Ceftolozane/tazobactam for the treatment of serious *Pseudomonas aeruginosa* infections: a multicentre nationwide clinical experience

Matteo Bassetti[a,*], Nadia Castaldo[a], Annamaria Cattelan[b], Cristina Mussini[c], Elda Righi[a], Carlo Tascini[d], Francesco Menichetti[e], Claudio Maria Mastroianni[f], Mario Tumbarello[g], Paolo Grossi[h], Stefania Artioli[i], Novella Carannante[d], Ludovica Cipriani[b], Davide Coletto[b], Alessandro Russo[a], Margherita Digaetano[c], Angela Raffaella Losito[g], Maddalena Peghin[a], Alessandro Capone[j], Stefano Nicolè[b], Antonio Vena[a,k,*], for the CEFTABUSE Study Group

[a] *Infectious Diseases Clinic, Department of Medicine, University of Udine and Azienda Sanitaria Universitaria Integrata, Udine, Italy*
[b] *Infectious Diseases Unit, Department of Internal Medicine, Azienda Ospedaliera–Universitaria di Padova, Padua, Italy*
[c] *Infectious Diseases Clinic, University of Modena and Reggio Emilia, Modena, Italy*
[d] *First Division of Infectious Diseases, Cotugno Hospital, AORN dei Colli, Naples, Italy*
[e] *Infectious Diseases Clinic, Nuovo Santa Chiara University Hospital, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy*
[f] *Department of Public Health and Infectious Diseases, 'Sapienza' University of Rome, Rome, Italy*
[g] *UOC Malattie Infettive, Fondazione Policlinico Universitario A. Gemelli IRCCS – Istituto Malattie Infettive, Università Cattolica del Sacro Cuore, Rome, Italy*
[h] *Department of Infectious and Tropical Diseases, University of Insubria, Ospedale di Circolo-Fondazioni Macchi, Varese, Italy*
[i] *Infectious Diseases and Hepatology Unit, Sant'Andrea Hospital La Spezia, La Spezia, Italy*
[j] *National Institute for Infectious Diseases 'Lazzaro Spallanzani' IRCCS, Rome, Italy*
[k] *Medicine Department, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain*

ARTICLE INFO

Accepted 4 November 2018

Editor: Professor A Tsakris

Keywords:
Ceftolozane/tazobactam
Pseudomonas aeruginosa
Ventilator-associated pneumonia

ABSTRACT

This study describes the largest clinical experience using ceftolozane/tazobactam (C/T) for different *Pseudomonas aeruginosa* infections. A retrospective study was performed at 22 hospitals in Italy (June 2016–March 2018). All adult patients treated with ≥4 days of C/T were enrolled. Successful clinical outcome was defined as complete resolution of clinical signs/symptoms related to *P. aeruginosa* infection and lack of microbiological evidence of infection. C/T treatment was documented in 101 patients with diverse infections, including nosocomial pneumonia (31.7%), acute bacterial skin and skin-structure infection (20.8%), complicated UTI (13.9%), complicated IAI (12.9%), bone infection (8.9%) and primary bacteraemia (5.9%). Over one-half of *P. aeruginosa* strains were XDR (50.5%), with 78.2% of isolates resistant to at least one carbapenem. C/T was used as first-line therapy in 39 patients (38.6%). When used as second-line or later, the most common reasons for discontinuation of previous antibiotics were in vitro resistance of *P. aeruginosa* and clinical failure of previous therapy. Concomitant antibiotics were reported in 35.6% of patients. C/T doses were 1.5 g q8h in 70 patients (69.3%) and 3 g q8h in 31 patients (30.7%); median duration of C/T therapy was 14 days. Overall clinical success was 83.2%. Significant lower success rates were observed in patients with sepsis or receiving continuous renal replacement therapy (CRRT). Mild adverse events were reported in only three patients. C/T demonstrated a favourable safety and tolerability profile regardless of the infection type. Clinicians should be aware of the risk of clinical failure with C/T therapy in septic patients receiving CRRT.

1. Introduction

Pseudomonas aeruginosa is a leading cause of nosocomial infections, which are often severe [1,2] and difficult to treat because of their increasing resistance to several antibiotics, including carbapenems [3–6]. There are limited therapeutic options for such infections, and old antibiotics such as colistin, aminoglycosides or fosfomycin are frequently prescribed [7]. Clinical failure [8], the

* Corresponding authors. Present address: Clinica di Malattie Infettive, Azienda Sanitaria Universitaria Integrata di Udine, Piazzale Santa Maria della Misericordia 15, 33010 Udine, Italy. Tel.: +39 0432 55 93 53, fax: +39 0432 55 93 71 (M. Bassetti); Tel.: +39 0432 55 93 99, fax +39 0432 55 93 71 (A. Vena).
E-mail addresses: matteo.bassetti@asuiud.sanita.fvg.it (M. Bassetti), anton.vena@gmail.com (A. Vena).

emergence of in vivo resistance [9], superinfection and nephrotoxicity [10,11] represent the main limitations of currently available drugs, leading to the search of new treatment options.

Ceftolozane/tazobactam (C/T) is a novel β-lactam/β-lactamase inhibitor combination with potent activity against Gram-negative bacteria, particularly against *P. aeruginosa* for which it is the most active available β-lactam antibiotic [5]. Although C/T has only been approved for the treatment of complicated urinary tract infections (cUTIs) and complicated intra-abdominal infections (cIAIs) [12,13], it has become a suitable and attractive option for the treatment of different infections caused by multidrug-resistant (MDR) or extensively drug-resistant (XDR) *P. aeruginosa* [14]. In recent years clinical experience with C/T is accumulating and expanding, but only a limited number of cases series have been published [15–21].

A multicentre nationwide study was performed to report the Italian experience with C/T in the treatment of severe *P. aeruginosa* infections and to evaluate risk factors associated with clinical failure.

2. Materials and methods

2.1. Study setting and design

A multicentre, retrospective, real-world study of hospitalised patients in 22 public hospitals in Italy who were treated for *P. aeruginosa* infections between June 2016 and March 2018 (21-month period) was performed. Hospitals were located in 12 Italian regions, namely Friuli Venezia Giulia, Veneto, Lombardia, Emilia Romagna, Liguria, Toscana, Lazio, Abruzzo, Campania, Puglia, Calabria and Sicilia. The Internal Review Board of Medical Area (D.A.M.E) of the co-ordinating centre (Azienda Ospedaliera Universitaria Integrata di Udine, Udine, Italy) approved this study. Because of its retrospective nature, informed consent was considered unnecessary.

Cases were eligible for the cohort study if the patient (i) was aged $\geq$18 years, (ii) received $\geq$4 days of C/T (with or without other antibiotics) and (iii) had a culture-confirmed *P. aeruginosa* infection.

