Real-world Use of Ceftolozane/tazobactam: a Systematic Literature Review

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Abstract

Background: Antibacterial-resistant gram-negative infections are a serious risk to global public health. Resistant Enterobacterales and *Pseudomonas aeruginosa* are highly prevalent, particularly in healthcare settings, and there are limited effective treatment options. Patients with infections caused by resistant pathogens have considerably worse outcomes, and significantly higher costs, relative to patients with susceptible infections. Ceftolozane/tazobactam (C/T) has established efficacy in clinical trials. This review aimed to collate data on C/T use in clinical practice.

Methods: This systematic literature review searched online biomedical databases for real-world studies of C/T for gram-negative infections. Relevant study, patient, and treatment characteristics, microbiology, and efficacy outcomes were captured.

Results: There were 83 studies comprising 3,701 patients were identified. The most common infections were respiratory infections (52.9% of reported infections), urinary tract infections (UTIs; 14.9%), and intra-abdominal infections (IAIs; 10.1%). Most patients included were seriously ill and had multiple comorbidities. The majority of patients had infections caused by *P. aeruginosa* (90.7%), of which 86.0% were antimicrobial-resistant. C/T was used as both a 1.5 g q8h and 3 g q8h dose, for a median duration of 7–56 days (varying between studies). Outcome rates were comparable between studies: clinical success rates ranged from 45.7–100.0%, with 27 studies (69%) reporting clinical success rates of >70%; microbiological success rates ranged from 31–100%, with 14 studies (74%) reporting microbiological success rates of >70%. Mortality rates ranged from 0–50%, with 31 studies (69%) reporting mortality rates of ≤20%. In comparative studies, C/T was as effective as aminoglycoside- or polymyxin-based regimens, and in some instances, significantly more effective.

Conclusions: The studies identified in this review demonstrate that C/T is effective in clinical practice, despite the diverse group of seriously ill patients, different levels of resistance of the pathogens treated, and varying dosing regimens used. Furthermore, comparative studies suggest that C/T offers a successful alternative to standard of care (SoC).

Background

Antibacterial resistance is a serious risk to global public health. The problem of resistance is especially acute for gram-negative pathogens. (1) Enterobacterales and *Pseudomonas aeruginosa* are the most prevalent gram-negative hospital-acquired infections (HAIs), collectively accounting for 30% of all HAIs in the United States (US). (2) Patients in intensive care units (ICUs) are particularly vulnerable to gram-negative infections and accounts for 70% of the HAIs acquired in ICUs. (2–4)

The burden of infections caused by these pathogens is intensified because of limited effective treatment options. Pathogen susceptibility to many of the available gram-negative antibacterial agents have diminished over time. (5) Patients with infections caused by resistant pathogens have considerably worse outcomes relative to their susceptible counterparts. (6, 7) In a US national database study, patients with multidrug-resistant (MDR) *P. aeruginosa* respiratory infections had higher mortality, an approximately 7-day longer length of stay (LOS), $20,000 excess costs, higher readmission rates, and >$10,000 excess net loss per case for the hospital relative to those with non–MDR *P. aeruginosa* infections. (7) Further, when the infection is caused by resistant pathogens, it increases the likelihood for receipt of initial inappropriate antibacterial therapy, which has been shown to diminish clinical outcomes and increase costs. (8, 9)

The challenge of resistance and deleterious impact on outcomes is further compounded by the serious drug-related toxicity associated with some of the current treatment options for resistant gram-negative pathogens. Aminoglycosides (e.g. gentamicin, tobramycin and amikacin) and polymyxins (e.g. colistin) are reported to cause nephrotoxicity and/or ototoxicity. (10, 11) Although these antibacterial agents tend to have higher susceptibility to many gram-negative pathogen, they come at a cost of toxicity.

Due to this imminent threat of drug-resistant Enterobacterales and *P. aeruginosa*, and the limited treatment options and toxic effects of some antibacterial agents, the World Health Organization (WHO) in 2017 designated both Enterobacterales and *P. aeruginosa* as the highest ‘critical’ priority in need of new therapies to counteract this crisis. (12)

Ceftolozane/tazobactam (C/T) is a β-lactam/β-lactamase inhibitor antibacterial agent, consisting of a fixed (2:1) combination of an antipseudomonal cephalosporin, ceftolozane, and the well-established β-lactamase inhibitor, tazobactam. (13) C/T is approved in the US and Europe for clinical use in adults with complicated urinary tract infections (cUTIs), including pyelonephritis, complicated intra-abdominal infections (cIAIs), and hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP). (13, 14) The approval of C/T was supported by three multinational, randomized, double-blind, active comparator-controlled trials: ASPECT-cUTI, ASPECT-cIAI and ASEPT-NP. (15–17) In the ASPECT trials, C/T demonstrated superiority over levofloxacin (ASPECT-cUTI), and noninferiority to meropenem (ASPECT-cIAI and -NP). (15–17) Since launch in 2014, real-world evidence (RWE) for the use of C/T in clinical practice has been
accumulating. The purpose of this systematic literature review (SLR) was to identify and collate published RWE to better understand the characteristics of patients treated with C/T and clinical outcomes.

**Methodology**

**4.1 Literature search**

A search of the literature for C/T RWE, published between 1st January 2009 and 3rd June 2020, was conducted in the following biomedical and economic databases via the OVID platform: Embase, MEDLINE, PsycInfo, Econlit, and EBM Reviews (ACP Journal Club, Cochrane Database of Systematic Reviews, Cochrane Methodology Register, Database of Abstracts of Reviews of Effects, Health Technology Assessment, NHS Economic Evaluation Database, Cochrane Clinical Answers). The search was conducted in January 2019 with a 10-year time horizon, then re-ran to capture literature published between January–November 2019, and November 2019–June 2020. The time horizon was chosen to minimize erroneous data identification given that C/T was approved for use in 2014 – using a longer horizon would capture any publications reporting on expanded access or compassionate use. The search was limited to English Language publications only.

Due to the heterogeneity of reporting of RWE, the search was designed to be broad to ensure relevant studies which may not be appropriately indexed were retrieved. Table 1 details the search strategy.

| #   | Search terms                                                                 |
|-----|-----------------------------------------------------------------------------|
| 1   | Ceftolozane/ OR Ceftolozane plus tazobactam/                               |
| 2   | ((Ceftolozane adj1 tazobactam) OR ZERBAXA OR MK-7625A).ti,ab.               |
| 3   | 1 OR 2                                                                      |
| 4   | (exp animals/ OR nonhuman/) NOT exp human/                                 |
| 5   | exp controlled clinical trial/                                             |
| 6   | 4 OR 5                                                                      |
| 7   | 3 NOT 6                                                                    |
|     | TOTAL (deduplicated and limits* applied)                                   |

*English and 2009–current.

A further search of internet-based sources relating to C/T RWE was also conducted (limited to English language only). This gray literature review involved searching conference proceedings of two conferences (European Congress of Clinical Microbiology and Infectious Diseases [ECCMID] and Infectious Disease Week [IDWeek]) — two of the largest infectious disease conferences in Europe and the US. Conference proceedings, when published as part of an abstract book, were also identified during the OVID search.

