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Ceftolozane/tazobactam for the treatment of *Pseudomonas aeruginosa* infections: A multicenter case series analysis



Inês Leonor Leitão^{a,b}, Carla Mimoso Santos^{a,b,*}, Paulo André^c, Sara Lino^{b,d}, Marcos Lemos^e, Filipe Froes^f

^a Infectious Diseases Department, Santa Maria Hospital – Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal

^b Infectious Diseases Clinic, Lisbon University Faculty of Medicine, Lisbon, Portugal

^c Intensive Care Unit, Centro Hospitalar Barreiro-Montijo, Barreiro, Portugal

^d Infectious Diseases Department, Curry Cabral Hospital – Centro Hospitalar Universitário Lisboa Central, Lisbon, Portugal

^e Clinical Hematology Department, Santo António dos Capuchos Hospital – Centro Hospitalar Universitário Lisboa Central, Lisbon, Portugal

^f Chest Department, Pulido Valente Hospital – Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal

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ABSTRACT

Introduction: *Pseudomonas aeruginosa* displays resistance to several available antibiotics. Infections caused by this pathogen are associated with a high mortality, morbidity, and considerable healthcare resource utilization and costs. This study was aimed at describing the use of ceftolozane/tazobactam (C/T) for the treatment of patients with *P. aeruginosa* infections.

Methods: Case series analysis of hospitalized patients treated with C/T for *P. aeruginosa* infections in five public Portuguese hospitals. Patients presenting with infections caused by this pathogen and receiving C/T for at least 72 h during hospitalization were eligible.

Results: Sixty-four hospitalized patients with *P. aeruginosa* infections treated with C/T were evaluated between December 2016 and July 2019. Most patients were aged between 60 and 79 years (53.9%). Patients presented a total of 68 *P. aeruginosa* infections, with respiratory infections being the most common (28.1%, 18 out of 64). Most *P. aeruginosa* strains (85.9%, 55 out of 64) were extensively drug-resistant (XDR). C/T was mostly used as targeted therapy (98.4%, 63 out of 64 patients) and as monotherapy (72.7%, 47 out of 64 patients). Combination therapy was used in 47.4% (9 out of 19) of patients with bacteremia. Most patients had successful microbiological (79.2%, 42 out of 53) and clinical (78.7%, 48 out of 61) outcomes. All-cause in-hospital mortality rate was 34.4%.

Conclusion: The present case series contributes to the body of evidence suggesting that C/T is an effective and safe option for treating *P. aeruginosa* infections, namely those caused by XDR strains, both when used as mono- or combination therapy.

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Ceftolozano/tazobactam para el tratamiento de infecciones por *Pseudomonas aeruginosa*: una serie de casos multicéntrica

R E S U M E N

Introducción: *Pseudomonas aeruginosa* presenta mecanismos de resistencia a diversos antibióticos. Las infecciones causadas por este patógeno aumentan la morbilidad, el uso de recursos y los costos asociados. Este estudio tuvo como objetivo describir el uso de ceftolozano/tazobactam (C/T) para el tratamiento de pacientes con infecciones por *P. aeruginosa*.

Palabras clave:

Ceftolozano/tazobactam

Pseudomonas aeruginosa

Infección hospitalaria

Multirresistencia

* Corresponding author.

E-mail address: carla.mimoso.santos@gmail.com (C. Mimoso Santos).

Métodos: Serie de casos de pacientes hospitalizados con infecciones por *P. aeruginosa* que fueron tratados con C/T en 5 hospitales portugueses. Fueron incluidos pacientes que presentaban infecciones por este patógeno y recibían terapéutica con C/T durante al menos 72 horas.

Resultados: Entre diciembre de 2016 y julio de 2019 fueron analizados 64 pacientes hospitalizados con infecciones por *P. aeruginosa* tratados con C/T. La mayoría tenían entre 60 y 79 años (53,9%). Se aislaron 68 infecciones por *P. aeruginosa*, siendo más frecuentes las respiratorias (28,1%; 18/64). La mayoría de las cepas de *P. aeruginosa* (85,9%; 55/64) eran extremadamente resistentes. El C/T se utilizó principalmente como terapia dirigida (98,4%; 63/64 pacientes) y en monoterapia (72,7%; 47/64 pacientes). La terapia combinada se utilizó en el 47,4% (9/19) de los pacientes con bacteriemia. La mayoría de los pacientes tuvieron resultados microbiológicos (79,2%; 42/53) y clínicos (78,7%; 48/61) satisfactorios. La tasa de mortalidad intrahospitalaria por todas las causas fue del 34,4%.