2.2. Data

Patients' medical records were retrospectively reviewed and data were collected using a pre-established form. The following data were recorded: age and sex; underlying diseases according to Charlson comorbidity index [22]; type of infection; presence of sepsis or septic shock at the time of the infection; susceptibility pattern of *P. aeruginosa* isolates; date of start and end of C/T therapy; source control of infection, when applicable; other antibiotics administered before, concomitant to and after C/T therapy; reasons for C/T use; dosage(s) of C/T and length of therapy; adverse events (AEs); clinical outcome; and recurrence of infection.

2.3. General definitions

Chronic renal disease was defined as the need of haemodialysis or the presence of renal impairment (serum creatinine >1.5 mg/dL) at the time of hospital admission. Diagnosis and classification of infection were defined according to the criteria of the US Centers for Disease Control and Prevention (CDC) [23]. Sepsis and septic shock were defined according to standard international criteria [24]. Source control of infection was considered adequate when any additional measures were taken to control the focus of the infection (i.e. removal of urinary catheter or intra-vascular catheter as well as surgical or radiological drainage of collection).

An infection was considered 'life-threatening' when a patient: (i) received C/T as rescue therapy because of clinical failure of a previous antibiotic regimen; (ii) had septic shock at the time of *P. aeruginosa* infection; or (iii) required intensive care unit (ICU) admission at the time of *P. aeruginosa* infection.

Recurrence was considered to have occurred if the infection reappeared after antibiotic discontinuation. Mortality was attributed to *P. aeruginosa* in patients who died with persistent positive culture for *P. aeruginosa* or with persistent signs or symptoms of *Pseudomonas* infection.

Indications for C/T as well as dosage, type of infusion and duration were established by infectious diseases specialists. C/T was dosed either as approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as an intravenous (i.v.) dose of 1.5 g every 8 h (q8h) (standard dosage), or as supported by recent pharmacokinetic data in patients with nosocomial pneumonia [25] as an i.v. dose of 3 g q8h (off-label dosage). Regardless of the dose administered, dose adjustment was required only for patients with moderate renal dysfunction (creatinine clearance <50 mL/min). In patients receiving continuous renal replacement therapy (CRRT), C/T was administered at 1.5 g q8h as suggested by recent pharmacokinetic studies [26,27].

AEs were classified according to World Health Organization (WHO) definitions [28]. Briefly, an AE was defined as severe when the drug reaction determined death and/or led to prolonged hospitalisation or a new hospital admission and/or caused temporary or permanent inability to carry on normal activities. Mild AEs comprised all the reactions of minor clinical significance not included in previous description.

2.4. Definition of patient outcome

Patient outcome was assessed as success or failure at the end of the follow-up period that ended at the end of April 2018. A successful clinical outcome was defined as complete resolution of clinical signs and symptoms related to *P. aeruginosa* infection and lack of microbiological evidence of infection. Clinical failure was defined as either lack of clinical response and/or recurrence and/or attributable mortality due to *P. aeruginosa* infection. This definition was used in order to compare the data with clinical failure rates reported in previous studies of C/T experience in daily clinical practice [20].

2.5. Microbiological methods

Cultures, identification of organisms and susceptibility testing were performed at each participating centre according to their own practise. Antimicrobial susceptibility was reported as interpreted by the local laboratories. The criteria for MDR, XDR or pandrug-resistant (PDR) *P. aeruginosa* was based on the standardized international definition proposed by Magiorakos et al. [29]; carbapenem resistance was defined when an isolate showed an imipenem and/or meropenem minimum inhibitory concentration (MIC) of $\geq$8 mg/L [30].

Isolates were tested for susceptibility to C/T by Etest (Liofilmchem®, Roseto degli Abruzzi, Italy) and the results were interpreted according to the breakpoints proposed by the Clinical and Laboratory Standards Institute (CLSI) [30].

2.6. Statistical analysis

Continuous variables were compared using Student's *t*-test and Mann–Whitney *U*-test for normally and non-normally distributed variables, respectively. The χ^2 test or Fisher's exact test was used to compare categorical variables. All tests of statistical significance

were two-tailed. Differences were considered statistically significant at a *P*-value of <0.05. Statistical analysis was performed with the software package PASW Statistics v.18.0 (SPSS Inc., Chicago, IL).

3. Results

A total of 101 patients treated with $\geq$4 days of C/T were evaluated. The clinical characteristics of the patients are shown in Table 1. The median patient age was 67 years (interquartile range 49–74 years) and 66 (65.3%) were male. Almost one-third of the patients (30.7%) showed a chronic renal disease prior to *P. aeruginosa* infection and, with the exception of seven cases, all patients had at least one serious underlying disease with a mean Charlson comorbidity index of 4.4. At the time of infection, 39 patients (38.6%) presented with sepsis or septic shock and 24 patients (23.8%) were admitted to the ICU owing to *P. aeruginosa* infection. Overall, 57 patients (56.4%) were classified as having a life-threating infection.

Infections included nosocomial pneumonia (32/101; 31.7%), acute bacterial skin and skin-structure infection (ABSSSI) (21/101; 20.8%), cUTI (14/101; 13.9%). cIAI (13/101; 12.9%), bone infection (9/101; 8.9%) and primary bacteraemia (6/101; 5.9%). A secondary bacteraemia was detected in 16 patients (15.8%). Among the 32 episodes of nosocomial pneumonia, 20 and 12 cases were classified as hospital-acquired pneumonia and ventilator-associated pneumonia, respectively.

3.1. Microbiological data

Information regarding susceptibility test results of the 101 *P. aeruginosa* isolates at the outset of C/T treatment are shown in Table 2. Approximately 70% of the isolates were non-susceptible to ceftazidime, ciprofloxacin, doripenem, levofloxacin, meropenem, piperacillin/tazobactam (TZP) and imipenem/cilastatin. Moreover, 58 (57.4%), 51 (50.5%) and 48 (47.5%) were non-susceptible to tobramycin, gentamicin and amikacin, respectively. Colistin retained in vitro activity against the majority of isolated strains, with a non-susceptibility rate of only 2.0%. According to their susceptibility profiles, 30 isolates (29.7%) were classified as non-MDR, 18 (17.8%) as MDR, 51 (50.5%) as XDR and 2 (2.0%) as PDR.

3.2. Antibiotic therapy and source control management

Thirty-nine patients (38.6%) received C/T as first-line therapy and 62 patients (61.4%) as second-line or later. The duration of previous antibiotic treatment ranged from 5–19 days and the most common classes of antibiotics used before the C/T regimen was implemented were carbapenems (meropenem), β-lactam/β-lactamase inhibitor (TZP), colistin and aminoglycosides (data not shown). The main reasons for administering C/T were in vitro resistance of *P. aeruginosa* strains in 67 patients (66.3%) and failure of previous therapy in 33 patients (32.7%). Interestingly, 17 patients (16.8%) received C/T due to an acute kidney injury related to previous antibiotics.

