with a high burden of comorbidity and preexisting organ impairment, such as those in this study.

Although it is difficult to make comparisons across studies due to differences in study design and case mix, the rates of clinical failure (37.6%) and 30-day mortality (17.3%) in the present study are broadly comparable to previous observational studies describing the use of C/T for MDR *P. aeruginosa* infections and suggest meaningful progress for patients compared with historical controls (16, 21–25). Clinical outcomes among patients with a respiratory tract infection in this study were remarkably similar to those reported for the recently completed ASPECT-NP study, a randomized controlled phase 3 study comparing C/T to meropenem in patients with ventilated nosocomial pneumonia (14). In this RCT, 28-day mortality in the intention-to-treat population randomized to C/T was 24.0% (compared to 24.2% for 30-day mortality in the present study) (14). Although less than 5% of patients in the ASPECT-NP study were infected with MDR *P. aeruginosa*, the comparison suggests that patients in routine clinical practice are achieving expected outcomes. However, the fact that less than 40% of patients in our study originally admitted from home were discharged directly home again is a sobering reminder that there is still much work to be done to return patients to their baseline state of health after surviving a serious infection.

It is notable that in this study C/T was used earlier in the course of the infection (median, 85 h after infection onset) than earlier observational studies where C/T was often reserved for salvage therapy (21, 23). This may suggest that clinical laboratories are streamlining the C/T susceptibility testing process and is a positive signal considering that a number of studies have shown that the treatment of serious infections is time sensitive with negative consequences for delays in appropriate therapy (33–36).

P. aeruginosa is remarkable for its ability to acquire new resistance mechanisms under selective antibiotic pressure (3). Among patients with follow-up cultures in this study, three (9.7%) isolates developed new C/T resistance as early as 3 days after C/T initiation. Two of these patients showed signs and symptoms of worsening infection at the time resistance was detected, suggesting it does impact outcomes. Moving forward, it will be important to identify risk factors for resistance development and to determine what strategies, if any, are preventative. No patients who developed C/T resistance received combination therapy. Whether combination therapy could attenu-

ate resistance development in some strains remains uncertain; however, it is clear that combination therapy carries definite risks of more adverse effects, as seen in this study and others (37, 38).

With regard to safety, our study provides important insights into potential C/T-related toxicities in real-world patients with multiple underlying risk factors. It is notable that all patients who experienced AKI on C/T were receiving other nephrotoxins and that the use of concomitant aminoglycoside or polymyxin therapy was significantly more common in these patients. This finding underscores the importance of limiting the administration of nephrotoxins whenever possible. Although we cannot exclude selection bias, combination antibiotic therapy was not associated with improved effectiveness, suggesting this common practice (approximately one in four patients in this study) should be reconsidered. The incidence of *C. difficile* infection in this study was over 16-fold higher than that in the C/T phase 3 cUTI and cIAI studies (3/1,015, 0.3% versus 13/259, 5.0%). It is not surprising that RCTs underestimate this adverse effect given the risk differences of the populations; in particular, 73% of patients in our study had recent antibiotic exposure, which is typical for patients with MDR infections (12, 13, 16). To the best of our knowledge, we are the first to report potential C/T-related encephalopathy in two patients. Neurotoxicity has been reported with virtually all cephalosporins and can range from mild headache and confusion to seizures (39). Consistent with the cases in this study, older age, higher doses, and renal impairment have been identified as risk factors (39). Data regarding C/T central nervous system (CNS) penetration have not yet been reported; however, the use of C/T for the treatment of meningitis has been described (40, 41). Although there are a wide spectrum of causes for CNS disturbances in patients with serious infections, our findings suggest that C/T-associated CNS disturbances should be considered in the differential for at-risk patients.

This study has important limitations. First, the study is subject to inherent biases and limitations with its retrospective design. Treatment-related factors, such as the time from infection onset to C/T initiation, C/T dose, and the use of combination therapy, were not assigned randomly, and it is, therefore, difficult to determine how these factors affected outcomes. Important information, such as the results of follow-up cultures, was available for only a minority of patients. Follow-up testing in this study is reflective of real-world practice. The fact that a greater proportion of patients who went on to experience clinical failure had follow-up cultures collected suggests that the incidence of resistance development found in this study (9.7%) may be an overestimate. Additionally, even though this represents the largest study to date evaluating the use of C/T for MDR infections, the sample size was still relatively small, limiting our ability to conduct meaningful subgroup analyses. We did not include a contemporary control group, and although our results suggest improvements over historical outcomes in patients with MDR *P. aeruginosa* infections, such comparisons are fraught with limitations due to changes over time in referral patterns, diagnostic modalities, ancillary care, and the underlying health of the population (42). Comparative outcome research of newer antibiotics, preferably in the form of prospective RCTs, designed, conducted, analyzed, and reported by independent groups without competing interests, is desperately needed.

