Experience With Ceftolozane-Tazobactam for the Treatment of Serious *Pseudomonas aeruginosa* Infections in Saudi Tertiary Care Center

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ABSTRACT

INTRODUCTION: Multidrug-resistant *Pseudomonas aeruginosa* isolates have multiple resistance mechanisms, and there are insufficient therapeutic options to target them. Ceftolozane-tazobactam is a novel antipseudomonal agent that contains a combination of an oxyimino-aminothiazolyl cephalosporin (ceftolozane) and a β-lactamase inhibitor (tazobactam).

METHODS: A single-center retrospective observational study between January 2017 and December 2018 for patients who had been diagnosed with carbapenem-resistant *P aeruginosa* infections and treated with ceftolozane-tazobactam for more than 72 hours. We assessed clinical success based on microbiological clearance as well as the clinical resolution of signs and symptoms of infection.

RESULTS: A total of 19 patients fit the inclusion criteria, with a median age was 57 years, and 53% were female. The types of infections were nosocomial pneumonia, acute bacterial skin, and skin structure infections; complicated intra-abdominal infections; and central line–associated bloodstream infections. All of the isolates were resistant to both meropenem and imipenem. The duration of therapy was variable (average of 14 days). At day 14 of starting ceftolozane-tazobactam, 18 of 19 patients had a resolution of signs and symptoms of the infection. Only 14 of 19 patients (74%) had proven microbiological eradication observed at the end of therapy. During therapy, there was no adverse event secondary to ceftolozane-tazobactam, and no *Clostridium difficile* infection was identified. The 30-day mortality rate was 21% (4/19).

CONCLUSIONS: Multidrug-resistant *P aeruginosa* infection is associated with high mortality, which would potentially be improved using a new antibiotic such as ceftolozane-tazobactam. Studies are required to explain the role of combination therapy, define adequate dosing, and identify the proper duration of treatment.

KEYWORDS: Ceftolozane-tazobactam, *Pseudomonas aeruginosa*, carbapenem-resistant, Saudi Arabia

Introduction

Hospital-acquired infections caused by resistant gram-negative bacteria have become a frequently encountered difficult clinical challenge. Those resistant organisms account for a significant percentage of hospital-acquired infections in many countries. Extended-spectrum β-lactamase (ESBL)-producing organisms have produced multiple hospital outbreaks and become a global health concern.[1,2] Moreover, increasing rates of carbapenem-resistant gram-negative bacteria are noticed in health care settings, especially with the increase of carbapenems used as essential agents to treat resistant isolates.[3,4] Because of multidrug resistance in gram-negative bacteria, the use of old abandoned antibiotics (ie, polymyxins) has been recalled by the World Health Organization[4] and reclassified as critically important for human medicine. Multidrug-resistant (MDR)

Pseudomonas aeruginosa isolates have multiple resistance mechanisms, and there are insufficient therapeutic options to target them.[5] As of today, aminoglycosides and polymyxins are the most consistently active antipseudomonal agents upon susceptibility testing. However, both are suboptimal for the treatment of pseudomonal infections due to pharmacokinetic limitations and their association with worse outcomes when given as a monotherapy.[6,7] In response to rising drug resistance, several new antibiotics are under development and investigation.[8] Ceftolozane-tazobactam is a novel antipseudomonal agent which contains a combination of an oxyimino-aminothiazolyl cephalosporin (ceftolozane) and a β-lactamase inhibitor (tazobactam) which has been approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of complicated intra-abdominal infections (with

concomitant metronidazole use) and complicated urinary tract infections.[9,10] Its potent activity against *P aeruginosa* arises from the stability of ceftolozane against AmpC enzymes, active efflux process, and porin-channel changes. Also, tazobactam gives ceftolozane further protection against destruction (by most ESBLs) without playing a role in its activity against *P aeruginosa*.[11,12] Ceftolozane-tazobactam was the most active β-lactam tested against *P aeruginosa* respiratory isolates of hospitalized patients in the United States from 2013 to 2015.[13] Although multicenter retrospective studies have demonstrated the efficacy of ceftolozane-tazobactam in MDR (including carbapenems) *P aeruginosa* infections,[14,15] further clinical studies are needed to establish substantial clinical evidence.