**4.2 Study selection**

All screening (by title and abstract, and by full-text) was performed by two reviewers and any uncertainties were resolved by a third reviewer. Predetermined inclusion and exclusion criteria were used to assess the eligibility of identified abstracts and full-texts for inclusion. PICOS eligibility criteria included observational and non-controlled studies reporting on the use of C/T to treat adult patients (≥ 18 years of age) with gram-negative infections in real-world clinical practice. Only studies in English were included. Studies were excluded if they did not meet the PICOS criteria, such as randomized controlled trials (RCTs) or other randomized or controlled experimental studies (Table S1; supplementary material).

**4.3 Data extraction and analysis**

Relevant study, patient, and treatment characteristics, microbiology, and efficacy outcomes were extracted into a data extraction form by one reviewer and checked by a senior reviewer. Efficacy outcomes included clinical cure (typically defined as the resolution of signs or symptoms
of infection following therapy and survival), microbiological cure (typically defined as large reduction or eradication in the number of pathogens following therapy), and mortality.

Results

5.1 SLR results

A total of 1,222 records were identified from the database searches, and 23 records were identified from the gray literature search. This resulted in 874 non-duplicate records that were subject to title and abstract screening. A total of 730 records were excluded according to the PICOS criteria and 144 were included for full-text review. Of these, 83 studies were determined to be eligible for data extraction and qualitative synthesis. The results of the SLR and study selection processes are presented in Fig. 1.

