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Real-world analysis of ceftolozane/tazobactam prescribing patterns and effectiveness: SPECTRA analysis on chronic pulmonary diseases and respiratory-related infections

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ABSTRACT

Objectives: In hospital settings, both pre-existing antibiotic-resistant Gram-negative (GN) bacteria and those that develop resistance during treatment pose significant challenges, often contributing to significant morbidity and mortality. This study focuses on chronic pulmonary disease (CPD) and respiratory-related infections (RRI), including pneumonia, from SPECTRA study. Understanding the real-world clinical use and outcomes for patients treated with ceftolozane/tazobactam (C/T) is essential.

Methods: The multi-national SPECTRA study utilised inpatient chart reviews to describe real-world practice and collect outcome data in hospitalised patients treated with C/T. This analysis focuses on secondary data from SPECTRA cohorts of CPD and RRI patients (the most common conditions comprising RRI included pneumonia and exacerbation of chronic respiratory infection [ECRI]).

Results: Between January 2016 and October 2020, 180 patients with CPD, 275 with RRI, 182 with pneumonia, and 91 with ECRI who received C/T for ≥48 h were included. The mean (standard deviation [SD]) age was 57.5 (18.7) years, 55.8 (18.2) years, 57.8 (17.4) years, and 51.8 (19.1) years in CPD, RRI, pneumonia, and ECRI patients, respectively. *Pseudomonas aeruginosa* was the most frequent pathogen, identified (91.5%, 91.8%, 88.0%, and 97.0% CPD, RRI, pneumonia, and ECRI patients, respectively), with MDR strains in 76.9%, 74.7%, 68.4%, and 80.3% CPD, RRI, pneumonia, and ECRI patients, respectively. Clinical success was achieved in 69.4%, 66.2%, 59.9%, 79.1% of CPD, RRI, pneumonia, and ECRI patients, respectively.

Conclusions: This SPECTRA subgroup analysis demonstrates significant real-world utilisation of C/T in treating patients with CPD and RRI, aligning with previous controlled studies.

1. Introduction

Gram-negative (GN) bacteria are a major cause of in-hospital-acquired infections and are notorious for developing antibiotic resistance [1]. This can result in treatments utilising several antibiotic agents (AA) and is associated with significant morbidity and mortality [1–3]. Treatment with AA may be employed in patients with chronic pulmonary disease (CPD), respiratory-related infections (RRI), including pneumonia, and bloodstream infections [1–4]. CPD may occur in response to alterations in lung function and may result in increased risk for RRI [5]. RRI usually includes exacerbation of chronic respiratory infection (ECRI) and pneumonia. Patients with pneumonia may be burdened with serious com-

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Table 1
Indications and conditions – by country.

	Australia N = 59	Austria N = 12	Germany N = 29	Italy N = 57	Mexico N = 59	Spain N = 313	UK N = 88	Total N = 617
Chronic pulmonary disease[1], n (%)	16 (27.1%)	2 (16.7%)	6 (20.7%)	16 (28.1%)	6 (10.2%)	92 (29.4%)	42 (47.7%)	180 (29.2%)
Respiratory-related infections[2], n (%)	16 (27.6%)	7 (58.3%)	12 (48.0%)	18 (32.1%)	31 (52.5%)	133 (43.5%)	58 (68.2%)	275 (45.8%)
Pneumonia, n (%)	13 (22.0%)	7 (58.3%)	9 (31.0%)	17 (29.8%)	30 (50.8%)	84 (26.8%)	22 (25.0%)	182 (29.5%)
Exacerbation of chronic respiratory infection, n (%)	6 (10.2%)	0	1 (3.4%)	1 (1.8%)	0	44 (14.1%)	39 (44.3%)	91 (14.7%)

[1] Missing data for CPD patients were reported for 1, 4, 1, 7, 3, and 16 patients in Australia, Germany, Italy, Spain, UK, and Total countries, respectively.
[2] Respiratory-related infections for patients who have at least one indication for Index event corresponding to a respiratory infection (prelisted indications 'Pneumonia' and 'Exacerbation of chronic respiratory infection' or other respiratory infections reported in the 'Other' category).

plications, contributing significantly to morbidity and mortality [1–3,6]. Patients with ECRI would experience acute worsening or flare-ups of symptoms [1].

Ceftolozane/tazobactam (C/T) is a broad-spectrum antibacterial agent comprised of an antipseudomonal cephalosporin (ceftolozane) in combination with an established β-lactamase inhibitor (tazobactam) [7]. The primary activity of C/T is against aerobic GN bacteria. C/T has been approved for complicated intra-abdominal infections (cIAI), complicated urinary tract infections (cUTI), and hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP) [8–10]. Given its broad-spectrum effectiveness against several multidrug-resistant (MDR) GN bacteria, including MDR *Pseudomonas aeruginosa*, AmpC-, and ESBL-producing Enterobacterales, it is vital to understand prescribing patterns in the real world [11–13]. Prescribing patterns of C/T from real-world data can demonstrate use in other indications and conditions [14–16].

SPECTRA was an international, retrospective study designed to describe real-world prescribing patterns of C/T in hospitalised patients [17]. SPECTRA was conducted in Australia, Austria, Germany, Italy, Spain, Mexico and the United Kingdom. This secondary analysis describes the real-world prescribing patterns and outcomes of C/T among patients with CPD and RRI. This work addresses gaps in knowledge of real-world C/T prescribing patterns.

2. Patients and methods

2.1. Study design

SPECTRA was an international, multi-centre, retrospective, descriptive inpatient chart review study [17]. It included adult patients who were treated with C/T for at least 48 h in a hospital setting from seven countries. To be eligible for inclusion, patients also had to receive their last dose of C/T at least 30 days before their chart abstraction. We report the prescribing patterns of C/T in patients with the comorbidity of CPD and/or with RRI.

