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ORIGINAL RESEARCH

# Impact of Ceftolozane–Tazobactam vs. Best Alternative Therapy on Clinical Outcomes in Patients with Multidrug-Resistant and Extensively Drug-Resistant *Pseudomonas aeruginosa* Lower Respiratory Tract Infections

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## ABSTRACT

***Introduction***: Infections caused by multidrug-resistant (MDR), extensively drug-resistant (XDR), and difficult-to-treat (DTR) *Pseudomonas aeruginosa* are increasingly challenging to combat. Ceftolozane–tazobactam (C/T) is a novel β-lactam–β-lactamase inhibitor combination now commonly used to treat MDR and XDR *P. aeruginosa*. Lower respiratory tract infections (LRTIs) remain the most common source of infection caused by MDR/XDR *P. aeruginosa*. Comparative effectiveness studies to date have been limited by the type of comparator agents (i.e., aminoglycosides and polymyxins) and the inclusion of multiple infection sources (i.e., urinary tract, abdominal, skin and soft tissue, etc.).

***Methods***: We performed a multicenter, retrospective analysis of adults with LRTI caused by MDR or XDR *P. aeruginosa* admitted from January 2014 to December 2019. We aimed to compare clinical outcomes between patients who received C/T ($n$ = 118) versus best alternative therapy ($n$ = 88). The primary outcome was

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clinical failure, defined as 30-day mortality and/or an adverse drug reaction on antibiotic therapy.

***Results***: Two hundred and six patients met inclusion criteria. The C/T group had a significantly higher proportion of XDR *P. aeruginosa* and ventilator-associated bacterial pneumonia (VABP). After multivariable logistic regression, C/T treatment was independently associated with a 73.3% reduction in clinical failure compared to those who received best alternative therapy ($P < 0.001$). The number needed to harm with best alternative therapy was 3.

***Conclusion***: Our results suggest that C/T is a safe and effective therapeutic regimen for patients with MDR and XDR *P. aeruginosa* LRTI.

**Keywords:** Ceftolozane–tazobactam; HABP/VABP; Multidrug resistance; Pneumonia; *Pseudomonas aeruginosa*

**Key Summary Points**

***Why carry out this study?***

Multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Pseudomonas aeruginosa* are serious public health concerns. High mortality is associated with lower respiratory tract infections caused by MDR/XDR *P. aeruginosa*, which may be due to the inconsistency of treatment strategies used to combat these infections.

This manuscript aims to compare the clinical outcomes of patients with lower respiratory tract infections caused by MDR/XDR *P. aeruginosa* treated with ceftolozane/tazobactam or best alternative therapy.

***What was learned from the study?***

Treatment with ceftolozane/tazobactam was associated with improved patient outcomes compared to those who received best alternative therapy.

These results confirm previous data regarding the treatment of MDR/XDR *P. aeruginosa* with ceftolozane/tazobactam and support its utility in patients with lower respiratory tract infection caused by MDR/XDR *P. aeruginosa*.

## INTRODUCTION

In 2019, over 1.2 million people died as a result of antibiotic-resistant infections worldwide [1]. The number of deaths attributed to antimicrobial resistance is estimated to rise to 10 million people by 2050, as projected in the Review on Antimicrobial Resistance [2]. *Pseudomonas aeruginosa* is of particular concern because of its extraordinary capacity to develop resistance. The respiratory tract is the most frequent infectious source of multidrug-resistant (MDR) and extensively drug-resistant (XDR) *P. aeruginosa* [3, 4]. MDR *P. aeruginosa* is defined as non-susceptible to at least one agent in three or more antimicrobial categories, and XDR is defined as non-susceptible to at least one agent in all but two or fewer categories [3]. Ceftolozane, a novel fifth-generation antipseudomonal cephalosporin, has independent activity against MDR *P. aeruginosa* and is formulated in combination with tazobactam, a β-lactamase inhibitor [5]. Ceftolozane–tazobactam (C/T) gained US Food and Drug Administration (FDA) approval for hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP) in June 2019, following the results of the ASPECT-NP trial, and has since become a preferred regimen in the treatment of drug-resistant *P. aeruginosa* [5–7]. Newer agents have since become available for the treatment of HABP/VABP caused by drug-resistant *P. aeruginosa*, including imipenem/cilastatin/relebactam and cefiderocol; however, these agents will not be covered in this article because of their novelty and lack of data associated with them.

Despite MDR/XDR *P. aeruginosa* having the largest incidence in HABP/VABP infections, clinical evidence supporting C/T for these infections is sparse. ASPECT-NP is the only

randomized controlled study examining the safety and efficacy of C/T for patients with HABP/VABP, and it demonstrated noninferiority of C/T to meropenem for Gram-negative pathogens; however, MDR/XDR *P. aeruginosa* was uncommon with only 50 patients ($n$ = 34 C/T, $n$ = 16 meropenem) in the microbiologic intention-to-treat population [8]. Furthermore, retrospective studies and case series have demonstrated clinical success rates for C/T of approximately 70–80% in patients with MDR *P. aeruginosa* infections, but their results are difficult to interpret because of inclusion of multiple disease states with comparator agents limited to aminoglycosides and/or polymyxins [9, 10].