Materials and Methods

This is a single-center retrospective observational study of patients treated between January 2017 and December 2018 at King Abdul Aziz Medical City-Riyadh (KAMC-RD) in Saudi Arabia. Eligible patients were those who had been diagnosed with MDR *P aeruginosa* infection from any source and who were at least 18 years old who received ceftolozane-tazobactam therapy for at least 72 hours. The clinical and demographic data of eligible patients were extracted from the electronic medical records using our local health information system (Best Care). *Pseudomonas aeruginosa* clinical isolates and their susceptibility results were identified using the routine microbiological methods applied at KAMC-RD microbiology labs using the automated machine VITEK 2. The date of initiation of ceftolozane-tazobactam, dosing, and duration was determined based on the clinical pharmacist, physician, and nursing documentation during hospitalization. We assessed clinical success based on microbiological clearance (whenever repeated cultures were available); clinical resolution of signs and symptoms of infection, and 30-day in-hospital survival after initiation of ceftolozane-tazobactam treatment. The persistence of *P aeruginosa*–positive clinical cultures after 72 hours of therapy was considered a microbiologic failure. All collected data were entered into Statistical Package for the Social Sciences software for analysis. This study was conducted in compliance with all the applicable institutional ethical guidelines in King Abdullah International Medical Research Center (KAIMRC), and consent was not required as there was no direct contact with patients.

Results

A total of 19 patients with MDR *P aeruginosa* had received ceftolozane-tazobactam and fit the inclusion criteria. The median age was 57 years (interquartile range: 36-71), and 10 (53%) were female, as indicated in Table 1.

Types of infection were nosocomial pneumonia (6/19, 32%), where half of them had ventilator-associated pneumonia, acute bacterial skin, and skin structure infections (3/19, 16%), and one of those had complicated bacteremia, pyelonephritis (2/19,

Table 1. Demographics and clinical characteristics of 19 patients.

FACTOR	NO. (%)
Age (median)	57 y (IQR: 36-71)
Female	10 (53%)
Underlying diseases	
Diabetes	9 (47%)
Hypertension	10 (53%)
Chronic kidney disease	5 (26%)
Hematologic malignancy	5 (26%)
Solid organ malignancy	2 (10%)
Specimen of culture	
Respiratory	6 (32%)
Skin tissue	3 (16%)
Urine	2 (10%)
Intra-abdominal fluid	3 (16%)
Bone tissue	1 (5%)
Blood	4 (21%)
ICU admission	12 (63%)
Required source control[a]	10 (53%)
Duration of therapy (average)	14 d (7-35 d)
Clinical improvement (day 14)	18 (95%)
Microbiological clearance (day 14)	14 (74%)
30-day mortality	4 (21%)

Abbreviations: ICU, intensive care unit; IQR, interquartile range.
[a]Central line removal, surgical debridement, drain insertion.

10%), complicated intra-abdominal infection (3/19, 16%), including cholangitis and intra-abdominal collection and bone infection (1, 5%). Central line–associated bloodstream infection was documented in 4 cases, and 1 had a complication with endocarditis.

Of 19 patients (63%), 12 were in intensive care unit (ICU) at the time of starting ceftolozane-tazobactam (Table 1). The rest of the patients did not require ICU admission during their hospitalization.

All the isolated *P aeruginosa* were carbapenem-resistant. Eight of the cultured *P aeruginosa* (42%) showed susceptibility to at least one of the aminoglycoside agents (gentamicin or amikacin). In total, 10 samples (53%) showed intermediate susceptibility to cefepime or ceftazidime. Most of the isolates were nonsusceptible to both ciprofloxacin and piperacillin-tazobactam (89%). Only 1 patient had a coinfection with other bacteria in the urine, which was an ESBL-producing *Klebsiella pneumoniae*, and the patients had a favorable outcome with

Table 2. Clinical and microbiological descriptions of cases associated with treatment failure.

