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A real-world investigation into prescribing patterns and effectiveness of ceftolozane/tazobactam among critically ill patients from SPECTRA

Alex Soriano [a], David L. Paterson [b], Florian Thalhalmmer [c], Stefan Kluge [d], Pierluigi Viale [e], Brune Akrich [f], Mike Allen [g], Stephanie Wirbel [h], Alexandre H. Watanabe [i], Emre Yücel [i,*], Engels N. Obi [i], Sundeep Kaul [j]

[a] Department of Infectious Diseases, Hospital Clinic, Calle de Villarroel 170, Helios Building, Barcelona 08036, Spain
[b] The University of Queensland, Unit 4, 455 Adelaide Street, Brisbane City, QLD 4000, Australia
[c] Department of Urology, Medical University of Vienna, Waehringer Guertel 18-20, Vienna A-1090, Austria
[d] University Hospital Hamburg-Eppendorf, Martini Street 52, Hamburg 20251, Germany
[e] Infectious Diseases Unit, Department of Medical and Surgical Sciences, IRCCS POL. Sant'Orsola Bologna, University of Bologna, Bologna, Italy
[f] MSD France, 10-12 Cr Michelet, Puteaux 92800, France
[g] MSD (UK) Limited, 120 Moorgate, London EC2M 6UR, UK
[h] ICON Plc, 27 rue de la Villette, Lyon 69003, France
[i] Merck & Co., Inc., 126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ 07065, USA
[j] Harefield Hospital, Hill End Road, Harefield UB9 6JH, UK

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ABSTRACT

Background: Ceftolozane/tazobactam (C/T) real-world use was examined in a global population of critical care patients treated in intensive care unit settings.
Methods: The Study of Prescribing patterns and Effectiveness of Ceftolozane/Tazobactam Real-world Analysis (SPECTRA) is a multinational, retrospective observational study of 617 adults treated with C/T conducted between 2016 and 2020. Population-associated clinical, treatment-related, and microbiologic characteristics, resource utilization, and clinical outcomes were assessed in critical care patients.
Results: In this SPECTRA critical care cohort (n=298), 81.5% had ≥1 comorbidity. Common infection sites were respiratory (50.0%), skin/wound/tissue (21.1%), blood (13.7%), and urine (10.3%); common pathogens were *Pseudomonas aeruginosa* (89.7%; 66.7% multidrug resistant), *Klebsiella* spp. (6.9%), and *Escherichia coli* (6.4%); 51.7% received C/T as third-line/salvage therapy. Thirty-day readmission rates were 3.4% (all cause) and 1.7% (infection related). Overall clinical success was 53.4% (95% confidence interval: 47.5% to 59.1%) and was greater with first-line C/T (62.2%) versus third line (45.5%). All-cause in-hospital mortality was 35.6%; infection-related mortality was 13.8%.
Conclusions: In this multinational, high-risk cohort, most patients had beneficial outcomes despite their clinical complexity and late intervention with C/T. These results support C/T use against a wide range of Gram-negative pathogens in critical care settings.
Trial registration: Not applicable due to retrospective design.

1. Introduction

The antibacterial management of critically ill patients with Gram-negative infections in the intensive care unit (ICU) has unique challenges [1]. Patients admitted to the ICU often have multiple comorbidities, requiring multimodal organ support with invasive devices (*e.g.*, mechanical ventilation), vasopressors and ionotropic support, and renal replacement therapy, which is associated with an increased risk of healthcare-acquired infections (HAI) [2–5]. Patients admitted to the ICU need early and appropriate treatment; however, it is challenging to select therapy that will be effective against all of the most prevalent infecting organisms [6]. Furthermore, patients managed in the ICU, particularly those with high Acute Physiologic Assessment and Chronic Health Evaluation (APACHE II) or Sequential Organ Failure Assessment

* Corresponding author.
E-mail address: emre.yucel@merck.com (E. Yücel).