Polymyxins and aminoglycosides may remain active against MDR/XDR isolates, but are associated with a higher risk of nephrotoxicity compared to the novel agents [9]. As a result of increased safety risks with aminoglycosides and polymyxins plus accessibility issues to newer agents (i.e., shortages and high costs), other traditional agents, such as meropenem and cefepime, have been administered at high doses as prolonged infusions to improve pharmacokinetic/pharmacodynamic (PK/PD) target exposures against drug-resistant pathogens [4, 11–13]. Combination therapy is another therapeutic approach to combat MDR *P. aeruginosa*; however, a clear benefit has not been demonstrated over monotherapy. The concept of difficult-to-treat (DTR) *P. aeruginosa* was introduced in 2018 and was defined by the Infectious Diseases Society of America (IDSA) as non-susceptibility to piperacillin–tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem–cilastatin, ciprofloxacin, and levofloxacin. According to the IDSA guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections, combination therapy against DTR *P. aeruginosa* is not routinely recommended [14, 15]. Although the DTR definition is comprehensive, its use in retrospective studies may be unrealistic because of limitations in susceptibility reporting. Needless to say, gaps remain within the IDSA guidance for treatment of MDR/XDR/DTR *P. aeruginosa*, specifically with regards to infection source. To address these gaps, we conducted a multicenter, retrospective cohort comparing safety and efficacy outcomes of patients with lower respiratory tract infection (LRTI) caused by MDR/XDR *P. aeruginosa* treated with C/T or best alternative therapy.

# METHODS

## Study Design and Population

We conducted a retrospective, observational cohort at the Detroit Medical Center (DMC) and Henry Ford Hospital (HFH) between 2014 and 2019. Cohorts included (1) patients who received C/T for 48 h or more for the index infection composed the C/T group; (2) best alternative therapy group, which included patients who received traditional beta-lactams (piperacillin/tazobactam, cefepime, meropenem, ceftazidime, or ceftazidime/avibactam), aminoglycosides, and/or polymyxins. Patients meeting the following criteria were eligible for inclusion: (1) age 18 years or older; (2) MDR or XDR *P. aeruginosa* isolated from at least one of the following samples: sputum, pleural fluid, tracheobronchial aspirate, or bronchoalveolar lavage; (3) diagnosis of LRTI defined as per Centers for Disease Control and National Healthcare Safety Network (CDC/NHSN) definitions [16, 17]. Patients with known *P. aeruginosa* colonization (two positive cultures at least 3 months apart over the course of 12 months), cystic fibrosis, and those who died or were discharged within 48 h of initiation of antimicrobials for empiric treatment of LRTI were excluded [18]. Inhaled aminoglycosides or polymyxins were allowed in both study arms. Patients with polymicrobial infections or concomitant infections were included.

## Outcomes

The primary outcome was composite clinical failure, defined as 30-day all-cause mortality and/or an adverse drug reaction (ADR) during antibiotic therapy. Secondary endpoints included individual components of the composite outcome, 30-day recurrence from end of

antibiotic treatment for index infection, hospital length of stay, time to active therapy, and 30-day readmission from discharge date. Time to active therapy was measured from index respiratory culture collection.

### Data Collection and Study Definitions

Relevant patient demographic, clinical, and treatment data between 2014 to 2019 were extracted from the electronic medical record and entered into a secured electronic data collection form [19]. The Wayne State Institutional Review Board (IRB) with Detroit Medical Center research authorization approved the study design and reporting, and waived the requirement for patient consent. Respiratory cultures were processed at the DMC and HFH microbiology laboratories according to Clinical and Laboratory Standards Institute (CLSI) procedures [20]. Bacterial identification and antimicrobial susceptibility testing were performed using Microscan (Siemens Healthcare Diagnostics), Phoenix (BD), or Vitek2 (bioMérieux). Clinical variables were collected on the basis of medical team notes and microbiological/diagnostic reports. Occurrence of side effects was collected on the basis of laboratory assessment or notes by the medical team and assessed using Common Terminology Criteria for Adverse Events (CTCAE) definitions and the Naranjo Adverse Drug Reaction Probability Scale [21, 22]. ADRs must have been documented in progress notes as related to the antibiotic(s) of interest. Severity of illness and patient comorbidities were assessed using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Charlson comorbidity index (CCI), respectively. APACHE II was assessed within 24 h of index respiratory infection. LRTI was defined according to the CDC/NHSN definitions and classified as hospital acquired if the index respiratory culture was obtained more than 48 h after admission [16]. Combination therapy was defined as concomitant use of two antimicrobials for at least 48 h for index infection. Active therapy was defined as in vitro susceptibility for organism(s) recovered on culture. MDR *P. aeruginosa* was defined as non-susceptible to at least one agent in three or more antimicrobial categories, and XDR was defined as non-susceptible to at least one agent in all but two or fewer categories [3]. Thirty-day all-cause mortality was defined as death from any cause within 30 days of index respiratory culture collection. Nephrotoxicity, defined as a serum creatinine increase of at least 0.5 mg/dL or a 50% increase from baseline on two consecutive measurements during antibiotic therapy for the index infection, was evaluated in patients not receiving hemodialysis or renal replacement [23]. Those receiving hemodialysis or renal replacement during antibiotic therapy were considered as not having nephrotoxicity.

### Statistical Analysis

Bivariate comparisons of baseline characteristics, infection-related variables, and outcomes between patients treated with C/T and best alternative therapy regimens were performed. The chi-squared or Fisher's exact test was utilized for categorical data, and the Student *t* test or Mann–Whitney *U* test were used to compare continuous parametric and nonparametric variables, respectively. Multivariable logistic regression was used to assess the independent association between best alternative therapy regimens and composite clinical failure while adjusting for confounding variables. All variables associated with the primary composite outcome of clinical failure in the bivariate analysis at a *P* value of less than 0.1 and at least 10% variability (variables covering at least 10% of total cases) were entered into the model simultaneously and removed using a backward stepwise approach. Covariates were retained in the model if the *P* value for the likelihood ratio test for their removal was less than 0.1. The variance of inflation factor was used to assess the multicollinearity of covariates in the model. Variables with a variance of inflation factor greater than 3 were not entered into the model. The Hosmer–Lemeshow goodness-of-fit test was used to assess the model's fit. All tests were two-tailed, with *P* values less than 0.05 considered statistically significant. IBM SPSS software,

version 28.0 (SPSS, Inc., Chicago, IL, USA), was used for all calculations.