AGE (SEX)	UNDERLYING DISEASES	TYPE OF INITIAL INFECTION	CONCOMITANT BACTEREMIA	SUSCEPTIBILITY OF THE ISOLATED *PSEUDOMONAS AERUGINOSA*[a]	TREATMENT REGIMEN (DURATION IN DAYS)	CEFTOLOZANE-TAZOBACTAM DOSE[b]	OUTCOME (AT 14D)	CAUSE OF TREATMENT FAILURE	30-D DEATH
73 (M)	DM, HTN, bowel perforation with complicated abdominal surgeries	Intra-abdominal abscesses	No	Ceftazidime=R Ciprofloxacin=R Amikacin=S Gentamicin=I	Ceftolozane-tazobactam[10] PLUS Amikacin[6]	1.5 g every 8 hours	Fever stopped, remained in ICU for circulatory support, repeated cultures remained positive	Lack of source control	YES
69 (M)	DM, HTN, CAD, CKD, rectal cancer	VAP	No	Ceftazidime=I Ciprofloxacin=S Amikacin=R Gentamicin=S	Ceftolozane-tazobactam[14] PLUS Aztreonam[14]	1.5 g every 8 hours	Clinically improved with persistent positive respiratory culture	Pneumonia on chronic tracheostomy	NO
61 (M)	HTN, non-small-cell lung cancer with long-term mechanical ventilation	VAP	No	Ceftazidime=I Ciprofloxacin=I Amikacin=S Gentamicin=S	Ceftolozane-tazobactam[10] PLUS Colistin[14]	3 g every 8 hours	Clinically improved with persistent positive respiratory culture	Recurrent pneumonia due to lung collapse and emphysematous changes	NO
57 (M)	HIV/AIDS, nasopharyngeal lymphoma	Complicated perianal abscesses	Yes	Ceftazidime=I Ciprofloxacin=R Amikacin=R Gentamicin=R	Ceftolozane-tazobactam[7] PLUS Colistin[13]	1.5 g every 8 hours	Clinically deteriorated with persistent positive blood cultures	Patient died while on antibiotics	YES
45 (F)	DM, HTN, polymyalgia rheumatica, postcardiac arrest	HAP	No	Ceftazidime=R Ciprofloxacin=R Amikacin=S Gentamicin=S	Piperacillin-tazobactam[7] PLUS Colistin[7] switched after cultures to ceftolozane-tazobactam[7]	1.5 g every 8 hours	Clinically improved with respiratory positive culture after treatment	Colonized with MDR *Pseudomonas aeruginosa* (did not require therapy)	NO

Abbreviations: AIDS, acquired immunodeficiency syndrome; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; F, female; HAP, hospital-acquired pneumonia; HIV, human immunodeficiency virus; HTN, hypertensionl, intermediate; ICU, intensive care unit; M, male; MDR, multidrug resistant; R, resistant; S, susceptible; VAP, ventilator-associated pneumonia.
[a]Minimum inhibitory concentrations (MICs) were determined using reference broth microdilution methods and interpreted according to the Clinical Laboratory Standards Institute (CLSI) criteria.[16]
[b]Before adjustment for renal impairment.

therapy. Intervention for source control was required for 6 of the patients, including surgical debridement, drains insertion, or fluid aspiration.

Ceftolozane-tazobactam was used as a single therapy in 11 patients, whereas the combination with other antibiotics was done in 8 patients with no apparent impact on the patient's outcome. Colistin, aztreonam, and amikacin were the antibiotics used as accompanying antipseudomonas agents. The average time between obtaining the culture and starting ceftolozane-tazobactam was 5 days. The antibiotic duration of therapy was widely variable between patients, ranging from 7 days to more than a month, with an average of 14 days. Only 2 patients required more than 3 weeks of therapy, and it was secondary to poor source control for osteomyelitis and persistent liver abscesses.

Among subjects with a creatinine clearance >50 mL/min, the approved dose of 1.5 g every 8 hours was used in 8 cases, and 2 patients received 3 g every 8 hours as decided by the treating physician. Ceftolozane-tazobactam dosing among the remaining patients was calculated according to the changes in creatinine clearance and requirement of hemodialysis, ranged from 1.5 to 0.375 g every 8 hours, following the recommended protocol.

At day 14 of starting ceftolozane-tazobactam, 18 of 19 patients had a resolution of signs and symptoms of the infection (as reported by treating physicians). Only 14 patients (74%) had proven microbiological eradication observed at the end of therapy. Of the 12 patients, 7 patients who were in ICU at the initiation of treatment were discharged to the medical/surgical ward, whereas the remaining 5 patients stayed for other reasons. During therapy, there was no adverse event secondary to ceftolozane-tazobactam in our cohort, and no cases with *Clostridium difficile* infection were identified.

