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New Perspectives on Antimicrobial Agents: Ceftolozane-Tazobactam

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ABSTRACT Ceftolozane-tazobactam (C/T) is a new fifth-generation cephalosporin/beta-lactamase inhibitor combination approved by the Food and Drug Administration and the European Medicines Agency for treatment of complicated intraabdominal infections, complicated urinary tract infections, and hospital-acquired pneumonia in adult patients. This review will briefly describe the pharmacology of C/T and focus on the emerging clinical trial and real-world data supporting its current utilization. Additionally, our synthesis of these data over time has set our current usage of C/T at Barnes-Jewish Hospital (BJH). C/T is primarily employed as directed monotherapy at BJH when Pseudomonas aeruginosa isolates are identified with resistance to other beta-lactams. C/T can also be used empirically in specific clinical situations at BJH prior to microbiological detection of an antibiotic-resistant P. aeruginosa isolate. These situations include critically ill patients in the intensive care unit (ICU) setting, where there is a high likelihood of infection with multidrug-resistant (MDR) P. aeruginosa; patients failing therapy with a carbapenem; specific patient populations known to be at high risk for infection with MDR P. aeruginosa (e.g., lung transplant and cystic fibrosis patients); and patients known to have previous infection or colonization with MDR P. aeruginosa.

KEYWORDS antimicrobial resistance

Infections are common causes of morbidity and mortality. Emergence of resistance to newly discovered antibiotics has been a constant challenge from the discovery of penicillin in 1928 by Alexander Fleming to the present (https://www.cdc.gov/drugresistance/about.html). Ceftolozane-tazobactam (C/T) is a new fifth-generation cephalosporin/beta-lactamase inhibitor combination approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for treatment of complicated intraabdominal infections (cIAIs), complicated urinary tract infections (cUTIs), and hospital-acquired pneumonia (HAP) in adult patients. This review will describe the pharmacology of C/T and focus on the emerging clinical trial and real-world data supporting its current utilization.

SPECTRUM OF ACTIVITY AND SURVEILLANCE DATA

C/T exhibits some activity against Gram-positive organisms; broad coverage against Gram-negative organisms, including multidrug-resistant (MDR) and extensively drug-resistant (XDR) Pseudomonas aeruginosa and extended spectrum beta-lactamase (ESBL)-producing Enterobacterales’ and limited activity against anaerobes. The limited or lack of activity of C/T against staphylococci, enterococci, Acinetobacter spp., Clostridiodes difficile, and other resistant organisms (e.g., carbapenemase producers) is noteworthy. The activity of C/T compared to that of other selected antibiotics targeting Gram-negative bacteria is summarized in Table 1.
Prior and recent surveillance data suggest superior potency of C/T compared to other beta-lactams against isolates of *P. aeruginosa* across various geographic, laboratory, microbiologic, and clinical settings (1). The activity of C/T against nonresistant Enterobacterales has been similarly encouraging; however, it appears to be less than that of carbapenems. Furthermore, the activity of C/T against beta-lactamase-producing organisms has been variable and dependent on the specific organism and beta-lactamase. Shortridge et al. assessed a total of 18,960 organisms (15,223 Enterobacterales and 3,737 *P. aeruginosa*) consecutively collected from 32 U.S. medical centers from 2013 to 2016 (2). C/T (94% susceptible), amikacin (99% susceptible), and meropenem (98% susceptible) were the most active compounds tested against Enterobacterales. Among the Enterobacterales isolates tested, 2% (n = 286) were resistant to all agents tested. The table below shows the antimicrobial activity of C/T and comparator agents by region/country.

**TABLE 1** Antimicrobial activity of ceftolozane-tazobactam and comparator agents by region/country

<table>
<thead>
<tr>
<th>Gram-negative bacteria</th>
<th>Antimicrobial agent</th>
<th>Ceftolozane-tazobactam</th>
<th>Piperacillin-tazobactam</th>
<th>Meropenem</th>
<th>Ceftazidime-avibactam</th>
<th>Cefepime</th>
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<td>85</td>
<td>71</td>
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</tbody>
</table>

*Beta-lactam resistant. Numeric values represent percent susceptibility.*

*Carbapenem nonsusceptible.*

*See reference 12.*

*See reference 10.*

*See reference 9.*

*MDR, multidrug resistant; XDR, extensively drug resistant.*

*Data derived from references 2 and 4–11.*
carbapenem-resistant *Enterobacterales* (CRE), and 10% \((n = 1,450)\) exhibited an ESBL-producing non-CRE phenotype. Although C/T showed good activity against ESBL-producing non-CRE phenotype strains of *Enterobacterales* (88% susceptible), it lacked useful activity against CRE.