## RESULTS

### Participants

During the study period, 241 patients with MDR/XDR *P. aeruginosa* LRTI were recorded. Of these, 35 were excluded from the analyses because of death or discharge within 48 h of initiation of antimicrobials for empiric treatment of LRTI ($n = 24$), had known *P. aeruginosa* colonization ($n = 7$) or cystic fibrosis ($n = 4$). The remaining 206 patients with MDR/XDR *P. aeruginosa* LRTI were included in the study (C/T, $n = 118$; best alternative therapy, $n = 88$) (Fig. 1).

### Descriptive Data

Within the entire cohort there were 144 (69.9%) men, the median age was 61.0 (53–72) years, and the patients had a median (interquartile range, IQR) APACHE II score of 24 (9–28). The XDR phenotype was more common in the C/T group (49.2% vs. 31.8%, $P = 0.013$) as was VABP (52.5% vs. 38.6%, $P = 0.048$) compared to the best alternative therapy group. The rate of polymicrobial infection (39.8% vs. 44.3%, $P = 0.518$) and acute kidney injury (AKI) on admission (36.4% vs. 30.6%, $P = 0.394$) was similar between groups. Among patients with polymicrobial infections, Gram-positive organisms were more common in the C/T group (6.8% vs. 18.6%, $P = 0.014$) whereas Gram-negative organisms *Klebsiella pneumoniae* (15.9% vs. 5.1%, $P = 0.009$) and *Stenotrophomonas maltophilia* (11.4% vs. 5.9%, $P = 0.161$) were more common in the best alternative therapy group. Of those with susceptibility data available, most patients with *S. maltophilia* (9/11, 81.8%) and *K. pneumoniae* (12/12, 100%) received active therapy against their respective organisms.

A comparison of baseline clinical characteristics between patients who received C/T for 48 h or more and those that received best alternative therapy is shown in Table 1. Some notable differences were observed between the two groups. *P. aeruginosa* with an XDR phenotype was more common in the C/T group compared with the best alternative therapy group, 49.2% vs. 31.8% ($P = 0.013$); as well as history of AKI, 29.7% vs. 17.0% ($P = 0.037$); and dementia, 15.3% vs. 4.5% ($P = 0.014$), respectively. Conversely, neutropenia and tumor with metastasis were more prominent in the best alternative therapy group compared to the C/T group, 19.3% vs. 0.0% ($P < 0.001$) and 14.8% vs. 2.5% ($P = 0.001$), respectively. Infection characteristics and polymicrobial organisms are also displayed in Table 1.

### Treatment Data

Overall, 118 patients with MDR/XDR *P. aeruginosa* LRTI received C/T (57.3%). Eighty-eight patients received best alternative therapy (42.7%), among which cefepime ($n = 45$), meropenem ($n = 35$), and piperacillin–tazobactam ($n = 18$) were the most common. Intravenous polymyxins were utilized less frequently with only 13 patients (6.3%) having received polymyxin B and 10 patients (4.9%) received

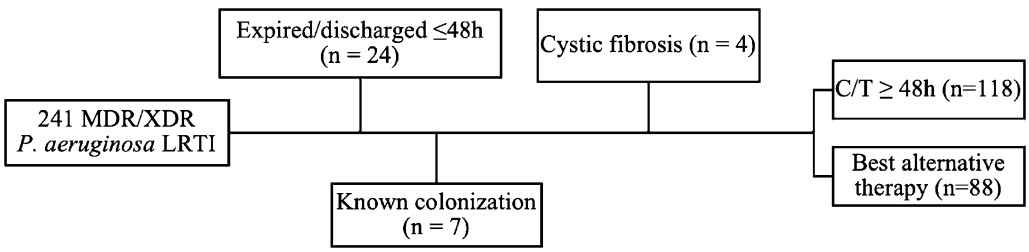


**Fig. 1** Flowchart of patients included in the study. *MDR* multidrug-resistant, *XDR* extensively drug-resistant, *LRTI* lower respiratory tract infection, *h* hours, *C/T* ceftolozane–tazobactam