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(SOFA) scores, who develop sepsis or septic shock can have wide-ranging pharmacokinetic responses to antibacterial treatment [7–9], making appropriate drug selection and dosing challenging.

Treating severe Gram-negative bacterial infections in critically ill patients can be even more difficult because they are often caused by organisms, including *Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae*, and *Acinetobacter baumannii*, that are resistant to commonly used antibacterial therapies [10,11]. Complicated Gram-negative infections that are resistant to antibacterial agents [12], especially those with hospital-onset disease, are associated with considerable healthcare resource utilization and negative patient outcomes [13–15]. Studies have shown 30-day readmission rates are 4% to 11% greater in patients infected with bacteria that are resistant to commonly used antibacterial agents compared with patients with infections caused by susceptible bacteria [13–15].

In addition, patients admitted to the hospital and the ICU are particularly at risk of acquiring severe infections caused by multidrug-resistant (MDR) pathogens [16]. A multicenter, retrospective, observational study of patients admitted to the ICU with severe Gram-negative infections showed that ~70% were transferred from surgical or medical wards and of those, 84% of infections were carbapenem resistant [17]. In a study of patients with pneumonia in the ICU setting, MDR infections were found in 62% (146/237) of cases and the length of stay in the ICU before infection was a significant risk factor of acquiring MDR pneumonia [18].

Appropriate dosing and treatment of patients with bacterial infections who are critically ill is often complicated due to physiological changes that contribute to altered antibacterial pharmacokinetics in these patients, including impaired [19,20] and augmented renal function [21]. Ceftolozane/tazobactam (C/T) is an antipseudomonal cephalosporin (ceftolozane) combined with an established β-lactamase inhibitor (tazobactam) used for the treatment of severe Gram-negative bacterial infections [22]. C/T has demonstrated efficacy in registrational trials for the treatment of complicated intra-abdominal infections (cIAI), complicated urinary tract infections (cUTI), as well as hospital-acquired and ventilator-associated bacterial pneumonia [10,23,24]. In a noninferiority trial, C/T also demonstrated higher susceptibility rates than meropenem in high-risk patients with ventilated hospital-acquired pneumonia and/or patients with renal dysfunction who were infected with *P. aeruginosa* [10].

While many studies have evaluated real-world use and outcomes associated with C/T in mixed cohorts of patients in critical care and general ward settings [25–27], few studies have reported outcomes specifically in a majority critical care cohort [17,28,29]. This study describes the real-world clinical utilization, including patient/treatment characteristics, and associated outcomes of C/T, focusing on a critical care cohort, employing retrospectively collected data from multiple sites in multiple countries. Such real-world data on C/T use and outcomes are important to help inform disease management and clinical practice.

2. Patients and methods

2.1. Study design and patients

Data were collected from the Study of Prescribing patterns and Effectiveness of Ceftolozane/Tazobactam Real-world Analysis (SPECTRA), a multicenter, retrospective inpatient observational study of patients treated with C/T between January 2016 and November 2020 in Australia, Austria, Germany, Italy, Mexico, Spain, and the United Kingdom [30]. The hospitalization during which the patient was first treated with C/T was considered as the index hospitalization and the infection for which the patient received C/T was considered as the index infection; the index date was the first date of administration of any antibacterial agent for any suspected Gram-negative infection for which C/T was administered for at least 48 h. C/T as salvage therapy was defined as C/T administered after at least 48 h of treatment with an initial Gram-negative antibacterial agent. Multidrug resistance was defined as resistant to at least three classes of antibacterial agents. Retrospective data were summarized from existing medical records for enrolled patients from 6 months before the index date, until death or 30 days from the last administration of C/T.