C/T was administered according to standard dosage in 70 patients (69.3%) for a mean $\pm$ standard deviation treatment duration of 19 $\pm$ 16 days. The remaining group of 31 patients (30.7%) received an off-label dosage for a mean duration of 16.7 $\pm$ 9.1 days. Among the patients with nosocomial pneumonia, 21/32 (65.6%) received an off-label dose, followed by 2/9 patients (22.2%) with bone infection (1 of them had concomitant nosocomial pneumonia without microbiological isolation) and 2/13 patients (15.4%) with cIAI. An adjusted dose was required in 20 patients with renal impairment.

Concomitant antibiotics for the treatment of *P. aeruginosa* infection were used in 36 patients (35.6%). The most commonly used

Table 1
Baseline demographics and clinical characteristics of 101 patients included in the efficacy population analysis

Variable	*n* (%)[a]
Age (years) [median (IQR)]	67 (49–74)
Male sex	66 (65.3)
Ward	
Medical	64 (63.4)
Surgical	21 (20.8)
ICU	16 (15.8)
Charlson comorbidity index (mean $\pm$ S.D.)	4.4 $\pm$ 4.0
Underlying diseases	
Cardiac disease	36 (35.6)
Neurological disease	33 (32.7)
Chronic renal disease	31 (30.7)
Diabetes mellitus	22 (21.8)
Gastrointestinal disease	21 (20.8)
Solid-organ tumour	17 (16.8)
Solid-organ transplant	11 (10.9)
Haematological malignancy	13 (12.9)
COPD	9 (8.9)
Bronchiectasis	6 (5.9)
Cystic fibrosis	8 (7.9)
Interstitial lung disease	7 (6.9)
Liver disease	2 (2.0)
Other predisposing conditions[b]	
Corticosteroids	32 (31.7)
Other immunosuppressive therapy	21 (20.8)
Chemotherapy	12 (11.9)
Neutropenia[c]	11 (10.9)
Invasive procedures	
Central venous catheter	63 (62.4)
Urinary catheter	57 (56.4)
Previous surgery[b]	41 (40.6)
Mechanical ventilation	19 (18.8)
Percutaneous endoscopic gastrostomy	9 (8.9)
Previous *P. aeruginosa* colonisation[b]	51 (50.5)
Severity of clinical presentation	
No sepsis	62 (61.4)
Sepsis	27 (26.7)
Septic shock	12 (11.9)
ICU admission due to *P. aeruginosa* infection	24 (23.8)
Type of infection	
Nosocomial pneumonia	32 (31.7)
ABSSSI	21 (20.8)
cUTI	14 (13.9)
cIAI	13 (12.9)
Bone infection	9 (8.9)
Primary bacteraemia	6 (5.9)
Other infections[d]	6 (5.9)
Concomitant *P. aeruginosa* bacteraemia	16 (15.8)
Life-threatening infection	57 (56.4)
Polymicrobial infection	36 (35.6)
Antibiotics before C/T treatment	
Received antibiotics before C/T for current infection	62 (61.4)
No. of antibiotics received [median (range)]	1 (1–4)
Days of antibiotic therapy [median (range)]	8 (5–19)
C/T treatment	
Combination therapy	36 (35.6)
Days of treatment [median (range)]	14 (9–23)
Extended infusion	14 (13.9)
Continuous infusion	5 (5.0)
Intermittent infusion	82 (81.2)
Standard dosage	70 (69.3)
Off-label dosage	31 (30.7)
Adequate source control of infection	27/41 (65.9)
Successful clinical outcome	84 (83.2)

IQR, interquartile range; ICU, intensive care unit; S.D., standard deviation; COPD, chronic obstructive pulmonary disease; ABSSSI, acute bacterial skin and skin-structure infection; cUTI, complicated urinary tract infection; cIAI, complicated intra-abdominal infection; C/T, ceftolozane/tazobactam.

[a] Data are *n* (%) unless otherwise stated.

[b] Within previous 30 days.

[c] Absolute neutrophil count $<500/mm^3$.

[d] Other infections include left ventricular assist device-specific infection ($n=1$), central venous catheter-related bacteraemia ($n=1$), deep brain stimulation hardware-related infection ($n=1$), pleural infection in patient with oesophageal fistula ($n=1$), acute proctitis ($n=1$) and community-acquired pneumonia ($n=1$).

Table 2
Antimicrobial susceptibility pattern of *Pseudomonas aeruginosa* isolates

Antimicrobial agent	*n* (%) non-susceptible
Amikacin	48 (47.5)
Cefepime	61 (60.4)
Ceftazidime	70 (69.3)
Ciprofloxacin	74 (73.1)
Colistin	2 (2.0)
Doripenem	76 (75.2)
Gentamicin	51 (50.5)
Fosfomycin	90 (89.1)
Levofloxacin	78 (77.2)
Meropenem	78 (77.2)
Piperacillin/tazobactam	78 (77.2)
Imipenem/cilastatin	76 (75.2)
Tobramycin	58 (57.4)

antibiotics were aminoglycosides in 11 patients (10.9%), colistin in 10 patients (9.9) and carbapenems in 5 patients (5.0%). Source control of infection was considered necessary in 41 patients (40.6%) and in 27/41 cases (65.9%) it was considered adequate.

3.3. Clinical outcome

Overall, 84 patients (83.2%) experienced a successful clinical outcome at the end of treatment. There were no differences in the clinical success rate with respect to the type of C/T treatment, i.e. monotherapy versus combination therapy [83.1% (54/65) vs. 83.3% (30/36); $P=1$] or primary versus second-line or later therapy [79.5% (31/39) vs. 85.5% (53/62); $P=0.58$] (Supplementary Fig. S1). Noteworthy, among the 53 patients with infections due to XDR or PDR *P. aeruginosa* strains, no decrease in clinical success rate was found in comparison with patients with infections due to non-MDR strains [81.1% (43/53) vs. 90.0% (27/30); $P=0.31$)] or MDR strains [81.1% (43/53) vs. 77.8% (14/18); $P=1$] (Supplementary Fig. S2). Similarly, there was no difference in clinical outcome among patients with infections due to carbapenem-susceptible and carbapenem-resistant *P. aeruginosa* isolates [86.4% (19/22) vs. 82.3% (65/79); $P=0.71$] (Supplementary Fig. S3).