**Table 1** Baseline demographics and clinical characteristics of the cohort

| Characteristics | C/T (*n* = 118) | Best alternative (*n* = 88) | All patients (*n* = 206) | *P* value |
|---|---|---|---|---|
| Demographics | | | | |
| Age in years, median (IQR) | 61.0 (54–73) | 63.5 (50–71) | 61.0 (53–72) | 0.894 |
| Age over 60 years | 60 (50.8) | 48 (54.5) | 108 (52.4) | 0.599 |
| Male sex | 83 (70.3) | 61 (69.3) | 144 (69.9) | 0.874 |
| BMI, median (IQR) | 25 (19–29) | 24 (20–28) | 24 (19–29) | 0.733 |
| XDR *P. aeruginosa* | 58 (49.2) | 28 (31.8) | 86 (41.7) | 0.013 |
| Race | | | | |
| African American | 64 (54.2) | 53 (60.2) | 117 (56.8) | 0.391 |
| Caucasian | 43 (36.4) | 29 (33.0) | 72 (35.0) | 0.604 |
| Hispanic | 2 (1.7) | 1 (1.1) | 3 (1.5) | 0.741 |
| Asian | 0 (0.0) | 1 (1.1) | 1 (0.5) | 0.246 |
| Other/unknown | 9 (7.6) | 4 (4.5) | 13 (6.3) | 0.368 |
| Severity of illness factors | | | | |
| Index culture collected in ICU | 84 (71.2) | 54 (61.4) | 138 (67.0) | 0.115 |
| SOFA score, median (IQR) | 6 (4–8) | 6 (4–8) | 6 (4–8) | 0.926 |
| APACHE II score, median (IQR) | 25 (19–29) | 23 (18–28) | 24 (19–28) | 0.403 |
| CCI, median (IQR) | 4 (2–6) | 5 (3–7) | 4 (2–7) | 0.033 |
| AKI present on admission | 39 (36.4) | 26 (30.6) | 65 (31.6) | 0.394 |
| AKIN stage 1 | 23 (59.0) | 14 (54.0) | 37 (56.9) | |
| AKIN stage 2 | 8 (20.5) | 8 (31.0) | 16 (24.6) | |
| AKIN stage 3 | 8 (20.5) | 4 (15.0) | 12 (18.5) | |
| Admission from NH/LTAC/SNF/LTCF | 44 (37.3) | 29 (33.0) | 73 (35.4) | 0.52 |
| Comorbid conditions | | | | |
| COPD | 37 (31.4) | 33 (37.5) | 70 (34.0) | 0.357 |
| Moderate to severe CKD | 29 (24.6) | 25 (28.4) | 54 (26.2) | 0.536 |
| Chronic dialysis | 12 (10.2) | 8 (9.1) | 20 (9.7) | 0.796 |
| Acute kidney injury | 35 (29.7) | 15 (17.0) | 50 (24.3) | 0.037 |
| Myocardial infarction | 7 (5.9) | 3 (3.4) | 10 (4.9) | 0.405 |
| Peripheral vascular disease | 13 (11.0) | 9 (10.2) | 22 (10.7) | 0.856 |
| Heart failure | 22 (18.6) | 22 (25.0) | 44 (21.4) | 0.271 |
| HIV | 1 (0.8) | 2 (2.3) | 3 (1.5) | 0.398 |

**Table 1** continued

| Characteristics | C/T ($n$ = 118) | Best alternative ($n$ = 88) | All patients ($n$ = 206) | $P$ value |
|---|---|---|---|---|
| Cerebrovascular disease | 29 (24.6) | 25 (28.4) | 54 (26.2) | 0.536 |
| Dementia | 18 (15.3) | 4 (4.5) | 22 (10.7) | 0.014 |
| Asthma | 7 (5.9) | 8 (9.1) | 15 (7.3) | 0.388 |
| Connective tissue disease | 12 (10.2) | 7 (8.0) | 19 (9.2) | 0.587 |
| Moderate or severe liver disease | 2 (1.7) | 1 (1.1) | 3 (1.5) | 0.741 |
| Diabetes | 18 (15.3) | 16 (18.2) | 34 (16.5) | 0.576 |
| Diabetes (with end-organ damage) | 28 (23.7) | 22 (25.0) | 50 (24.3) | 0.833 |
| Hemiplegia | 12 (10.2) | 10 (11.4) | 22 (10.7) | 0.784 |
| Tumor without metastasis | 5 (4.2) | 2 (2.3) | 7 (3.4) | 0.441 |
| Tumor with metastasis | 3 (2.5) | 13 (14.8) | 16 (7.8) | 0.001 |
| IV drug use | 5 (4.2) | 4 (4.5) | 9 (4.4) | 0.915 |
| Immunosuppression factors | | | | |
| Neutropenia[a] | 0 (0.0) | 17 (19.3) | 17 (8.3) | < 0.001 |
| Solid organ transplant | 1 (0.8) | 0 (0.0) | 1 (0.5) | 0.387 |
| Chemotherapy within 90 days[b] | 3 (2.5) | 7 (8.0) | 10 (4.9) | 0.074 |
| High dose corticosteroids | 3 (2.5) | 2 (2.3) | 5 (2.4) | 0.901 |
| MDR risk factors | | | | |
| Antimicrobials within 90 days[b] | 83 (70.3) | 53 (60.2) | 136 (66.0) | 0.13 |
| Hospitalization within 90 days[b] | 71 (60.2) | 58 (65.9) | 129 (62.6) | 0.4 |
| Admitted from nursing home/LTCF | 41 (34.7) | 41 (46.6) | 82 (39.8) | 0.086 |
| Chronic dialysis within last 30 days[b] | 11 (9.3) | 7 (8.0) | 18 (8.7) | 0.731 |
| Home wound care | 4 (3.4) | 2 (2.3) | 6 (2.9) | 0.637 |
| Surgery within 30 days[b] | 9 (7.6) | 10 (11.4) | 19 (9.2) | 0.359 |
| Infection characteristics | | | | |
| VABP | 62 (52.5) | 34 (38.6) | 96 (46.6) | 0.048 |
| Polymicrobial infections | 47 (39.8) | 39 (44.3) | 86 (41.7) | 0.518 |
| Two organisms | 31 (66.0) | 30 (76.9) | 61 (70.9) | 0.224 |
| Three organisms | 14 (29.8) | 9 (23.1) | 23 (26.7) | 0.712 |
| Four organisms | 2 (4.3) | 0 (0.0) | 2 (2.3) | 0.508 |
| Concomitant pathogens | | | | |
| *Acinetobacter baumannii* | 4 (3.4) | 6 (6.8) | 10 (4.9) | 0.257 |