The Index infection refers to the first infection for which the patient received C/T. CPD was identified as a comorbidity in medical history and was associated with the Index infection. RRI included pneumonia, ECRI, and other respiratory infections. Patients with pneumonia were defined based on their condition during the Index event of pneumonia. Similarly, patients with ECRI were defined by their condition during the Index event of ECRI.

We analysed demographics, clinical characteristics, microbiological findings, treatment patterns, and clinical outcomes (including clinical success, mortality, and readmission) for patients with CPD and RRI. Clinical success was defined by investigator assessments based on several criteria:

- No additional GN therapy required after a minimum of 48 h of treatment with C/T (excluding discharge antibiotics or de-escalation).
- No further inpatient antibiotic treatment for exacerbation of respiratory infection within 28 days of stopping C/T.
- Resolution of ECRI.
- No death attributed to GN infection.
- Discharge from the hospital or intensive care unit (ICU).
- No need for re-operation for source infection control.
- Microbiological eradication, as assessed by the investigator, since microbiological data for recalculation were not collected.

Each criterion for clinical success was independently assessed and reported.

The study was conducted in accordance with the relevant ethical standards and approved by the appropriate local Ethics Committees. Obtaining patient informed consent was waived for all sites due to the retrospective nature of the study, except for Italy.

2.2. Statistical analysis

SAS software 9.4 (SAS Institute, North Carolina, USA) was used for statistical analysis. Analyses were performed on the Analysis population who met the inclusion and exclusion criteria.

3. Results

3.1. Demographics and baseline characteristics

Among the seven countries and 617 patients comprising the Analysis population of the multi-national SPECTRA study, there were 180 patients with CPD, 275 with RRI, 182 with pneumonia, and 91 with ECRI (Table 1). There was also a smaller subset of patients ($N = 19$) that were categorised initially as other by the study investigators but later reclassified as other respiratory that did not fall into the larger subgroups in this sub-study and were not analysed further. Index dates spanned from January 2016 to October 2020. Although this period covered the COVID-19 pandemic, there were only 18 patients. Due to the small sample size, this patient group was excluded from the final analysis.

The mean (standard deviation [SD]) age was 57.5 (18.7) years, 55.8 (18.2) years, 57.8 (17.4) years, and 51.8 (19.1) years in CPD, RRI, pneumonia, and ECRI patients, respectively

(Table 2). There were 63.9%, 66.5%, 68.7%, and 60.4% of patients who were male in CPD, RRI, pneumonia, and ECRI patients, respectively. Renal impairment (creatinine clearance $\leq$80 mL/min) was shown in 44.9%, 44.7%, 50.6%, and 36.7% of CPD, RRI, pneumonia, and ECRI patients, respectively. There were 55.6%, 52.0%, 47.8%, and 60.4% of patients who were hospitalised within 6 months of the Index date in CPD, RRI, pneumonia, and ECRI patients, respectively; and among them, 11.0%, 25.2%,32.2%, and 16.4% had an ICU stay in CPD, RRI, pneumonia, and ECRI patients, respectively. In total, there were 188, 258, 133, and 115 prior hospitalisations within 6 months of the Index date reported in CPD, RRI, pneumonia, and

Table 2
Patient demographics and baseline characteristics.