Conclusión: La presente serie de casos sustenta que la terapéutica con C/T es una alternativa efectiva y segura para las infecciones por *P. aeruginosa*, particularmente por cepas extremadamente resistentes, en monoterapia o en terapia combinada.

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Introduction

The growing number of infections due to multidrug resistant (MDR) Gram-negative pathogens, together with the scarcity of new and effective antibiotics in the last years, has hindered the selection of appropriate treatments, with negative consequences on patients' morbidity and mortality.^{1–3}

The treatment of *Pseudomonas aeruginosa* infections is particularly challenging, as this pathogen displays resistance to several available antibiotics, namely aminoglycosides, quinolones, and β -lactams (including carbapenem).^{4,5} Inappropriate empiric therapy is common within the context of these infections due to the high prevalence of resistance and restricted treatment options.^{6,7} Consequentially, infections caused by resistant *P. aeruginosa* are characterized by a high mortality, morbidity, and considerable healthcare resource utilization and costs.^{3,8–10} Worrisomely, the prevalence of resistant strains of *P. aeruginosa* has been growing in the past decades.^{7,11–13} In Portugal, a recent study conducted in intensive care units reported high rates of resistance among *P. aeruginosa* isolates (21.2% and 23.2% were MDR and extensively drug-resistant [XDR], respectively).¹⁴

The rise of antimicrobial resistance among Gram-negative bacteria has sparked the development of new therapeutic agents.¹⁵ In 2017, the World Health Organization (WHO) listed *P. aeruginosa*, Enterobacterales and *Acinetobacter baumannii* as pathogens of critical priority for the development of new antibiotics.¹⁶ In this context, novel antibiotics, such as β -lactam/ β -lactamase inhibitor combinations (ceftolozane-tazobactam [C/T] and ceftazidime/avibactam), have been developed and introduced in recent years. C/T is currently indicated for the treatment of adults with complicated intra-abdominal and urinary tract infections, acute pyelonephritis, and hospital-acquired pneumonia, including ventilator-associated pneumonia.¹⁷

Various observational studies have demonstrated that C/T is an effective alternative for the treatment of MDR and XDR *P. aeruginosa* infections.^{1,18–23} Indeed, clinical success was documented in more than 70% patients treated with C/T in six of the seven referenced studies, with percentages ranging from 63.8% to 88.0%.^{1,18–23} Favourable safety results have also been reported – namely a low incidence (3.0%) of adverse events (AEs) (mild severity only) – regardless of infection type.¹⁸

Real-world data on the use of C/T for the treatment of *P. aeruginosa* infections are still scarce. We herein describe the experience of five Portuguese public hospitals with this antimicrobial for the treatment of patients with *P. aeruginosa* infections.

Methods

Study design

Case series analysis of hospitalized patients treated with C/T for *P. aeruginosa* infections in five public Portuguese hospitals. Four participating hospitals belong to tertiary hospital centers – Santa Maria Hospital and Pulido Valente Hospital are part of the Centro Hospitalar Universitário Lisboa Norte, and the Curry Cabral Hospital and Santo António dos Capuchos Hospital are part of the Centro Hospitalar Universitário Lisboa Central. One (Centro Hospitalar Barreiro-Montijo) is a district hospital. Patients presenting with infections caused by *P. aeruginosa* and receiving C/T for at least 72 h during hospitalization were eligible for inclusion in this case series.

This project was approved by the independent ethics committees of the participating hospitals, all of which provided a waiver of informed consent.

Data collected

Data were retrospectively collected from the clinical records of eligible patients using a pre-defined form. The following variables were collected: patients' demographic (age, sex), anthropometric (weight), and clinical characteristics (neutropenia <500 cells/mm³, other immunosuppression), and comorbidities; site and type of infection; microbiological data, including susceptibility test results and resistance profile of *P. aeruginosa* isolated strains; presence of bacteremia, septic shock, coinfection with other pathogens, and ventilator-dependent respiratory failure during C/T courses; C/T treatment-related characteristics, namely empiric/targeted, monotherapy/combination therapy, duration, and dose, minimum inhibitory concentration (MIC), creatinine clearance (CrCl), and adverse reactions; outcomes, including microbiological and clinical success after C/T treatment, development of resistance, and all cause in-hospital mortality.