Fig. 1 shows clinical success rates according to different type of infections treated with C/T. The response rates to C/T therapy was 85.2% for the 27 patients receiving the drug for cUTI or cIAI (FDA and EMA approved indications for C/T) compared with 82.4% for the other 74 patients who received the drug as off-label indications ($P=1$). Among the latter group, the highest success rate was observed for patients with primary bacteraemia (100%), followed by ABSSSI (90.5%), bone infection (88.9%) and nosocomial pneumonia (75.0%).

Epidemiological and clinical characteristics of the 17 patients who experienced clinical failure are shown in the Supplementary Table S1. Clinical failure was due to death (five patients), persistence of clinical signs and symptoms related to *P. aeruginosa* infections despite C/T treatment (five patients) and recurrence of the infection (seven patients). Among the latter group, the median time between the first episode and recurrence was 14 days (range 7–42 days).

When patients with clinical success were compared with those who experienced clinical failure, characteristics significantly more common among patients with clinical failure were sepsis (22.6% vs. 47.1%; $P=0.05$), CRRT (8.3% vs. 29.4%; $P=0.03$) and polymicrobial infection (29.8% vs. 64.7%; $P=0.01$) (Table 3). By multivariate analysis, sepsis [odds ratio (OR) = 3.02, 95% confidence interval (CI) 1.01–9.2; $P=0.05$] and receipt of CRRT (OR = 4.5, 95% CI 1.18–17.39; $P=0.02$) were the only independent predictors of clinical failure.

Overall, C/T resistance was detected in only 3 patients (3.0%), of whom none had a fatal outcome. One patient developed C/T resistance during a 7-day course of colistin and C/T combination for nosocomial pneumonia (see patient number 16 in Supplementary Table S1). Because the isolate showed intermediate susceptibility to meropenem, this patient's treatment was switched to high-dose carbapenem and he recovered. In the remaining two patients, the emergence of C/T resistance led to airway colonisation and urinary tract colonisation, respectively. In these patients, C/T-resistant strains emerged 8 days and 17 days after a treatment course of C/T for nosocomial pneumonia and cUTI, respectively. Neither patients received other treatment courses and both were alive during the follow-up period. We could not perform a risk factor analysis for development of C/T resistance owing to the low number of strains developing.

3.4. Safety and tolerability

The overall incidence of AEs considered by treating physicians as related to C/T therapy was low, with at least one potential event reported in only 3 (3.0%) of 101 patients. The time from starting C/T to AE onset varied widely from 5 days to 72 days. AEs consisted of gastrointestinal symptoms (i.e. nausea, abdominal pain and diarrhoea), rash and an asymptomatic increase in liver function test results. Among the three patients who experienced AEs, all were receiving C/T for other than FDA-approved indications, two with a standard approved dosage (one patient with left ventricular assist device infection and one with bone infection) and one with a higher dosage (one patient treated for hospital-acquired pneumonia). All episodes were considered as mild in severity. Despite this, C/T was discontinued early in two of the three patients (one with increased serum liver function test and one with gastrointestinal symptoms).

4. Discussion

Here we present the largest clinical experience with C/T therapy for the treatment of serious *P .aeruginosa* infection published so far. We showed that C/T is an effective and safe drug for treating different types of *P. aeruginosa* infection, including those with off-label indications. Of importance, clinical success was observed in nearly 85% of the patients, notwithstanding the fact that almost 70% of the isolates were MDR or XDR. Importantly, this analysis also indicated that CRRT and sepsis are associated with a significantly increased risk of clinical failure.

Pseudomonas aeruginosa represents a common cause of severe healthcare-associated infections [31] and its intrinsic resistance to many antibiotics is a cause of concern [31–34]. In many countries, carbapenem resistance is detected in ca. 25–50% of *P. aeruginosa* strains and up to 50% of these isolates are classified as MDR [33–35]. In this scenario, colistin and/or aminoglycosides are the only antimicrobials retaining satisfactory activity, but they show a high risk of nephrotoxicity [36,37] and resistance has been increasingly reported [33–35]. For these reasons, use of highly efficacious and well-tolerated new options for the treatment of severe *P. aeruginosa* infections is of particular clinical interest.

C/T is a new cephalosporin with potent in vitro activity against *P. aeruginosa* that is not affected by the most common mechanisms of resistance, including efflux pumps, reduced uptake through porin channels, and modifications of the penicillin-binding proteins [38,39]. Previous results [40,41] evaluating C/T for the treatment of cUTI and cIAI have demonstrated a high degree of clinical efficacy and tolerability of the drug, leading to an approval for the treatment of complicated of cUTIs and cIAIs [12,13].

None the less, reflecting an unmet need for licensed treatment options, C/T is currently frequently used for off-label indications, and data regarding how C/T performs overall in the treatment of *P. aeruginosa* infections is expanding. Seven case series have