**Table 1** continued

| Characteristics | C/T ($n$ = 118) | Best alternative ($n$ = 88) | All patients ($n$ = 206) | $P$ value |
|---|---|---|---|---|
| *Citrobacter freundii* | 1 (0.8) | 0 (0.0) | 1 (0.5) | 0.387 |
| *Enterobacter cloacae* | 1 (0.8) | 0 (0.0) | 1 (0.5) | 0.387 |
| *Escherichia coli* | 2 (1.7) | 3 (3.4) | 5 (2.4) | 0.429 |
| *Klebsiella oxytoca* | 1 (0.8) | 0 (0.0) | 1 (0.5) | 0.387 |
| *Klebsiella pneumoniae* | 6 (5.1) | 14 (15.9) | 20 (9.7) | 0.009 |
| *Morganella morganii* | 1 (0.8) | 1 (1.1) | 2 (1.0) | 0.834 |
| *Proteus mirabilis* | 7 (5.9) | 3 (3.4) | 10 (4.9) | 0.405 |
| *Providencia stuartii* | 9 (7.6) | 5 (5.7) | 14 (6.8) | 0.583 |
| *Serratia marcescens* | 3 (2.5) | 0 (0.0) | 3 (2.5) | 0.132 |
| *Stenotrophomonas maltophilia* | 7 (5.9) | 10 (11.4) | 17 (8.3) | 0.161 |
| Gram-positive bacteria | 22 (18.6) | 6 (6.8) | 28 (13.6) | 0.014 |
| Fungal pathogen | 1 (0.8) | 0 (0.0) | 1 (0.5) | 0.387 |

Data are presented as number (%) unless stated otherwise

*AIDS* acquired immunodeficiency syndrome (CD4 < 200), *AKIN* Acute Kidney Injury Network, *APACHE* Acute Physiology and Chronic Health Evaluation, *BMI* body mass index, *CCI* Charlson comorbidity index, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disorder, *HIV* human immunodeficiency virus, *ICU* intensive care unit, *IQR* interquartile range, *IV* intravenous, *LTAC* long-term acute care facility, *LTCF* long-term care facility, *MDR*, multidrug-resistant, *moderate to severe CKD* KDOQI CKD stage III–V or GFR < 60 ml/min or on chronic dialysis, *n* number of patients, *NH* nursing home, *SNF* skilled nursing facility, *SOFA* sequential organ failure assessment, *VABP* ventilator-associated bacterial pneumonia (mechanically ventilated ≥ 48 h prior to pneumonia diagnosis), *XDR* extensively drug-resistant

[a]Neutropenia defined as absolute neutrophil count or white blood cell count < 500

[b]From time of index culture collection

colistin, and most of those patients received a polymyxin for at least 48 h (14/23, 60.9%). Intravenous aminoglycosides were administered in 59/206 patients (28.6%). In total, 48/206 patients (23.3%) received combination therapy for at least 48 h. Interestingly, combination therapy was more common in the C/T group (29.7%) compared to best alternative therapy (14.8%) ($P$ = 0.012). Of those cases where C/T was used in combination with another agent ($n$ = 35), the most common combination agents were aminoglycosides (22/35) and polymyxins (8/35). Empiric therapy with C/T was employed in eight patients (6.8%). Most patients (88/118) received appropriate C/T dosing, 3 g every 8 h, per package insert for HABP/VABP, with a portion of patients receiving renally adjusted C/T dosing of 1.5 g every 8 h (15/118).

## Resistance Data

Among the entire cohort, C/T susceptibilities were available for most patients (61.7%). Of those MDR/XDR *P. aeruginosa* isolates with reported C/T susceptibility data, 87.4% were susceptible to C/T (MIC ≤ 4/4). Specifically, 27/31 (87.1%) were susceptible to C/T in the best alternative therapy group, and 87/96 (90.6%) were susceptible in the C/T group. The

**Table 2** Antibiotic treatment and resistance data for the cohort

| Characteristics | C/T ($n$ = 118) | Best alternative ($n$ = 88) | All patients ($n$ = 206) | $P$ value |
|---|---|---|---|---|
| Antibiotics | | | | |
| Tobramycin | 29 (24.6) | 13 (14.8) | 42 (20.4) | 0.084 |
| Amikacin | 13 (11.0) | 3 (3.4) | 16 (7.8) | 0.044 |
| Gentamicin | 1 (0.8) | 0 (0.0) | 1 (0.5) | 0.387 |
| Colistin | 6 (5.1) | 4 (4.5) | 10 (4.9) | 0.859 |
| Polymyxin B | 6 (5.1) | 7 (8.0) | 13 (6.3) | 0.402 |
| Cefepime | 37 (31.4) | 45 (51.1) | 82 (39.8) | 0.004 |
| Meropenem | 40 (33.9) | 35 (39.8) | 75 (36.4) | 0.386 |
| Piperacillin–tazobactam | 22 (18.6) | 18 (20.5) | 40 (19.4) | 0.745 |
| Ceftazidime–avibactam | 6 (5.1) | 10 (11.4) | 16 (7.8) | 0.096 |
| Aztreonam | 1 (0.8) | 5 (5.7) | 6 (2.9) | 0.041 |
| Imipenem | 1 (0.8) | 1 (1.1) | 2 (1.0) | 0.834 |
| Ceftazidime | 0 (0.0) | 2 (2.3) | 2 (1.0) | 0.1 |
| Levofloxacin | 1 (0.8) | 0 (0.0) | 1 (0.5) | 0.387 |
| Inhaled antibiotics | 23 (19.5) | 15 (17.0) | 38 (18.4) | 0.654 |
| Tobramycin | 18 (15.3) | 8 (9.1) | 26 (12.6) | 0.188 |
| Colistin | 7 (5.9) | 8 (9.1) | 15 (7.3) | 0.388 |
| Nephrotoxicity risk factors | | | | |
| Aminoglycoside or polymyxin ≥ 48 h | 49 (41.5) | 23 (26.1) | 72 (35.0) | 0.022 |
| Aminoglycoside ≥ 48 h | 21 (17.8) | 8 (9.1) | 29 (14.1) | 0.076 |
| Polymyxin ≥ 48 h | 9 (7.6) | 5 (5.7) | 14 (6.8) | 0.583 |
| Combination therapy | 35 (29.7) | 13 (14.8) | 48 (23.3) | 0.012 |
| *P. aeruginosa* resistance[a] | | | | |
| Resistant to C/T (MIC ≥ 16/4) | 4 (4.2) | 2 (6.5) | 6 (4.8) | 0.637 |
| Intermediate to C/T (MIC 8/4) | 5 (5.2) | 2 (6.5) | 7 (5.5) | 0.701 |
| Resistant ≥ 1 carbapenem | 97 (83.6) | 63 (74.1) | 160 (79.6) | 0.099 |
| Resistant ≥ 1 aminoglycoside | 16 (13.7) | 7 (8.2) | 23 (11.4) | 0.241 |
| Resistant ≥ 1 polymyxin | 9 (22.5) | 5 (17.9) | 14 (20.6) | 0.641 |