The 30-day mortality rate was 21% (4/19). Two of those deaths were related to the primary infection. Although 1 of those 2 had shown a clinical improvement initially, the cultures remained positive due to lack of source control (Table 2). The other 2 patients deteriorated later and died due to complications of catastrophic antiphospholipid syndrome and severe aspiration.

Discussion

In this report, we are presenting a real-world experience with ceftolozane-tazobactam treatment of MDR *P aeruginosa* infections with various indications. Our data suggest that ceftolozane-tazobactam is an effective and safe drug for treating different types of carbapenem-resistant *P aeruginosa* infections. Clinical success was observed in nearly 95% of the patients with a 30-day mortality of 21%. Such a success rate was also noted in previous reports.[13,14] In a recent multicenter study,[15] 205 critically ill patients infected with MDR *P aeruginosa* and treated with ceftolozane-tazobactam were reviewed, and the overall mortality rate was 19%. Pneumonia was the most common infection, and the isolated organisms were nonsusceptible to antipseudomonal carbapenems in 96.8% of the patients. A similar result was also observed in another multicentral retrospective study.[17] The average course duration of ceftolozane-tazobactam was 14 days, which is similar to our study.

It is difficult to evaluate the actual effects of the use of concomitant intravenous antibiotics or high-dose ceftolozane-tazobactam due to the small number of patients. Recent studies are now recommending using high-dose ceftolozane-tazobactam for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia in patients ≥18 years old. Ceftolozane-tazobactam monotherapy may be sufficient for the treatment of *P aeruginosa* infections that are susceptible to this agent. Early initiation of proper antibiotics and identification of the susceptibility pattern for these new antibiotics are anticipated to associate with lowered mortality, greater clinical success, and microbiological cure. It is essential to highlight that ceftolozane-tazobactam is not active against carbapenemase-producing strains. Still, it has good activity against *P aeruginosa* strains that are resistant to carbapenems via mechanisms other than carbapenemase production.

The median time from culture collection to the start of ceftolozane-tazobactam dosing in our study was 5 days. This indicates that a de-escalation approach was used in these cases, which is commonly recommended by clinical guidelines for severe infections. The emergence of resistance after courses of ceftolozane-tazobactam has been described in some reports highlighting the importance of setting strict standards for the drug's use and the continued urgency for new antibiotics.[18]

The limitations of this study include the retrospective nature of the data and dependence on documentation for assessing clinical outcomes via medical records review. Moreover, the decision to use ceftolozane-tazobactam as well as different doses and antibiotic combinations was at the consideration of the treating clinicians rather than prespecified in a protocol. Finally, the presence of different types of infections also limited the analysis. However, considering the severity and high mortality rates of such infections, it is necessary to have clinical data on the efficiency of new antibiotics with potent activity against resistant *P aeruginosa*.

In conclusion, our results suggest that ceftolozane-tazobactam shows an anticipated great advantage for treating severe infections caused by carbapenem-resistant *P aeruginosa*. More studies are required to explore the role of combination therapy, define adequate dosing of ceftolozane-tazobactam during different types of infections from the appropriate pharmacokinetic/pharmacodynamic data, and identify the proper duration of treatment.

Author Contributions

MB contributed to conception or design of the work, data analysis and interpretation, drafting the article, and final approval of the version to be published. AAh contributed to conception or design of the work, data collection, drafting the article, and critical revision of the article. AAla contributed to conception or design of the work, data collection, and critical

revision of the article. EM contributed to conception or design of the work, data collection, data analysis and interpretation, drafting the article, and critical revision of the article. LA contributed to data collection, data analysis and interpretation, drafting the article, and critical revision of the article. AbA contributed to data collection, data analysis and interpretation, and critical revision of the article. SA and MA contributed to data analysis and interpretation, drafting the article, and critical revision of the article. BA contributed to data collection, drafting the article, and critical revision of the article. AAlo contributed to conception or design of the work, data analysis and interpretation, critical revision of the article, and final approval of the version to be published.

Ethical Approval

This study was conducted in compliance with all the applicable institutional ethical guidelines in King Abdullah International Medical Research Center (KAIMRC), and consent was not required as there was no direct contact with patients.

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