Definitions and microbiological methods

A successful clinical outcome was defined as a positive evolution of clinical signs/symptoms and an improvement in inflammation laboratory parameters. Independently of this evolution, though usually in its sequence, hospital discharge was documented as a “success” while in-hospital death due to the infectious process was considered a “failure”. A successful microbiological outcome was defined as the occurrence of negative microbiological test(s), or tests with isolation of pathogen(s) other than the one which

motivated antimicrobial therapy with C/T, in previously positive product samples and after suspension of antibiotic therapy. The definitions of MDR and XDR bacteria published by Magiorakos A.P. et al. were followed.²⁴

Cultures, identification of microorganisms, and susceptibility testing were performed at each participating hospital according to their own practice. The minimum inhibitory concentrations for C/T were determined using E-test or Vitek 2 antibiotic susceptibility testing cards and interpreted according to the European Committee on Antimicrobial Susceptibility Testing breakpoints.

Ceftolozane/tazobactam dose in patients with pneumonia

Though C/T was not yet indicated for the treatment of pneumonia during the period encompassed by this case series, we explored whether patients with these infections received the dose currently recommended in the most recent summary of product characteristics.¹⁷ C/T dose should be adjusted based on the patients' renal function, with progressively lower doses being recommended for patients with CrCl between 30 and 50 mL/min, 15–29 mL/min, and those with end stage renal disease on hemodialysis. No dose adjustment is necessary for patients with mild renal impairment (CrCl >50 mL/min). Generally, the dose recommended for the treatment of pneumonia is double of that recommended for other indications of C/T (complicated intra-abdominal infections, complicated urinary tract infections, and acute pyelonephritis), except for patients with end stage renal disease on hemodialysis. For these patients, the recommended maintenance dose is three times higher than that recommended for the remaining indications.

For this assessment, we first determined the number of patients who received one of the recommended doses for the treatment of pneumonia infections, regardless of whether it was correctly adjusted to their renal function. For instance, a patient with CrCl between 30 and 50 mL/min treated with 3 g of C/T every 8 h was considered to have received a dose recommended for the treatment of pneumonia, despite this dose not being correctly adjusted to renal function. We then assessed, among these patients, how many had their dose correctly adjusted to renal function. Lastly, for those who did not, we determined the number of patients who received doses that were higher/lower than those recommended for their renal function.

Statistical analysis

Continuous variables were summarized by descriptive statistics, namely mean, median, standard deviation, minimum and maximum, while categorical variables were summarized by absolute and relative frequencies. Comparison of categorical variables between subgroups was performed with the Chi-Square test and Fisher Exact test.

All hypothesis tests were two-sided and a *p* value ≤0.05 was considered statistically significant. All statistical procedures were performed using SAS 9.4 software.

Results

A total of 64 hospitalized patients treated for at least three days with C/T for *P. aeruginosa* infections were evaluated. The cases herein reported occurred between December 2016 and July 2019.

Patient characteristics

Most patients were male (60.9%) and between 60 and 79 years (53.1%) – Table 1. Median weight was 73 kg (range: 37–120 kg). Diabetes mellitus was the most common comorbidity (33.9% of patients), followed by cancer (32.2%). Twenty-five patients

Table 1
Patient characteristics.

	Total (n = 64)
Sex, n (%)	
Male	39 (60.9%)
Age, n (%)	
18–29	3 (4.7%)
30–39	3 (4.7%)
40–49	6 (9.4%)
50–59	9 (14.1%)
60–69	19 (29.7%)
70–79	15 (23.4%)
80 or older	9 (14.1%)
Weight (kg)	
Mean	72.45
Median	73.00
Standard deviation	17.95
Minimum	37.00
Maximum	120.00
Missing values	15
Main comorbidities, n (%) ^a	
Diabetes mellitus	20 (33.9%)
Cancer	19 (32.2%)
Chronic kidney disease	13 (22.0%)
Chronic lung disease	11 (18.6%)
Congestive heart failure	2 (3.4%)
Other	33 (55.0%)
Missing values	5
Neutropenia < 500 cells/mm ³ , n (%)	
Yes	8 (12.5%)
No	56 (87.5%)
Other immunosuppression, n (%)	25 (39.1%)
End-stage renal disease	8 (12.5%)
Chemotherapy	6 (9.4%)
HIV	4 (6.3%)
Organ transplant	4 (6.3%)
Other immunosuppressive therapy	2 (3.1%)
Metastatic malignancy	1 (1.6%)

^a Percentages determined based on non-missing values.