Characteristics	Chronic pulmonary disease, *N* = 180	Respiratory-related infections		
		Respiratory-related infections total *N* = 275	Pneumonia *N* = 182	Exacerbation of chronic respiratory infection *N* = 91
Age in years, median (Q1; Q3)	61.5 (44.5; 72.0)	59.0 (42.0; 70.0)	61.0 (47.0; 72.0)	54.0 (35.0; 68.0)
Age in years, mean (SD)	57.5 (18.7)	55.8 (18.2)	57.8 (17.4)	51.8 (19.1)
Males, n (%)	115 (63.9%)	183 (66.5%)	125 (68.7%)	55 (60.4%)
BMI (kg/m^2), median (Q1; Q3)	24.9 (20.8; 28.9)	25.0 (20.7; 27.7)	25.2 (21.5; 27.8)	22.9 (19.8; 26.1)
Previous care setting, n (%)				
Home/community	150 (83.3%)	221 (80.4%)	142 (78.0%)	78 (85.7%)
Other hospital	11 (6.1%)	32 (11.6%)	24 (13.2%)	4 (4.4%)
Other skilled care facility	16 (8.9%)	12 (4.4%)	7 (3.8%)	8 (8.8%)
Renal impairment is defined as creatinine clearance ≤80 mL/min, n (%)	79 (44.9%)	117 (44.7%)	86 (50.6%)	33 (36.7%)
Mechanical ventilation within 7 days prior to Index date, n (%)	27 (15.0%)	63 (22.9%)	54 (29.7%)	10 (11.0%)
Hospitalisations in 6 months prior to Index date[1], n (%)	100 (55.6%)	143 (52.0%)	87 (47.8%)	55 (60.4%)
If Yes:				
ICU Stay in 6 months prior to Index date[1], n (%)	11 (11.0%)	36 (25.2%)	28 (32.2%)	9 (16.4%)
Total number of hospitalisations[1,2], n	188	258	133	115
Duration of hospitalisation (days)[1,2,3], median (Q1; Q3)	12.0 (7.0; 20.0)	13.0 (7.0; 22.0)	14.0 (7.0; 28.0)	13.0 (8.0; 20.0)
mean (SD)	17.7 (21.2)	21.0 (34.7)	26.7 (46.6)	15.7 (11.9)
Hospitalisations related to infections[1,2,3], n (%)	122 (64.9%)	139 (54.7%)	53 (40.8%)	85 (74.6%)
Hospitalisations related to GN infections[1,2,3], n (%)	97 (51.6%)	107 (42.1%)	37 (28.5%)	69 (60.5%)
Total number of ICU stays[1,2], n	18	45	37	9
Duration of ICU stays[1,2,3],	9.5	8.0	8.0	9.0
median (Q1; Q3)	(6.0; 15.0)	(6.0; 18.0)	(5.0; 16.0)	(7.0; 40.0)
mean (SD)	18.1 (26.4)	19.5 (27.2)	17.3 (25.2)	26.7 (33.7)
ICU stays related to infections[1,2,3], n (%)	7 (38.9%)	18 (40.0%)	16 (43.2%)	3 (33.3%)
ICU stays related to GN infections[1,2,3], n (%)	4 (22.2%)	8 (17.8%)	7 (18.9%)	1 (11.1%)
Surgeries[1], n (%)	37 (20.6%)	54 (19.6%)	39 (21.4%)	12 (13.2%)
Number of comorbidities per patient[4], median (Q1; Q3)	3.0 (2.0; 4.0)	2.0 (1.0; 3.0)	2.0 (1.0 – 3.0)	2.0 (1.0 – 4.0)
At least 1 comorbidity/ medical history[4], n (%)	180 (100%)	232 (84.4%)	142 (78.0%)	90 (98.9%)
Comorbidities[4], n (%)				
Heart disease	55 (30.6%)	70 (25.5%)	51 (28.0%)	19 (20.9%)
Chronic kidney disease	28 (15.6%)	35 (12.7%)	25 (13.7%)	11 (12.1%)
Acute kidney injury	13 (7.2%)	22 (8.0%)	16 (8.8%)	6 (6.6%)
Living kidney donation	2 (1.1%)	2 (0.7%)	2 (1.1%)	1 (1.1%)
End-stage renal disease	4 (2.2%)	7 (2.5%)	6 (3.3%)	1 (1.1%)
Requirement for dialysis	11 (6.1%)	18 (6.5%)	13 (7.1%)	5 (5.5%)
Chronic pulmonary disease	180 (100.0%)	129 (46.9%)	61 (33.5%)	74 (81.3%)
cystic fibrosis	45 (25.0%)	51 (18.5%)	15 (8.2%)	36 (39.6%)
Liver disease, mild	19 (10.6%)	23 (8.4%)	9 (4.9%)	13 (14.3%)
Live disease, moderate to severe	6 (3.3%)	8 (2.9%)	5 (2.7%)	1 (1.1%)
Acute hepatitis	2 (1.1%)	3 (1.1%)	2 (1.1%)	0
Chronic hepatitis	8 (4.4%)	8 (2.9%)	4 (2.2%)	4 (4.4%)
Cirrhosis	12 (6.7%)	12 (4.4%)	5 (2.7%)	5 (5.5%)
Diabetes mellitus, uncomplicated	40 (22.2%)	60 (21.8%)	31 (17.0%)	27 (29.7%)
Diabetes mellitus, end-organ damage	12 (6.7%)	11 (4.0%)	9 (4.9%)	2 (2.2%)
IV drug use	10 (5.6%)	10 (3.6%)	4 (2.2%)	6 (6.6%)
Hematologic malignancy	15 (8.3%)	39 (14.2%)	34 (18.7%)	4 (4.4%)
Solid tumour, metastatic	5 (2.8%)	10 (3.6%)	7 (3.8%)	1 (1.1%)
Transplant	46 (25.6%)	62 (22.5%)	44 (24.2%)	19 (20.9%)
Immunocompromised[5]	75 (41.7%)	109 (39.6%)	79 (43.4%)	28 (30.8%)
Antibacterials/fungal therapy received in the 30 days before the Index date[1], n (%)	123 (68.3%)	176 (64.0%)	112 (61.5%)	59 (64.8%)
Antibacterials/fungal therapy, n (%)				
Clostridium difficile antimicrobials	6 (3.3%)	12 (4.4%)	10 (5.5%)	1 (1.1%)
Gram-positive antimicrobials	42 (23.3%)	74 (26.9%)	49 (26.9%)	19 (20.9%)
Aminoglycoside	34 (18.9%)	50 (18.2%)	28 (15.4%)	19 (20.9%)
Polymyxin	25 (13.9%)	35 (12.7%)	11 (6.0%)	21 (23.1%)
Fluroquinolone	37 (20.6%)	55 (20.0%)	34 (18.7%)	20 (22.0%)
Cephalosporin	29 (16.1%)	43 (15.6%)	30 (16.5%)	15 (16.5%)
Carbapenem	48 (26.7%)	82 (29.8%)	55 (30.2%)	24 (26.4%)
Ceftazidime/avibactam	1 (0.6%)	4 (1.5%)	4 (2.2%)	0
Pipercillin/tazobactam	36 (20.0%)	65 (23.6%)	50 (27.5%)	13 (14.3%)
B-lactam, other	27 (15.0%)	30 (10.9%)	21 (11.5%)	13 (14.3%)
Ceftolozane/tazobactam	4 (2.2%)	7 (2.5%)	5 (2.7%)	4 (4.4%)

(*continued on next page*)

Table 2 (*continued*)

Characteristics	Chronic pulmonary disease, $N = 180$	Respiratory-related infections		
		Respiratory-related infections total $N = 275$	Pneumonia $N = 182$	Exacerbation of chronic respiratory infection $N = 91$
Other	49 (27.2%)	61 (22.2%)	38 (20.9%)	25 (27.5%)
Antibacterials/fungal therapy, n (%)				
Fungal therapy	45 (25.0%)	72 (26.2%)	47 (25.8%)	23 (25.3%)