This analysis focused on patients in the critical care setting, defined as those admitted to the ICU during the index hospitalization. All adult patients (aged 18 years or older) admitted to the ICU during the index hospitalization and treated with C/T for at least 48 h, irrespective of pathogen isolation, were included. Patients must have received their last administration of C/T at least 30 days before their chart abstraction to be enrolled. Patients were excluded if they had participated in an interventional clinical trial for Gram-negative infection at the time of C/T administration. All analyses were performed on those patients who met the inclusion and exclusion criteria and for whom C/T was received within the treatment period related to the index infection.

The study was conducted in compliance with the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices [31], the ethical principles arising from the Declaration of Helsinki [32], the European Union good pharmacovigilance practices [33], European and national laws with respect to data protection [34], and applicable local regulations. Approval from each of the local independent ethics committee or institutional review boards was obtained before patients were enrolled in the study, where required by national laws and guidelines.

2.2. Measurements and outcomes

Clinical, treatment-related, and microbiologic characteristics of the study population were assessed. Healthcare resource utilization outcomes that were evaluated included all-cause and infection-related 30-day readmission rates. Clinical outcomes evaluated included clinical success and all-cause and infection-related in-hospital mortality. Clinical success was defined as no additional Gram-negative therapy required after a minimum of 48 h of treatment with C/T (not including discharge antibacterial agents or de-escalation), and/or no death attributed to Gram-negative infection, and/or discharge from hospital or ICU, and/or no need for re-operation for source infection control, and/or microbiologic eradication (negative culture at the site of index infection after C/T).

2.3. Statistical analysis

Analyses were mainly descriptive. Continuous variables were summarized with number, mean, standard deviation, median, first and third quartiles (Q1, Q3), minimum and maximum, and number of missing data, where applicable. Categorical variables were summarized with frequencies, percentages, and number of missing data, where applicable. For each parameter, percentages were based on the number of data points available. Univariate and multivariable logistic regression models were performed to assess factors associated with clinical success among clinical, treatment-related, and microbiologic characteristics. Those variables with P-values <0.2 in univariate analyses were included in the multivariable analyses, and a backward selection procedure was applied. Analyses were conducted using SAS® software, version 9.4 (SAS Institute Inc, Cary, NC, USA).

3. Results

Of 617 patients included in SPECTRA, 298 patients were included in the final cohort of critical care patients (mean age of 57 years, 68.8% male; Table 1). Respiratory-related infections were reported for 154 (53.1%) patients, of which 122 (79.2%) had pneumonia. Approximately 81.5% of patients had at least one comorbidity. Key comorbidities included heart disease (29.2%) and chronic pulmonary disease (27.2%). Admission to the ICU was related to the index infection in 41.9% of

Table 1
Patient characteristics.

Parameter	*N*=298
Age (years)	
Mean (SD)	57.0 (16.7)
Median (Q1–Q3)	59.5 (45.0–70.0)
Male, *n* (%)	205 (68.8)
BMI (kg/m^2)	
Mean (SD)	26.2 (7.2)
Median (Q1–Q3)	25.3 (21.8–28.7)
Admission to the ICU related to index infection, *n* (%)	125 (41.9)
At least one comorbidity, *n* (%)	243 (81.5)
Heart disease	87 (29.2)
Chronic pulmonary disease	81 (27.2)
Diabetes mellitus	72 (24.2)
Chronic kidney disease	52 (17.4)
Liver disease	41 (13.8)
Cystic fibrosis	25 (8.4)
Immunocompromised*	133 (44.6)
Hematologic malignancy	52 (17.4)
Solid tumor	17 (5.7)
Transplant	82 (27.5)
Vasopressors received within 7 days preindex, *n* (%)	66 (22.1)
Corticosteroids received within 7 days preindex, *n* (%)	92 (30.9)
Mechanical ventilation within 7 days preindex, *n* (%)	86 (28.9)
Previous hospitalizations in the 6 months before the index date, *n* (%)	138 (46.3)
ICU stay in the 6 months before the index date, *n* (%)	51 (37.0)
C/T use 30 days before index hospitalization, *n* (%)	8 (2.7)
Indication for index event, *n* (%)	
Any respiratory-related infection†	154 (53.1)
Pneumonia	122 (40.9)
cIAI	52 (17.4)
cUTI	31 (10.4)
Exacerbation of chronic respiratory infection	29 (9.7)
Other respiratory infection	16 (5.4)
Febrile neutropenia	16 (5.4)
Bone and joint infection	12 (4.0)
Sepsis during index hospitalization, *n* (%)	124 (41.6)
Renal status, *n* (%)	
First renal replacement therapy during index hospitalization	64 (21.5)
Continuous renal replacement therapy	43 (14.4)
New acute kidney injury	110 (36.9)