Walkty et al. studied 3,229 *P. aeruginosa* isolates obtained as part of the CANWARD surveillance program (3). C/T was the most active antimicrobial evaluated, with 98% of isolates testing susceptible. The percentage of antimicrobial-nonsusceptible isolates that remained susceptible to C/T ranged from 85% (amikacin-nonsusceptible subset) to 95% (ciprofloxacin-nonsusceptible subset). A total of 462 *P. aeruginosa* isolates were MDR (14% of all isolates tested), and 84 were XDR (3% of all isolates tested). C/T demonstrated excellent *in vitro* activity versus the MDR and XDR isolates, with 90% and 79% remaining susceptible, respectively. An examination of the 89 *P. aeruginosa* isolates from the ASPECT-NP trial demonstrated 66% susceptibility to C/T, while susceptibility to piperacillin-tazobactam was only 45% (4). However, for the 262 *Enterobacterales* isolates in the ASPECT-NP trial, susceptibility to C/T was 43% (highest for ESBL-producing *Escherichia coli* [90%] and lowest for ESBL-producing *Klebsiella pneumoniae* [36%] and carbapenemase-producing *Enterobacterales* [0%] isolates). Similar patterns were seen for respiratory Gram-negative bacteria in the SMART Asia-Pacific surveillance program, where 93% of ESBL-producing *E. coli* and 66% of ESBL-producing *K. pneumoniae* isolates were susceptible to C/T, while *P. aeruginosa* susceptibility to C/T was 92% for all strains and 73% for carbapenem-nonsusceptible strains (5). Similar findings were recently described from the CHINET surveillance program in China and the SUPERIOR study from Spain (6, 7).

Susceptibility patterns to C/T will differ by region, making local antibiogram data critical for clinical decision making. A European surveillance study found C/T to be the most active compound (after colistin) tested against *P. aeruginosa* isolates, with overall susceptibility rates of 94% in Western Europe and 81% in Eastern Europe (8). C/T was active against 95% of all *Enterobacterales* isolates from Western Europe and 79% of those from Eastern Europe. Similar findings were demonstrated from a U.S. surveillance study of 1,209 *P. aeruginosa* isolates that demonstrated 95% susceptibility to C/T (9). However, C/T susceptibility to MDR and XDR isolates of *P. aeruginosa* is also important to assess. Hirsch et al. compared the activity of C/T to that of ceftazidime-avibactam (C/A) against 119 ESBL-producing *Enterobacterales* and 60 beta-lactam-resistant *P. aeruginosa* isolates from 3 U.S. hospitals (10). Susceptibility to C/T and C/A, respectively, was 98% and 100% for ESBL-producing *E. coli*, 77% and 100% for ESBL-producing *K. pneumoniae*, 89% and 91% for MDR *P. aeruginosa*, and 57% and 71% for XDR *P. aeruginosa* isolates. These findings differ from those of other studies (Table 1), including data from Grupper et al. who found the C/A and C/T inhibitory activities for carbapenem-resistant *P. aeruginosa* to be 81% and 91%, respectively (11). However, the activity of C/T against *Enterobacterales* is generally less than that of meropenem and ceftazidime-avibactam (6, 10, 12).

MIC breakpoints released by the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) differ for several organisms, including *P. aeruginosa* and *Enterobacterales* (13, 14). Current breakpoints for *P. aeruginosa* and *Enterobacterales* are \(\leq 4/4 \mu g/ml\) and \(\leq 2/4 \mu g/ml\), respectively, and are based on 1,000 mg to 500 mg dosing of C/T intravenously (i.v.) every 8 h. Compelling pharmacokinetic/pharmacodynamic (PK/PD) data discussed in more detail below, coupled with the above breakpoint information, may lead clinicians to consider higher-dose C/T, particularly in the setting of elevated MICs.