5.2 Study characteristics

Of the 83 studies included in the SLR, 61 were published as peer-reviewed publications,\(^{(18-78)}\) and 22 were conference proceedings (availability as abstracts or posters).\(^{(79-100)}\) Including studies that recruited patients from multiple countries, the most common study locations were the US \((N = 50),\(^{(21, 22, 24, 27-29, 33, 34, 39-41, 43-45, 50, 51, 54, 56, 57, 59, 61, 62, 68-71, 73-77, 79-85, 87-92, 94, 95, 97-100})\) Spain \((N = 15),\(^{(26, 28, 30-32, 35-37, 42, 47, 49, 58, 66, 79, 96})\) and Italy \((N = 13).\(^{(18, 20, 23, 25, 48, 52, 53, 55, 64, 67, 72, 79, 86})\) A variety of study designs were captured: 27 were non-comparative retrospective studies,\(^{(18, 19, 22, 24, 25, 28, 32, 33, 40, 41, 79, 81, 84-92, 94-99})\) 14 were case series,\(^{(20, 21, 29, 31, 34-39, 42, 43, 82, 100})\) five were comparative (including two cohort studies,\(^{(80, 83})\) and three case-control studies,\(^{(23, 26, 27})\) and one was a non-comparative prospective study.\(^{(30})\) There were thirty-six single-patient case reports identified.\(^{(44-78, 93})\) Case reports were included to capture uses of C/T in special clinical situations. Table S2 in the supplementary material summarizes the single-patient case reports identified by the SLR. There were 47 studies (24 multicenter) reporting on more than one patient, as summarized in Table 2.\(^{(18, 22, 23, 25, 27, 28, 33, 37, 38, 40, 79-81, 83-85, 87-91, 94, 97, 99})\)
| Citation, study design, location | N | Patient/infection description | Disease severity | C/T treatment | Outcome, % (n/N) |
|--------------------------------|---|-------------------------------|------------------|---------------|-----------------|
| **2020 studies**               |   |                               |                  |               |                 |
| **Peer-reviewed literature**   |   |                               |                  |               |                 |
| **Bassetti et al. 2020(18)**   | 153| ESBL-producing Enterobacterales infections, including NP (30.0%), cUTI (22.2%), and clAI (16.3%). | > ICU N = 74  
> CCI mean = 4.9 | > Dose C/T: 1.5 g q8h (75.0%; of which 6 patients received creatinine clearance adjusted dose) or 3 g q8h (24.8%) | 83.7 (128/153)  
9.8 (15/153) |
| Retrospective, multicenter, Italy |   |                               |                  |               |                 |
| **Bosaeed et al. 2020(19)**    | 19 | MDR PsA infections, including NP (32%), CLABSIs (21%), and ABSSSIs (16%), and clAI (16%). | > ICU N = 12 | > Dose C/T: 1.5 g q8h (42.1%) or 3 g q8h (10.5%) or creatinine clearance adjusted (47.4%) | 95 (18/19)  
74 (14/19)  
21 (4/19) |
| Retrospective, single center, Saudi Arabia |   |                               |                  |               |                 |
| **Buonomo et al. 2020(20)**    | 4  | PsA (50% MDR; 50% XDR) cSSTIs in patients with chronic kidney disease. | -                | > Dose C/T: creatinine clearance adjusted (100.0%) – 0.75 g q8h (75.0%), 0.375 g q8h (25%) | 100.0 (4/4)  
-  
0 |
| Retrospective, single center, case series, Italy |   |                               |                  |               |                 |
| **Jones et al. 2020(21)**      | 7  | PsA (57.1% non-MDR; 42.9% MDR) infections (one patient also had an *E. coli* infection), including pneumonia (42.9%), cUTI (28.6%), and bacteremia (14.3%). | -                | > Dose C/T: 4.5 g qd (CI; 85.7%), 9 g qd (CI; 14.3%) | 85.7 (6/7)  
100.0 (3/3)  
0\(^a\) |
| Retrospective, single center, case series, case series, US |   |                               |                  |               |                 |
| Citation, study design, location | N | Patient/infection description | Disease severity | C/T treatment | Outcome, % (n/N) |
|---------------------------------|---|--------------------------------|-----------------|--------------|-----------------|
| **Citation, study design, location** | **N** | **C/T** | **Patient/infection description** | **Disease severity** | **C/T treatment** | **Outcome, % (n/N)** |
| | | | | | | **Clinical** | **Micro.** | **Mortality** |
| **Jorgensen et al. 2020(22)** | 259 | Retrospective, multicenter, US | MDR gram-negative infections (91.1% PsA; 23.2% Enterobacteriales) including, RTIs (62.9%), SSTIs (10.8%), and UTIs (10.0%). Patients with MDR PsA infections (N = 226) were used as the primary analysis set. | > ICU N = 131 | > Dose C/T: 1.5 g q8h (36.3%) or 3 g q8h (63.7%), creatinine clearance adjusted (30.5%) | MDR PsA (N = 226) | - | MDR PsA (N = 226) |
| | | | | > IMC N = 23 | > Duration: med. (IQR): 10 (6–15) days | Clinical failure: 37.6 | (85/226) | - |
| | | | | > APACHE II med. = 21 | | | | | 17.3 |
| | | | | > CCI med. = 3 | | | | | (39/226) |
| | | | | > SOFA med. = 5 | | | | | |
| **Vena et al. 2020(23)** | 16 | Retrospective, multicenter, case-control, Italy | Drug-resistant PsA (62.5% MDR; 37.5% XDR) pneumonia and bacteremia | > ICU N = 2 | > Duration: mean (SD): 12.1 (5.8) days | 81.3 | - | 18.8 |
| | | | | | (13/16) | | | | (3/16) |
| **Conference proceedings** | | | | | | | | | |
| **Caffrey et al. 2020(80)** | 57 | Retrospective, multicenter, cohort, US | MDR PsA infections, including RTIs (36.8%), UTIs (22.8%), and SSTIs (17.5%) | > ICU N = 36 | > Duration med. (IQR): 12 (5–18) days | - | 31.0 | 17.5 |
| | | | | > APACHE II med. = 40 | | | | | (13/42) |
| | | | | > CCI med. = 4 | | | | | (10/57) |
| **Gudiol et al. 2020(79)** | 31 | Retrospective, multicenter, International | PsA (90.3% MDR; 41.9% XDR) bloodstream infections in neutropenic cancer patients. | > ICU N = 7 | > Empiric C/T: 25.8% | - | - | 16.1 |
| | | | | > IMC N = 31 | > Confirmed C/T: 96.8% | - | - | (5/31) |
| **2019 studies** | | | | | | | | | |
| **Peer-reviewed literature** | | | | | | | | | |
| **Bassetti et al. 2019(25)** | 101 | Retrospective, multicenter, Italy | PsA (70% drug resistant) infections, including NP (31.7%), ABSSSI (20.8%), and cUTI (13.9%). | > ICU N = 24 | > Dose C/T: 1.5 g q8h (69.3%) or 3 g q8h (30.7%) | 83.2 | - | 5.0 |
| | | | | > CCI mean = 4.4 | > Duration: med. (range): 14 (9–23) days | (84/101) | - | (5/101) |
| **Fernández-Cruz et al. 2019(26)** | 19 | Retrospective, single center, case-control, Spain | PsA (52.6% MDR; 47.4% XDR) infections, including pneumonia (26.3%), catheter-related BSI (21.1%), and primary BSI (21.1%) in patients with hematological malignancy. | > ICU N = 5 | > Empiric C/T: 15.8% | 89.5 | - | 5.3 |
| | | | | > IMC N = 19 | > Confirmed C/T: 84.2% | (17/19) | - | (1/19) |
| Citation, study design, location | N/C/T | Patient/infection description | Disease severity | C/T treatment | Outcome, % (n/N) |
|---------------------------------|-------|--------------------------------|------------------|--------------|-----------------|
|                                |       |                                |                  |              | Clinical | Micro. | Mortality |
| Gerlach et al. 2019(24)        | 18    | MDR PsA osteomyelitis          | ICU N = 11       | Dose C/T: 1.5 g q8h (27.7%) or 3 g q8h (55.6%), or creatinine clearance adjusted (16.7%) | 50.0 (9/18) | 75.0 | 22.2 (4/18) |
| Retrospective, single center US |       |                                | APACHE II med. = 13.5 | Empiric C/T: 0.0% |                  |       |           |
|                                |       |                                | CCI med. = 5.5    | Confirmed C/T: 100.0% |                  |       |           |
|                                |       |                                |                  | Duration: med. (range): 39 (3–98) days |                  |       |           |
| Pogue et al. 2019(27)          | 100   | MDR or XDR PsA infections, including NP (VABP [52.0%], HABP [12.0%]), cUTIs (16.0%), and wound (13.0%). | ICU N = 70       | Dose C/T: 3 g q8h (63%), 1.5 g q8h (38%) | 81.0 (81/100) |       | 20.0 (20/100) |
| Retrospective, multicenter, case-control US |       |                                | IMC N = 14     | Duration: med. (IQR): 9.5 (7–14) days |                  |       |           |
|                                |       |                                | CCI mean = 3    |                  |                  |       |           |
|                                |       |                                | SOFA = 8        |                  |                  |       |           |
| Rodriguez-Nunez et al. 2019(28) | 90    | Drug-resistant PsA RTIs (76.7% XDR; 23.3% MDR) | CCI med. = 5 | Dose C/T: standard (1.5 g q8h or creatinine clearance adjusted; 40%), high (3 g q8h or double creatinine clearance 60%). | 56.7 (51/90) |       | 27.8 (25/90) |
| Retrospective, multicenter, International |       |                                |                  | Duration: med. (IQR): 14 (10–16) days |                  |       |           |
|                                | 5     | MDR gram-negative (60% PsA; 40% A. baumannii) osteomyelitis |                  | Dose C/T: 1.5 g q8h (20%), 3 g q8h (80%) | 60.0 (3/5) |       | 20.0 (1/5) |
| Tan et al. 2019(29)            |       |                                |                  | Empiric C/T: 0% |                  |       |           |
| Retrospective, single center, case series US |       |                                |                  | Confirmed C/T: 100% |                  |       |           |
|                                |       |                                |                  | Duration mean: 37.8 days |                  |       |           |
| Conference proceedings         |       |                                |                  |                  |                  |       |           |
| Cabrera et al. 2019(85)        | 45    | Gram-negative (84.4% PsA; 71.1% MDR PsA) infections, including pneumonia (38%), UTI (20%), wound (9%), and bone (9%). | ICU N = 19 | Empiric C/T: 21.7% | 68.9 (31/45) |       | 0 |
| Retrospective, multicenter US   |       |                                | IMC N = 6       | Confirmed C/T: 78.3% |                  |       |           |
|                                |       |                                |                  | Duration med. (IQR): 8 (4–12) days |                  |       |           |
| Citation, study design, location | N  | C/T treatment | Outcome, % (n/N) |
|----------------------------------|----|---------------|------------------|
| **Patient/infection description** |    |               | Clinical | Micro. | Mortality |
| Hart et al. 2019(84) | 70 | > ICU N = 33  | 69 (48/70) | - | 19 (13/70) |
| Retrospective, multicenter | US | > IMC N = 70 | > Duration mean (SD): 13 (10.8) days | - | - |
| MDR PsA infections, including pneumonia (56%), wound (11%), IAI (10%) in immunocompromised patients. | | > APACHE II med. = 18 | > CCI med. = 5 | - | - |
| Mills et al. 2019(83) | 62 | > ICU N = 49 | 72.6 (45/62) | - | 29 (18/62) |
| Retrospective, multicenter cohort | US | > IMC N = 13 | > Duration mean: 16.1 days | - | - |
| Sheffl et al. 2019(82) | 4 | - | - | - | 0 (2/4) |
| Retrospective, case series | US | > Dose C/T med.: 6 g CI qd | > Duration range: 6–91 days | - | - |
| Trisler et al. 2019(81) | 35 | > Empiric C/T: 0.0% | 63.8 (37/58) | - | 27.6 (16/58) |
| Retrospective, multicenter | US | > Confirmed C/T: 100.0% | > Duration med. (IQR): CF = 18.5 (14–37.5) days, non-CF = 15.0 (10–25) days | - | - |
| **2018 studies** | | > Empiric C/T: 1.5 g q8h (46.6%), 3 g q8h (41.4%), 0.75 g q8h (12.1%) | Clinical failure: 54.3 (19/35) | - | - |
| **Citation, study design, location** | **Patient/infection description** | **Disease severity** | **C/T treatment** | **Outcome, % (n/N)** |
| **Peer-reviewed literature** | | | | |
| Diaz-Cañestro et al. 2018(30) | 58 | > ICU N = 16 | 63.8 (37/58) | - | 27.6 (16/58) |
| Prospective, single center | Spain | > IMC N = 7 | > Dose C/T: 1.5 g q8h (46.6%), 3 g q8h (41.4%), 0.75 g q8h (12.1%) | - | - |
| PsA (86.2% XDR) infections, including RTIs (60.3%), UTIs (17.2%), and IAI (6.9%). | | > CCI med. = 4 | > Empiric C/T: 1.7% | - | - |
| | | > SOFA med. = 3 | > Confirmed C/T: 91.4% | - | - |
| | | > Duration mean (SD): 11.4 (6.2) days | - | - | - |
| Citation, study design, location | N | Patient/infection description | Disease severity | C/T treatment | Outcome, % (n/N) |
|---------------------------------|---|--------------------------------|-----------------|---------------|-----------------|
| **Dietl et al. 2018(31)** | 7 | XDR PsA SSTIs (43%) and osteomyelitis (57%). | > CCI med. = 6 | > Dose C/T: 1.5 g q8h (43%), 0.75 g q8h (29%), 0.375 g q8h (29%) | 86 (6/7) 100 (4/4) |
| Retrospective, single center, case series | Spain | | | > Empiric C/T: 0% | |
|  | | | | > Confirmed C/T: 71% | |
|  | | | | > Duration med. (range): SSTI 13 (4–27)/ osteo. 48 (21–66) days | |
| **Escolà-Vergé et al. 2018(32)** | 38 | XDR PsA infections, including RTIs (36.8%), SSTIs (15.8%), and UTIs (15.8%). | > ICU N = 12 | > Dose C/T: 3 g q8h (60.5%), 1.5 g q8h (35.5%) | 68.4 (26/38) 31.6 (12/38) |
| Retrospective, single center | Spain | | > CCI med. = 3.5 | > Duration med. (range): 15.5 (3–62) days | |
| **Gallagher et al. 2018(33)** | 205 | MDR PsA infections, including 59% pneumonia, UTI (13.7%), and wound (12.7%). | > ICU N = 105 | > Dose C/T: 3 g q8h (47.3%), 1.5 g q8h (52.7%) | 73.7 (151/205) 70.7 (145/205) 19.0 (39/205) |
| Retrospective, multicenter | US | | > APACHE II med. = 19 | > Duration med. (IQR): 10 (7–14) days | |
| **Hakki et al. 2018(34)** | 6 | 7 episodes of MDR PsA infections, including bacteremia (42.9%), pneumonia (42.9%), and soft tissue (14.3%) in patients with hematological malignancy or hematopoietic stem cell transplant. | > IMC N = 6 | > Dose C/T: 3 g q8h (100%) | 71.4 (5/7)b |
| Retrospective, single center, case series | US | | | > Empiric C/T: 33.3% | |
|  | | | | > Confirmed C/T: 66.7% | |
|  | | | | > Duration med. (range): 29 (14–103) days | |
| **Xipell et al. 2018(35)** | 23 | 24 episodes of MDR PsA infections, including RTI (33.3%), UTI (29.2%), and SSTI (25.0%). | > ICU N = 4 | > Dose C/T: 3 g q8h or 1.25 g q8h or 0.75 g q8h (%=NR) | 88 (21/24) 75 (12/16) 22 (5/23) |
| Retrospective, single center, case series | Spain | | | > Empiric C/T: 13% | |
|  | | | | > Confirmed C/T: 87% | |
|  | | | | > Duration mean (SD): 14.3 (9.4) days | |