In conclusion, this study adds considerably to the growing body of literature describing C/T treatment patterns and outcomes for MDR infections. Our study suggests that C/T can be an effective antibiotic for patients with limited treatment options. We describe hitherto unrecognized safety signals that may prompt increased vigilance and earlier detection. This study also identifies patient groups at higher risk for poor outcomes, such as those with renal impairment and critical illness, for whom continued advancement is needed.

MATERIALS AND METHODS

Study design and population. This was a multicenter, retrospective, noncomparative cohort study conducted at eight academic and community medical centers in the United States between 2015 and 2019. Inclusion criteria were the following: (i) age of ≥18 years and (ii) receipt of ≥72 hours of C/T for suspected or confirmed MDR Gram-negative infection. For each patient, only the initial eligible C/T treatment course during the study period was included.

Ethics. Approval was obtained from each medical center's institutional review board with a waiver for informed consent.

Data collection and study definitions. Pharmacy records were screened for all patients who received at least one dose of C/T during the study period. Relevant demographic, clinical, microbiological, and treatment data were extracted from the electronic medical record and entered into a secure online data collection form (43). Comorbidity burden was quantified using the Charlson comorbidity score (44). The severity of illness at infection onset was assessed using the SOFA and APACHE II scores (28, 45). Infection onset was considered to be the time that the index culture was collected or, for patients that did not have cultures collected, when signs and symptoms were first documented. Sources of infection were based on available clinical, microbiological, and diagnostic data. The infection was considered hospital acquired if the index culture was obtained greater than 48 h after admission (31). Bacterial identification and antibiotic susceptibilities were performed at each center according to standard procedures. C/T susceptibility was determined using disk diffusion or gradient strips, when available. MDR *P. aeruginosa* was defined by nonsusceptibility to at least one antibiotic in at least three classes that are typically active against wild-type *P. aeruginosa* (29). Extensively drug resistant (XDR) was defined as nonsusceptible to at least one antibiotic in all but two classes (29). Carbapenem-resistant *Enterobacterales* (CRE) was defined by current U.S. Centers for Disease Control and Prevention (CDC) criteria (7). Standard- and high-doses were defined as 1.5 g of intravenous (i.v.) C/T every 8 hours and 3 g of i.v. C/T every 8 hours, respectively, with dose adjustments for renal impairment according to the manufacturer's recommendations (1). For the purposes of this study, C/T combination therapy was defined as the receipt of a concomitant i.v. antipseudomonal antibiotic for ≥48 hours with C/T. Microbiological failure was defined as microbiologically confirmed recurrence after 7 days of C/T therapy to the end of follow-up plus signs and symptoms of infection. Patients were followed for 30 days after hospital discharge. Clinical failure was defined as a composite of all-cause 30-day mortality, microbiological failure, and/or failure to resolve or improve signs and symptoms of infections during C/T therapy. Acute kidney injury (AKI) was evaluated in patients not receiving hemodialysis at the start of C/T and was defined as a serum creatinine increase of ≥0.5 mg/dl or 50% from baseline on two consecutive measurements while on C/T and up to 72 h following the last dose. Hepatotoxicity was defined as previously described (14).

Statistical analysis. Baseline characteristics of the overall cohort and in the subgroup of patients with MDR *P. aeruginosa* infections were evaluated using descriptive statistics; categorical data were reported as counts and percentages, and continuous data were reported as medians and interquartile ranges (IQRs). The primary efficacy outcome was composite clinical failure in patients from whom MDR *P. aeruginosa* was isolated. An additional *post hoc* analysis was also conducted in patients with an MDR *P. aeruginosa* isolate confirmed to be susceptible to C/T. Multivariable logistic regression analysis was performed to identify independent predictors of clinical failure. Clinically relevant variables were selected for model entry based on bivariate comparisons ($P < 0.2$) and biological plausibility. Some variables were collapsed into single composite variables when the number of patients in subgroups was too small to allow for meaningful analysis. The selected model was simplified based on the Akaike information criterion (AIC) in backward fashion. Multicolinearity of candidate regression models was assessed via the variance inflation factor, with values less than three considered acceptable. Secondary outcomes of interest included individual components of the composite outcome, discharge disposition, emergence of C/T resistance, and hospital length of stay. Safety outcomes were evaluated in the total cohort and included AKI, dermatological reactions, gastrointestinal intolerance, cytopenias, central nervous system disturbances, and *Clostridioides difficile*-associated diarrhea.

All analyses were performed using SPSS Statistics version 25.0 (IBM Corp., Armonk, NY) and SAS 9.4 Statistical Software (SAS Institute Inc., Cary, NC). A two-tailed *P* value less than 0.05 was statistically significant.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.2 MB.

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