[1] Index date: first date of administration of any antibiotic for any suspected Gram-negative infection in which C/T was administered. Characteristic is for 6 months prior to Index date unless otherwise described.
[2] Several Hospitalisations may have been experienced by the same patient. Several ICU stays may have been experienced by the same patient.
[3] Duration of hospitalisation missing data reported for 1, 9, 6 and 2 patients in CPD, RRI, pneumonia, and ECRI groups, respectively; hospitalisation related to infections/GN infections missing data reported for 4, 3 and 1 patients in RRI, pneumonia, and ECRI groups, respectively; duration of ICU stay missing data reported for one patient in RRI and pneumonia groups.
[4] For CPD patients, CPD is counted as a comorbidity.
[5] Immunocompromised defined as: 'Immunocompromised present' (raw item) or 'hematologic malignancy present' or 'solid tumour present' or 'transplant = yes'.Abbreviations: Q1, first quartile; Q3, third quartile; n, frequency; %, percentage; BMI, body mass index; GN, Gram negative; kg, kilogram; m, meter; mL, millilitre; min, minute; ICU, intensive care unit; IV, intravenous; SD, standard deviation.

Table 3
Characteristics of C/T administration.

Characteristics	Chronic pulmonary disease, $N = 180$	Respiratory-related infections		
		Respiratory-related infections total $N = 275$	Pneumonia $N = 182$	Exacerbation of chronic respiratory infection $N = 91$
Duration of C/T treatment (days) (treatment interruptions not included)				
Mean (SD)	14.2 (10.0)	12.9 (7.8)	12.8 (8.3)	13.6 (5.9)
Median (Q1; Q3)	13.0 (8.0; 16.0)	12.0 (8.0; 16.0)	11.0 (7.0; 16.0)	14.0 (8.0; 16.0)
C/T: Rank of initiation, n (%)				
First	38 (21.1%)	78 (28.4%)	61 (33.5%)	16 (17.6%)
Second	50 (27.8%)	67 (24.4%)	43 (23.6%)	23 (25.3%)
Third	52 (28.9%)	54 (19.6%)	33 (18.1%)	22 (24.2%)
Fourth	17 (9.4%)	32 (11.6%)	22 (12.1%)	9 (9.9%)
Fifth	11 (6.1%)	22 (8.0%)	11 (6.0%)	10 (11.0%)
Sixth or more	12 (6.7%)	22 (8.0%)	12 (6.6%)	11 (12.1%)
Timing of C/T initiation, n (%)				
Empiric therapy[1]	48 (26.7%)	81 (29.5%)	58 (31.9%)	22 (24.2%)
Definitive therapy[2]	113 (62.8%)	157 (57.1%)	103 (56.6%)	56 (61.5%)
Undetermined	12 (6.7%)	24 (8.7%)	15 (8.2%)	6 (6.6%)
C/T not given before culture availabilities, given within 2 days after microbiological sample and no other antibacterial was given before	7 (3.9%)	13 (4.7%)	6 (3.3%)	7 (7.7%)
If definitive therapy:				
Missing	24	47	28	17
C/T early directed therapy[3]	52 (58.4%)	55 (50.0%)	37 (49.3%)	19 (48.7%)
C/T late directed therapy[4]	37 (41.6%)	55 (50.0%)	38 (50.7%)	20 (51.3%)

[1] Empiric therapy: C/T was initiated before receipt of susceptibility testing and the time from the first microbiological (MB) sample for Index infection to the first dose of C/T was ≤5 days or was missing.
[2] Definitive therapy: C/T was initiated after receipt of susceptibility testing and the time from the first microbiological sample for Index infection to the first dose of C/T was >2 days or missing or was within 0–2 days and another antibacterial was given before C/T.
[3] C/T early directed therapy: C/T was given between 3 and 7 days after the date of the microbiological sample or C/T was given within 0–2 days and another antibacterial was given before C/T.
[4] C/T late-directed therapy: C/T was given more than 7 days after the date of the microbiological sample.Abbreviations: n, frequency; %, percentage; SD, standard deviation; Q1, first quartile; Q3, third quartile; g, gram; h, hour.

ECRI patients, respectively: the median (Q1; Q3) duration of hospitalisation was 12.0 (7.0; 20.0) days, 13.0 (7.0; 22.0) days, 14.0 (7.0; 28.0) days, and 13.0 (8.0; 20.0) days in CPD, RRI, pneumonia, and ECRI patients, respectively, (the mean [SD] duration of hospitalisation was 17.7 [21.2] days, 21.0 [34.7] days, 26.7 [46.6] days, and 15.7 [11.9] days in CPD, RRI, pneumonia, and ECRI patients, respectively); 64.9%, 54.7%, 40.8%, and 74.6% of hospitalisations were related to infections, and 51.6%, 42.1%, 28.5%, and 60.5% were related to GN infections in CPD, RRI, pneumonia, and ECRI patients, respectively. The median (Q1; Q3) duration of ICU stays was 9.5 (6.0; 15.0) days, 8.0 (6.0; 18.0) days, 8.0 (5.0; 16.0), and 9.0 (7.0; 40.0) days in CPD, RRI, pneumonia, and ECRI patients, respectively, (the mean [SD] duration of ICU stays was 18.1 [26.4] days, 19.5 [27.2] days, 17.3 [25.2], and 26.7 [33.7] days in CPD, RRI, pneumonia, and ECRI patients, respectively); 38.9%, 40.0%, 43.2%, and 33.3% of ICU stays were related to infections and 22.2%, 17.8%, 18.9%, and 11.1% were related to GN infections in CPD, RRI, pneumonia, and ECRI patients, respectively. There were 20.6%, 19.6%, 21.4%, and 13.2% patients who had surgery within 6 months prior to the Index date in CPD, RRI, pneumonia, and ECRI patients, respectively.