(39.1%) were immunosuppressed and eight (12.5%) had neutropenia <500 cells/mm³.

Infection characteristics

The 64 patients included in this case series presented a total of 68 *P. aeruginosa* infections. The great majority of patients (95.3%) had single-site *P. aeruginosa* infections. Multiple-site infections were observed in three patients (4.7%) – two patients had two infection sites and one patient had three. Various sites of infections were observed (Table 2), with respiratory infections being the most common – recorded in 28.1% of patients. Regarding infection types, the most frequently observed were pneumonia (21.0%), urinary tract infections (14.5%), and diabetic foot (12.9%).

Patients' clinical presentation during ceftolozane/tazobactam treatment courses

Patients presented with bacteremia and septic shock in 29.7% and 4.8% of C/T courses, respectively – Table 3. Coinfection with other pathogens was observed in 22 patients (35.5%). The most common co-pathogens were *Enterococcus* spp. and Enterobacterales, each being found in eight of the 14 co-infections (57.1%) for which pathogens were recorded.

Microbiological data

Antibiotic susceptibility testing was carried out for all 64 isolated *P. aeruginosa* strains. Most tested isolates were resistant

Table 2Site and type of *Pseudomonas aeruginosa* infections treated with ceftolozane/tazobactam.

	Total (n = 64)
Site of infection, n (%)	
Respiratory	18 (28.1%)
Osteoarticular	10 (15.6%)
Urinary	10 (15.6%)
Skin and soft tissue	10 (15.6%)
Intra-abdominal	5 (7.8%)
Bloodstream infection without focus	5 (7.8%)
Vascular device infection	2 (3.1%)
Genital	1 (1.6%)
Osteoarticular + skin and soft tissue	1 (1.6%)
Respiratory + skin and soft tissue	1 (1.6%)
Intra-abdominal + respiratory + vascular device infection	1 (1.6%)
Type of infection, n (%)^a	
Pneumonia	13 (21.0%)
Urinary tract infection	9 (14.5%)
Diabetic foot	8 (12.9%)
Ventilator-associated tracheobronchitis	5 (8.1%)
Sepsis without focus	5 (8.1%)
Surgical site infection	5 (8.1%)
Cellulitis	2 (3.2%)
Prosthesis infection	2 (3.2%)
Peritonitis	2 (3.2%)
Septic knee arthritis + fasciitis	1 (1.6%)
Tracheobronchitis + burn infection	1 (1.6%)
Tertiary peritonitis + vascular prosthesis infection + pneumonia	1 (1.6%)
Other	8 (12.9%)
Missing values	2

^a Percentages determined based on non-missing values.**Table 3**

Patients' clinical presentation during ceftolozane/tazobactam treatment courses.

	Total (n = 64)
Bacteremia, n (%)	
Yes	19 (29.7%)
No	45 (70.3%)
Septic shock, n (%)^a	
Yes	3 (4.8%)
No	60 (95.2%)
Missing values	1
Coinfection, n (%)^a	
Yes	22 (35.5%)
No	40 (64.5%)
Missing values	2
Coinfection – pathogens, n (%)^{a,b}	
Enterobacterales	8 (57.1%)
<i>Klebsiella pneumoniae</i> ^c	6 (42.9%)
<i>Enterobacter aerogenes</i>	1 (7.1%)
<i>Proteus mirabilis</i>	1 (7.1%)
<i>Enterococcus</i> spp.	8 (57.1%)
<i>Enterococcus faecalis</i>	6 (42.9%)
<i>Enterococcus faecium</i>	2 (14.3%)
Anaerobic	5 (35.7%)
<i>Bacteroides fragilis</i>	2 (14.3%)
<i>Lactobacillus rhamnosus</i>	1 (7.1%)
<i>Finegoldia magna</i>	1 (7.1%)
<i>Peptostreptococcus anaerobius</i>	1 (7.1%)
<i>Staphylococcus aureus</i> ^d	2 (14.3%)
<i>Candida tropicalis</i>	1 (7.1%)
<i>Pseudomonas aeruginosa</i> ^e	1 (7.1%)
Missing values	8
Ventilator-dependent respiratory failure, n (%)	
Yes	20 (31.3%)
No	44 (68.8%)

^a Percentages determined based on non-missing values.^b Coinfections could be due to more than one pathogen.^c Four extended spectrum β -lactamase and one carbapenemase-producing.^d One methicillin-resistant.^e *Pseudomonas aeruginosa* with a different susceptibility profile (only resistant to aminoglycosides).**Table 4**

Ceftolozane/tazobactam treatment-related characteristics.

