MSD

Essential Medicines List Secretariat
Expert Committee on the Selection and Use of Essential Medicines World Health Organization
20 Avenue Appia
CH-1211 Geneva 27, Switzerland

December 20, 2022

Dear Essential Medicines Committee:

MSD submits this application to request the inclusion of ceftolozane/tazobactam (C/T) (ZERBAXA) on the World Health Organization (WHO) Model List of Essential Medicines (EML). Ceftolozane belongs to the cephalosporin class of antimicrobials and exerts bactericidal activity through binding to important penicillin-binding proteins resulting in inhibition of bacterial cell-wall synthesis and subsequent cell death. Tazobactam is a beta-lactam structurally related to penicillins that is an inhibitor of many molecular Class A beta-lactamases, including CTX-M, SHV, and TEM enzymes, that break down beta-lactam antibiotics like ceftolozane. Tazobactam blocks action of these enzymes and allows ceftolozane to act against bacteria that are otherwise resistant.

In the US and EU C/T is indicated for the treatment of complicated intra-abdominal infections, acute pyelonephritis, and complicated urinary tract infections in adult and pediatric patients. Since 2019 C/T is also indicated for treatment of hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP) in adult patients (18 years or older); studies for this indication in pediatric patients are ongoing.

Antimicrobial resistance (AMR) is a major global health threat, taking 1.27 million lives in 2019, mostly concentrated in low- and middle-income countries (LMICs). We are seeking inclusion of C/T as individual drug on the EML as a Reserve Antibiotic. The inclusion of C/T can support access to effective treatment options that can reduce mortality from resistant infections, in particular from the WHO priority pathogen *Pseudomonas aeruginosa*. Often countered in HAP/VAP patients in the hospital setting, *P. aeruginosa* can be co-resistant to several antipseudomonal agents with high mortality rates. During the COVID-19 pandemic there has been a continued increase in healthcare associated infections observed in many countries. Therefore, it is critical to expand the choice of antipseudomonal agents – both in general and to HAP/VAP patients specifically.

We propose C/T inclusion on the EML to address this need for the following reasons:

- Several multi-country *in vitro* and clinical studies have demonstrated that C/T offers excellent coverage of *Pseudomonas aeruginosa* as well as ESBL-producing Enterobacterales. The coverage of multidrug-resistant pathogens when there are limited, or no treatment options available is especially important in critically ill hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia patients where C/T has demonstrated mortality benefit.

- C/T is the only β-lactam/β-lactamase inhibitor that has demonstrated concentrations of both components in the epithelial lining fluid of persons with pneumonia exceeding target concentrations for 100% of the dosing interval for both *Enterobacterales* and *P. aeruginosa*; no other antibiotic has lung concentration data measured directly in critically ill patients with pneumonia.

- C/T offers the most comprehensive coverage of multi-drug-resistant (MDR)-*Pseudomonas aeruginosa* clinical isolates and provides coverage in the setting of ceftazidime/avibactam resistance in most regions. C/T has emerged as the preferred agent for the treatment of *P. aeruginosa* and MDR-*P. aeruginosa* in the most recent IDSA and ESCMID guidelines due to this combined surveillance and real-world evidence.

- C/T is one of the most widely filed on-patent novel antibiotics to date.[1] It is currently registered in 79 countries globally, including 25 LMICs. Additionally, C/T has been filed in 7 more countries, 6 of which are LMICs, and filings in several other countries are pending regulatory approval. MSD is also working to implement an access pricing framework for C/T.

- Given the rapid rise in antimicrobial resistance where a single agent or limited number of initially effective agents are utilized, having several agents available on the EML can help minimize the risk of pan-resistance while offering continued treatment options should there be interruptions in supply.

Consistent with the AWaRE classification of antibiotics, we support C/T's designation as a Reserve Group antibiotic that should only be deployed for treatment of confirmed or suspected infections due to multidrug-resistant organisms. With Reserve classification, we recommend that access of C/T is informed with appropriate use and strong stewardship activities.

We strongly recommend the inclusion of C/T on the EML and appreciate your consideration of our application. We are happy to provide the Expert Committee with any additional information if requested.

Sincerely,

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Elizabeth Rhee, MD, Vice President and Therapeutic Area Head, Infectious Disease Clinical Research, MSD

Application for Inclusion of Ceftolozane/Tazobactam (C/T) to the WHO Model List of Essential Medicines

Submitted to:
Essential Medicines List Secretariat

Expert Committee on the Selection and Use of Essential Medicines

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Summary Statement of Proposal for Inclusion

Ceftolozane/tazobactam (C/T; ZERBAXA®) is a combination product with two active substances:

- Ceftolozane belongs to the cephalosporin class of antimicrobials. Ceftolozane exerts bactericidal activity through binding to important penicillin-binding proteins (PBPs), resulting in inhibition of bacterial cell-wall synthesis and subsequent cell death.[2]
- Tazobactam is a beta-lactam structurally related to penicillins. It is an inhibitor of many molecular Class A beta-lactamases, including CTX-M, SHV, and TEM enzymes. These enzymes enable bacteria to break down beta-lactam antibiotics like ceftolozane, making the bacteria resistant to the antibiotic's action. By blocking the action of these enzymes, tazobactam allows ceftolozane to act against bacteria that would otherwise be resistant to this antibiotic.

In the US and EU C/T is indicated for the treatment of complicated intra-abdominal infections, acute pyelonephritis, and complicated urinary tract infections in adult and pediatric patients. Since 2019 C/T is also indicated for treatment of hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP) in adult patients (18 years or older); studies for this indication in pediatric patients are ongoing.