Among patients with CPD, 41.7% of CPD patients were immunocompromised, which included those with organ transplants and hematologic malignancies. In addition to CPD, the most common

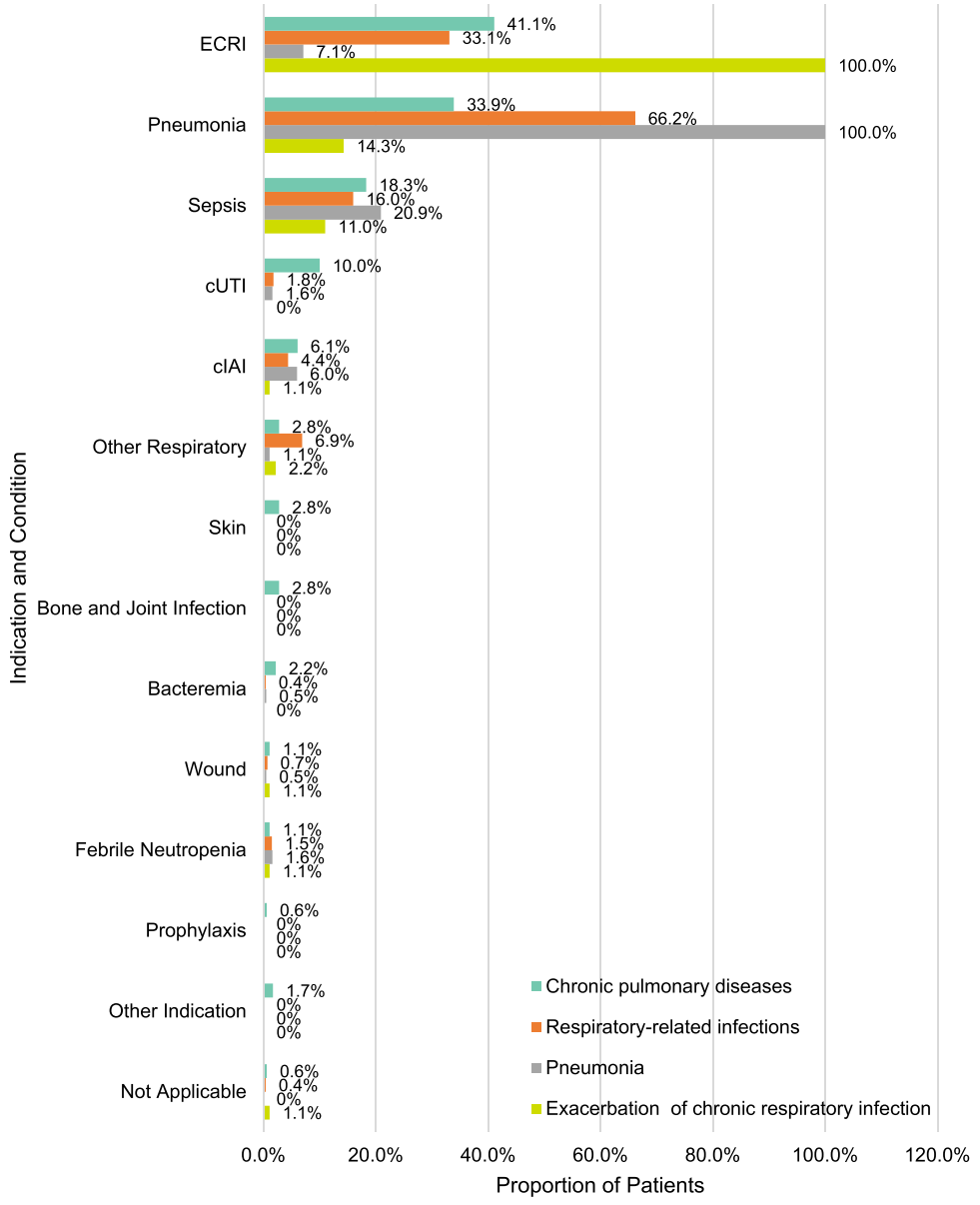

Fig. 1. Indications and conditions for which patients received C/T. Several indications/conditions may have been reported for the same patient. Fig. 1 shows indications and conditions for which CPD, (*green*), RRI (*orange*), pneumonia (*grey*), and ECRI (*yellow*) patients received C/T. The proportion of patients (%) is graphed for each indication or condition with the horizontal bars.
Abbreviations: cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; ECRI, exacerbation of chronic respiratory infection.

comorbidities observed were diabetes mellitus (both uncomplicated and with end-organ damage, 28.9%), heart disease (30.6%), and cystic fibrosis (25.0%).

Comorbidities were reported in RRI (84.4%), pneumonia (78.0%), and ECRI (98.9%) patients. CPD as a comorbidity was reported in 129 (46.9%) patients with RRI, 61 (33.5%) patients with pneumonia, and 74 (81.3%) patients with ECRI. Significant overlap was shown between RRI and CPD (the 129 patients that had CPD within the RRI cohort accounted for 71.7% of patients in the CPD cohort). There were 39.6%, 43.4%, and 30.8% of RRI, pneumonia, and ECRI patients, respectively, who were immunocompromised (including patients with organ transplant and hematologic malignancy). Other comorbidities consisted of diabetes mellitus (uncomplicated and end organ damage) (25.8%, 21.9%, and 31.9%), heart disease (25.5%, 28.0%, and 20.9%), and cystic fibrosis (18.5%, 8.2%, and 39.6%) in RRI, pneumonia, and ECRI patients, respectively.