	Total (n = 64)
Decision to initiate C/T, n (%)	
Empirical ^a	1 (1.6%)
Targeted	63 (98.4%)
Mono- or combination therapy, n (%)	
Monotherapy	47 (73.4%)
Combination therapy	17 (26.6%)
Combined antibiotics for <i>Pseudomonas aeruginosa</i> infections, n (%)	
Colistin	10 (58.8%)
Aminoglycosides	6 (35.3%)
Colistin + aminoglycoside	1 (5.9%)
Concomitant antimicrobial therapy for non-<i>Pseudomonas aeruginosa</i> infections, n (%)	
Yes	20 (31.3%)
No	44 (68.7%)
MIC (mg/L)	
Mean	2.18
Median	2.00
Standard deviation	0.97
Minimum	0.75
Maximum	4.00
Missing values	12
CrCl (mL/min)	
Mean	63.15
Median	53.00
Standard deviation	42.99
Minimum	10.00
Maximum	183.00
Missing values	9
Dose (g)	
Mean	1.52
Median	1.50
Standard deviation	0.96
Minimum	0.15
Maximum	3.00
Missing values	2
Treatment duration (days)	
Mean	14.84
Median	14.00
Standard deviation	7.76
Minimum	3.00
Maximum	50.00

^a C/T was started after isolation of *Pseudomonas aeruginosa* and while waiting for antibiotic susceptibility testing results.

C/T, ceftolozane/tazobactam; MIC, minimum inhibitory concentration; CrCl, creatinine clearance.

to piperacillin-tazobactam (98.4%, 63 out of 64), carbapenems (meropenem and/or imipenem) (95.3%, 61 out of 64), quinolones (90.0%, 54 out of 60), and ceftazidime (86.5%, 45 out of 52). All tested isolates were susceptible to colistin (44 out of 44) and more than half to aminoglycosides (59.0%, 36 out of 61). The great majority of *P. aeruginosa* strains were XDR (85.9%, 55 out of 64) and 12.7% (8 out of 64) were MDR. One strain was susceptible to all tested antibiotics.

Ceftolozane/tazobactam treatment characterization

C/T was used empirically in one patient only (1.6%), being started after isolation of *P. aeruginosa* and while waiting for antibiotic susceptibility testing results (Table 4). C/T was most commonly used as monotherapy (73.4%). In the cases in which C/T was used in combination with other antibiotics (26.6%) for the treatment of *P. aeruginosa* infections, the most frequently used were colistin (58.8%) and aminoglycosides (35.3%). Combination therapy was used in approximately half of the patients with bacteremia (47.4%, 9 out of 19) and in 87.5% (7 out of 8) of neutropenic patients.

Table 5
Microbiological and clinical outcomes by subgroups.