Antimicrobial resistance (AMR) is a major global health threat, taking 1.27 million lives in 2019, mostly concentrated in low- and middle-income countries (LMICs). We are seeking inclusion of C/T as individual drug on the EML as a Reserve Antibiotic. The inclusion of C/T can support access to effective treatment options that can reduce mortality from resistant infections, in particular from the WHO priority pathogen *Pseudomonas aeruginosa*. Often countered in HAP/VAP patients in the hospital setting, *P. aeruginosa* can be co-resistant to several antipseudomonal agents with high mortality rates. During the COVID-19 pandemic there has been a continued increase in healthcare associated infections observed in many countries. Therefore, it is critical to expand the choice of antipseudomonal agents – both in general and to HAP/VAP patients specifically.

We propose C/T inclusion on the EML to address this need for the following reasons:

- Several multi-country *in vitro* and clinical studies have demonstrated that C/T offers excellent coverage of *Pseudomonas aeruginosa* as well as ESBL-producing Enterobacterales. The coverage of multi-drug-resistant pathogens when there are limited, or no treatment options available is especially important in critically ill hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia patients where C/T has demonstrated mortality benefit.

- C/T is the only β-lactam/β-lactamase inhibitor that has demonstrated concentrations of both components in the epithelial lining fluid of persons with pneumonia exceeding target

concentrations for 100% of the dosing interval for both *Enterobacterales* and *P. aeruginosa*; no other antibiotic has lung concentration data measured directly in critically ill patients with pneumonia.

- C/T offers the most comprehensive coverage of MDR-*Pseudomonas aeruginosa* clinical isolates and provides coverage in the setting of ceftazidime/avibactam resistance in most regions. C/T has emerged as the preferred agent for the treatment of *P. aeruginosa* and MDR-*P. aeruginosa* in the most recent IDSA and ESCMID guidelines due to this combined surveillance and real-world evidence.

- C/T is one of the most widely filed on-patent novel antibiotics to date.[1] It is currently registered in 79 countries globally, including 25 LMICs. Additionally, C/T has been filed in 7 more countries, 6 of which are LMICs, and filings in several other countries are pending regulatory approval. MSD is also working to implement an access pricing framework for C/T.

- Given the rapid rise in antimicrobial resistance where a single agent or limited number of initially effective agents are utilized, having several agents available on the EML can help minimize the risk of pan-resistance while offering continued treatment options should there be interruptions in supply.

Consistent with the AWaRE classification of antibiotics, we support C/T's designation as a Reserve Group antibiotic that should only be deployed for treatment of confirmed or suspected infections due to multidrug-resistant organisms. With Reserve classification, we recommend that access of C/T is informed with appropriate use and strong stewardship activities.

Consultation with WHO Technical Departments

WHO Expert Committee on Selection and Use of Essential Medicines
Essential Medicines Team
Department of Health Products Policy and Standards

Organizations Consulted and/or Supporting the Submission

Merck, Sharp, and Dohme Corp.

Key Information for Proposed Medicine

INN: ceftolozane/tazobactam
ATC: J01DI54

Dose Form and Strengths Proposed for Inclusion, Including Adult and Age-Appropriate Pediatric Dose Forms/Strengths

The recommended dosage of C/T for adult patients with cUTI, cIAI or HABP/VABP without renal impairment is presented in Table 1.[2,3]

Table 1. Dosage of C/T by infection in adult patients with CrCL greater than 50 mL/min[2,3]

Infection	Dose	Frequency	Infusion time (hours)	Duration of treatment*
cUTIs, including Pyelonephritis	1.5 g (1 g ceftolozane/ 0.5 g tazobactam)	q8h	1	7 days
cIAIs**	1.5 g (1 g ceftolozane/ 0.5 g tazobactam)	q8h	1	4-14 days
HABP/VABP	3 g (2 g ceftolozane/ 1 g tazobactam)	q8h	1	8-14 days

*The duration of therapy is based on the length of therapy planned in the respective clinical trial. For example, in ASPECT-cIAI, patients were planned to receive 4–14 days of C/T.
**In combination with metronidazole 500 mg every 8 hours.
cIAI: complicated intra-abdominal infection; CrCL: creatinine clearance; cUTI: complicated urinary tract infection; HABP: hospital-acquired bacterial pneumonia; q8h: every 8 hours; VABP: ventilator-associated bacterial pneumonia.

Renal Impairment

As C/T is predominantly eliminated by the kidneys, dose adjustment is required for adult patients whose CrCL is 50 mL/min or less.[2,3] Renal dose adjustments for adult patients are listed in Table 2. For patients with changing renal function, CrCL should be monitored by healthcare professionals at least daily and the dosage of C/T adjusted accordingly.[2,3]

Table 2. Recommended dosage regimen for C/T in patients with renal impairment[2,3]

Estimated CrCL (mL/min)*	cUTIs, including pyelonephritis and cIAIs**	HABP/VABP
30 to 50	750 mg (500 mg and 250 mg) IV q8h	1.5 g (1 g and 0.5 g) IV q8h
15 to 29	375 mg (250 mg and 125 mg) IV q8h	750 mg (500 mg and 250 mg) IV q8h

Estimated CrCL (mL/min)*	cUTIs, including pyelonephritis and cIAIs**	HABP/VABP
End-stage renal disease on hemodialysis	A single loading dose of 750 mg (500 mg and 250 mg) followed by a 150 mg (100 mg and 50 mg) maintenance dose administered q8h for the remainder of the treatment period (on hemodialysis days, administer the dose at the earliest possible time following completion of dialysis)	A single loading dose of 2.25 g (1.5 g and 0.75 g) followed by a 450 mg (300 mg and 150 mg) maintenance dose administered q8h for the remainder of the treatment period (on hemodialysis days, administer the dose at the earliest possible time following completion of dialysis)

*CrCL estimated using Cockcroft-Gault formula.
**All doses of ZERBAXA® are administered intravenously over 1 hour.
cIAI: complicated intra-abdominal infection; CrCL: creatinine clearance; cUTI: complicated urinary tract infection; HABP: hospital-acquired bacterial pneumonia; IV: intravenous; q8h; every 8 hours; VABP: ventilator-associated bacterial pneumonia.