Data are presented as number (%) unless stated otherwise. Antibiotics are listed if patient received at least one dose
*MIC* minimum inhibitory concentration, *C/T* ceftolozane–tazobactam, *h* hours
[a]Of those patients with resistance data available

**Table 3** Bivariate comparison of primary and secondary outcomes between patients with C/T and best alternative therapy

| Outcomes | C/T ($n$ = 118) | Best alternative ($n$ = 88) | $P$ value |
|---|---|---|---|
| Primary outcome | | | |
| Composite clinical failure | 28 (23.7) | 43 (48.9) | < 0.001 |
| 30-day mortality | 18 (15.3) | 18 (20.5) | 0.331 |
| Adverse drug reaction, any | 12 (10.2) | 29 (33.0) | < 0.001 |
| Secondary outcomes | | | |
| 30-day recurrence | 18 (15.3) | 14 (15.9) | 0.898 |
| 30-day readmission | 21 (17.8) | 13 (14.8) | 0.563 |
| 60-day readmission | 19 (16.1) | 16 (45.7) | 0.667 |
| LOS from index culture, median (IQR) | 23.1 (9.4–25.7) | 10.3 (4.3–13.3) | < 0.001 |
| Discharge non-home | 98 (56.6) | 75 (43.4) | 0.674 |
| Time to active therapy, days | 2.3 (0.3–4.0) | 0.7 (− 0.9 to 2.6) | < 0.001 |
| Admitted to ICU during hospital stay | 104 (88.1) | 75 (85.2) | 0.541 |
| Multiple ICU admissions during hospital stay | 27 (22.9) | 11 (12.5) | 0.057 |
| Admitted to ICU (× 2) | 19 (16.1) | 9 (10.2) | 0.224 |
| Admitted to ICU (× 3) | 8 (6.8) | 2 (2.3) | 0.137 |
| ID consult | 115 (97.5) | 69 (78.4) | < 0.001 |
| Surgical consult | 6 (5.1) | 14 (15.9) | 0.009 |
| Surgical interventions | 8 (6.8) | 8 (9.1) | 0.54 |
| IV catheter removal | 0 (0.0) | 4 (4.5) | 0.032 |
| Incision and drainage | 1 (0.8) | 0 (0.0) | 1 |
| Debridement | 3 (0.8) | 2 (2.3) | 1 |
| Other | 4 (3.4) | 2 (2.3) | 1 |
| Adverse drug reactions | 12 (10.2) | 29 (33.0) | < 0.001 |
| Nephrotoxicity[a] | 6 (5.1) | 12 (13.6) | 0.032 |
| Nephrotoxin within 72 h[b] | 5 (83.3) | 5 (41.7) | 0.152 |
| Gastrointestinal (nausea, vomiting, diarrhea) | 1 (0.8) | 2 (2.3) | 0.577 |
| Cardiac (arrhythmias, QTc prolongation) | 0 (0.0) | 3 (3.4) | 0.076 |
| Lactic acidosis | 0 (0.0) | 6 (6.8) | 0.005 |
| *Clostridioides difficile* infection | 6 (5.1) | 1 (1.1) | 0.243 |
| Encephalopathy (AMS or new onset seizures) | 0 (0.0) | 6 (6.8) | 0.005 |
| Hepatotoxicity (e.g., AST/ALT elevations) | 2 (1.7) | 0 (0.0) | 0.508 |

**Table 3** continued

| Outcomes | C/T ($n$ = 118) | Best alternative ($n$ = 88) | $P$ value |
|---|---|---|---|
| Neutropenia[c] | 0 (0.0) | 16 (18.2) | < 0.001 |

Data are presented as number (%) unless stated otherwise

*ALT* alanine aminotransferase, *AMS* altered mental status, *AST* aspartate aminotransferase, *h* hours, *ICU* intensive care unit, *IQR* interquartile range, *LOS* length of stay, *QTc* QT corrected for heart rate

[a]Defined as a serum creatinine increase ≥ 0.5 mg/dL or a 50% increase from baseline on 2 consecutive measurements during antibiotic therapy for the index infection

[b]Receipt of aminoglycosides, amphotericin B, vancomycin, or IV contrast within 72 h timeframe of this nephrotoxicity episode