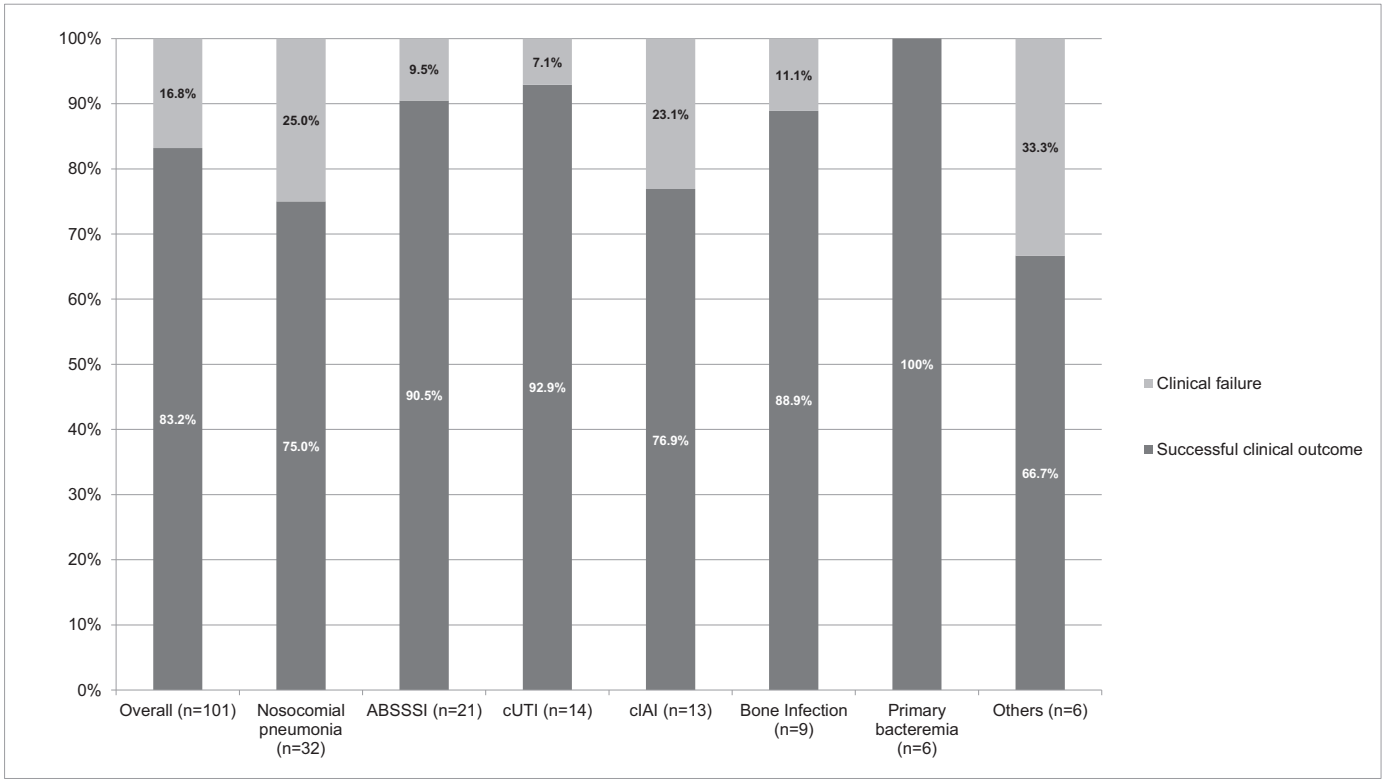

Fig. 1. Clinical success rates according to type of *Pseudomonas aeruginosa* infection. ABSSSI, acute bacterial skin and skin-structure infection; cUTI, complicated urinary tract infection; cIAI, complicated intra-abdominal infection.

been published to date, with a cumulative success rate of 79.3% [15–21]. Similar to these studies, an excellent clinical success (overall 83.2%), not influenced by the type of infection, was observed in the current study. Indeed, the clinical success rates were 100%, 92.9%, 90.5% and 88.9% for treating primary bacteraemia, cUTI, ABSSSI and bone infection, respectively. Interestingly, the high clinical success rate was also retained in patients who received C/T as secondary therapy (28/33; 84.8%) or salvage therapy (25/29; 86.2%) as well as those with life-threatening infection (46/57; 80.7%).

Regarding nosocomial pneumonia, the rate of clinical success in patients treated with C/T varies from 50% in earlier studies [15,16,20,21] to ca. 80% in more recent studies. In the present report, the overall clinical success for nosocomial pneumonia treated with C/T was 75%, which is consistent with that recently observed by Escolà-Vergé et al. [17]. The differences in outcome reported in previous studies are likely to be related to the widespread use of a C/T dosage of 3 g q8h (in our experience 65.6% versus 42.7% reported in previous reports [15,16,20,21]), with a greater probability to attain an adequate pharmacodynamic target in epithelial lung fluid [25,42].

Risk factors for clinical failure during C/T therapy have been investigated in only two previous studies including 21 and 38 patients, respectively [17,20]. These studies showed that higher Simplified Acute Physiology Score (SAPS) II [20] and inadequate source control [17] were associated with clinical failure in patients receiving C/T for *P. aeruginosa* infections. The current study is the first reporting an association between clinical failure and receipt of CRRT during C/T therapy. Optimal dosing of C/T in patients receiving CRRT is an unresolved issue and no dosing recommendations are currently available in this specific setting [14]. Previous preliminary reports [26,27] suggested that a standard dosage of 1.5 g q8h should ensure appropriate C/T exposure for the treatment of pneumonia in patients undergoing CRRT. However, considering that all patients with CRRT in the current study received a C/T dosage of 1.5 g q8h, we suggest to consider an increased posology of C/T in these patients or, if available, to routinely perform therapeutic drug monitoring.

When used in the context of infection due to *P. aeruginosa*, selection of C/T-resistant strains during and after C/T therapy is a matter of concern. Specifically, of the 21 patients treated by Haidar et al., 3 (14%) developed C/T resistance following a short course of C/T therapy (8 days) [20]. Previous studies demonstrated that the in vitro selection of C/T-resistant *P. aeruginosa* strains was primarily linked to mutations in or overexpression of the resident AmpC β-lactamase [43,44]. In the current study, the propensity for selection of resistance was not an issue: only 3 (3.0%) of 101 patients developed C/T resistance, with only 1 presenting a recurrent infection.

Consistent with previous reports [15–21], no differences in clinical response rates between patients treated with combination therapy or monotherapy were observed in this study. However, further investigations are needed to address the potential role that a combination regimen could have in improving the outcome among septic patients or those receiving CRRT.

In our experience, C/T had an excellent safety profile, similar to that reported in phase III trials. Mild AEs were observed in only three patients [40,41].

This study has several limitations that should be addressed. First, it was an observational, retrospective study; therefore, we may not have been able to control for all measured and unmeasured variables that may have had a clinical impact on patient evolution. Second, in many cases C/T was given as second- or third-line therapy and the role of prior therapy on clinical outcome is unclear. Third, susceptibility testing was performed at each individual centre and we do not have molecular analysis

Table 3
Univariate analysis of risk factors for clinical failure of ceftolozane/tazobactam (C/T) therapy among patients with *Pseudomonas aeruginosa* infection