Hepatic Impairment

No dose adjustment is necessary in patients with hepatic impairment.[2,3]

Dosing in Pediatric Population Age Birth to less than 18 years old

Recommended dosage of ceftolozane/tazobactam by infection in pediatric patients (birth to less than 18 years of age (with an estimated glomerular filtration rate (eGFR) greater than 50 mL/min/1.73m^2		
Infection	Dose	Duration of Treatment
Complicated intra-abdominal infections*	30 mg/kg up to a maximum dose of 1.5 g**	5-14 days
Complicated urinary tract infections including pyelonephritis	30 mg/kg up to a maximum dose of 1.5 g**	7-14 days
+ Estimated GFR using an age-appropriate equation for use in the pediatric population * Used in conjunction with metronidazole **Pediatric patients weighing greater than 50 kg should not exceed a maximum dose of 1.5g.		

Indication(s)

In the US, C/T is indicated for the treatment of pediatric populations (birth to less than 18 years old) and adults with the following infections caused by designated susceptible pathogens:[2]

- Complicated urinary tract infections (cUTIs), including pyelonephritis, with or without concurrent bacteremia, caused by the following GN susceptible pathogens: *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* and *Pseudomonas aeruginosa*.[2]

- Complicated intra-abdominal infections (cIAIs), in combination with metronidazole, caused by the following GN and Gram-positive susceptible pathogens: *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Bacteroides fragilis*, *Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus salivarius*.[2]

Additionally, C/T is indicated for the treatment of adults with HABP and VABP:

- Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) caused by the following GN susceptible pathogens: *Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, and Serratia marcescens*.[2]

In the European Union (EU), C/T is indicated for the treatment of children and adults with the following infections:[3]

- cUTIs, including acute pyelonephritis. C/T has demonstrated clinical efficacy against the following GN bacteria: *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*.[3]
- cIAIs in combination with metronidazole when anaerobic bacteria are suspected. C/T has demonstrated clinical efficacy against the following Gram-negative and Gram-positive bacteria: *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus salivarius*.[3]
- Hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP). C/T has demonstrated clinical efficacy against the following Gram-negative and Gram-positive bacteria: *Enterobacter cloacae*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Serratia marcescens.*[3]

Proposal for Individual Medicine or Representative of a Pharmacological Class/Therapeutic Group

This proposal is for C/T to be included as an individual medicine, classified as a Reserve Group Antibiotic.

Information Supporting Public Health Relevance

Epidemiology

Gram-negative bacteria are a common cause of hospital-acquired infections (HAIs) – collectively *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* accounted for 30% of all pathogens responsible for HAIs between 2011 and 2014.[4] Among all of the issues generated by bacterial resistance, GN pathogens present a particular threat as they have

intrinsic or acquired resistance to most drugs that would be considered for treatment.[5] More recently, in a multinational multicenter surveillance study of carbapenem resistant *Pseudomonas aeruginosa*, Gill et al. found CR-PA to be present in not only hospitals in high income countries but also low and middle income countries, more frequently isolated from respiratory tract specimens, and while prevalent in the ICUs more frequently isolated in non-ICU patients.[6]

Furthermore, Enterobacterales (formerly categorized as *Enterobacteriaceae*; including *E. coli* and *K. pneumoniae*) and *P. aeruginosa* are designated by the World Health Organization (WHO) as the highest 'critical' priority in need of new therapeutic options to counteract growing resistant to available treatments.[7] A recent study estimated that drug resistant *E. coli, K. pneumoniae,* and, *P. aeruginosa* were directly responsible for 496,600 deaths in 2019 globally.[8]

Likewise, the Centers for Disease Control and Prevention (CDC) have stated that HAIs are the most serious GN infections and the most common pathogens are Enterobacterales, *P. aeruginosa* and *Acinetobacter* spp.[5] Resistant pathogens are highly prevalent in the US, with approximately 13% of Enterobacterales isolated from hospital-onset infections producing an Extended-spectrum β-lactamase (ESBL),[9] and up to 20% of *P. aeruginosa* isolates resistant to carbapenems,[10] antibacterials typically used as last-line therapy. With growing global resistant rates, the ability to treat infections such as complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI), and HABP/VABP has become increasingly more complex.

Antibacterial resistance increases the risk of administering initial inappropriate antibacterial therapy (IIAT), where a patient is treated with a drug with little or no *in vitro* activity against the causative pathogen and delays the treatment of effective therapy.[11,12] IIAT is associated with longer hospital stays, higher mortality rates, and increased economic burden compared with patients who receive appropriate initial therapy.[12-18]

Furthermore, some current treatment options for cUTI, cIAI and HABP/VABP have been associated with serious drug-related toxicity. Specifically, aminoglycosides (eg, gentamicin, tobramycin, and amikacin) and polymyxins (eg, colistin) are reported to cause nephrotoxicity and/or ototoxicity;[19] aminoglycosides are additionally associated with a higher rate of treatment failure.[20,21] In the case of HABP/VABP, some therapies may have limited pulmonary penetration, may not reach favorable local pulmonary pharmacokinetics (PK) or may require higher doses, which could increase the risk of toxicity.[22-29]

Therefore, there is an unmet need for additional therapeutic options that can treat prevalent GN pathogens with a high probability of susceptibility, target attainment and penetration at site of infection.