**Conference proceedings**
| Citation, study design, location | N | C/T | Patient/infection description | Disease severity | C/T treatment | Outcome, % (n/N) |
|----------------------------------|---|-----|-------------------------------|-----------------|--------------|-----------------|
| **Elabor et al. 2018(97)**       | 65|     | MDR PsA infections, including pneumonia, wound/bone/joint infections, UTIs, and IAIs (% NR) in immunocompromised patients. | > ICU N = 37 | > Dose C/T: 3 g q8h (35.4%), 1.5 g q8h (35.4%), < 1.5 g q8h (29.2%) | 78.4 (51/65) |
| **Giola et al. 2018(96)**        | 15|     | MDR PsA infections, including RTI (53%), IAI (27%), and wound (13%). | > ICU N = 8 | > Dose C/T: 1.5 g q8h (67%), < 1.5 g q8h (13%), 3 g q8h (20%) | 60 (9/15) |
| **Henry et al. 2018(95)**        | 29|     | 42 treatment courses for gram-negative infections (86% PsA; 7% *Klebsiella* spp.; 7% *E. coli*), including pneumonia (26%), IAIs (21%), and UTI (21%). | > ICU N = 15 | > Dose C/T: med. (range) = 1.5 g (0.15-3 g) q8h | 76 (32/42) |
| **Hirsch et al. 2018(94)**       | 35|     | Gram-negative infections (79% PsA: 60.7% MDR; 21.4% XDR), including RTIs (33%), BSIs (21%), and bone/joint infections (18%) | > ICU N = 26 | > Dose C/T: 3 g q8h (42.9%), 1.5 g q8h (31.4%), 0.75 g q8h (17.1%), 0.375 g q8h (2.9%), Other (5.7%) | 77.4 (24/31) |
| **Jayakumar et al. 2018(92)**    | 22|     | PsA (95%; 90% MDR) sepsis and/or bacteremia infections. | - | > Dose C/T: 3 g q8h (55%), Other (45%) | 77 (17/22) |
| Citation, study design, location | N | Patient/infection description | Disease severity | C/T treatment | Outcome, % (n/N) |
|--------------------------------|---|-------------------------------|-----------------|--------------|-----------------|
| **Jorgensen et al. 2018(90)**  | 116 | MDR PsA infections, including RTI (65%), UTI (10.3%), and SSTI (9.4%). |  > ICU N = 72  
> IMC N = 22  
> APACHE II med. = 21  
> CCI med. = 3.5 | - | 38.8 (45/116) |
| Retrospective, multicenter, US | | | | | |
| **Jorgensen et al. 2018(91)**  | 137 | MDR PsA infections |  > ICU N = 87  
> IMC N = 11 | - | -  
-  
17.2 (20/116) |
| Retrospective, multicenter, US | | | | | |
| **Pogue et al. 2018(89)**     | 113 | PsA cUTI (64%) and cIAI (36%). | -  
> Empiric C/T: 31%  
> Confirmed C/T: early definite 28% and late definite 41% | - | -  
12.4 (14/113) |
| Retrospective, multicenter, US | | | | | |
| **Puzniak et al. 2018(87)**   | 1,490 | Gram-negative infections (78% PsA [202/259 patients with microbiological results]). |  > ICU N = 824  
> CCI mean = 3 | - | -  
-  
9.1 (NR) |
| Retrospective, multicenter, US | | | | | |
| **Puzniak et al. 2018(88)**   | 199 | PsA infections, including RTIs (57%) and UTIs (17%). |  > ICU N = 107  
> CCI mean = 2.9 |  > Empiric C/T: 34%  
> Confirmed C/T: early direct 50% and late direct 16%  
> Duration med. (IQR): 8 (4–13) days | - | 14 (28/199) |
| Retrospective, multicenter, US | | | | | |
| **Tordato et al. 2018(86)**   | 11 | PsA infections (73% XDR), including RTIs (54%), BSIs (27%), and IAIs (18%). |  > ICU N = 6  
> IMC N = 3  
> CCI med. = 4 |  > Duration med. (range): 16 (6–27) days | 100.0 (11/11) | 36.4 (4/11) |
| Retrospective, single center, Italy | | | | | |