**RESISTANCE MECHANISMS**

Reports of C/T resistance followed its introduction and have led to investigations of underlying mechanisms. Common mechanisms of cross-resistance such as upregulation of efflux pumps and structure/functional changes of porin channels have not been shown to significantly impact the susceptibility profile of C/T against *P.
aeruginosa (15). In an analysis of Pseudomonas isolates from the BSAC Bacteraemia Surveillance program, 94 to 99.7% of isolates were susceptible to C/T, with resistance patterns consistent with raised efflux (16). In strains of Pseudomonas with AmpC hyperproduction, C/T was susceptible in 96.6% of isolates, reflecting the improved stability of ceftolozane against AmpC-producing strains. Resistance to imipenem, a surrogate for OprD deletion, was not associated with reduced susceptibility to C/T. Still, production and/or overexpression of other beta-lactamases (e.g., metallo-beta-lactamases, GES beta-lactamases, OXA beta-lactamases, and carbapenemases) not inhibited by tazobactam may result in hydrolysis of ceftolozane. In the same BSAC substudy, Pseudomonas isolates with MBL- and VEB-type beta-lactamases were nearly uniformly resistant to C/T, but isolates with GES-type beta-lactamases remained largely susceptible (84.2%). Whole-genome sequencing (WGS) analyses have been conducted in a number of cohorts to further elucidate mechanisms of acquired resistance to C/T. AmpC-AmpR region mutations have frequently been identified (17–22). This is of great significance, as the omega loop of AmpC is the substrate-binding site for ceftolozane. Other mechanisms of C/T resistance identified by WGS include mutations in penicillin binding protein 3 (PBP3) (17), the multidrug efflux transporter mexB (19), and the DNA polymerase subunits gamma and tau (17). Although mutations in the porin D precursor OprD were identified, these mutations did not independently confer resistance to C/T (17, 19). Acquisition of OXA-14 β-lactamase via horizontal transfer was also commonly identified among C/T-resistant isolates (18, 22).

Enterobacterales spp. demonstrate various degrees of susceptibility to C/T. Morganella spp. with AmpC hyperproduction are likely to remain susceptible due to the effectiveness of tazobactam against Morganella AmpC (16). In Klebsiella spp., where AmpC production is plasmid mediated, C/T is active in cases where plasmid-encoded bla_tha was present. Among clinical isolates of the Enterobacter cloacae complex (ECC), susceptibility to C/T is largely dependent on the beta-lactamase-producing profile exhibited. In an analysis by Robin et al., C/T demonstrated 100% susceptibility in wild-type strains; however, the susceptibility rate decreased in ECC strains that produced ESBL (67%), high levels of cephalosporinase (HL-CASE, 24%), or were ESBL and HL-CASE coproducers (11%) (23). The decreased rate of activity, particularly among strains producing HL-CASE, is likely reflective of the poor activity of tazobactam in AmpC-producing Enterobacter spp. In addition, 30% of the isolates tested demonstrated resistance to ertapenem. In ertapenem-resistant isolates, only 1 of the 28 isolates (4%) demonstrated susceptibility to C/T. This suggests that in clinical isolates of ECC demonstrating reduced susceptibility to carbapenems, C/T is less likely to be a viable treatment option.

PHARMACOKINETICS/PHARMACODYNAMICS: DOSING IMPLICATIONS

The PK/PD profile of ceftolozane is consistent with that of other cephalosporins. Ceftolozane exhibits dose-linear pharmacokinetics, a mean plasma half-life of 2 to 3 h, a volume of distribution at steady state of 12 to 18 liters, minimal metabolism and accumulation, protein binding of approximately 20%, and a renal excretion rate of over 90% ranging from 5 to 7 liters/h across a variety of doses (24). Results of preclinical and clinical studies have led to recommended dose adjustments of C/T for patients with varying degrees of renal function, including intermittent or continuous renal replacement therapy (25). Ceftolozane exhibits time-dependent bactericidal activity best predicted by the percentage of time the free drug concentration is above the MIC across a dosing interval (%fT>MIC) (24).