Treatment Details

C/T is a β-lactam/β-lactamase inhibitor antibacterial, consisting of a fixed (2:1) combination of the novel antipseudomonal cephalosporin, ceftolozane, and the established β-lactamase inhibitor, tazobactam. Ceftolozane exerts bactericidal activity through binding to important penicillin-binding proteins (PBPs), resulting in inhibition of bacterial cell wall synthesis and subsequent cell death.[2,3] Ceftolozane is an inhibitor of PBPs of *P. aeruginosa* (eg, PBP1b, PBP1c, and PBP3) and *E. coli* (eg, PBP3).[2,3]

Tazobactam is a β-lactam structurally related to penicillin.[2,3] It is an inhibitor of many Molecular Class A β-lactamases, including CTX-M, SHV, and TEM enzymes.[2,3] C/T demonstrated *in vitro* activity against *Enterobacterales* in the presence of some ESBLs and other β-lactamases of the following groups: TEM, SHV, CTX-M, and OXA.[2,3] C/T also demonstrated *in vitro* activity against *P. aeruginosa* isolates tested that had chromosomal AmpC, loss of outer membrane porin (OprD), or up-regulation of efflux pumps (MexXY, MexAB).[2,3]

Of note, tazobactam does not contribute to the antipseudomonal activity of ceftolozane; ceftolozane in itself is active.[30]

C/T provides an effective treatment option for patients who are at risk of serious GN infections caused by indicated pathogens, including those with certain mechanisms of resistance with a safety profile similar to comparators, both in adult and pediatric patients. C/T demonstrated a statistically significant difference in clinical cure rates favoring C/T compared to levofloxacin in ASPECT-cUTI and demonstrated comparable efficacy with meropenem in ASPECT-cIAI (C/T in combination with metronidazole) and ASPECT-NP. As such, C/T presents as an antibacterial option for patients with cUTI, cIAI or HABP/VABP caused by susceptible GN pathogens, including resistant strains. C/T is effective against ESBL-producing *E. coli* and *K. pneumoniae* (excluding those which are CR) and MDR *P. aeruginosa* (including CR strains). C/T is not active against bacteria that produce serine carbapenemases (*K. pneumoniae* carbapenemase [KPC]), and metallo-beta-lactamases.

This antibiotic offers a safe and effective alternative to drugs like polymyxins and aminoglycosides, while supplementing the MDR-GN coverage of ceftazidime/avibactam (C/A) and meropenem/vaborbactam (M/V) particularly in the settings of emergence of resistance on treatment (C/A) or in the setting of a Pseudomonas infection (M/V). Finally, there are robust diagnostic testing options for C/T that cover simple to perform manual susceptibility testing methods to the automated testing methods.

Utilization of C/T in the Pediatric Population

UTIs are the second most common bacterial infection in children in the US;the number annually diagnosed with a UTI before the age of 6 years old is in excess of 180,000. Recurrent

UTIs will develop in 12% to 30% of these cases.[31,32] If these cases develop without effective therapies, they can become classified as complicated UTIs (cUTIs) and become more difficult to treat, leading to more serious outcomes such as sepsis, renal scarring, hypertension, and chronic renal insufficiency.[31,33] In the US, the number of pediatric inpatient and outpatient encounters for a UTI has steadily increased since 2000, likely due to increased resistance to antibiotics or poor initial diagnosis.[31]

The incidence rate of cIAIs remains relatively high in developing countries, despite decreasing across the world population.[34] Most of the studies reporting secondary peritonitis cIAIs are not comparable with each other because of wide variations of inclusion criteria. Thus, the true incidence of cIAIs is difficult to assess.[35]

The same GN bacteria that cause cUTIs and cIAIs in the adult population will affect children, however there are less antibiotics approved by national health services available to adequately manage these infections.[36] Clinical trials show that C/T can be used as a safe and effective treatment option for cUTIs and cIAIs in the adult population. Extension to the pediatric population may help address the clinical need for safe and effective antibiotics, thus providing an alternative treatment for DR pathogens.[37-39]

Robust sponsored studies in pediatric patients in cUTI including pyelonephritis and cIAI demonstrates efficacy and safety in children from birth to less than 18 years of age.

Dose Regimen and Duration of Treatment for Adults

Each vial contains ceftolozane sulfate equivalent to 1 g ceftolozane and tazobactam sodium equivalent to 0.5 g tazobactam. After reconstitution with 10 mL diluent, the total volume of the solution in the vial is 11.4 mL, which contains 88 mg/mL of ceftolozane and 44 mg/mL of tazobactam.

Excipient with Known Effect

Each vial contains 10 mmol (230 mg) of sodium. When the powder is reconstituted with 10 mL of sodium chloride 9 mg/mL (0.9%) solution for injection, the vial contains 11.5 mmol (265 mg) of sodium.

The recommended dosage of C/T for patients with cUTI, cIAI or HABP/VABP is presented in Table 3.[2,3]

Table 3. Dosage of C/T by infection in adult patients with CrCL greater than 50 mL/min[2,3]

Infection	Dose	Frequency	Infusion time (hours)	Duration of treatment*
cUTIs, including Pyelonephritis	1.5 g (1 g ceftolozane/ 0.5 g tazobactam)	q8h	1	7 days
cIAIs**	1.5 g (1 g ceftolozane/ 0.5 g tazobactam)	q8h	1	4–14 days
HABP/VABP	3 g (2 g ceftolozane/ 1 g tazobactam)	q8h	1	8–14 days

*The duration of therapy is based on the length of therapy planned in the respective clinical trial. For example, in ASPECT-cIAI, patients were planned to receive 4–14 days of C/T.
**In combination with metronidazole 500 mg every 8 hours.
cIAI: complicated intra-abdominal infection; CrCL: creatinine clearance; cUTI: complicated urinary tract infection; HABP: hospital-acquired bacterial pneumonia; q8h: every 8 hours; VABP: ventilator-associated bacterial pneumonia.