Variable	*n* (%)[a]		*P*-value
	Clinical success ($n=84$)	Clinical failure ($n=17$)	
Age (years) (mean ± S.D.)	61.3 ± 18.3	58.2 ± 16.7	0.51
Sex male	55 (65.5)	11 (64.7)	1
Charlson comorbidity index (mean ± S.D.)	4.5 ± 2.5	4.1 ± 2.2	0.50
Underlying diseases			
Cardiac disease	29 (34.5)	7 (41.2)	0.59
Neurological disease	27 (32.1)	6 (35.3)	0.78
Chronic renal disease	25 (29.8)	6 (35.3)	0.77
Diabetes mellitus	17 (20.2)	5 (29.4)	0.51
Gastrointestinal disease	17 (20.2)	4 (23.5)	0.75
Solid-organ tumour	14 (16.7)	3 (17.6)	1
Solid-organ transplant	8 (9.5)	3 (17.6)	0.39
Haematological malignancy	11 (13.1)	2 (11.8)	1
COPD	6 (7.1)	3 (17.6)	0.17
Cystic fibrosis	5 (6.0)	3 (17.6)	0.13
Liver disease	2 (2.4)	0	1
Other predisposing conditions [b]			
Corticosteroids	28 (33.3)	4 (23.5)	0.57
Other immunosuppressive therapy	17 (20.2)	4 (23.5)	0.74
Chemotherapy	11 (13.1)	1 (5.9)	0.68
Neutropenia [c]	9 (10.7)	2 (11.8)	1
Invasive procedures			
Central venous catheter	50 (59.5)	13 (76.5)	0.27
Urinary catheter	44 (52.4)	13 (76.5)	0.10
Previous surgery [b]	32 (38.1)	9 (52.9)	0.28
Mechanical ventilation	15 (17.9)	4 (23.5)	0.73
Percutaneous endoscopic gastrostomy	7 (8.3)	2 (11.8)	0.64
Severity of clinical presentation			
No sepsis	54 (64.3)	8 (47.1)	0.27
Sepsis	19 (22.6)	8 (47.1)	0.05
Septic shock	11 (13.1)	1 (5.9)	0.68
ICU admission due to *P. aeruginosa* infection	17 (20.2)	7 (41.2)	0.11
Polymicrobial infection	25 (29.8)	11 (64.7)	0.01
Off-label indication	61 (72.6)	13 (76.5)	1
Type of infection			
Nosocomial pneumonia	24 (28.6)	8 (47.1)	0.15
ABSSSI	19 (22.6)	2 (11.8)	0.51
cUTI	13 (15.5)	1 (5.9)	0.45
cIAI	10 (11.9)	3 (17.6)	0.45
Bone infection	8 (9.5)	1 (5.9)	1
Primary bacteraemia	6 (7.1)	0	0.58
Other infections	4 (4.8)	2 (11.8)	0.26
Life-threatening infection	46 (54.8)	11 (64.7)	0.59
C/T treatment			
Combination therapy	30 (35.7)	6 (35.3)	1
Days of treatment (mean ± S.D.)	18.3 ±13.7	18.3 ± 16.6	0.99
Standard dosage	61 (72.6)	9 (52.9)	0.14
Off-label dosage	23 (27.4)	8 (47.1)	0.14
Intermittent haemodialysis	5 (6.0)	1 (5.9)	1
CRRT	7 (8.3)	5 (29.4)	0.03
Adequate source control of the infection	23/33 (69.7)	4/8 (50.0)	0.59

S.D., standard deviation; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; ABSSSI, acute bacterial skin and skin-structure infection; cUTI, complicated urinary tract infection; cIAI, complicated intra-abdominal infection; CRRT, continuous renal replacement therapy.

[a] Data are *n* (%) unless otherwise stated.

[b] Within previous 30 days.

[c] Absolute neutrophil count <500 mm^3.

to determine the presence of enzymes associated with antibiotic resistance in the isolates. Moreover, although colistin susceptibility was reported for *P. aeruginosa* strains, in vitro polymyxin susceptibility testing is influenced by several different factors and its interpretation could be challenging [45].

Fourth, we did not analyse antibiotic levels in the blood and we cannot exclude that clinical failure in some patients could be related to the high renal creatinine clearance of β-lactams during sepsis [46–49].

Lastly, the findings in this study are limited by the inability to perform a risk factor analysis for the development of in vivo C/T resistance. Study strengths include the fact that it was carried out in 22 medical centres, therefore the findings could be reasonably applied to other sites.

In conclusion, the current study suggests that C/T has a relevant role in the therapeutic armamentarium for treatment of different *P. aeruginosa* infections. However, clinicians should be aware of the risk of clinical failure with C/T therapy in septic patients receiving CRRT. The results of this study are relevant to physicians in hospital settings who attend patients with a wide variety of diseases (bloodstream infections, nosocomial pneumonia) and severity of illness (medical, critically ill patients).

Acknowledgments

The authors acknowledge as co-authors all of the following CEFTABUSE-IT Study Group members: Matteo Bassetti, Antonio Vena, Nadia Castaldo, Davide Pecori, Elda Righi, Alessia Carnellutti, Filippo Givone, Elena Graziano, Maria Merelli, Barbara Cadeo and Maddalena Peghin (Infectious Diseases Division, Santa Maria della Misericordia University Hospital, Udine, Italy); Annamaria Cattelan, Ludovica Cipriani and Davide Coletto (Unit of Infectious Diseases, Department of Internal Medicine, Azienda Ospedaliera-Universitaria di Padova, Padua, Italy); Cristina Mussini and Margherita Digaetano (Division of Infectious Diseases, University of Modena, Modena, Italy); Carlo Tascini and Novella Carannante (First Division of Infectious Diseases, Cotugno Hospital, AORN dei Colli, Naples, Italy); Francesco Menichetti, Stefano Verdenelli and Silvia Fabiani (Infectious Diseases Clinic, Nuovo Santa Chiara University Hospital, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy); Claudio Maria Mastroianni, Russo Gianluca, Alessandra Oliva, Maria Rosa Ciardi, Camilla Ajassa and Tiziana Tieghi (Infectious Diseases Unit, Sapienza University of Rome, Latina, Italy; Department of Public Health and Infectious Diseases, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; Polo Pontino, Ospedale Santa Maria Goretti, 'Sapienza' University of Rome, Latina, Italy); Mario Tumbarello, Angela Raffaella Losito and Francesca Raffaelli (UOC Malattie Infettive, Fondazione Policlinico Universitario A. Gemelli IRCCS – Istituto Malattie Infettive, Università Cattolica del Sacro Cuore, Rome, Italy); Paolo Grossi and Cristina Rovelli (Department of Infectious and Tropical Diseases, University of Insubria, Ospedale di Circolo-Fondazioni Macchi, Varese, Italy); Stefania Artioli and Giorgia Caruana (Infectious Diseases and Hepatology Unit, Sant'Andrea Hospital La Spezia, La Spezia, Italy); Roberto Luzzati and Giulia Bontempo (Infectious Diseases Division, University Hospital of Trieste, Trieste, Italy); Nicola Petrosillo and Alessandro Capone (Clinical and Research Department for Infectious Diseases, Unit of Systemic and Immunedepression-Associated Infections, National Institute for Infectious Diseases L. Spallanzani, Rome, Italy); Giuliano Rizzardini, Massimo Coen and Matteo Passerini (Department of Infectious Diseases I, L. Sacco University Hospital, Milan, Italy); Antonio Mastroianni, Filippo Urso and Maria Francesca Bianco (Infectious Diseases Unit, 'Annunziata' Hospital, Cosenza, Italy); Guglielmo Borgia, Ivan Gentile and Alberto Enrico Maraolo (Department of Clinical Medicine and Surgery, Section of Infectious Diseases, University of Naples Federico II, Naples, Italy); Massimo Crapis and Sergio Venturini (Azienda per l'Assistenza Sanitaria n 5 Friuli Occidentale Ringgold Standard Institution – Infectious Diseases Unit, Pordenone, Friuli-Venezia Giulia, Italy); Giustino Parruti and Francesca Trave (Infectious Diseases Unit, Pescara General Hospital, Pescara, Italy); Gioacchino Angarano, Sergio Carbonara and Michele Fabiano Mariani (Clinic of Infectious Diseases, University of Bari, Bari, Italy); Massimo Girardis (Department of Anesthesia and Intensive Care, University Hospital of Modena, Modena, Italy); Antonio Cascio and Claudia Gioé (Infectious Diseases Division, Department of Health Promotion Sciences and Mother and Child Care 'G. D'Alessandro', University of Palermo, Palermo, Italy); and Marco Anselmo and Emanuele Malfatto (Infectious Diseases Unit, S. Paolo Hospital, ASL 2 Savona, Italy).