[c]ANC decrease to < 1500 cells/mm$^3$; or 50% decrease in ANC if baseline ANC < 1500 cells/mm$^3$ from initiation of antibiotic

four patients with C/T-resistant isolates in the C/T group were all treated with combination therapy consisting of C/T plus another agent for at least 48 h. Carbapenem resistance was evaluated in 201 patients with susceptibility information and carbapenem-resistant (CR) *P. aeruginosa* was found to be prevalent among the cohort with 79.6% of isolates demonstrating resistance (MIC ≥ 8) to at least one carbapenem (meropenem, imipenem–cilastatin, or doripenem) (Table 2). The frequency of CR-*P. aeruginosa* in the C/T group (97/116, 83.6%) and best alternative therapy group (63/85, 74.1%) was assessed, although the difference in frequency between groups was not statistically significant ($P$ = 0.099). Resistance to one or more aminoglycosides was found in 11.4% of patients with susceptibility information available (23/202) and there was no significant difference between C/T and best alternative therapy groups, 13.7% vs. 8.2%, respectively ($P$ = 0.241). Resistance to polymyxins (MIC ≥ 4 for polymyxin B or colistin) was 20.6% among patients with susceptibility data (14/68) [20]. There was no statistically significant difference in the frequency of polymyxin-resistant isolates between C/T and best alternative therapy groups, 22.5% and 17.9%, respectively ($P$ = 0.641) (Table 2).

## Outcomes Data

A bivariate comparison of clinical outcomes between C/T and best alternative therapy patients is presented in Table 3. In bivariate analysis, clinical failure was significantly higher in the best alternative therapy group compared to the C/T group, 48.9% vs. 23.7%, respectively ($P$ < 0.001). The individual components of composite clinical failure, i.e., ADR (33.0% vs. 10.2%, $P$ < 0.001) and 30-day mortality (20.5% vs. 15.3%, $P$ = 0.331), were also found to be higher in the best alternative therapy group, although 30-day mortality was not significantly different between groups. Hospital length of stay (LOS) was higher in the C/T group compared to the best alternative therapy group (23.1 vs. 10.3 days, $P$ < 0.001) although ICU admission was comparable between groups, 88.1% vs. 85.2%, respectively ($P$ = 0.541). Among patients with susceptibility information, time to active therapy was significantly longer in the C/T group compared to the best alternative therapy group (2.3 vs. 0.7 days, $P$ < 0.001) although no significant differences were found in microbiologic recurrence or readmission between groups (Table 3). Overall, patients who received best alternative therapy were more likely to experience ADRs, including nephrotoxicity (33.0% vs. 10.2%, $P$ < 0.001), encephalopathy (6.8% vs. 0%, $P$ = 0.005), and neutropenia (16.0% vs. 0%, $P$ < 0.001), respectively (Table 3).

A bivariate comparison of baseline criteria between all patients with and without clinical failure was assessed (Table S1 in the supplementary material). Notable variables with differences between the two groups at the prespecified $P$ value of less than 0.1 were

**Table 4** Multivariable logistic regression for factors independently associated with clinical failure

| Variables | OR | *P* value | 95% CI | aOR | *P* value | 95% CI |
|---|---|---|---|---|---|---|
| C/T treatment group | 0.326 | < 0.001 | 0.179–0.591 | 0.267 | < 0.001 | 0.140–0.507 |
| APACHE II score | 1.088 | < 0.001 | 1.042–1.137 | 1.102 | < 0.001 | 1.052–1.154 |

Variables included (1) treatment with C/T, (2) moderate-severe CKD, (3) APACHE II, (4) age over 60, (5) CCI, (6) SOFA, (7) COPD, (8) tobramycin. Hosmer–Lemeshow goodness-of-fit test $P = 0.336$; variance inflation factor $\leq 3$ for all variables included at model entry

*OR* odds ratio, *CI* confidence interval, *aOR* adjusted odds ratio, *C/T* ceftolozane–tazobactam

included in the stepwise selection process for the multivariable logistic regression model. The final model had an area under the receiver operating characteristic (ROC) curve of 0.73, indicating that successful classification of clinical failure was achieved with the fitted model. The Hosmer–Lemeshow goodness-of-fit test demonstrated an acceptable *P* value ($P = 0.336$). Treatment with C/T was significantly associated with a 73.3% lower likelihood of clinical failure (adjusting for APACHE II) compared with best alternative therapy (aOR 0.267, 95% CI 0.140–0.507, $P < 0.001$). Independent associations between clinical failure and included variables are listed in Table 4.

## DISCUSSION

To our knowledge, this is the largest study to date evaluating C/T for the treatment of MDR/XDR *P. aeruginosa* LRTI. Further, this is the first analysis to compare safety and efficacy outcomes of C/T vs. best alternative therapy specifically for the treatment of MDR/XDR *P. aeruginosa* LRTI. The population included was largely critically ill, demonstrated by high APACHE II scores and CCIs, ICU admission, and VABP diagnoses. Susceptibility to C/T was consistent with previously reported susceptibility rates in MDR/XDR *P. aeruginosa* (76.9–92.2%) [20, 24, 25]. Although C/T demonstrates excellent activity against MDR/XDR *P. aeruginosa*, it is important to consider the predominant, local resistance mechanisms in order to apply empirical therapy with C/T due to loss of activity against *K. pneumoniae* carbapenemase (KPC) and metallo-β-lactamases [26]. Combination therapy with C/T was used in nearly 30% of patients with a variety of agents including colistin, polymyxin B, tobramycin, amikacin, ciprofloxacin, and levofloxacin. Interestingly, polymicrobial infection was not associated with clinical failure during bivariate comparison, likely owing to appropriate administration of active therapy (Table S1 in the supplementary material). After we controlled for confounders, C/T was associated with a 73.3% reduction in clinical failure ($P < 0.001$), despite having longer time to active therapy (2.3 vs. 0.7 days) and longer LOS (23.1 vs. 10.3 days), respectively. Greater incidence of XDR *P. aeruginosa* and VABP in the C/T group likely contributed towards longer time to active therapy and LOS, respectively. These findings are consistent with recent data in MDR/XDR *P. aeruginosa* invasive infections, including those outside of the respiratory tract (e.g., urinary tract and wound infections) that demonstrate improved outcomes with novel beta-lactam/beta-lactamase inhibitors (i.e., C/T and CZA) compared to traditional regimens for the management of MDR/XDR Gram-negative infections [9]. While this retrospective analysis cannot determine the true extent of clinical failure risk in this complex, critically ill population, our results are clinically relevant because treatment regimen was the only modifiable factor contributing to significantly reduced clinical failure after multivariable regression.