Animal models of ceftolozane revealed an approximately 30% to 40% fT>MIC is likely to achieve a 1- to 2-log killing with the approved 1.5 g every 8 h (q8h) intermittent infusion dosing (26, 27). Subsequent PK/PD studies have shown that this dosing scheme is able to achieve a high probability of target attainment (PTA) when considering a 30% to 60% fT>MIC against MICs of up to 8 to 16 mg/liter for Enterobacterales and/or P. aeruginosa (28–31). While intermittent infusions of C/T 1.5 g q8h are likely
adequate for susceptible infections, practitioners must evaluate the generalizability of these data to individual patients and consider described associations of increased MIC with risk of clinical failure and mortality (32, 33).

Recent data highlighted the potential benefit of targeting 100% ft>MIC, compared with other PK/PD targets, with improved clinical outcomes in critically ill patients who are known to exhibit altered PK (34). Sime et al. analyzed the impact of various C/T regimens on the PTA across various MICs in 12 critically ill patients (28). When considering a 100% ft>MIC, intermittent infusions of C/T 1.5 g q8h only achieved a ≥90% PTA for an MIC of ≤2 mg/liter. Similarly, this regimen only achieved optimal fractional target attainment (FTA) in patients with a creatinine clearance (CLCR) of ≤140 ml/min/1.73 m², hence calling into the question the appropriateness of this regimen in critically ill patients with augmented renal clearance (ARC). These results are concordant with those of Xiao et al., who observed a PTA of ≥90% in non-critically ill patients with normal or augmented renal clearance only when considering a 32.2% ft>MIC for an MIC of ≤4 mg/liter (29).

Given the above PK/PD considerations, practitioners may consider alternative dosing regimens as a means of optimizing the PK/PD profile of C/T. Sime et al. observed intermittent infusions of C/T 3.0 g q8h achieved a PTA of ≥90% when considering a 100% ft>MIC for an MIC of up to 8 mg/liter, while maintaining optimal PTA in patients with ARC for directed therapy (28). Use of a 1.5-g loading dose, followed by a continuos infusion of 4.5 g C/T achieved ≥90% PTA when considering a 100% ft>MIC for an MIC of up to 16 mg/liter, with improved FTA in patients with ARC compared to 3.0 g q8h intermittent infusions. Higher loading and continuous infusion doses of C/T were more effective in achieving ≥90% PTA when considering a 100% ft>MIC and a more aggressive 100% ft>4-5×MIC. Natesan et al. completed a Monte Carlo simulation to identify the C/T dosing schemes able to optimize the PTA against P. aeruginosa with an MIC of up to 32 mg/liter with a 40% ft>MIC PK/PD target (31). They observed that infusion times of 4 to 5 h were required to ensure ≥90% PTA with the C/T 1.5 g q8h dosing regimen for an MIC of ≤16 mg/liter and the 3 g q8h dosing regimen for an MIC of ≤32 mg/liter in patients with ARC. Similarly, a recent phase I study of critically ill adults with ARC suggested that a 3-g dose of C/T was generally well tolerated and was able to achieve PK/PD targets (35).

The generalizability of the above discussed plasma concentration-based studies to alternative sites of infection, such as the epithelial lining fluid (ELF) should also be considered. Pulmonary penetration of antibiotics may be a predictor of appropriate treatment (36). Data in healthy volunteers revealed a penetration ratio of approximately 0.50, suggestive of adequate penetration of C/T into the ELF (36, 37). However, Xiao et al. conducted Monte Carlo simulations in 25 healthy subjects and observed a PTA of 95.6% and 85% when considering a 40% ft>MIC up to an MIC of 8 mg/liter in ELF for the 3.0-g and 1.5-g doses, respectively. A similar trend was observed with a 50% ft>MIC (37). In a recent phase 1 trial of critically ill patients with pneumonia requiring mechanical ventilation, a 3.0-g dose of C/T via intermittent infusion q8h provided mean ELF concentrations of >4 mg/liter and 1 mg/liter for ceftolozane and tazobactam, respectively, for the entire dosing interval (38).