Funding

None.

Competing interests

MB serves on scientific advisory boards for Angelini, AstraZeneca, Bayer, Cubist, Pfizer, Menarini, MSD, Nabriva, Paratek, Roche, Shionogi, Tetraphase, The Medicine Company and Astellas Pharma Inc., and has received funding for travel or speaker honoraria from Algorithm, Angelini, Astellas Pharma Inc., AstraZeneca, Cubist, Pfizer, MSD, Gilead Sciences, Menarini, Novartis, Ranbaxy and Teva; CT has received funds for speaking at symposia organised on behalf of Pfizer, Gilead, Novartis, Merck, Angelini, Thermo Fisher, Biotest and Astellas. All other authors declare no competing interests.

Ethical approval

The Internal Review board of Medical Area (D.A.M.E) of Azienda Ospedaliera Universitaria Integrata di Udine (Udine, Italy) approved this study [18/I.R.B_Bassetti_18], which waived the requirement of informed consent owing to the retrospective design of the study.

References

[1] Kang CI, Kim SH, Kim HB, Park SW, Choe YJ, Oh MD, et al. *Pseudomonas aeruginosa* bacteremia: risk factors for mortality and influence of delayed receipt of effective antimicrobial therapy on clinical outcome. Clin Infect Dis 2003;37:745–51.

[2] Vidal F, Mensa J, Almela M, Martinez JA, Marco F, Casals C, et al. Epidemiology and outcome of *Pseudomonas aeruginosa* bacteremia, with special emphasis on the influence of antibiotic treatment. Analysis of 189 episodes. Arch Intern Med 1996;156:2121–6.

[3] Livermore DM. Multiple mechanisms of antimicrobial resistance in *Pseudomonas aeruginosa*: our worst nightmare? Clin Infect Dis 2002;34:634–40.

[4] Pena C, Suarez C, Gozalo M, Murillas J, Almirante B, Pomar V, et al. Prospective multicenter study of the impact of carbapenem resistance on mortality in *Pseudomonas aeruginosa* bloodstream infections. Antimicrob Agents Chemother 2012;56:1265–72.

[5] Pfaller MA, Bassetti M, Duncan LR, Castanheira M. Ceftolozane/tazobactam activity against drug-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* causing urinary tract and intraabdominal infections in Europe: report from an antimicrobial surveillance programme (2012–15). J Antimicrob Chemother 2017;72:1386–95.

[6] Shortridge D, Castanheira M, Pfaller MA, Flamm RK. Ceftolozane–tazobactam activity against *Pseudomonas aeruginosa* clinical isolates from U.S. hospitals: report from the PACTS Antimicrobial Surveillance Program, 2012 to 2015. Antimicrob Agents Chemother 2017;61 pii: e00465-17. doi:10.1128/AAC.00465-17.

[7] Karaiskos I, Giamarellou H. Multidrug-resistant and extensively drug-resistant Gram-negative pathogens: current and emerging therapeutic approaches. Expert Opin Pharmacother 2014;15:1351–70.

[8] Paul M, Bishara J, Levcovich A, Chowers M, Goldberg E, Singer P, et al. Effectiveness and safety of colistin: prospective comparative cohort study. J Antimicrob Chemother 2010;65:1019–27.

[9] Bergen PJ, Li J, Nation RL, Turnidge JD, Coulthard K, Milne RW. Comparison of once-, twice- and thrice-daily dosing of colistin on antibacterial effect and emergence of resistance: studies with *Pseudomonas aeruginosa* in an in vitro pharmacodynamic model. J Antimicrob Chemother 2008;61:636–42.

[10] Hartzell JD, Neff R, Ake J, Howard R, Olson S, Paolino K, et al. Nephrotoxicity associated with intravenous colistin (colistimethate sodium) treatment at a tertiary care medical center. Clin Infect Dis 2009;48:1724–8.

[11] Destache CJ. Aminoglycoside-induced nephrotoxicity—a focus on monitoring: a review of literature. J Pharm Pract 2014;27:562–6.

[12] US Food and Drug Administration (FDA). *Zerbaxa® full prescribing information*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206829lbl.pdf [accessed 30 October 2017].

[13] European Medicines Agency (EMA). *Zerbaxa. Annex I. Summary of product characteristics*. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003772/WC500194595.pdf [accessed 30 October 2017].

[14] Giacobbe DR, Bassetti M, De Rosa FG, Del Bono V, Grossi PA, Menichetti F, et al. Ceftolozane/tazobactam: place in therapy. Expert Rev Anti Infect Ther 2018;16:307–20.

[15] Caston JJ, De la Torre A, Ruiz-Camps I, Sorli ML, Torres V, Torre-Cisneros J. Salvage therapy with ceftolozane–tazobactam for multidrug-resistant *Pseudomonas aeruginosa* infections. Antimicrob Agents Chemother 2017;61 pii: e02136-16. doi:10.1128/AAC.02136-16.

[16] Dinh A, Wyplosz B, Kerneis S, Lebeaux D, Bouchand F, Duran C, et al. Use of ceftolozane/tazobactam as salvage therapy for infections due to extensively drug-resistant *Pseudomonas aeruginosa*. Int J Antimicrob Agents 2017;49:782–3.

[17] Escolà-Vergé L, Pigrau C, Los-Arcos I, Arévalo Á, Viñado B, Campany D, et al. Ceftolozane/tazobactam for the treatment of XDR *Pseudomonas aeruginosa* infections. Infection 2018;46:461–8.

[18] Xipell M, Bodro M, Marco F, Martinez JA, Soriano A. Successful treatment of three severe MDR or XDR *Pseudomonas aeruginosa* infections with ceftolozane/tazobactam. Future Microbiol 2017;12:1323–6.

[19] Dietl B, Sanchez I, Arcenillas P, Cuchi E, Gomez L, Gonzalez de Molina FJ, et al. Ceftolozane/tazobactam in the treatment of osteomyelitis and skin and soft-tissue infections due to extensively drug-resistant *Pseudomonas aeruginosa*: clinical and microbiological outcomes. Int J Antimicrob Agents 2018;51:498–502.