Renal Impairment

As C/T is predominantly eliminated by the kidneys, dose adjustment is required for patients whose CrCL is 50 mL/min or less.[2,3] Renal dose adjustments are listed in Table 4. For patients with changing renal function, CrCL should be monitored by healthcare professionals at least daily and the dosage of ceftolozane/tazobactam adjusted accordingly.[2,3]

Table 4. Recommended dosage regimen for C/T in patients with renal impairment[2,3]

Estimated CrCL (mL/min)*	cUTIs, including pyelonephritis and cIAIs**	HABP/VABP
30 to 50	750 mg (500 mg and 250 mg) IV q8h	1.5 g (1 g and 0.5 g) IV q8h
15 to 29	375 mg (250 mg and 125 mg) IV q8h	750 mg (500 mg and 250 mg) IV q8h
End-stage renal disease on hemodialysis	A single loading dose of 750 mg (500 mg and 250 mg) followed by a 150 mg (100 mg and 50 mg) maintenance dose administered q8h for the remainder of the treatment period (on hemodialysis days, administer the dose at the earliest possible time following completion of dialysis)	A single loading dose of 2.25 g (1.5 g and 0.75 g) followed by a 450 mg (300 mg and 150 mg) maintenance dose administered q8h for the remainder of the treatment period (on hemodialysis days, administer the dose at the earliest possible time following completion of dialysis)

*CrCL estimated using Cockcroft-Gault formula.
**All doses of ZERBAXA® are administered intravenously over 1 hour.
cIAI: complicated intra-abdominal infection; CrCL: creatinine clearance; cUTI: complicated urinary tract infection; HABP: hospital-acquired bacterial pneumonia; IV: intravenous; q8h; every 8 hours; VABP: Ventilator-associated bacterial pneumonia.

Hepatic Impairment

No dose adjustment is necessary in patients with hepatic impairment.[2,3]

Dosing in pediatric population age birth to less than 18 years old with GFR >50 mL/min/1.73m^2

Recommended dosage of ceftolozane/tazobactam by infection in pediatric patients (birth to less than 18 years of age (with an estimated glomerular filtration rate [eGFR] greater than 50 mL/min/1.73m^2		
Infection	Dose	Duration of Treatment
Complicated Intra-abdominal Infections*	30 mg/kg up to a maximum dose of 1.5 g**	5-14 days
Complicated urinary tract infections including pyelonephritis	30 mg/kg up to a maximum dose of 1.5 g**	7-14 days
+Estimated GFR using an age-appropriate equation for use in the pediatric population. *Used in conjunction with metronidazole. **Pediatric patients weighing greater than 50 kg should not exceed a maximum dose of 1.5g.		

Requirements to Ensure Appropriate Use

To reduce the development of drug-resistant bacteria and maintain the effectiveness of C/T and other antibacterial drugs, C/T should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.[2,3] Currently, there are 6 FDA-cleared *in vitro* diagnostic methods for ceftolozane and tazobactam susceptibility testing. The diagnostic methods are outlined below:

1. **ETEST® C/T 256 Strip** is available for order from BioMérieux. The test is a quantitative technique of antimicrobial susceptibility testing (AST) for determining mean inhibitory concentration (MIC) for C/T
    - Additional information can be found online at, www.biomerieux-usa.com/etest.

2. **MIC Test Strip** is available for order from Liofilchem S.R.L. Currently there are interpretive criteria for *Pseudomonas aeruginosa* and Enterobacterales.
    - Additional information can be found online at, https://www.liofilchem.com.

3. **HardyDisk™ Ceftolozane/Tazobactam** are impregnated paper disks for antimicrobial susceptibility testing (AST) for *Pseudomonas aeruginosa* and Enterobacterales and are available from Hardy Diagnostics. These disks are used in disk diffusion, also known as Kirby-Bauer testing.
    - Additional information can be found online at, https://hardydiagnostics.com/

4. **Sensititre™ GN6F Standard MIC Plates** for C/T testing on microbroth dilution are available from Thermo Scientific™. Currently there are interpretive criteria for *Pseudomonas aeruginosa* and Enterobacterales.
    - Additional information can be found online at: www.thermofisher.com/AST.

5. **Vitek® 2 AST/XN08 Gram-Negative Susceptibility Card** is used to determine the susceptibility of select aerobic Gram-negative bacilli to antimicrobial agents. The cards are available from BioMérieux.
    - Additional information can be found online at: https://biomerieuxdirect.com/clinical

6. **MicroScan® Detect Neg MIC 2 Gram-Negative Susceptibility Panel** is available from Beckman Coulter. The panel is used to determine the susceptibility of select aerobic gram-negative bacilli to antimicrobial agents.
    - Additional information can be found online at: https://www.beckman.com/

7. **Phoenix panels** are available from Becton Dickinson. There are 5 panels: BD Phoenix NMIC 305, BD Phoenix NMIC 306, BD Phoenix NMIC 311, BD Phoenix Combo NMIC/ID 308 and BD Phoenix AST only 308. These panels are used to determine the susceptibility or identification of selects aerobic Gram-negative bacilli to antimicrobial agents.
    - Additional information can be found at: www.bd.com

When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the initial selection of therapy.[2,3]

Recommendations in Clinical Guidelines

Ceftolozane was specifically designed to evade resistance mechanisms (ie, oprD loss, efflux, AmpC) that are common among clinical *P. aeruginosa* isolates. Ceftolozane does not rely on its partner beta-lactamase inhibitor tazobactam to restore susceptibility to an otherwise inactive drug (ie, ceftolozane has independent activity against wild-type and resistant strains of *P. aeruginosa*), which may explain slightly higher likelihood of activity against resistant *P. aeruginosa* compared to other novel β-lactam-β-lactamase inhibitors.