**2017 studies**

**Peer-reviewed literature**
| Citation, study design, location | N C/T | Patient/infection description | Disease severity | C/T treatment | Outcome, % (n/N) |
|----------------------------------|-------|------------------------------|-----------------|--------------|-----------------|
| Álvarez Lerma et al. 2017(36)    | 2     | PDR PsA ventilation-associated respiratory infections | > ICU N = 2     | > Dose C/T: 1.5 g q8h then 0.75 g q8h (50%), 0.75 g q8h (50%) | 100 (2/2) |
|                                 |       |                              | > APACHE II mean = 25.5 | > Empiric C/T: 0% | 100 (2/2) |
|                                 |       |                              | > Confirmed C/T: 100% | > Duration: mean = 15.5 days | 50 (1/2) |
| Castón et al. 2017(37)          | 12    | MDR PsA infections, including RTIs (50%) and IAIs (25.0%). 83% of patients had septic shock. | > IMC N = 4     | > Dose C/T: 1.5 g q8h (67%), 3 g q8h (33%) | 75.0 (9/12) |
|                                 |       |                              | > Empiric C/T: 0% | > Confirmed C/T: 100% | 63.6 (7/11) |
|                                 |       |                              | > Duration med. (range): 12 (9–18) days | > Duration med. (range): 15 (4–63) days | 25.0 (3/12) |
| Dinh et al. 2017(38)            | 15    | XDR PsA infections, including RTIs (46.7%), UTIs (20.0%), and IAIs (13.3%). | > ICU N = 8     | > Dose C/T: med. (range) = 6 g (3-7.5 g) | 67 (10/15) |
|                                 |       |                              | > IMC N = 10    | > Empiric C/T: 0% | 75 (6/8) |
|                                 |       |                              | > SOFA mean = 7.6 | > Confirmed C/T: 100% | 27 (4/15) |
|                                 |       |                              | > Duration med. (range): 15 (4–63) days | > Duration med. (range): 14 (3–52) days |       |
| Haidar et al. 2017(39)          | 21    | MDR PsA infections, including 86% RTIs, 5% cUTIs, 5% cIAIs, and 5% bacteremia. | > IMC N = 9     | > Dose C/T: 1.5 g q8h (48%), 0.75 g q8h (24%), 0.375 g q8h (5%), Other (23%) | 67 (10/15) |
|                                 |       |                              | > CCI med.=5    | Clinical failure: | 29 (6/21) |
|                                 |       |                              | > SOFA med.=6   | - | 10 (2/21) |
|                                 |       |                              | > Duration med. (range): 14 (3–52) days | > Duration med. (range): 16 (5–27) days |       |
| Munita et al. 2017(40)          | 35    | CR PsA infections, including pneumonia (51.0%) and secondary BSI (17.1%). | > CCI med.=4    | > Dose C/T: 3 g q8h (26%), 0.375–1.25 g q8h (%=NR) | 74 (26/35) |
|                                 |       |                              |                  | > Duration med. (range): 16 (5–27) days | 100 (25/25) |
|                                 |       |                              |                  |                  | 22.8 (8/35) |
| Citation                                           | N  | C/T  | Patient/infection description                                                                 | Disease severity | C/T treatment                                                                 | Outcome, % (n/N)       | 2016 studies                                                                 |
|----------------------------------------------------|----|------|-----------------------------------------------------------------------------------------------|------------------|--------------------------------------------------------------------------------|------------------------|------------------------------------------------------------------------------|
| Sacha et al. 2017(41)                              | 49 |      | 60 courses of therapy for gram-negative infections (86.7% PsA; 34.6% non-MDR; 40.4% MDR; 25.0% XDR), including NP (56.7%), IAI (18.3%), and bacteremia (6.7%) | 60               | > ICU N = 37<br> > IMC N = 25<br> > Dose C/T: 3 g q8h (1.7%), 1.5 g q8h (51.7%), 0.75 g q8h (26.7%), 0.375 g q8h (8.3%), 0.15 g q8h (11.7%)<br> > Empiric C/T: 36.7%<br> > Confirmed C/T: 63.3%<br> > Duration med.: 1–8 days | 64.1 (25/39) 38.5 (5/13) 16.7 (10/60) | - 100% mortality. |
| Xipell et al. 2017(42)                             | 3  |      | MDR or XDR PsA infections, including mediastinitis, liver abscess, and septic shock.         | 30               | > Dose C/T: 1.5 g q8h (100%)<br> > Empiric C/T: 0%<br> > Confirmed C/T: 100%<br> > Duration mean (range): 30.3 (21–42) days | 100 - 0               | - 100% mortality. |
| Conference proceedings                             |    |      |                                                                                              |                  |                                                                                 |                        |                                                                              |
| Leuthner et al. 2017(98)                           | 30 |      | Gram-negative infections (93% PsA; 3% E. coli; 3% P. stuartii), including RTIs (67%), cUTIs (27%), and BSIs (20%). | 30               | > ICU N = 8<br> > IMC N = 4<br> > Dose C/T: 3 g q8h (57%), Other (43%)<br> > Empiric C/T: 23%<br> > Confirmed C/T: 77%<br> > Duration med.: 10 days | 80 (24/30) 92 (11/12) 20 (6/30) | - 100% mortality. |
| Conference proceedings                             |    |      |                                                                                              |                  |                                                                                 |                        |                                                                              |
| Iovleva et al. 2016(100)                           | 2  |      | Imipenem-resistant PsA HCAP.                                                                 | 2                | > APACHE II mean = 13<br> > CCI mean = 2 | 100 (2/2) 100 (2/2) 0 (2/2) | - 100% mortality. |
| Nathan et al. 2016(99)                             | 28 |      | Gram-negative infections (68% resistant pathogens, including 36.4% MDR PsA and 15.2% ESBL-producing E. coli), including RTI (28.6%), cIAI (25%), and cUTI (25%). | 28               | > ICU N = 0<br> > Duration: med. = 12 days for RTI, 12 days for cIAI and 15 days for cUTI | 89 (24/27) - - | - 100% mortality. |
| 2015 studies                                       |    |      |                                                                                              |                  |                                                                                 |                        |                                                                              |
| Peer-reviewed literature                           |    |      |                                                                                              |                  |                                                                                 |                        |                                                                              |
### 5.3 Patient characteristics

Identified studies included a total 3,701 distinct patients treated with C/T. Excluding the single-patient case reports, the median number of patients included was 30 (range: 2(100)–1,490(87)). Patient populations were heterogeneous, with a number of different sources of infections and pathogens reported. There were 3,735 total infections. Of these, there were 1,807 infections where the source of infection was not reported (48.4%); excluding those publications, the most common source of infection(s) were pneumonia/respiratory tract infections (RTIs; 52.9% of reported infections), UTIs (14.9%), and IAIs (10.1%). There was also report of C/T use in SSTIs (7.1%), bone and joint infections (6.1%), and primary bacteremia (4.2%). Over time, the number of patients treated with C/T has grown, but the proportion of each infection type has remained relatively consistent (Fig. 2). The number of patients treated for RTIs was consistently high over the time period studied (Fig. 2) – 100.0% of identified patients treated with C/T in 2015, 35.3% in 2016, 65.5% in 2017, 44.9% in 2018, 62.9% in 2019, and 49.1% in 2020 had RTIs, and the number of patients treated with C/T for these infections has grown year-on-year.