These data support the routine use of higher dose and/or continuous infusion C/T to optimize PTA. These regimens should be considered for empirical treatment, particularly in patients with critical illness, ARC, pneumonia, and/or a known history of MDR P. aeruginosa with elevated MIC.

**CLINICAL TRIALS LEADING TO REGULATORY APPROVAL**

C/T was approved by the FDA and EMA on the basis of a series of three international, multicenter, randomized, controlled clinical trials. The similarly structured ASPECT trials were phase III trials that were designed to test the noninferiority of C/T against active comparators in hospitalized patients older than 18 years of age. In the ASPECT-cUTI trial, patients with signs of pyelonephritis or complicated lower urinary
tract infection (cLUTI) were randomized in a 1:1 allocation to receive i.v. treatment consisting of C/T 1.5 g q8 h or levofloxacin 750 mg once daily for 7 days (39). In more than 1,000 patients, the most frequent pathogens included *E. coli* (629 patients, 78.6%) and other Gram-negative uropathogens, many of which were levofloxacin resistant (26.5%) or were ESBL-producing strains (14.8%). Exceeding the noninferiority margin, C/T demonstrated superior rates of composite cure in the microbiological modified intention-to-treat (mMITT) (76.9% versus 68.45%) and per-protocol populations (83.3% versus 75.4%). Several subgroup analyses demonstrated superiority of C/T over levofloxacin, including in patients greater than 65 years of age (70.0% versus 53.5%), those with cLUTI (67.1% versus 47.3%), and those infected with levofloxacin-resistant (60.0% versus 39.3%) or ESBL-producing strains (62.3% versus 35.1%). As with other cephalosporins that lack activity toward *Enterococcus* species, C/T demonstrated poor rates of eradication for patients with *Enterococcus faecalis* (31.3%) and *Enterococcus faecium* (50.0%) infections. Compared to the levofloxacin group, similar rates of headache, constipation, nausea, and diarrhea were observed in the treatment groups. Two serious cases of *C. difficile* infection (CDI) were noted in the C/T group.

In the ASPECT-cIAI trial, hospitalized patients with evidence of cIAI with planned or recently completed drainage of an infectious nidus were randomized in a 1:1 ratio to i.v. therapy with C/T 1.5 g q8h plus metronidazole 500 mg i.v. q8h or meropenem 1 g q8h plus matching placebo for 4 to 10 days (40). Up to 14 days of therapy was permitted if evidence of multiple abscesses, non-appendix-related diffused peritonitis, prior antimicrobial therapy, or hospital-acquired infection was present. Notable trial exclusions consisted of staged abdominal repair with open fascia or poor source control. In the primary outcome of clinical cure assessed 24 h following the last dose of study treatment, C/T plus metronidazole was deemed to be noninferior to meropenem in the microbiological intention-to-treat (ITT) population (83.0% versus 87.3%, respectively). Similar rates of treatment failure at the test-of-cure visit were observed in both treatment groups (8.2% versus 8.2%) owing to persistent infection requiring further intervention or additional antibiotics. C/T plus metronidazole demonstrated numerically higher rates of clinical cure in patients with ESBL-positive (95.8% versus 88.5%) and CTX-M-14/15 (100.0% versus 72.7%) infections, suggesting a potential role for C/T as an alternative antimicrobial for resistant *Enterobacterales* infections. CDI developed in 1 patient in each treatment group.

In the ASPECT-NP trial, mechanically ventilated patients with nosocomial bacterial pneumonia (NBP) were randomized to i.v. treatment with C/T 3 g q8h or meropenem 1 g q8h for 8 to 14 days (41). Permitted adjunctive empirical agents included linezolid (until absence of *Staphylococcus aureus* from lower respiratory tract specimens was confirmed) and amikacin for up to 72 h in centers where a high rate of carbapenem-resistant *P. aeruginosa* was present based on institution-specific antibiograms. In the primary endpoint of 28-day mortality, C/T demonstrated noninferiority to meropenem (24.0% versus 25.3%, respectively) in the intention-to-treat population. Clinical cure in the ITT population was similar to that for C/T compared to meropenem in the ventilator-associated pneumonia (55.9% versus 57.0%) and ventilated hospital-acquired pneumonia (50.5% versus 44.4%) subgroups. In patients that failed prior antimicrobial therapy, C/T demonstrated a 28-day mortality rate of 22.6% versus 45.0% in the meropenem group (percentage difference, 22.4%; 95% confidence interval [CI], 3.1 to 40.1%). For patients with infections caused by ESBL-producing *Enterobacterales*, 18 (21%) of 84 in the C/T group and 21 (29%) of 73 in the meropenem group died by 28 days (percentage difference, 8.0%; 95% CI, −28.7 to 13.9%). Adverse events were common in both treatment groups. The most frequently reported events included CDI (4 patients in the C/T group and 1 patient in the meropenem group), diarrhea, and abnormal liver function tests.