	Microbiological outcome			Clinical outcome		
	Failure (n = 11)	Success (n = 42)	p value	Failure (n = 13)	Success (n = 48)	p value
<i>Site of infection, n (%)</i>						
Respiratory	3 (18.8%)	13 (81.3%)	NA	2 (11.1%)	16 (88.9%)	NA
Urinary	0 (0.0%)	6 (100.0%)		1 (11.1%)	8 (88.9%)	
Osteoarticular	2 (20.0%)	8 (80.0%)		2 (25.0%)	6 (75.0%)	
Skin and soft tissue	1 (14.3%)	6 (85.7%)		2 (20.0%)	8 (80.0%)	
Intra-abdominal	0 (0.0%)	5 (100.0%)		1 (20.0%)	4 (80.0%)	
Bloodstream infections without focus	2 (40.0%)	3 (60.0%)		2 (40.0%)	3 (60.0%)	
Vascular device infection	–	0 (0.0%)	1 (100.0%)	–	0 (0.0%)	2 (100.0%)
Genital	–	–		0 (0.0%)	1 (100.0%)	
Respiratory + skin and soft tissue	1 (100.0%)	0 (0.0%)		1 (100.0%)	0 (0.0%)	
Osteoarticular + skin and soft tissue	1 (100.0%)	0 (0.0%)		1 (100.0%)	0 (0.0%)	
Intra-abdominal + respiratory + vascular device infection	1 (100.0%)	0 (0.0%)		1 (100.0%)	0 (0.0%)	
<i>Coinfection, n (%)</i>						
Yes	5 (25.0%)	15 (75.0%)	0.7325	6 (27.3%)	16 (72.7%)	0.5240
No	6 (19.4%)	25 (80.6%)		7 (18.9%)	30 (81.1%)	
<i>Mono- versus combination therapy, n (%)</i>						
Monotherapy	7 (17.9%)	32 (82.1%)	0.4532	10 (22.7%)	34 (77.3%)	>0.9999
Combination therapy	4 (28.6%)	10 (71.4%)		3 (17.6%)	14 (82.4%)	
<i>Empirical versus targeted therapy, n (%)</i>						
Empirical	0 (0.0%)	1 (100.0%)	>0.9999	0 (0.0%)	1 (100.0%)	>0.9999
Targeted	11 (21.2%)	41 (78.8%)		13 (21.7%)	47 (78.3%)	
<i>XDR versus MDR <i>Pseudomonas aeruginosa</i> strains, n (%)</i>						
XDR	9 (20.5%)	35 (79.5%)	>0.9999	12 (23.1%)	40 (76.9%)	0.6727
MDR	2 (25.0%)	6 (75.0%)		1 (12.5%)	7 (87.5%)	
<i>Bacteremia, n (%)</i>						
Yes	–	–		5 (26.3%)	14 (73.7%)	0.5196
No	–	–	–	8 (19.0%)	34 (81.0%)	
<i>Neutropenia < 500 cells/mm³, n (%)</i>						
Yes	–	–		2 (25.0%)	6 (75.0%)	>0.9999
No	–	–	–	11 (20.8%)	42 (79.2%)	
<i>Other immunosuppression, n (%)</i>						
Yes	–	–		5 (20.0%)	20 (80.0%)	0.8349
No	–	–	–	8 (22.2%)	28 (77.8%)	
<i>Creatinine clearance ≤ 50 mL/min, n (%)</i>						
Yes	–	–		8 (23.5%)	26 (76.5%)	0.6350
No	–	–	–	5 (18.5%)	22 (81.5%)	
<i>Ventilator-dependent respiratory failure, n (%)</i>						
Yes	–	–		5 (26.3%)	14 (73.7%)	0.5196
No	–	–	–	8 (19.0%)	34 (81.0%)	

Ceftolozane/tazobactam dose in patients with pneumonia

Among the 14 patients with pneumonia, ten (71.4%) received a dose that is currently recommended for the treatment of these infections. Of these ten, the dose was correctly adjusted to renal function in six patients (60.0%). In the four patients for whom the dose was not correctly adjusted to renal function, three received a dose higher than that recommended, and one patient received a dose lower than recommended. Three of the four patients for whom the dose was not correctly adjusted were on hemodialysis.

Outcomes following ceftolozane/tazobactam treatment

Successful microbiological and clinical outcomes were observed for most patients with available data on these variables – 79.2% (42 out of 53) and 78.7% (48 out of 61), respectively. Regarding infection site, the lowest percentages of microbiological and clinical success were observed for bloodstream infections without focus ($n = 3$, 60.0%). No statistically significant differences in microbiological and clinical success percentages were found between compared subgroups – Table 5.

Development of C/T resistance was documented in five patients (7.8%) – Table 6. All these patients received monotherapy for

difficult to treat infections, namely osteoarticular and device-associated infections. The C/T dose was correctly adjusted to renal function in three of the five patients. In the two remaining patients, although the initial dose was correctly defined according to the patients' renal function at the time of treatment start, no adjustment (i.e., dose increase) was made as renal function recovered during the treatment period. Thus, these patients were treated with doses lower than those recommended after renal function improved. Despite not having pneumonia, one patient received the dose recommended for the treatment of these infections in patients without renal insufficiency. The three patients with multiple-site infections developed resistance. Median treatment duration was 21 days (range: 10–33 days) – higher than that observed for patients not developing resistance (14 days [range: 1–50 days]). Two of the patients who developed resistance died during the hospitalization.

All-cause in-hospital mortality rate was 34.4%.

Safety and tolerability

One adverse drug reaction (ADR) – leucopenia – was reported in the 64 patients for whom C/T was administered. This ADR occurred in an HIV patient with a diffuse large B-cell lymphoma, who did not have chemotherapy-induced marrow aplasia at the time of the

Table 6

Characterization of patients who developed Ceftolozane/tazobactam resistance.