The patient population included in these RWE publications were often classified as seriously ill with multiple comorbidities. In total, 1,751 patients (47.3% of 3,701 patients reported) were admitted to the ICU. The literature review recorded three commonly used measures of patient illness severity – Acute Physiology and Chronic Health Evaluation (APACHE) II, Sequential Organ Failure Assessment (SOFA), and Charlson Comorbidity (CC) index. APACHE and SOFA are systems for predicting ICU mortality. Nine publications, comprising 794 patients treated with C/T, reported APACHE scores ranging from 13–40, with larger studies (>50 patients) ranging from 18–40.(22, 24, 33, 36, 80, 84, 90, 97, 100) Six publications, comprising 472 patients treated with C/T, reported SOFA scores ranging from 3–8.(22, 26, 27, 30, 38, 39) The CC index quantifies the comorbidity burden of included patients by predicting the mortality of patients with multiple comorbidities. Twenty-one publications, comprising 2,930 patients, reported CC index scores ranging from 2–6.(18, 22, 24–28, 30–33, 39, 40, 80, 84, 86, 87, 90, 96, 97, 100) These measures show the high severity of illness of patients included in the RWE of C/T treatment.

Furthermore, this review identified 30 publications reporting a total of 364 immunocompromised patients.(22, 26, 27, 30, 34, 37–39, 41, 43, 48, 49, 51, 53, 59–61, 63, 68, 73, 79, 83–86, 90, 91, 96–98) Immunocompromised patients include those with a history of organ transplant, disease suppressing immunity (e.g. human immunodeficiency virus [HIV]/acquired immunodeficiency syndrome [AIDS], lymphoma,
leukemia), receipt of chemotherapy, or immunosuppressive treatment (e.g. corticosteroids). Of these studies, 5 reported only immunocompromised patients.\(^{26, 34, 43, 79, 84}\)

A total of 1,294 (35.0\%) patients did not have a causative pathogen specified (note that the majority of these came from a single publication (Puźniak \textit{et al.} 2018).\(^{87}\) For publications that reported a causative pathogen, the majority of patients (90.7\%; \(N = 2,184\)) had infections that were caused by \textit{P. aeruginosa}, of which 14.0\% were caused by non-drug resistant \textit{P aeruginosa}, or the level of resistance was not specified, 72.3\% by MDR \textit{P aeruginosa}, 13.4\% extensively-drug-resistant (XDR), and 0.2\% pan-drug-resistant (PDR). Note that the level of resistance specified (MDR/XDR/PDR) was recorded as described in the publication. Resistant infections comprised the majority of infections treated in studies published in the first three-year period captured (2015–2017) vs. the second three-year period (Fig. 3).

### 5.4 Treatment characteristics

C/T is indicated for use at two doses: either 1.5 g q8h (for cIAI and cUTI) or 3 g q8h (for patients with HABP/VABP). For patients with renal insufficiency, doses are reduced according to level of creatinine clearance. In studies that reported dosing information (\(N = 1,418\) patients), C/T was used as a 1.5 g q8h dose in 619 (43.7\%) patients, as a 3 g q8h dose in 621 (43.8\%) patients, and as a creatinine clearance adjusted dose in 178 (12.6\%) patients. Note, however, that reporting of dosing was inconsistent between studies and the specific dose by type of infection (i.e., 3 g q8h for respiratory) was not always delineated. Of studies that reported the timing of C/T treatment (\(N = 893\) patients), C/T was administered empirically (i.e. prior to susceptibility results) in 222 (24.9\%) patients and administered confirmed (i.e. following susceptibility results) in 671 (75.1\%). There was little year-on-year change in the proportion of patients treated empirically or confirmed, or treated with a 1.5 g q8h or 3 g q8h regimen – despite the approval of the 3 g q8h dose in 2019.

There was large variation in the duration of C/T therapy reported, often different to the label dose of 4–14 (cIAI), 7 (cUTI), or 8–14 (HABP/VABP) days. In all studies, the median duration of C/T therapy ranged from 7–56 days, irrespective of dose. Median duration in larger studies (> 50 patients) ranged from 8–16.1 days, consistent with the indicated duration.

### 5.5 Outcomes

#### 5.5.1 Overall outcomes

All 47 studies that included more than one patient reported clinical outcomes with C/T treatment: 39 reported clinical outcomes (\(18–21, 23–43, 81, 83–86, 90, 92, 94–100\)) 19 reported microbiological outcomes,\(^{19, 21, 24, 31–33, 35–38, 40, 41, 43, 80, 94, 96–98, 100}\) and 45 reported mortality rates. \(^{18–43, 79, 80, 82–92, 94–98, 100}\) Clinical success rates ranged from 45.7–100.0\%, with 27 studies (69\%) reporting clinical success rates of > 70\%. In larger studies (> 50 patients; 10 studies), clinical success rates ranged from 56.7–83.7\%. Microbiological success rates were similar, ranging from 31–100\%, with 14 studies (74\%) reporting microbiological success rates of > 70\%. In larger studies (> 50 patients; three studies), microbiological success rates ranged from 31–75.3\%. Mortality rates ranged from 0–50\%, with 31 studies (69\%) reporting mortality rates of ≤ 20\%. In larger studies (> 50 patients; 16 studies), mortality rates ranged from 5–29\%.

With each of these outcomes, note that definitions used, and assessments performed, were variable.

Outcomes were consistent in the 36 single-patient case reports – clinical cure was reported in 28 of 32 studies (87.5\%), microbiological cure in 18 of 23 studies (78.3\%), and mortality in 4 of 32 studies (11.4\%).

#### 5.5.2 Outcomes by treatment characteristics

Seven studies reported on the treatment characteristics that were risk factors for clinical outcomes.\(^{18, 25, 28, 30, 32, 33, 39}\) Patient cohort size ranged from 21–205, with a median of 90. Five studies included patients with \textit{P aeruginosa} infections,\(^{25, 28, 30, 32, 33, 39}\) one included patients with Enterobacteriales infections.\(^{18}\) There was a diverse range of infection types included.

Five studies found mixed evidence that a delay in receipt of C/T led to worse outcomes.\(^{18, 28, 30, 33, 39}\) Bassetti \textit{et al.} 2020 found that a significantly higher proportion of patients who achieved clinical success received empiric C/T and had a significantly shorter latency between infection onset and C/T administration (both \(p < 0.001\)).\(^{18}\) Similarly, Gallagher \textit{et al.} 2018 found that starting C/T less than four days after positive culture was associated with significantly higher clinical and microbiological cure rates, and that starting C/T more than four days after positive culture was associated with significantly higher mortality.\(^{33}\) In contrast, three studies found no association between initiating C/T within 48 hours of \textit{P aeruginosa} isolation, time to C/T, or type of treatment (empiric, semi-empiric, or confirmed) (all \(p > 0.05\)).\(^{28, 30, 39}\) These three studies were of smaller size (169 combined patients vs. 258 for the two previously mentioned studies), and, importantly, Rodriguez-Nunez \textit{et al.} included some patients that were also reported in Díaz-Cañestro \textit{et al.} 2018, effectively double-counting these patients and possibly giving them disproportionate influence over the conclusion drawn in this review.\(^{28, 30}\)