Limitations of these data include the omission of patients with impaired renal function (creatinine clearance [CLCr], <30 ml/min) from the ASPECT-cUTI and cIAI trials. While ASPECT-NP permitted inclusion of patients with a baseline CLCr of >15 ml/min, any use of renal replacement therapy was excluded. Clinicians looking for guidance in
dosing C/T in these scenarios may be forced to adopt nonstandard dosing strategies based on PK models from various dialytic modalities (42).

**USE OF C/T FOR DIFFICULT-TO-TREAT GRAM-NEGATIVE INFECTIONS IN CLINICAL PRACTICE**

Recent published IDSA guidance recommends C/T as a preferred antibiotic for difficult-to-treat *P. aeruginosa* as a cause of uncomplicated cystitis, cUTI, and infections outside the urinary tract, based on its high strain coverage and clinical trial data (43). To maximize the effectiveness of treatment, a novel C/T dosing modality of 3 g i.v. q8h, with each dose infused over 3 h, is recommended in the same guidance document for all infections other than cystitis (43). C/T infusion for at least 3 h has been shown to be associated with maximizing %fT>MIC likelihood for *P. aeruginosa* infections and reduced resistance development (17, 44). Use of these escalated C/T doses, especially when delivered as extended or continuous infusions, represents a novel approach to maximizing PD and clinical outcomes of *P. aeruginosa* infections and may also help facilitate outpatient parenteral antimicrobial therapy delivery when warranted. (32, 45, 46). Strong consideration should also be given to selecting C/T doses in critically ill patients upon their initial presentation based on what creatinine clearance (CLCR) is expected to be in 48 h, rather than on the first estimated CLCR (47). This suggestion is supported by higher rates of clinical failure in patients with MDR *P. aeruginosa* respiratory tract infections complicated by renal dysfunction (CLCR, <50 ml/min), potentially stemming from inappropriate renal-adjusted escalated doses of C/T (48).

Real-world experience suggests that C/T can be effective at both the 1.5-g and 3-g doses. Balandin et al. evaluated the use of C/T in critically ill patients with infections due to *P. aeruginosa* in Spanish intensive care units (ICUs) (49). They found that both the standard dose and the high dose were associated with similar outcomes. Moreover, the primary determinants of mortality in their study were severity of illness and comorbidities. This was similar to the results of another Spanish study focusing on lower respiratory tract infection due to *P. aeruginosa* that could not demonstrate superior outcomes with high-dose C/T (32). A recent Italian study described real-world experience with C/T in 122 consecutively treated patients with Gram-negative infections, primarily urinary tract and intraabdominal infections (50). *P. aeruginosa* was the most common isolate, and 30-day all-cause mortality was 20.5% for all infections. Microbiological cure was shown in 81% of the patients treated with C/T alone and in 78.3% of those treated with combination therapy. A recent U.S. real-world experience of C/T for MDR *P. aeruginosa* infections assessed 259 patients, with *P. aeruginosa* being isolated in 236 (91.1%) (48). The MDR and XDR phenotypes were detected in 95.8% and 37.7% of *P. aeruginosa* isolates, respectively, and the respiratory tract (62.9%) was the most common infection site. High-dose C/T was used in 71.2% of patients with a respiratory tract infection. In the primary efficacy population (n = 226), clinical failure and 30-day mortality occurred in 85 (37.6%) and 39 (17.3%) patients, respectively. Another multicenter study of 205 patients treated with C/T for MDR *P. aeruginosa* infections, 59% of which were pneumonia, reported clinical success in 151 (73.7%), microbiological cure in 145 (70.7%), and a 30-day mortality rate of 19% (39/205). In addition, initiation of C/T within 4 days of culture collection was statistically associated with clinical success, microbiological eradication, and survival (51). C/T was also found to be independently associated with clinical cure and was protective against acute kidney injury (AKI) in a multicenter study of drug-resistant *P. aeruginosa* infections, 52% of which were ventilator-associated pneumonias, versus polymyxin or aminoglycoside-based comparator therapy (52). These real-world experiences highlight the potential role for C/T in current medical practice to treat antibiotic-resistant *P. aeruginosa* infections.