* Immunocompromised: 'Immunocompromised' (raw item) as collected in the electronic data capture or hematologic malignancy or solid tumor or transplant.
† *n*=290 (*n*=8 missing data).

BMI: Body mass index; cIAI: Complicated intra-abdominal infection; C/T: Ceftolozane/tazobactam; cUTI: Complicated urinary tract infection; ICU: Intensive care unit; SD: Standard deviation.

patients. Renal replacement therapy was initiated in 21.5% of patients during the index hospitalization, and 14.4% were on continuous renal replacement therapy. Within 7 days before the index date, 22.1% of patients were treated with vasopressor therapy, 30.9% were treated with corticosteroids, and 28.9% were on mechanical ventilation.

Microbiologic data related to the index event were available for 68.5% of the study population (204 patients). For these patients, the most common sites of infection were respiratory (50.0%), skin/wound/tissue (21.1%), blood (13.7%), urine (10.3%), and pleural fluid/cerebrospinal fluid/other fluid (9.3%) (Table 2). The most common pathogens isolated among patients with microbiologic data were *P. aeruginosa* (89.7%), *Klebsiella* spp. (6.9%), and *E. coli* (6.4%), and MDR *P. aeruginosa* was identified in 66.7% of patients, with 39.3% of infections determined to be polymicrobial (Table 2). Extended-spectrum β-lactamase (ESBL)–positive pathogens were isolated from 45 (22.1%) patients.

Treatment characteristics for the overall population are shown in Table 3. The most common C/T regimen was 1.5 g every 8 h (36.9% of patients); 21.8% of patients received 3 g every 8 h. Of those patients with pneumonia (*n*=122), 28.3% received the recommended C/T dose

Table 2
Microbiologic findings.

Infection	*n/N* (%)
Polymicrobial infections	117/298 (39.3)
Culture results available*	204/298 (68.4)
Sites of infection†	
Respiratory	102/204 (50.0)
Skin/wound or tissue	43/204 (21.1)
Blood	28/204 (13.7)
Urine	21/204 (10.3)
Pleural fluid/cerebrospinal fluid/other fluid	19/204 (9.3)
Line/device	6/204 (2.9)
Other	4/204 (2.0)
Pathogens‡	
Pseudomonas aeruginosa	183/204 (89.7)
ESBL positive$^{\delta}$	27/183 (14.8)
MDR *P. aeruginosa*	136/204 (66.7)
Escherichia coli	13/204 (6.4)
ESBL positive$^{\delta}$	7/13 (53.8)
Klebsiella spp.	14/204 (6.9)
ESBL positive$^{\delta}$	7/14 (50.0)
Enterobacter spp.	6/204 (2.9)
ESBL positive$^{\delta}$	1/6 (16.7)
Acinetobacter spp.	5/204 (2.5)
ESBL positive$^{\delta}$	2/5 (40.0)

* Microbiologic data were available for 204 patients out of 298; patients were not required to have pathogens isolated for enrollment.
† Patients may have several sites of infection.
‡ Pathogens that were detected, but present in ≤2 patients (≤1.0%) included *Pantoea* spp., *Serratia* spp., *Proteus* spp., *Citrobacter freundii*, and ESBL-positive *K. pneumoniae*.
$^{\delta}$ ESBL positivity assessed among patients with pathogen.
ESBL: Extended-spectrum β-lactamase; MDR: Multidrug resistant.