Overall, 68.3%, 64.0%, 61.5%, and 64.8% of CPD, RRI, pneumonia, and ECRI patients, respectively, received antibacterials or fungal therapy in the 30 days before the Index date. More specifically, these included fungal therapy (25.0%, 26.2%, 25.8%, and 25.3%), carbapenem (26.7%, 29.8%, 30.2%, and 26.4%), Gram positive antimicrobials (23.3%, 26.9%, 26.9%, and 20.9%), fluroquinolone (20.6%, 20.0%, 18.7%, and 22.0%), and piperacillin/tazobactam (20.0%, 23.6%, 27.5%, and 14.3%) in CPD, RRI, pneumonia, and ECRI patients, respectively.

3.2. Therapy characteristics

The mean (SD) duration of C/T treatment was 14.2 (10.0) days (median: 13.0 days) in CPD patients, 12.9 (7.8) days (median: 12.0 days) in RRI patients, 12.8 (8.3) days (median: 11.0 days) in pneumonia patients, and 13.6 (5.9) days (median: 14.0 days) in ECRI patients (Table 3). C/T was given as empiric therapy in 26.7%, 29.5%,

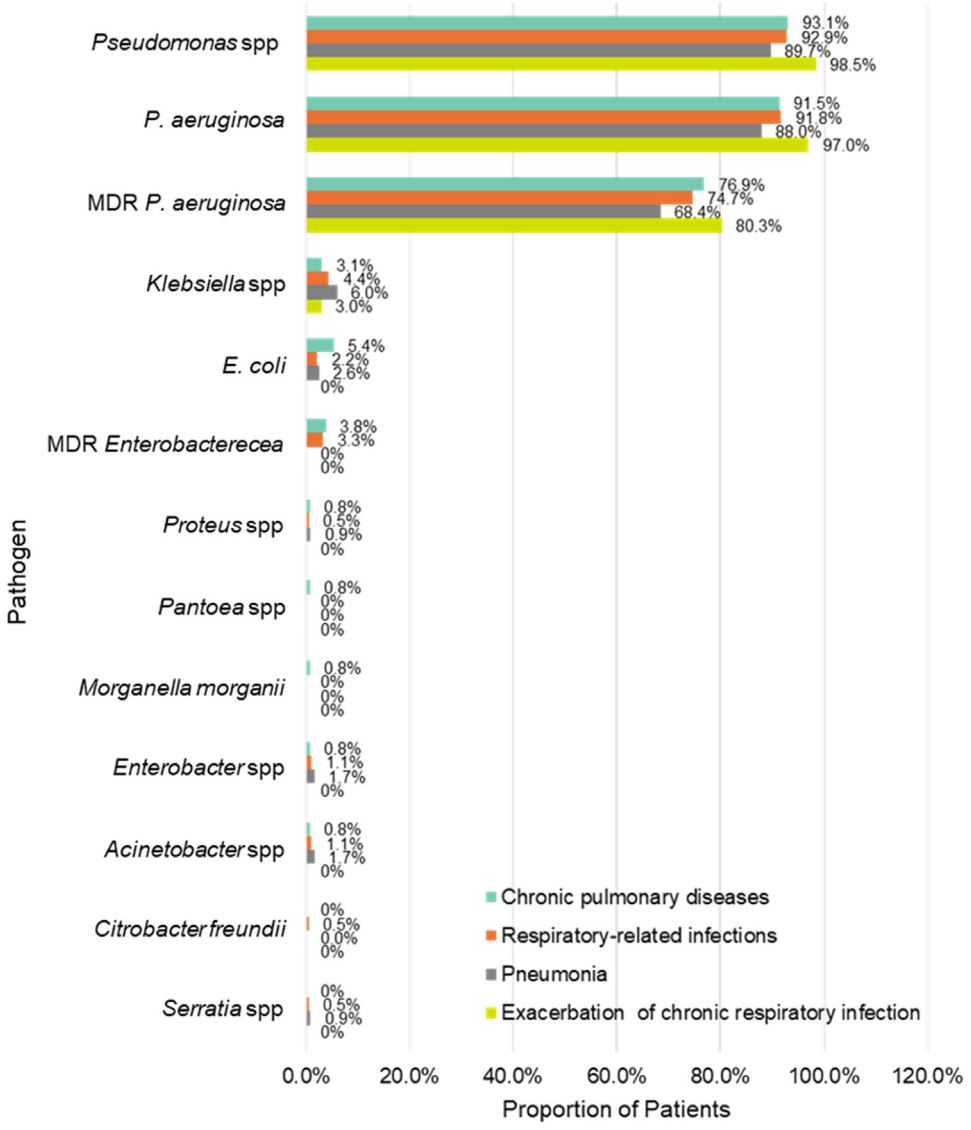

Fig. 2. Pathogens. A positive culture for more than one organism may apply to one patient. Fig. 2 shows pathogens identified for which CPD (*green*), RRI (*orange*), pneumonia (*grey*), and ECRI (*yellow*) patients received C/T. The proportion of patients (%) is graphed for each pathogen with the horizontal bars.
Abbreviations: spp, species; *P. aeruginosa, Pseudomonas aeruginosa*; MDR, multidrug resistant; *E. coli, Escherichia coli.*

31.9%, and 24.2% of CPD, RRI, pneumonia, and ECRI patients, respectively, and in 62.8%, 57.1%, 56.6%, and 61.5% as definitive therapy, respectively (among them, 58.4%, 50.0%, 49.3%, and 48.7% received early directed therapy and 41.6%, 50.0%, 50.7%, and 51.3% received late directed therapy in CPD, RRI, pneumonia, and ECRI patients, respectively). C/T was given as a first line therapy in 21.1%, 28.4%, 33.5%, and 17.6%, second line therapy in 27.8%, 24.4%, 23.6%, and 25.3%, third line therapy in 28.9%, 19.6%, 23.6%, and 25.3%, fourth line therapy in 9.4%, 11.6%, 12.1%, and 9.9%, fifth line therapy in 6.1%, 8.0%, 6.0%, and 11.0%, and sixth line therapy or more in 6.7%, 8.0%, 6.6%, and 12.1% CPD, RRI, pneumonia, and ECRI patients, respectively.