The question of whether including C/T as a component of combination therapy is clinically superior to C/T monotherapy was recently examined. In a systematic review and meta-analysis that included 8 nonrandomized studies of C/T for treatment of
severe, predominantly *P. aeruginosa* infections in 432 patients, C/T as a component of combination therapy was associated with similar clinical improvement and microbiological eradication versus C/T monotherapy (odds ratio [OR], 0.97; 95% CI, 0.54 to 1.74; \( P = 0.954 \)). However, when the outcome of mortality at 30 days was assessed in a less robust 4-study subset of this analysis that included 186 patients, C/T as a component of combination therapy was associated with statistically lower mortality at 30 days than C/T monotherapy (OR, 0.31; 95% CI, 0.10 to 0.97; \( P = 0.045 \)). Thus, due to the aforementioned mixed results, it appears that the question of whether C/T is best deployed as a monotherapy or combination therapy for severe *Pseudomonas* infections remains unsettled and warrants further prospective study (53).

Our real-world use of C/T at Barnes-Jewish Hospital (BJH) is supported by our local antibiogram, which shows that 98% of all clinical *P. aeruginosa* isolates are susceptible to C/T and that 60% of multiple-beta-lactam resistant *P. aeruginosa* isolates (resistant to piperacillin-tazobactam, cefepime, imipenem, and meropenem) are susceptible to C/T (54). C/T is primarily employed as directed monotherapy at BJH when *P. aeruginosa* isolates are identified with resistance to other beta-lactams (Fig. 1). C/T can also be used empirically at BJH prior to microbiological detection of an antibiotic-resistant *P. aeruginosa* isolate in specific clinical situations (Fig. 1). These situations include critically ill patients in the ICU setting, where there is a high likelihood of infection with MDR *P. aeruginosa*; patients failing therapy with a carbapenem; specific patient populations known to be at high risk for infection with MDR *P. aeruginosa* (e.g., lung transplant and cystic fibrosis patients); and patients known to have previous infection or colonization with MDR *P. aeruginosa*. It is important to note that once microbiology results are available, patients are deescalated to narrower spectrum antibiotics if possible. C/T is initially dosed as 1.5 g q8h for patients with cUTI or IAI unless augmented

FIG 1 Current strategy for the clinical use of ceftolozane-tazobactam at Barnes-Jewish Hospital.
renal clearance is present. In cases where augmented renal clearance or nosocomial pneumonia is present, the dose is increased to 3 g q8h. At least initially, aggressive dose reductions for poor renal clearance are often delayed until renal function can be more definitively assessed. Although no formal policy exists, individual clinicians may choose to employ prolonged or continuous infusion C/T in difficult cases.

The Barnes-Jewish Hospital Antimicrobial Stewardship Program implemented a novel stewardship approach involving C/T in fall of 2019. This policy allows any prescriber the ability to order an initial 24 h of C/T without any prior authorization or justification. Such orders are quickly verified and dispensed by the pharmacy department to help facilitate rapid initiation of therapy. A concomitant order for an infectious diseases (ID) consult at the time of initial ordering of the agent is also required, except from lung transplant physicians. The expectation is that the ID consult take place within the initial 24-h period of C/T use, after which time continuation of the drug in patients with ongoing clinical need can only be ordered by ID physicians granted this right through electronic medical record (EMR) login credentials. Patients in whom continuation is not judged by the ID consult to be warranted would be expected to have their antibiotic therapy deescalated accordingly, typically shortly after the initial 24 h.