Table 3
Treatment, resource use, and clinical outcomes.

	N=298
Initial dose of C/T / frequency, *n* (%)	
1.5 g/q8h	110 (36.9)
3.0 g/q8h	65 (21.8)
1.0 g/q8h	36 (12.1)
2.0 g/q8h	33 (11.1)
Other regimens	54 (18.1)
C/T initiation*, *n* (%)	
First-line therapy	74 (24.8)
Second-line therapy	70 (23.5)
Third-line or salvage therapy	154 (51.7)
C/T treatment duration†, median (Q1–Q3) (days)	11.0 (7.0–16.5)
All-cause 30-day readmission, *n* (%)	10 (3.4)
Infection-related 30-day readmission, *n* (%)	5 (1.7)
Clinical success‡, *n* (%) (95% CI)	159 (53.4) (47.5–59.1)
All-cause in-hospital mortality, *n* (%) (95% CI)	106 (35.6) (30.1–41.3)
Infection-related in-hospital mortality, *n* (%)	41 (13.8)

* Line of therapy was determined by considering the start date of each Gram-negative antibacterial agent taken for index infection and sorting them by chronological order.
† Treatment interruptions not included.
‡ Defined as no additional Gram-negative therapy required after a minimum of 48 h of treatment with C/T (not including discharge antibacterials or de-escalation), no death attributed to Gram-negative infection, discharge from hospital or ICU, no need for re-operation for source infection control, or microbiologic eradication (negative culture at the site of index infection after C/T).

CI: Confidence interval; C/T: Ceftolozane/tazobactam; ICU: Intensive care unit; q8h: Every 8 h.

of 3 g every 8 h. A little over half (51.7%) of patients received C/T as third-line or salvage therapy, 24.8% as first-line treatment, and 23.5% as second-line treatment. The median time from microbiologic sample for the index infection to the initiation of C/T was 6.0 days (Q1–Q3, 3.0–12.0 days). Median C/T treatment duration was 11.0 days (Q1–Q3:

7.0–16.5 days).

All-cause and infection-related 30-day admission rates were 3.4% and 1.7%, respectively (Table 4). Overall clinical success as determined by the investigators was 53.4% (95% CI: 47.5% to 59.1%). Clinical success by line of treatment (first line, second line, and third line/salvage) was 62.2%, 61.4%, and 45.5%, respectively. All-cause in-hospital mortality was 35.6% (95% CI: 30.1% to 41.3%). All-cause in-hospital mortality rates by line of C/T treatment were 37.8% (first line), 30.0% (second line), and 37.0% (third line/salvage). Infection-related in-hospital mortality was 13.8%. By line of C/T treatment, infection-related in-hospital mortality rates were 9.5% (first line), 11.4% (second line), and 16.9% (third line/salvage).

Nine clinical, treatment-related, and microbiologic characteristics were qualified for the multivariable analysis ($P<0.2$ in univariate analysis) and are shown in Table 5. On a multivariable analysis, only positive culture for *E. coli* was significantly ($P<0.05$) associated with a lower likelihood of clinical success (odds ratio [95% CI] of clinical success was 0.230 [0.057 to 0.922]; $P=0.038$).

4. Discussion

This multinational real-world study included a large number of patients with critical illness who presented with severe Gram-negative infections in the ICU, and reports outcomes associated with C/T use. This was a high-risk study population with >80% of the study sample having at least one comorbidity, renal replacement therapy initiated in 21.5% of patients, and significant vasopressor, corticosteroid, and mechanical ventilation use within 7 days before the index date. Additionally, 41.9% of included patients had an infection-related ICU admission. These characteristics contribute to the overall challenge of antibacterial management in patients with critical illness and underscore the need for early and appropriate treatment.