Due to these product characteristics, the results from phase 3 trials, and the large volume of real-world effectiveness data published, prominent societies such as the Infectious Diseases Society of America (IDSA) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) have positioned C/T as a preferred treatment option for drug resistant *P. aeruginosa* in their most recent pathogen directed guidance/guidelines publications.[40,41] In the IDSA guidance on the treatment of *P. aeruginosa* with difficult-to-treat resistance (DTR-*P.*

aeruginosa), C/T is a preferred treatment option for all types of infections included in their guidance document (ie, uncomplicated urinary tract infections, acute pyelonephritis and complicated urinary tract infections, and infections outside the urinary tract). Moreover, for patients with moderate to severe disease or poor source control with *P. aeruginosa* isolates resistant to carbapenems but susceptible to traditional β-lactams, use of C/T is also a reasonable treatment option.[40]

Similar to the IDSA, ESCMID recently published their guideline for the treatment of infections caused by multi-drug-resistant Gram-negative bacilli.[41] Their recommendations were more prescriptive for C/T as the preferred treatment option. They state in patients with severe infections due to difficult to treat carbapenem resistant *P. aeruginosa*, we suggest therapy with C/T if active *in vitro*.

Consistent with recommendations in these society guidance/guideline statements, C/T is listed as a preferred treatment option for resistant *P. aeruginosa* in numerous country-specific guidelines, expert opinion papers, and prominent clinical bedside references including the Sanford Guide[42] and UpToDate[43] as well.

The tick box table below (Table 5) indicates country, and guideline that has included C/T as a recommended treatment option.

Table 5. Summary of treatment recommendations including C/T

Country	Reference	cIAI	cUTI	HABP/VABP
Global	World Society of Emergency Surgery (WSES) guidelines for the treatment of cIAIs Sartelli et al. 2017[44]	X		
Global	Surgical Infection Society (SIS) guidelines for the treatment of IAIs Mazuski et al. 2017[45]	X		
US	Infectious Disease Society of American (IDSA) guidance on difficult-to-treat resistance (DTR) *Pseudomonas aeruginosa* Tamma et al. 2022[40]	X	X	X
European	European Respiratory Society (ERS) initial antibacterial treatment recommendations for HABP/VABP Torres et al. 2017, 2018[46,47]			X
European	European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment	X	X	X

	of infections caused by multidrug-resistant Gram-negative bacilli Paul et al. 2022[41]			
Germany	Germany S2k guideline 2018 Bodmann et al. 2018[48]	X	X	X
Germany	Germany pneumonia guidelines 2018 Dalhoff et al. 2018[49]			X
Spain	Spanish Society of Chemotherapy Mensa et al. 2018[50]	X	X	X
	Society of Clinical Microbiology and Infectious Diseases Cueto et al. 2017[51]		X	
Italy	How to manage *Pseudomonas aeruginosa* infections Bassetti et al. 2018[52]	X	X	X

Review of Benefits: Summary of Evidence of Comparative Effectiveness

Efficacy of C/T in cUTI, including pyelonephritis in adults

NOTE: This trial has been published as Wagenlehner et al. *Lancet*. 2015;385(9981):1949-1956.[53]

The efficacy and safety of C/T for the treatment of cUTI (including pyelonephritis) was evaluated in a multicenter, double-blind, randomized, Phase III study (ASPECT-cUTI).[53,54] ASPECT-cUTI employed a noninferiority clinical trial design in accordance with the Food and Drug Administration (FDA) draft guidance regarding the use of noninferiority trials to support product approval of antibacterials. The primary objective of the ASPECT-cUTI trial was to demonstrate the noninferiority of intravenous (IV) C/T (1.5 g every 8 hours [q8h]) vs. IV levofloxacin (750 mg once daily) over a 7-day course of treatment in adult patients with cUTI, including pyelonephritis.[53,54]

As per the FDA, C/T met the primary endpoint by achieving noninferior composite cure rates to levofloxacin (95% confidence interval [CI], 10% noninferiority margin) in the microbiological modified intent-to-treat (mMITT) population, at a one-sided 0.025 significance level (Table 6).[53,54] C/T also met its key secondary endpoint by achieving noninferior composite cure rates in the microbiologically evaluable at test-of-cure (ME at TOC) population. Furthermore, as the lower bound of the two-sided 95% and 99% CIs constructed around the treatment difference excluded zero, superiority of C/T over levofloxacin was indicated.

As per the European Medicines Agency (EMA), C/T met the primary endpoint by achieving noninferior microbiological success rates to levofloxacin (99% CI, 10% noninferiority margin) in the ME at TOC population, at a one-sided 0.005 significance level. C/T also met its key secondary endpoint by achieving noninferior microbiological success rates in the mMITT population (Table 6). Again, as the lower bound of the two-sided 99% CI around the treatment difference excluded zero, superiority of C/T over levofloxacin was indicated (Table 6).[55]

Table 6. Efficacy results for primary and key secondary analyses in ASPECT-cUTI (mMITT and ME at TOC populations)[53-55]

Population response	Ceftolozane/ tazobactam n/N (%)	Levofloxacin n/N (%)	% Difference (95% CI) [99% CI]
FDA			
Primary analysis (mMITT)			
Composite success	306/398 (76.9)	275/402 (68.4)	8.5 (2.31, 14.57)* 8.5 [0.36, 16.46]*
Key secondary analysis (ME at TOC)			
Composite success	284/341 (83.3)	266/353 (75.4)	8.0 (1.95, 13.97)* 8.0 [0.01, 15.84]*
EMA			
Primary analysis (ME at TOC)			
Microbiological success	288/340 (84.7)	266/353 (75.4)	9.4 [1.54, 17.12]*
Key secondary analysis (mMITT)			
Microbiological success	313/398 (78.6)	281/402 (69.9)	8.7 [0.77, 16.57]*

'Composite' is a combination of microbiological and clinical success.
*Superiority demonstrated by the lower bound of the two-sided CI around the treatment differences excluding zero.
CI: confidence interval; EMA: European Medicines Agency; FDA: Food and Drug Administration; ME: microbiologically evaluable; mMITT: microbiological modified intent-to-treat; TOC: test-of-cure.