Unlike previous comparative effectiveness studies, the present study includes meropenem, among other traditional beta-lactam agents, for the treatment of MDR/XDR *P. aeruginosa*, which adds to the literature to support C/T over these

traditional therapies. A recent retrospective evaluation by Pogue et al. investigated the impact of C/T vs. polymyxin or aminoglycoside-based regimens on clinical outcomes in 200 patients with drug-resistant *P. aeruginosa* infections. Like the present analysis, the cohort represented a complex patient population, with 69% of patients admitted to the ICU, a median SOFA score of 8, and 63% mechanically ventilated at the onset of infection. The study compared rates of clinical cure, defined as resolution of signs/symptoms of infection, between patients who received C/T ($n = 100$) and polymyxin or aminoglycoside-based regimens ($n = 100$). In their analysis, higher clinical cure ($P = 0.002$) and lower AKI rates ($P < 0.001$) were demonstrated in patients receiving C/T compared to those who received polymyxin- or aminoglycoside-based regimens [9]. However, other commonly utilized monotherapy regimens (i.e., carbapenems, cefepime, etc.) were not included, and other infection sites, including urinary tract and wound, comprised over 30% of the population. In response, Vena et al. reported results from a multicenter, retrospective 1:2 matched case–control analysis of 48 patients with MDR/XDR *P. aeruginosa* HABP/VABP or bloodstream infection [27]. Although limited by small sample size, their findings corroborated the results from Pogue et al. with C/T-based regimens demonstrating a trend towards higher cure rates and lower incidence of AKI compared to colistin- or aminoglycoside-based regimens. Taken with the results of the current study, these data support preferential use of C/T over alternative therapy options for MDR/XDR *P. aeruginosa* LRTIs.

Our study improves upon the previous investigations by comparing all conventional agents to C/T for the treatment MDR/XDR *P. aeruginosa*, as opposed to only including polymyxins and aminoglycosides as comparators. As demonstrated in our data, cefepime, meropenem, and piperacillin–tazobactam are still utilized in the treatment of MDR *P. aeruginosa*. As a result, our study has high external validity by including a representative population with real-world treatment regimens. The present study also includes detailed resistance data, which allows us to describe the frequency of MDR and XDR *P. aeruginosa*, further characterize the *P. aeruginosa* isolates, and improve internal validity. Furthermore, by excluding other disease states (i.e., bacteremia, urinary tract, etc.) we are better able to extrapolate our results with more precision to patients with respiratory infection caused by MDR/XDR *P. aeruginosa*.

There are several limitations to the present study that should be considered. In addition to the retrospective nature of data collection, the *P. aeruginosa* respiratory culture data were collected from two centers in Michigan, and therefore antibiotic formularies, patient populations, and institutional prescribing patterns may affect the applicability of these results to other institutions. Second, infectious disease (ID) consultations, which have been associated with improved outcomes in previous studies, were more frequent in the C/T group than the best alternative therapy group likely as a result of antibiotic restriction tiers [28, 29]. When ID consult was included as a study variable and was considered as a component of C/T intervention in the logistic regression, the results of the primary analysis remained unchanged. Lastly, an inherent limitation exists within the composite outcome, which includes nephrotoxicity, for which a small portion of patients were ineligible to achieve because of hemodialysis. However, the proportion of patients with hemodialysis was very similar between the C/T and best alternative therapy groups (10.2% vs. 9.1%, $P = 0.796$), and hemodialysis was not found to be significantly different between those with clinical failure and those without (11.3% and 7.4%, $P = 0.351$). Limiting the type of infection to the lower respiratory tract narrows our analysis and including all antimicrobials represents a real-world approach to treatment and outcomes in this complicated patient population.

## CONCLUSION

Overall, we found that C/T-based regimens were well tolerated and showed significant reduction in clinical failure compared to best alternative therapy regimens in patients with MDR/XDR *P. aeruginosa* LRTI. Our study adds to the

mounting evidence that C/T appears to be a safe and effective therapy for treatment of LRTI caused by MDR/XDR *P. aeruginosa*. Further studies are needed to assess the impact of combination therapy with C/T and other agents on patient outcomes in those with severe infection caused by drug-resistant *P. aeruginosa*.

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***Prior Presentation.*** Data from a proportion of patients in this analysis have been presented, in part, in the following publications: Jorgensen et al. [30, 31].

***Compliance with Ethics Guidelines.*** The Wayne State Institutional Review Board (IRB) with Detroit Medical Center research authorization approved the study design and reporting and waived the requirement for patient consent.

***Data Availability.*** Data are available on request to m.rybak@wayne.edu given patient confidentiality regulations from a limited dataset under the Health Insurance Portability and Accountability Act (HIPAA).

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## Publisher's Note