In the current study, C/T was used to treat multisource, polymicrobial infections, including 53.1% of patients with respiratory-related infections, of which 79.2% had pneumonia. The most common infecting pathogens were *P. aeruginosa, E. coli*, and *Klebsiella* spp. These results are consistent with a large European prevalence study that evaluated HAIs of all types and found that *E. coli, K. pneumoniae*, and *P. aeruginosa* were among the top five infecting bacterial types [35]. The current study findings also align with a study of Gram-negative lower respiratory tract isolates obtained from United States clinical laboratories in 2018–2019 as part of the Study for Monitoring Antimicrobial Resistance Trends (SMART) that reported *P. aeruginosa, K. pneumoniae*, and *E. coli* as the most common Gram-negative bacterial pathogens isolated from lower respiratory tract infections (33%, 12%, and 10%, respectively) [36]. In addition, resistant Gram-negative pathogens are

Table 4
Clinical success and mortality by line of C/T therapy, % (95% CI).

Line of therapy	All-cause in-hospital mortality	Infection-related in-hospital mortality	Clinical success*
First (*n*=74)	37.8 (26.8–49.9)	9.5 (3.9–18.5)	62.2 (50.1–73.2)
Second (*n*=70)	30.0 (19.6–42.1)	11.4 (5.1–21.3)	61.4 (49.0–72.8)
Third or salvage (*n*=154)	37.0 (29.4–45.2)	16.9 (11.3–23.8)	45.5 (37.4–53.7)

* Defined as no additional Gram-negative therapy required after a minimum of 48 h of treatment with C/T (not including discharge antibacterial agents or de-escalation), no death attributed to Gram-negative infection, discharge from hospital or ICU, no need for re-operation for source infection control, or microbiologic eradication (negative culture at the site of index infection after C/T).

CI: Confidence interval; C/T: Ceftolozane/tazobactam; ICU: Intensive care unit.

Table 5
Factors associated with clinical success: results of univariate analyses for factors with $P<0.2$.

Condition present	Index infection considered as a clinical success by the investigator		Univariate logistic model *P*-value
	Yes	No	
Source of infection: urine			0.183
Yes (*n*=18)	14 (77.8%)	4 (22.2%)	
No (*n*=161)	99 (61.5%)	62 (38.5%)	
Missing (*n*=78)	46 (59.0%)	32 (41.0%)	
Source of infection: skin/ wound or tissue			0.057
Yes (*n*=33)	16 (48.5%)	17 (51.5%)	
No (*n*=146)	97 (66.4%)	49 (33.6%)	
Missing (*n*=78)	46 (59.0%)	32 (41.0%)	
Indication for index event: cIAI			0.196
Yes (*n*=45)	24 (53.3%)	21 (46.7%)	
No (*n*=212)	135 (63.7%)	77 (36.3%)	
Missing (*n*=0)			
Indication for index event: sepsis			0.080
Yes (*n*=73)	39 (53.4%)	34 (46.6%)	
No (*n*=184)	120 (65.2%)	64 (34.8%)	
Missing (*n*=0)			
Enterobacterales ESBL positive			0.111
Yes (*n*=14)	6 (42.9%)	8 (57.1%)	
No (*n*=165)	107 (64.8%)	58 (35.2%)	
Missing (*n*=78)	46 (59.0%)	32 (41.0%)	
Positive culture for *Escherichia coli*			0.038
Yes (*n*=10)	3 (30.0%)	7 (70.0%)	
No (*n*=169)	110 (65.1%)	59 (34.9%)	
Missing (*n*=78)	46 (59.0%)	32 (41.0%)	
Renal impairment			0.114
Yes (*n*=127)	74 (58.3%)	53 (41.7%)	
No (*n*=116)	79 (68.1%)	37 (31.9%)	
Missing (*n*=14)	6 (42.9%)	8 (57.1%)	
Heart disease			0.157
Yes (*n*=68)	47 (69.1%)	21 (30.9%)	
No (*n*=187)	111 (59.4%)	76 (40.6%)	
Missing (*n*=2)	1 (50.0%)	1 (50.0%)	
Time from first microbiologic sample to start of C/T			0.093
<3 days (*n*=41)	29 (70.7%)	12 (29.3%)	
3–7 days (*n*=62)	43 (69.4%)	19 (30.6%)	
>7 days (*n*=76)	41 (53.9%)	35 (46.1%)	
Missing (*n*=78)	46 (59.0%)	32 (41.0%)	