#### 5.5.3 Outcomes by PsA resistance subtype
Two studies were identified that conducted an analysis to understand whether *P. aeruginosa* resistance was a factor in clinical outcome.(28, 30) In univariate analysis, Rodriguez-Nunez et al. found that similar proportions of survivors and non-survivors had XDR PsA infections.(28) Whereas, Diaz-Cañestro et al. found that resistance profile (the proportion of patients with MDR vs. XDR infections) was significantly different between patients who were clinical successes or failures (Table 3). (30)

| Citation, study design, location | N C/T | Patient/infection description | Analysis | Variable | Proportion of patients with either outcome with variable | p-value |
|----------------------------------|-------|-------------------------------|----------|----------|---------------------------------------------------------|---------|
| **Rodriguez-Nunez et al. 2019(28)** | **90** | Drug-resistant PsA RTIs (76.7% XDR; 23.3% MDR). | Univariate regression | Survivors (N = 65) | Non-survivors (N = 25) | .308 |
| Retrospective, multicenter International | | | | | | |
| **Diaz-Cañestro et al. 2018(30)** | **58** | PsA (86.2% XDR; 10.3% MDR) infections, including RTIs (60.3%), UTIs (17.2%), and IAIIs (6.9%). | Univariate regression | Clinical cure (N = 35) | Clinical failure (N = 21) | .045 |
| Prospective, single center Spain | | | | | | |

C/T: Ceftolozane/tazobactam; IAI: Intra-abdominal infection; MDR: Multidrug-resistant; PsA: *Pseudomonas aeruginosa*; RTI: Respiratory tract infection; UTI: Urinary tract infection; XDR: Extensively-drug-resistant.

### 5.6. Comparative studies

Five studies were identified that compared C/T with other treatment regimens (Table 4): three included aminoglycoside/polymyxin-based regimens as comparator,(23, 27, 80) two either used standard of care (SoC).(26, 83) Each study included patients with *P. aeruginosa* infections, with four including patients with resistant *P. aeruginosa*. (23, 27, 80, 83)

In the three studies with aminoglycoside-/polymyxin-based comparators, all reported mortality rates,(23, 27, 80) two reported clinical cure rates,(23, 27) and one reported microbiological cure rate. (80) In Pogue et al., patients treated with C/T had significantly higher clinical cure rate (p = 0.002), but there was no difference in in-hospital mortality.(27) In response, Vena et al. conducted a similar case-control study, but balanced the proportion of patients with pneumonia in each arm, ensured patients received a sufficient polymyxin dosage, and ensured that all included patients had an infectious disease consultation.(23) Results were comparable with Pogue et al. – patients treated with C/T had a numerically higher clinical cure rate and lower mortality rate than patients treated with aminoglycoside/polymyxin regimen, though this did not reach statistical significance.(23) Caffrey et al. showed that patients treated with C/T were significantly less likely to die as inpatients than patients treated with aminoglycoside/polymyxin-based regimens, although there was no difference in 30-day mortality rates or microbiological cure rates, and clinical cure rates were not reported.(80)

In the two studies that compared patients treated with C/T with mixed SoC antibacterial agents, both reported clinical cure rates and mortality.(26, 83) Both studies found that patients treated with C/T had numerically higher clinical cure rates than patients treated with other antibacterial agents. Fernández-Cruz et al. additionally found that patients treated with C/T had significantly lower mortality rates (p < 0.05); (26) such a difference was not apparent in Mills et al. (83)
| Citation, study design, location | Study design | Patient/infection description | Treatment groups | Outcome description | Outcome, % (n/N) | p-value/aOR |
|-------------------------------|-------------|-------------------------------|------------------|-------------------|----------------|-------------|
| **Aminoglycoside/polymyxin comparator** | | | | | | |
| Caffrey et al. 2020(80) | Cohort | Patients had MDR PsA infections. | C/T (N = 57) vs. aminoglycoside/polymyxin-based (N = 155) | Clinical cure | - | - |
| | | | | Mortality, 30-day | 17.5 (10/57) | 18.1 (28/155) | aOR: 0.78 95% CI: 0.30–2.03 |
| | | | | Mortality, inpatient | 15.8 (9/57) | 27.7 (43/155) | aOR: 0.39 95% CI: 0.16–0.93 |
| | | | | Microbiological cure | 31.0 (13/42) | 30.6 (33/108) | aOR: 0.88 95% CI: 0.35–2.21 |
| Vena et al. 2020(23) | Case-control | Patients had pneumonia or bacteremia caused by MDR or XDR PsA. | C/T (N = 16) vs. aminoglycoside/polymyxin-based (N = 32) | Clinical cure | 81.3 (13/16) | 56.3 (18/32) | 0.11 |
| | | | | Mortality, 30-day | 18.8 (3/16) | 28.1 (9/32) | 0.72 |
| | | | | Microbiological cure | - | - | - |
| Pogue et al. 2019(27) | Case-control | Patients had an MDR or XDR PsA infection. | C/T (N = 100) vs. aminoglycoside/polymyxin-based (N = 100) | Clinical cure | 81.0 (81/100) | 61.0 (61/100) | 0.002 |
| | | | | Mortality, in hospital | 20.0 (20/100) | 25.0 (25/100) | 0.400 |
| | | | | Microbiological cure | - | - | - |
| **Other comparator** | | | | | | |
| Fernández-Cruz et al. 2019(26) | Case-control | Patients had hematological malignancies and PsA infection. | C/T (N = 19) vs. mixed SoC antibacterial agents (N = 38) | Clinical cure, 14-day | 89.5 (17/19) | 71.1 (27/38) | 0.183 |
| | | | | Mortality, 30-day | 5.3 (1/19) | 28.9 (11/38) | 0.045 |
| | | | | Microbiological cure | - | - | - |
| Mills et al. 2019(83) | Cohort | Patients had pneumonia with an MDR PsA culture. | C/T (N = 62) vs. mixed SoC antibacterial agents (N = 53) | Clinical cure, 14-day | 72.6 (45/62) | 67.9 (36/53) | 0.683 |
| | | | | Mortality | 29.0 (18/62) | 26.4 (14/53) | 0.840 |
| | | | | Microbiological cure | - | - | - |

aOR: Adjusted odds ratio; CI: Confidence interval; C/T: Ceftolozane/tazobactam; IV: Intravenous; MDR: Multidrug-resistant; PsA: *Pseudomonas aeruginosa*; SoC: Standard of care; US: United States; XDR: Extensively-drug-resistant.

**Discussion**

The principal finding of this SLR was that there is a body of RWE that establishes the effectiveness of C/T in real-world clinical practice, including patients described as severely ill patients and/or with resistant infections. Considering the patient disease severity measures, publications reported APACHE scores ranging from 13–40, with larger studies (> 50 patients) ranging from 18–40. This is higher than the APACHE score reported in ASPECT-NP (median 17),(15) and significantly higher than reported in ASPECT-IAI.
(mean 6.2). Furthermore, inclusion of immunocompromised patients, typically excluded by clinical trials, offers valuable insights into C/T effectiveness in this underrepresented population. A key limitation of many clinical trials is the exclusion of these seriously ill patients, and the restriction of recruitment to only patients with a narrow range of infections. By filling this gap, the RWE therefore provides valuable data on the outcomes of these patients seen in clinical practice.