We believe that this novel stewardship approach to C/T helps minimize delays to appropriate therapy, while maintaining ID oversight to facilitate therapy continuation or deescalation as clinically warranted. We thought it important to allow clinicians unimpeded access to the agent for initial empirical usage in patients deemed to be at very high risk for MDR Pseudomonas, and include C/T on our initial P. aeruginosa in vitro susceptibility testing panel to help inform timely treatment decision making. In addition, adoption of rapid molecular diagnostics has shown promise in identifying the presence or absence of resistance genes in P. aeruginosa and is expected to further assist with empirical therapy decision making involving C/T for P. aeruginosa infections (55).

It is important to emphasize that empirical use of C/T is predominantly reserved for patients at high risk of MDR Pseudomonas, as previously mentioned (Table 2) (56–58). Other therapies are often preferable for infections caused by ESBL-producing Enterobacteriales. While C/T consistently demonstrates in vitro activity against most E. coli isolates carrying different ESBL enzymes, the same cannot be said for all isolates of K. pneumoniae or Enterobacter cloacae with ESBL-encoding genes (59). Despite the

**TABLE 2** Risk factors for antibiotic-resistant *Pseudomonas aeruginosa* infection

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Antibiotic selection pressure</th>
<th>Patient related</th>
<th>Therapy related</th>
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<tbody>
<tr>
<td>Parenteral antibiotic administration in the past 3–6 mo</td>
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<td>Chronic lung disease (COPD, bronchiectasis, pulmonary fibrosis, cystic fibrosis)</td>
<td>Imunosuppressive therapy</td>
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<td>Prior colonization or infection with <em>Pseudomonas aeruginosa</em></td>
<td>Home wound care</td>
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<td></td>
<td>Residence in a high-risk environment (LTAC, nursing home for debilitated patients)</td>
<td>Hospitalization for more than two days in the past 90 days</td>
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<td></td>
<td>Poor functional status (not ambulatory, gastrostomy tube)</td>
<td>Inhaled corticosteroid use</td>
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<td></td>
<td>Tracheostomy</td>
<td>Indwelling vascular catheter</td>
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<td></td>
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<td>Septic shock</td>
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<td></td>
<td></td>
<td>ARDS preceding VAP</td>
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<td>≥5 days of hospitalization preceding HAP/VAP</td>
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<td></td>
<td></td>
<td>Acute renal replacement therapy preceding HAP/VAP</td>
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<tr>
<td></td>
<td></td>
<td>&gt;20% local threshold for antibiotic resistance</td>
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</tr>
</tbody>
</table>

*a* Derived from references 35–57. COPD, chronic obstructive pulmonary disease; LTAC, long term acute care; ARDS, acute respiratory distress syndrome; VAP, ventilator-associated pneumonia; HAP, hospital-acquired pneumonia.
suggestion that C/T may have a potential role in ESBL-positive cIAI infections (40), generalization to all ESBL-expressing bacteria and sources of infection could be problematic. Successful clinical outcome, defined as complete resolution of clinical signs and symptoms related to ESBL producer infection and lack of microbiological evidence of infection, was reported in 67/74 (91%) cases of E. coli, 28/45 (84%) cases of K. pneumoniae, and 15/22 (68%) cases of Enterobacter spp. in a multicenter, retrospective cohort study. Moreover, in the same study, use of standard-dose C/T in septic patients requiring continuous renal replacement therapy was associated with clinical failure (60).

CONCLUSIONS
Antibiotic resistance continues to be a major problem impacting the treatment of serious infections, especially those due to Gram-negative bacteria. The availability of novel antimicrobial agents like C/T allows for potentially better outcomes and less toxicity in the treatment of these infections. The main challenge for clinicians is to develop local practices that allow appropriate empirical and directed treatment with novel antibiotics, including C/T, while also minimizing the emergence of resistance to these agents. Identifying appropriate patients for empirical treatment with antimicrobials like C/T will require careful understanding of local risk factors for infection with antibiotic-resistant pathogens, including MDR P. aeruginosa (Table 2), and the enhanced use of rapid microbiological diagnostics.

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