The most frequent indications and conditions for which patients received C/T (Fig. 1) included ECRI (41.1%, 33.1%, 7.1%, and 100%), pneumonia (33.9%, 66.2%, 100%, and 14.3%), and sepsis (18.3%, 16.0%, 20.9%, and 11.0%) in CPD, RRI, pneumonia, and ECRI patients, respectively.

The most frequent pathogens in which patients received C/T included *Pseudomonas* species (93.1%, 92.9%, 89.7%, and 98.5%) followed by *P. aeruginosa* (91.5%, 91.8%, 88.0%, and 97.0%) and *Klebsiella* species (3.1%, 4.4%, 6.0%, and 3.0%) in CPD, RRI, pneumonia, and ECRI patients, respectively (Fig. 2). Furthermore, MDR *P. aeruginosa* was identified in 76.9%, 74.7%, 68.4%, and 80.3% CPD, RRI, pneumonia, and ECRI patients, respectively.

3.3. Clinical outcomes

The 30-day all-cause readmission rate was 10.0%, 9.8%, 6.6%, and 15.4% and the 30-day infection-related readmission rate was 5.6%, 4.4%, 2.2%, and 7.7% in CPD, RRI, pneumonia, and ECRI patients, respectively (Table 4). ICU admission during the Index hospitalisation occurred in 45.0%, 56.0%, 67.0%, and 31.9% of CPD, RRI, pneumonia, and ECRI patients, respectively. There were 11.7%, 17.1%, 20.9%, and 12.1% of CPD, RRI, pneumonia, and ECRI patients, respectively, that had microbiological eradication. The all-cause in-hospital mortality was 18.3%, 24.7%, 32.4%, and 6.6% in CPD, RRI, pneumonia, and ECRI patients, respectively. Clinical success was achieved in 69.4%, 66.2%, 59.9%, 79.1% of CPD, RRI, pneumonia, and ECRI patients, respectively. The majority (58.4%, 59.9%, 51.4%, and 77.8% CPD, RRI, pneumonia, and ECRI patients, respectively) did not require further inpatient antibiotic treatment within 28 days of stopping C/T.

Table 4
Clinical outcomes.

Characteristics	Chronic pulmonary disease, $N = 180$	Respiratory-related infections		
		Respiratory-related infections total $N = 275$	Pneumonia $N = 182$	Exacerbation of chronic respiratory infection $N = 91$
Index infection considered as a clinical success by the investigator, n (%)				
Yes	125 (69.4%)	182 (66.2%)	109 (59.9%)	72 (79.1%)
95% CI	(62.2%, 76.1%)	(60.3%, 71.8%)	(52.4%, 67.1%)	(69.3%, 86.9%)
No	40 (22.2%)	67 (24.4%)	54 (29.7%)	11 (12.1%)
95% CI	(16.4%, 29.0%)	(19.4%, 29.9%)	(23.1%, 36.9%)	(6.2%, 20.6%)
Unknown	15 (8.3%)	26 (9.5%)	19 (10.4%)	8 (8.8%)
95% CI	(4.7%, 13.4%)	(6.3%, 13.5%)	(6.4%, 15.8%)	(3.9%, 16.6%)
If yes, the clinical success was assessed based on:				
No additional Gram-negative antibacterial therapy required for a minimum of 48H targeted to Index infection after a minimum of 48H of C/T, not including discharge antibiotics or de-escalation	98 (78.4%)	129 (70.9%)	73 (67.0%)	61 (84.7%)
No death attributed to Gram-negative infection	86 (68.8%)	121 (66.5%)	64 (58.7%)	59 (81.9%)
No further inpatient antibiotic treatment for exacerbation of respiratory infection ≤28 days of stopping C/T	73 (58.4%)	109 (59.9%)	56 (51.4%)	56 (77.8%)
Resolution of exacerbation of chronic respiratory infection	64 (51.2%)	85 (46.7%)	30 (27.5%)	59 (81.9%)
Discharge from hospital, ICU, or step-down unit signifying clinical stability	103 (82.4%)	139 (76.4%)	73 (67.0%)	68 (94.4%)
No need for re-operation for source control	18 (14.4%)	33 (18.1%)	24 (22.0%)	9 (12.5%)
Documented microbiological eradication as assessed by investigator	21 (16.8%)	47 (25.8%)	38 (34.9%)	11 (15.3%)
Admission in ICU during the Index hospitalisation, n (%)				
Yes	81 (45.0%)	154 (56.0%)	122 (67.0%)	29 (31.9%)
No	99 (55.0%)	121 (44.0%)	60 (33.0%)	62 (68.1%)
All-cause in-hospital mortality, n (%)	33 (18.3%)	68 (24.7%)	59 (32.4%)	6 (6.6%)
95% CI	(13.0%, 24.8%)	(19.7%, 30.3%)	(25.7%, 39.7%)	(2.5%, 13.8%)
30-day all-causes readmission, n (%)				
Yes	18 (10.0%)	27 (9.8%)	12 (6.6%)	14 (15.4%)
No	98 (54.4%)	128 (46.5%)	73 (40.1%)	56 (61.5%)
Not applicable[1]	57 (31.7%)	110 (40.0%)	92 (50.5%)	16 (17.6%)
Unknown	7 (3.9%)	10 (3.6%)	5 (2.7%)	5 (5.5%)
30-day infection-related readmission, n (%)				
Yes	10 (5.6%)	12 (4.4%)	4 (2.2%)	7 (7.7%)
No	105 (58.3%)	141 (51.3%)	80 (44.0%)	61 (67.0%)
Not applicable[1]	57 (31.7%)	110 (40.0%)	92 (50.5%)	16 (17.6%)
Unknown	8 (4.4%)	12 (4.4%)	6 (3.3%)	7 (7.7%)
Microbiological eradication, n (%)				
No	144 (80.0%)	202 (73.5%)	125 (68.7%)	72 (79.1%)
Yes	21 (11.7%)	47 (17.1%)	38 (20.9%)	11 (12.1%)
Unknown	15 (8.3%)	26 (9.5%)	19 (10.4%)	8 (8.8%)

[1] Not applicable: Patient died during Index hospitalisation or was still hospitalised 30 days past ceftolozane/tazobactam treatment.A patient may be in more than one subgroup/column (columns not mutually exclusive).Abbreviations: n, frequency; %, percentage; CI, confidence interval; H, hour; ICU, intensive care unit.