Site of infection	Type of infection	C/T MIC (mg/L)	Renal insufficiency	C/T dose	Correct adjustment of C/T dose to renal function	Monotherapy	Treatment duration	All-cause in-hospital death
Osteoarticular	Diabetic foot	1	Acute (nadir CrCl 15–29 mL/min)	Dose recommended for non-pneumonia infections	No, lower than the recommended adjusted dose	Yes	21	No
Osteoarticular	Diabetic foot	2	Acute (nadir CrCl 30–50 mL/min)	Dose recommended for non-pneumonia infections	No, lower than the recommended adjusted dose	Yes	22	No
Osteoarticular + skin and soft tissue	Septic knee arthritis + fasciitis	1	End stage renal disease on hemodialysis	Dose recommended for non-pneumonia infections	Yes	Yes	15	Yes
Respiratory + skin and soft tissue	Tracheobronchitis + burn infection	3	No	Dose recommended for pneumonia infections	Not applicable	Yes	10	No
Intra-abdominal + respiratory + skin and soft tissue	Tertiary peritonitis + osteoarticular prosthesis infection + pneumonia	4	Acute (nadir CrCl 15–29 mL/min)	Dose recommended for pneumonia infections	Yes	Yes	33	Yes

CT, ceftolozane/tazobactam; MIC, minimum inhibitory concentration; CrCl, creatinine clearance.

event. This was a profound and prolonged neutropenia (nadir leucocyte of 260 cells/ μ L, with zero neutrophils) that developed at the fourth day of treatment with C/T. The treatment was suspended at the tenth day and the patient was treated with human granulocyte colony stimulating factor. The leucopenia event was resolved 15 days after treatment suspension.

Discussion

This project aimed at describing the experience of five Portuguese public hospitals with using C/T for the treatment of patients with *P. aeruginosa* infections. To the best of our knowledge, this is the first analysis of cases regarding the real-world use of C/T in Portugal.

As mentioned in the introduction, the treatment of *P. aeruginosa* infections is particularly challenging due to the growing resistance of this pathogen to various antibiotics, namely carbapenems.^{25,26} Indeed, in the present case series, most isolated strains of *P. aeruginosa* were resistant to carbapenems (95.3%), as well as to piperacillin-tazobactam (98.4%), quinolones (90.0%), and ceftazidime (86.5%). The high rate of resistance among *P. aeruginosa* strains likely represented the main reason for using C/T for the targeted treatment of high-risk patients with severe infections, who accounted for the majority of patients in our case series.

This case series suggests that C/T is an effective option for the treatment of *P. aeruginosa* infections, as evidenced by the high percentages of microbiological and clinical success observed for included patients (79.2% and 78.7%, respectively). The significance of these results is further highlighted when one considers that the great majority of isolated *P. aeruginosa* strains were XDR (85.9%). Clinical success rate results are in line with past research.^{1,18–23}

Previous studies focusing on *P. aeruginosa* infections have reported no differences in clinical response when comparing patients who received C/T as monotherapy with those receiving combination therapy, indicating that the former may be sufficient for the treatment of these infections.^{2,18,19,21,22,27} In this case series, percentages of clinical success were similar for cases treated with C/T monotherapy (77.3%) versus combination therapy (82.4%). The slight difference observed for microbiological success (10.7% higher among courses during which patients received monotherapy) may be due to selection bias, as proposed by Gallagher JC et al.²⁰ That

is, physicians likely choose to administer additional antibiotics in patients performing worse. This explanation is supported by the fact that a considerably higher proportion of patients treated with combination therapy presented bacteremia when compared to those that received monotherapy (52.9% vs. 21.3%, respectively).

In line with past research,¹⁸ our data also support the safety and tolerability profile of C/T treatment, in a wide range of *P. aeruginosa* infections. Leucopenia was the only ADR reported during the 64 courses of treatment with this antimicrobial, occurring once in one patient.

Development of resistance to novel β -lactam/ β -lactamase inhibitor combinations – the introduction of which have lightened the pressing demand of new agents for the treatment of MDR/XDR *P. aeruginosa* infections – is a matter of concern.²⁸ Emergence of resistance to C/T has indeed been documented in previous studies, ranging from 3% to 14% of patients treated for *P. aeruginosa* infections.^{18,19,21} Our data fall within the range reported in the literature, with five patients (7.8%) developing resistance to C/T. Whether combination therapy is able to protect against the development of resistance is still up to debate.²⁹ Our results seem to support this hypothesis, as all five patients who developed resistance received monotherapy. Still, one should note that use of monotherapy was considerably more frequent in this case series (73.4% vs. 26.6% of combination therapy).