Despite the heterogeneity in the patient population, outcomes of treatment with C/T were consistent with those found in the ASPECT clinical trials. In larger RWE studies (> 50 patients), clinical cure rates ranged from 56.7–83.7%, microbiological cure rates ranged from 31–75.3%, and mortality rates ranged from 5–29%. By way of descriptive comparison, C/T outcomes in the ASPECT trials were: ASPECT-cUTI, clinical cure = 92.0%, microbiological eradication = 80.4%, and mortality = 0.2%;(17, 101) ASPECT-cIAI, clinical cure = 83.0%, microbiological cure = 85.3%, and mortality = 2.3%;(16, 102) and ASPECT-NP, clinical cure = 54.4%, microbiological eradication = 73.1%, and 28-day mortality = 24.0%.(15)

Treatment characteristics were broadly aligned with the approved use of C/T and both indicated doses of C/T were used approximately equally; however, it was unclear which dose was used for which indication and often the outcomes were not stratified by dose and indication. This result is concerning, since the indicated dose for pneumonia is based on optimized pharmacokinetic and pharmacodynamic properties. C/T was more commonly used as confirmed therapy than as an empiric therapy (75.1% vs. 24.9%). This is consistent with the principles of antimicrobial stewardship, whereby broader-spectrum antibacterial agents are reserved for special clinical situations when other treatments have failed. However, there were two studies that suggested patients who were treated earlier, either empirically, or sooner after infection onset, had better clinical outcomes.(18, 33) Although a similar association was not found in three other studies,(28, 30, 39) comparison of early vs. late use of C/T warrants further investigation. Late use of C/T may be indicative of initial inappropriate antibacterial therapy with other agents, which has been shown in the literature to have deleterious effects on outcomes.(8, 9)

Data from the comparative studies suggest that C/T is at least as effective as, and in several cases, significantly better than, aminoglycoside- or polymyxin-based regimens for serious, MDR infections.(23, 27, 80) Outside the scope of this review, though pertinent to clinicians, is the lower risk of nephrotoxicity with C/T compared to aminoglycosides or polymyxins. Both comparative studies that assessed safety found a significantly lower incidence of acute kidney injury with C/T than with aminoglycoside/polymyxin-based comparators.(23, 27) This combination of comparable effectiveness and lower risk of nephrotoxicity means that C/T can be an alternative to these therapies, particularly in patients with decreased renal function.

This SLR highlights the inconsistent reporting that is common within published RWE. Due to differences in study design, objectives, outcome assessment and definitions, there were often incomplete data for the variables of interest, as set out in this SLR. This variability in turn imposes challenges in attributing outcomes to the exposure studied. The inclusion of conference proceedings, which are not subject to the same rigorous peer-review, may have affected evidence included within this review, and thus the conclusions drawn. As mentioned in the results, some studies included data that were reported in part by other studies – this may be more widespread than thought as some large database studies collected patients across hundreds of hospitals, possibly capturing patients reported in other studies. As this is a qualitative review, this double counting was not adjusted for. However, given the consistency of outcomes between studies conducted in different locations, in different years, and by different authors, it is likely that the outcomes reported approximate the true treatment effect.

As was to be expected, many studies had small sample sizes and did not include comparison groups for statistical inference purposes. In the comparative cohort studies that did, C/T had comparable efficacy to standard of care, and was significantly better in several outcomes. Furthermore, identified risk factors may have been subject to a reporting bias: with some studies only reporting multivariate analysis, it was difficult to recognize which risk factors were non-significant, and therefore excluded, in univariate analysis. Many studies had industry authors and/or were sponsored by grants from industry which may lead to publication bias; however, the results were consistent regardless of authorship or sponsorship. The vast majority of publications were of a retrospective design. This may lead to selection bias, as both exposure and outcome of patients are already known. Finally, this review did not include a comprehensive search of all relevant microbiology conferences or search for studies that were not captured in biomedical databases. These are pragmatic limitations associated with all literature reviews and are not expected to influence the findings of this review.

In conclusion, this SLR identified and summarized the published RWE on the use of C/T in clinical practice. These studies demonstrate the clinical effectiveness of C/T, despite the diverse group of seriously ill patients and level of resistance of the pathogens treated. The RWE body of literature provides additional insights into patient types that are commonly encountered in everyday practice and may have been excluded from the registration trials. Further studies are needed that evaluate homogenous patient sub-types and that account for other treatments that were received prior to C/T to properly attribute outcomes to the effectiveness of C/T.

List Of Abbreviations
| Abbreviation | Full Form |
|--------------|-----------|
| ABSSSI       | Acute bacterial skin and skin structure infection |
| AIDS         | Acquired immunodeficiency syndrome |
| aOR          | Adjusted odds ratio |
| BSI          | Bloodstream infection |
| CC(I)        | Charlson comorbidity (index) |
| CF           | Cystic Fibrosis |
| CI           | Confidence interval |
| cIAI         | Complicated intra-abdominal infection |
| CLABSI       | Central-line-associated bloodstream infection |
| CNS          | Central nervous system |
| CR           | Carbapenem-resistant |
| cSSTI        | Complicated skin and soft tissue infection |
| C/T          | Ceftolozane/tazobactam |
| cUTI         | Complicated urinary tract infection |
| ECCMID       | European Congress of Clinical Microbiology and Infectious Diseases |
| ESBL         | Extended-spectrum β-lactamase |
| HABP         | Hospital-acquired bacterial pneumonia |
| HAI          | Hospital-acquired infection |
| HCAP         | Healthcare-associated pneumonia |
| HIV          | Human immunodeficiency syndrome |
| IAI          | Intra-abdominal infection |
| ICU          | Intensive care unit |
| IDWeek       | Infectious Disease Week |
| IMC          | Immunocompromised |
| IQR          | Interquartile range |
| LOS          | Length of stay |
| LVAD         | Left-ventricular assist device |
| MDR          | Multidrug-resistant |
| NP           | Nosocomial pneumonia |
| NR           | Not reported |
| OR           | Odds ratio |
| PDR          | Pandrug-resistant |
| PK/PD        | Pharmacokinetics/pharmacodynamics |
| PsA          | Pseudomonas aeruginosa |
| RCT          | Randomized controlled trial |
| RTI          | Respiratory tract infection |
| RWE          | Real-world evidence |
| SD           | Standard deviation |
| SLR          | Systematic literature review |
Declarations

10.1 Ethics approval and consent to participate
Not applicable.

10.2 Consent for publication
Not applicable.

10.3 Availability of data and materials
All data analyzed during this study are included in this published article (and its supplementary information).

10.4 Competing interests
LP and RD are employees of Merck & Co., Inc., who may own stock and/or hold stock options in the Company. TP, HC, and AE are employees of Adelphi Values PROVE, which received funding for this research.

10.5 Funding
Funding for this research was provided by Merck & Co., Inc., Kenilworth, NJ, USA. Employees of the study sponsor were involved in the study design, as well as collection, analysis, and interpretation of the data, and in critically revising the manuscript for important intellectual content.

10.6 Authors' contributions
LP and RD conceived and designed the research, contributed to the interpretation of results, and critically revised the manuscript for important intellectual content. TP, HC, and AE conducted the literature review, analyzed the data, interpreted the results, and drafted the manuscript. All authors have approved the manuscript to be submitted for publication.

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Figures

A. *P. aeruginosa* resistance profile, 2015–2017 studies (N=27 studies; n=195 patients)  

B. *P. aeruginosa* resistance profile, 2018–2020 studies (N=56 studies; n=1,989 patients)

![Figure 3](image)

P. aeruginosa resistance profile in studies identified in 2015–2017 and 2018–2020 MDR: Multidrug-resistant; PDR: Pandrug-resistant; XDR: Extensively-drug-resistant.