Efficacy of C/T in cIAI in Adults

NOTE: This trial has been published as Solomkin et al. *Clin Infect Dis*. 2015;60(10):1462-1471.[56]

The efficacy and safety of C/T for the treatment of cIAI was evaluated in a multicenter, double-blind, randomized, phase 3 study (ASPECT-cIAI).[56] ASPECT-cIAI employed a noninferiority clinical trial design in accordance with the FDA draft guidance regarding the use of noninferiority trials to support product approval in antibacterial clinical efficacy evaluations. The primary objective of the ASPECT-cIAI trial was to demonstrate the noninferiority of IV C/T (1.5 g q8h) + metronidazole (500 mg every 8 hours) vs. IV meropenem (1 g q8h) + placebo for treatment of patients with cIAI requiring surgical intervention.[56]

As per the FDA, C/T + metronidazole met the primary endpoint by achieving noninferior clinical cure rates to meropenem (95% CI, 10% noninferiority margin) in the microbiological intent-to-treat (mITT) population, at a one-sided 0.025 significance level (Table 7).[56] C/T +

metronidazole also met the key secondary endpoint by achieving noninferior clinical cure rates in the ME population (Table 7).[56]

As per the EMA, C/T plus metronidazole met the primary endpoint by achieving noninferior clinical cure rates to meropenem (99% CI, 12.5% noninferiority margin) in the clinically evaluable (CE) population, at a one-sided 0.005 significance level (Table 7).[57,58] C/T + metronidazole also met the key secondary endpoint by achieving noninferior clinical cure rates in the intent-to-treat (ITT) population (Table 7).[57,58]

Table 7 Efficacy results for primary and key secondary analyses at the TOC visit in ASPECT-cIAI (mITT, ME, CE, and ITT populations)[57-59]

Population response	Ceftolozane/ tazobactam plus metronidazole n/N (%)	Meropenem n/N (%)	% Difference (95% CI) [99% CI]
FDA			
Primary analysis (mITT)			
Clinical cure	323/389 (83.0)	364/417 (87.3)	-4.2 (-8.91, 0.54)
Secondary analysis (ME)			
Clinical cure	259/275 (94.2)	304/321 (94.7)	-0.5 (-4.52, 2.59)
EMA			
Primary analysis (CE)			
Clinical cure	353/375 (94.1)	375/399 (94.0)	0.0 [-4.16, 4.30]
Secondary analysis (ITT)			
Clinical cure	399/476 (83.8)	424/494 (85.8)	-2.2 [-7.95, 3.44]

CE: clinically evaluable; CI: confidence interval; EMA: European Medicines Agency; FDA: Food and Drug Administration; ITT: intent-to-treat; ME: microbiologically evaluable; mITT: microbiological intent-to-treat; TOC: test-of-cure.

Efficacy of C/T in HABP/VABP in adults

Note: The results of ASPECT-NP were published as Kollef et al. *Lancet Infect Dis.* 2019;19(12):1299-1311.[60]

The efficacy and safety of C/T for the treatment of ventilated HABP (ventilated HABP) and VABP was evaluated in a multicenter, double-blind, randomized, phase 3 study (ASPECT-NP).[61] ASPECT-NP employed a noninferiority clinical trial design in accordance with the FDA draft guidance regarding the use of noninferiority trials to support product approval in antibacterial clinical efficacy evaluations. The primary objective of the ASPECT-NP trial was to demonstrate the noninferiority of IV C/T (3 g q8h) vs. IV meropenem (1 g q8h) for treatment of patients with ventilated HABP/VABP.[61] At randomization, patients were stratified by diagnosis (VABP or ventilated HABP) and by age (<65 or ≥65 years) to facilitate balanced distribution of high-risk subjects between the two treatment groups. The target enrollment for patients with VABP was planned to be at least 50% of the randomized population.[61]

As per the FDA, C/T met the primary endpoint by achieving noninferior Day 28 all-cause mortality rates to meropenem (95% CI, 10% noninferiority margin) in the ITT population, at the 0.05 significance level (Table 8). C/T also met the key secondary endpoint by achieving noninferior clinical cure rates in the ITT population (Table 8). Results in the diagnosis subgroups were consistent with the overall population.[61]

As per the EMA, C/T met the primary endpoint by achieving noninferior clinical cure rates to meropenem (97.5% CI, 12.5% noninferiority margin) in the ITT population, at the 0.05 significance level (Table 8). C/T also met the key secondary endpoint by achieving noninferior Day 28 all-cause mortality rates in the ITT population (Table 8). Results in the diagnosis subgroups were consistent with the overall population.[61]

Table 8. Efficacy results for primary and key secondary analyses in ASPECT-NP (ITT population)[61]

Analysis in the ITT population	Ceftolozane/ tazobactam n/N (%)	Meropenem n/N (%)	% Difference (95.0% CI)* [97.5% CI]**
Day 28 all-cause mortality (FDA primary, EMA key secondary)			
Overall	87/362 (24.0)	92/364 (25.3)	1.1 (-5.13, 7.39) [-5.92, 8.39]
VABP subgroup	63/263 (24.0)	52/256 (20.3)	-3.6 (-10.74, 3.52) [-11.75, 4.55]
Ventilated HABP subgroup	24/99 (24.2)	40/108 (37.0)	12.8 (0.18, 24.75) [-1.63, 26.37]
Clinical cure (EMA primary, FDA key secondary)			
Overall	197/362 (54.4)	194/364 (53.3)	1.1 (-6.17, 8.29) [-7.20, 9.31]
VABP subgroup	147/263 (55.9)	146/256 (57.0)	-1.1 (-9.59, 7.35) [-10.79, 8.55]
Ventilated HABP subgroup	50/99 (50.5)	48/108 (44.4)	6.1 (-7.44, 19.27) [-9.31, 21.06]