Analysis includes only those with known status for clinical success. Responses of 'unknown' were considered as missing data.

cIAI: Complicated intra-abdominal infection; C/T: Ceftolozane/tazobactam; ESBL: Extended-spectrum β-lactamase.

more likely in hospital-onset than community-acquired infections [37–39]. The current study showed high rates of MDR *P. aeruginosa*, with 66.7% of the study sample being positive for MDR *P. aeruginosa*. This is higher than rates reported in prior studies conducted in hospitalized populations in the United States, where up to 20% of *P. aeruginosa* isolates from respiratory sources in the hospital setting were MDR [36,37,40]. This is expected since C/T is considered for treating MDR Gram-negative infections.

More than half of patients received C/T as third-line or salvage therapy, and our results suggest that early use of C/T may be associated with better outcomes. Previous studies have demonstrated that initial inappropriate treatment with antimicrobial agents results in significantly higher mortality and longer hospital stays than appropriate therapy [41–45]. Also, patients who experienced a delay in receiving appropriate antibacterial therapy have been reported to experience longer durations of antimicrobial therapy, longer lengths of stay, a lower chance of being discharged to home, and an increased risk of in-hospital mortality or being discharged to hospice [41,46]. In addition, a study on ventilator-acquired bacterial pneumonia and ventilated hospital-acquired bacterial pneumonia reported that early treatment with C/T was more cost-effective than waiting until pathogen confirmation [47]. The Infectious Diseases Society of America (IDSA) 2022 guidelines, recommend antibacterial agents that can treat ESBL-producing bacteria for HAI caused by resistant pathogens, and in the absence of identification of the infecting pathogen, patient characteristics could be used to help select antibacterial therapy [48]. The IDSA also acknowledges the challenge presented by current identification methods and the need to balance timely treatment of resistant infections with potential unnecessary first-line use in patients with nonresistant infections [48]. However, the IDSA guidelines, updated in 2023, recommend against the use of C/T for the treatment of ESBL-Enterobacterales, with the exception of polymicrobial infections because of concerns regarding the ability of tazobactam to inhibit ESBL production despite *in vitro* and clinical data showing efficacy [49].

All-cause and infection-related 30-day readmission rates were low (3.4% and 1.7%, respectively) compared with other studies. In a large, multicenter study of patients hospitalized with Gram-negative infections, all-cause 30-day readmission rates for carbapenem-susceptible infections ranged from 16.5% to 24.0% and 23.2% to 28.3% for carbapenem-nonsusceptible infections, with higher rates reported for principal diagnoses other than cUTI, and for HAI compared with community-acquired infections [50]. In another study of carbapenem resistance in patients hospitalized with respiratory infections, 30-day readmission rates ranged from 13.5% to 20.4% regardless of susceptibility to carbapenem [14]. In a small single-center study of hospitalized patients with sepsis and/or bacteremia treated with C/T, the all-cause 30-day readmission rate was 14%, of which 67% were infection related [51]. This may be explained by the fact that patients in the present study were largely in the ICU and therefore, closely monitored and actively managed.