[20] Haidar G, Philips NJ, Shields RK, Snyder D, Cheng S, Potoski BA, et al. Ceftolozane–tazobactam for the treatment of multidrug-resistant *Pseudomonas aeruginosa* infections: clinical effectiveness and evolution of resistance. Clin Infect Dis 2017;65:110–20.

[21] Munita JM, Aitken SL, Miller WR, Perez F, Rosa R, Shimose LA, et al. Multicenter evaluation of ceftolozane/tazobactam for serious infections caused by carbapenem-resistant *Pseudomonas aeruginosa*. Clin Infect Dis 2017;65:158–61.

[22] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.

[23] Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988;16:128–40.

[24] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801–10.

[25] Xiao AJ, Miller BW, Huntington JA, Nicolau DP. Ceftolozane/tazobactam pharmacokinetic/pharmacodynamic-derived dose justification for phase 3 studies in patients with nosocomial pneumonia. J Clin Pharmacol 2016;56:56–66.

[26] Bremmer DN, Nicolau DP, Burcham P, Chunduri A, Shidham G, Bauer KA. Ceftolozane/tazobactam pharmacokinetics in a critically ill adult receiving continuous renal replacement therapy. Pharmacotherapy 2016;36:e30–3.

[27] Kuti JL, Ghazi IM, Quintiliani R Jr, Shore E, Nicolau DP. Treatment of multidrug-resistant *Pseudomonas aeruginosa* with ceftolozane/tazobactam in a critically ill patient receiving continuous venovenous haemodiafiltration. Int J Antimicrob Agents 2016;48:342–3.

[28] Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000;356:1255–9.

[29] Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18:268–81.

[30] Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. 28th ed. Wayne, PA: CLSI; 2018. CLSI supplement M100.

[31] Driscoll JA, Brody SL, Kollef MH. The epidemiology, pathogenesis and treatment of *Pseudomonas aeruginosa* infections. Drugs 2007;67:351–68.

[32] Rossolini GM, Mantengoli E. Treatment and control of severe infections caused by multiresistant *Pseudomonas aeruginosa*. Clin Microbiol Infect 2005;11(Suppl 4):17–32.

[33] The Center for Disease Dynamics, Economics & Policy (CDDEP). ResistanceMap database: The Surveillance Network. Washington, DC: CDDEP; 2013 http://www.cddep.org/map accessed 17 March 2016.

[34] European Centre for Disease Prevention and Control (ECDC). Antimicrobial resistance surveillance in Europe 2013. Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm, Sweden: ECDC; 2014 https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/antimicrobial-resistance-surveillance-europe-2013.pdf accessed 17 March 2016.

[35] European Centre for Disease Prevention and Control (ECDC). Antimicrobial resistance surveillance in Europe. Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2015. Stockholm, Sweden: ECDC; 2017 https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/antimicrobial-resistance-europe-2015.pdf accessed 30 October 2017.

[36] Martis N, Leroy S, Blanc V. Colistin in multi-drug resistant *Pseudomonas aeruginosa* blood-stream infections: a narrative review for the clinician. J Infect 2014;69:1–12.

[37] Nakamura I, Yamaguchi T, Tsukimori A, Sato A, Fukushima S, Matsumoto T. New options of antibiotic combination therapy for multidrug-resistant *Pseudomonas aeruginosa*. Eur J Clin Microbiol Infect Dis 2015;34:83–7.

[38] Zhanel GG, Chung P, Adam H, Zelenitsky S, Denisuik A, Schweizer F, et al. Ceftolozane/tazobactam: a novel cephalosporin/β-lactamase inhibitor combination with activity against multidrug-resistant Gram-negative bacilli. Drugs 2014;74:31–51.

[39] Pai H, Kim J, Kim J, Lee JH, Choe KW, Gotoh N. Carbapenem resistance mechanisms in *Pseudomonas aeruginosa* clinical isolates. Antimicrob Agents Chemother 2001;45:480–4.

[40] Wagenlehner FM, Umeh O, Steenbergen J, Yuan G, Darouiche RO. Ceftolozane—tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). Lancet 2015;385:1949–56.

[41] Solomkin J, Hershberger E, Miller B, Popejoy M, Friedland I, Steenbergen J, et al. Ceftolozane/tazobactam plus metronidazole for complicated intra-abdominal infections in an era of multidrug resistance: results from a randomized, double-blind, phase 3 trial (ASPECT-cIAI). Clin Infect Dis 2015;60:1462–71.

[42] Chandorkar G, Xiao A, Mouksassi MS, Hershberger E, Krishna G. Population pharmacokinetics of ceftolozane/tazobactam in healthy volunteers, subjects with varying degrees of renal function and patients with bacterial infections. J Clin Pharmacol 2015;55:230–9.

[43] Cabot G, Bruchmann S, Mulet X, Zamorano L, Moya B, Juan C, et al. *Pseudomonas aeruginosa* ceftolozane–tazobactam resistance development requires multiple mutations leading to overexpression and structural modification of AmpC. Antimicrob Agents Chemother 2014;58:3091–9.

[44] Berrazeg M, Jeannot K, Ntsogo Enguene VY, Broutin I, Loeffert S, Fournier D, et al. Mutations in β-lactamase AmpC increase resistance of *Pseudomonas aeruginosa* isolates to antipseudomonal cephalosporins. Antimicrob Agents Chemother 2015;59:6248–55.

[45] Humphries RM. Susceptibility testing of the polymyxins: where are we now? Pharmacotherapy 2015;35:22–7.

[46] Carrie C, Petit L, d'Houdain N, Sauvage N, Cottenceau V, Lafitte M, et al. Association between augmented renal clearance, antibiotic exposure and clinical outcome in critically ill septic patients receiving high doses of β-lactams administered by continuous infusion: a prospective observational study. Int J Antimicrob Agents 2018;51:443–9.

[47] Udy AA, Dulhunty JM, Roberts JA, Davis JS, Webb SAR, Bellomo R, et al. Association between augmented renal clearance and clinical outcomes in patients receiving β-lactam antibiotic therapy by continuous or intermittent infusion: a nested cohort study of the BLING-II randomised, placebo-controlled, clinical trial. Int J Antimicrob Agents 2017;49:624–30.

[48] Tsai D, Stewart P, Goud R, Gourley S, Hewagama S, Krishnaswamy S, et al. Total and unbound ceftriaxone pharmacokinetics in critically ill Australian Indigenous patients with severe sepsis. Int J Antimicrob Agents 2016;48:748–52.

[49] Wrenn RH, Cluck D, Kennedy L, Ohl C, Williamson JC. Extended infusion compared to standard infusion cefepime as empiric treatment of febrile neutropenia. J Oncol Pharm Pract 2018;24:170–5.