4. Discussion

This SPECTRA subgroup analysis highlights the real-world application and effectiveness of C/T in patients with CPD and RRI (inclusive of pneumonia and ECRI). These data also included patients who received C/T for off-label indications. In this report, patients had complicated GN infections and serious illnesses. Comorbidities or medical history were abundant (100% of CPD patients, 84.4% of RRI patients, 78.0% of pneumonia patients, and 98.9% of ECRI patients). RRI in this SPECTRA study included pneumonia, ECRI and other respiratory infections. CPD was largely a condition that many (46.9%) patients treated with RRI were challenged with. Overall C/T clinical success (69.4%, 66.2%, 59.9%, and 79.1% of CPD, RRI, pneumonia, and ECRI patients, respectively) align with a previous cohort of nosocomial pneumonia patients treated with C/T in a Phase 3 comparator-controlled clinical trial, ASPECT-NP (54.4%) [8–10]. C/T clinical success in all patient groups was also similar to the overall SPECTRA study clinical success and previous real-world evidence studies that provide valuable insights into its use in broader patient populations [16–19]. The clinical success for patients with ECRI was particularly noteworthy as patients with ECRI are frequently colonised with multidrug-resistant *P. aeruginosa* that presents a complicated challenge for antibiotic therapy [20]. This correlated to an incidence of 80.3% MDR *P. aeruginosa* in this SPECTRA ECRI cohort. Real-world usage data such as these can help inform subgroup evidence-based guidance for new agents. National guidance on the appropriate use of new agents and/or new indications would aid in optimal and appropriate use.

Varying pathogens were identified as the Index infection. These included predominantly *P. aeruginosa* (91.5%, 91.8%, 88.0%, and 97.0% in CPD, RRI, pneumonia, and ECRI patients, respectively), consistent with the overall SPECTRA results and previous studies including a systematic literature review where *P. aeruginosa* was also present in the majority of patients treated with C/T and underscores the importance of C/T in treating infections caused by this challenging pathogen [15,21–23]. This was consistent with another previous study, which showed that *P. aeruginosa* was susceptible to C/T in over 92% of cases [24].

Patients treated with C/T received previous treatment(s) within 30 days prior to the Index date. The majority, 68.3%, 64.0%, 61.5%, and 64.8% of CPD, RRI, pneumonia, and ECRI patients, respectively, received previous antibacterials and/or fungal therapy. This was also consistent with the overall SPECTRA result [17]. Antibiotics used to treat severe bacterial infections (e.g., carbapenems), were used in the 30 days prior to the Index date for C/T in 26.7%, 29.8%, 30.2%, and 26.4% of CPD, RRI, pneumonia, and ECRI patients, respectively.

4.1. Limitations

In this SPECTRA subgroup analysis for patients with CPD and RRI, the study's retrospective design and reliance on existing med-

ical records may have introduced biases and limited causality. An effort was made to obtain accurate and complete medical records to limit those biases. Moreover, the study focused on hospitalised patients from selected countries, which may affect the generalisability of results. There may have been Investigator selection bias since this study used a sponsor-provided list, and some Investigators did not respond. However, enrolment of all eligible patients treated within the study period helped to avoid patient selection bias. Among the data, there was missing microbiological data (50 [27.8%)] CPD, 93 [33.8%) RRI, 65 [35.7%] pneumonia, and 25 [27.5%] ECRI patients, respectively) that may have affected some conclusions. There was also potential for loss to follow-up that may have occurred if events after the patient Index hospitalisation occurred at another facility. This study was analysed descriptively to avoid inaccurate reporting and conclusions of results. Future CPD and RRI studies are needed to further analyse outcomes associated with C/T use in patients with drug-resistant GN pathogens.

4.2. Conclusions

In conclusion, this subgroup analysis underscores the critical role of real-world evidence in informing clinical practice, particularly in the context of antibiotic prescribing for CPD and RRI. The compelling data on the effectiveness and utilisation of C/T not only validate its application in managing multidrug-resistant pathogens but also highlight the urgent need for evidence-based guidelines that reflect actual clinical experiences. As the healthcare landscape continues to evolve amid rising antibiotic resistance, integrating real-world insights into clinical decision-making is imperative for optimising patient outcomes and steering the future of antimicrobial stewardship. The findings of this SPECTRA subgroup analysis serve as a clarion call for clinicians, policymakers, and researchers alike to prioritise real-world evidence in shaping effective treatment strategies and public health initiatives.

5. Transparency declarations

AHW, ENO, NS, and EY are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. LPK was an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, at the time of the study. MA is an employee of Merck Sharp & Dohme (UK) Limited, London, UK. SK received research support from Biotest, CytoSorbents, Daiichi Sankyo, Fresenius Medical Care. He also received lecture fees from ADVITOS, CSL Behring, Fresenius Medical Care, Gilead, MSD, Pfizer, Shionogi and Zoll. He received consultant fees from ADVITOS, AstraZeneca, Fresenius, Gilead, MSD and Pfizer.

Declaration of competing interests

None declared.

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