In the present study, clinical success was reported in 53.4% of patients, overall. These findings are similar to the ASPECT-NP trial where most of the patients with nosocomial pneumonia who were treated with C/T were severely ill and admitted to the ICU (334/362, 92%) [10]. In the ASPECT-NP trial, clinical success rates were 40% for extensively drug-resistant *P. aeruginosa*, 54% for MDR *P. aeruginosa*, and 57% for ESBL-producing Enterobacterales [10]. The multivariable analysis found that only positive culture for *E. coli* was associated with lack of clinical success. It is possible that other clinical, treatment-related, and microbiologic characteristics may have been associated with clinical success, but there were very few patients in this analysis. In the present study, in-hospital mortality was 35.6% in patients with complex comorbidities and severe infections who were admitted to critical care settings and had received C/T. Similarly, in ASPECT-NP, an all-cause 28-day mortality rate of 24% in the C/T-treated cohort was observed [10]. All-cause mortality associated with ventilator-associated bacterial pneumonia has been found in the literature to range widely from 20% to 50% for ICU-acquired pneumonia with unspecified treatment regimens [52].

While the results of this study may be generalizable to the critically ill population with similar infections and treatments, potential biases were present. These include patient selection bias, as participants were selected at the discretion of the treating physician, and site selection bias since sites were primarily in developed countries. Lack of microbiology data for 31.5% of the study sample may have also affected the results, and a lack of control group could have influenced the interpretation of the data. Consequently, caution should be taken when extrapolating the results to broader populations. In addition, antimicrobial resistance is rapidly expanding and the results achieved in this study may not be reproducible in the near future due to the shifting antimicrobial resistance landscape [53]. Nevertheless, this study represents one of the largest datasets of C/T use in the ICU and encompasses a worldwide population; thus, the results should be applicable to clinicians at other institutions who treat patients in this setting.

Specific data on the prevalence of combination therapy among the studied cohort were unavailable for analysis and is a limitation of this study. Future research should aim to capture this information to provide a more comprehensive understanding of treatment practices. In addition, this study does not include difficult-to-treat *P. aeruginosa* prevalence and outcomes data, which is another limitation that should be addressed in future studies to better understand the effectiveness of C/T in treating these challenging infections.

5. Conclusions

This multinational real-world study included a high number of patients who were critically ill and reports encouraging outcomes associated with C/T use. In this very high-risk cohort presenting with severe Gram-negative infections, 53.4% of patients receiving C/T had clinical success despite their clinical complexity and late administration of C/T. Although antibacterial utilization is shaped by local resistance patterns, infection severity, patient characteristics, and drug safety profile, C/T is a well-established antibacterial combination agent active against a wide range of Gram-negative pathogens, including those with antibacterial resistance, making it a valuable option in critical care settings.

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CRediT authorship contribution statement

Alex Soriano: Writing – review & editing, Validation, Project administration, Methodology, Investigation, Data curation. **David L. Paterson:** Writing – review & editing, Validation, Project administration, Methodology, Investigation. **Florian Thalhalmmer:** Writing – review & editing, Validation, Project administration, Methodology, Investigation, Formal analysis. **Stefan Kluge:** Writing – review & editing, Validation, Project administration, Methodology, Investigation. **Pierluigi Viale:** Writing – review & editing, Validation, Project administration, Methodology, Investigation. **Brune Akrich:** Writing – review & editing, Validation, Project administration, Methodology, Investigation. **Mike Allen:** Writing – review & editing, Validation, Project administration, Methodology, Investigation. **Stephanie Wirbel:** Writing – review & editing, Validation, Project administration, Methodology, Investigation, Formal analysis. **Alexandre H. Watanabe:** Writing – review & editing, Validation, Project administration, Methodology, Investigation. **Emre Yücel:** Writing – review & editing,

Validation, Methodology, Investigation, Formal analysis. **Engels N. Obi:** Writing – review & editing, Validation, Project administration, Methodology, Investigation. **Sundeep Kaul:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships, which may be considered as potential competing interests:

EY, AHW, and ENO are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD). BA is an employee of MSD France, and MA is an employee of MSD (UK) Limited, London, UK.

AS has received honoraria for lectures and advisory boards from Advance Pharma, Angelini Pharma, Pfizer, Menarini, MSD, Shionogi, and Gilead. AS has received research grants from Gilead and Pfizer.

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