As previously stated, options for the treatment of MDR and XDR *P. aeruginosa* infections are limited.^{6,7} As C/T is one of the best antipseudomonal agents currently available,³⁰ efforts should be made to avoid the development of resistance to this antimicrobial caused by selective antibiotic pressure. Thus, the authors consider that C/T should mainly be reserved for the targeted treatment of infections caused by carbapenem-resistant MDR and XDR *P. aeruginosa* infections, while the use of C/T for the treatment of extended-spectrum beta-lactamases-producing Enterobacterales as a carbapenem-sparing strategy should be avoided. Risk factors for MDR *P. aeruginosa* and carbapenemase-producing Enterobacterales frequently overlap in the context of MDR infections. As carbapenemase-producing Enterobacterales are outside the spectrum of C/T, empirical treatment for high mortality risk infections in this context should be based on new β -lactam/ β -lactamase inhibitor combinations (e.g., ceftazidime/avibactam, meropenem/vaborbactam, imipenem/relebactam). In these scenarios of high risk of resistance, the authors consider that the

empirical use of C/T should be limited to those cases in which *P. aeruginosa* has been isolated but the antibiotic susceptibility testing results have not yet become available. In these cases, the association of a non β -lactam antibiotic should be considered to broaden the spectrum of activity. The preference for the use of C/T as a targeted treatment across the participating hospitals is clearly reflected in our results, as only one instance of empirical use of C/T was recorded among the 64 included patients.

Establishing adequate comparisons of mortality rates with past studies is challenging due to the different methodologies adopted. While we considered all-cause in-hospital mortality, previous studies mainly assessed mortality at fixed time points (30- and 90-day rates), with the exception of Munita JM et al.²² In this study, which evaluated C/T treatment for serious infections caused by carbapenem-resistant *P. aeruginosa*, a lower all-cause in-hospital mortality rate was observed (22.8% vs. 34.4% in our case series). When compared to the studies assessing fixed time point mortality, the in-hospital mortality rate obtained in our case series was higher than the 30-day mortality rates (10.0%–27.6%)^{1,20,21} and lower than the 90-day mortality rate (48%)²¹ reported. The patients' characteristics should be taken into account when interpreting mortality results, as they allow us to infer about the clinical presentation severity of the patients included in this case series. Specifically, included patients were mostly over 60 years old and approximately 32% had cancer. Moreover, in an appreciable proportion of treatment courses, patients were immunosuppressed (39.1%) and presented with bacteremia (29.7%), coinfection with other pathogens (35.5%), and ventilator-dependent respiratory failure (31.3%).

This case series has some limitations. First, it is limited by the retrospective nature of the data and the reliance on medical records to determine clinical and microbiological outcomes. Second, though multiple hospitals participated in this series, our findings might not be representative of other institutions across Portugal. Third, the cases herein reported pertain only to patients treated for at least 72 h with C/T during the hospitalization. As a result, more severe cases (e.g., patients who died prior to completing 72 h of the antibiotic course) were excluded from this case series. Lastly, as only all-cause in-hospital mortality was collected, it's not possible to determine the proportion of deaths that were due to *P. aeruginosa* infection.

In conclusion, the present case series contributes to the body of evidence suggesting that C/T is an effective and safe option for treating *P. aeruginosa* infections, namely those caused by XDR strains, both when used as mono- or combination therapy. Our results are relevant to physicians responsible for the management of in-hospital patients presenting with infections caused by this pathogen.

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Conflict of Interest

Dr. Mimoso Santos reports personal fees and non-financial support from Pfizer, MSD and Gilead, outside the submitted work. Dr. André reports personal fees and non-financial support from Pfizer and MSD, outside the submitter work. Dr. Lino reports personal fees and non-financial support from MSD, Gilead, ViiV and Pfizer, outside the submitted work. Dr. Froes reports personal fees and non-financial support from Pfizer, MSD, Sanofi, AstraZeneca and Novartis, outside the submitted work. Dr. Leitão and Dr. Lemos have no relevant financial or non-financial interests to disclose.

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