*FDA analysis. The 95% CIs of % difference are stratified Newcombe CIs for the overall population and unstratified Newcombe CIs for the ventilated HABP/VABP subgroups.
**EMA analysis. The 97.5% CIs of % difference are stratified Newcombe CIs for the overall population and unstratified Newcombe CIs for the ventilated HABP/VABP subgroups.
CI: confidence interval; EMA: European Medicines Agency; FDA: Food and Drug Administration; ITT: intent-to-treat; TOC: test-of-cure; VABP: ventilator-associated bacterial pneumonia; ventilated HABP: ventilated hospital-acquired bacterial pneumonia.

Subgroup analyses also support the primary analysis. The subgroup of patients with ventilated HABP and the subgroup of patients who were failing their current nosocomial pneumonia therapy prior to enrollment in the study, had lower mortality in the C/T arm than the meropenem arm with the 95% CI of the between-group difference excluding zero. However, significance could not be inferred as adjustment for multiplicity was not performed.[61] In the subgroup of patients with ESBL-positive/AmpC-overproducing Enterobacterales isolated that were sensitive to the study therapies, 28-day all-cause mortality was 6.7% (2/30) with C/T and 32.3% (10/31) with meropenem (25.6% difference, 95% CI: 5.54 to 43.84). Clinical cure rate at test-of-cure, 7–14 days after end of therapy, was 73.3% (22/30) with C/T and 61.3% (19/31) with meropenem (12.0% difference, 95% CI: −11.21 to +33.51).[62] Mortality rates were generally comparable between treatment arms by geographic region and in other patient subgroups, including patients with augmented renal clearance and patients who received adjunctive GN therapy.[61]

Emergence of non-susceptibility in the ASPECT-NP study

In the ASPECT-NP study, emergence of nonsusceptibility was not observed among the 59 participants with baseline susceptible *P. aeruginosa* isolates in the C/T arm. Among 58 participants with baseline susceptible *P. aeruginosa* isolates in the meropenem arm, emergence of nonsusceptibility was observed in 13 (22.4%). Among participants who received C/T and meropenem, 5.1% and 3.4% had a new infection with a nonsusceptible strain, respectively. None of the isolates with emergence of nonsusceptibility to meropenem developed co-resistance to C/T.[63]

Susceptibility to C/T in adult studies

The activity of C/T have been well characterized in a comprehensive series of *in vivo* and *in vitro* microbiology studies.[64] C/T is active against some β-lactamase-producing *E. coli* and *K. pneumoniae* (excluding those which are carbapenem resistant [CR] and those harboring metallo-β-lactamases [MBLs]) and multidrug-resistant (MDR) *P. aeruginosa* (including CR strains, but excluding those harboring MBLs). These susceptibility data reflect good potency against both resistant and wild-type *E. coli*, *K. pneumoniae*, and *P. aeruginosa*, with high susceptibility rates in isolates from different patient populations. The Study for Monitoring Antimicrobial Resistance Trends (SMART) and the Program to Assess C/T Susceptibility (PACTS) are global surveillance studies evaluating C/T activity against GN organisms.[65,66] Surveillance data provides a source of evidence on C/T *in vitro* activity against strains that may be underrepresented in clinical trials.

Clinical evidence for C/T in pediatric patients

The phase 1 clinical trial consisted of an open-label, multicenter study to characterize PK, safety, and tolerability of single IV dose of C/T in children with GN infection or receiving perioperative prophylaxis. Patients from birth to <18 years of age were eligible for inclusion and enrolled into 1 of 6 groups dependent on their age.[37]

The initial doses of C/T were chosen based on adult PK data and followed by an interim review doses of safety parameters after the first 3. PK parameters of C/T were similar across all groups, while the clearance was decreased in groups 5 and 6 (<3 months of age) due to reduced renal function. Based on an interim dose increase in group 3, the PK of C/T was demonstrated to be dose proportional. All children achieved the PK/PD target for both ceftolozane and tazobactam. Acceptable PK/PD exposure was defined as the % time of the dosing interval that free concentrations were greater than a minimum inhibitory concentration (MIC) of 8 μg/mL.[37]

No SAEs or deaths were reported for the population of 37 patients. Two patients had DR-AEs that resolved by study completion (dizziness and tachycardia/bradycardia). No clinically significant abnormalities or changes in ECGs were observed after study drug administration.[37]

C/T Real-World Evidence

Since the launch of C/T there have been a variety of real-world data analyses for C/T including case reports and observational studies.[67-125] A wide range of infection types and patient types have been included in these studies that may have had limited or no representation in the clinical trials.

Out of 25 case reports published among patients treated with C/T across the US (16), Italy (4), Spain (2), Australia (1), France (1), and the UK (1) respiratory infections were the most commonly reported (36%).[83-107] The predominant pathogen reported was *Pseudomonas*: 76% were MDR *Pseudomonas*, 16% were XDR *Pseudomonas* and 4% were pan β-lactam resistant *Pseudomonas*. The majority (68%) of the patients had received IIAT. Duration of C/T varied from seven days to eight weeks depending on type of infection. The majority (88% and 81%, respectively) of case reports demonstrated clinical and/or microbiological cure of the infection and only one reported a 30-day mortality.

In addition to the case reports, there were real-world retrospective case-controlled and cohort observational studies. These studies included 2-205 patients in the analysis and respiratory infections represented 26-94% of the infection types reported. A summary of some of the real-world studies follows.

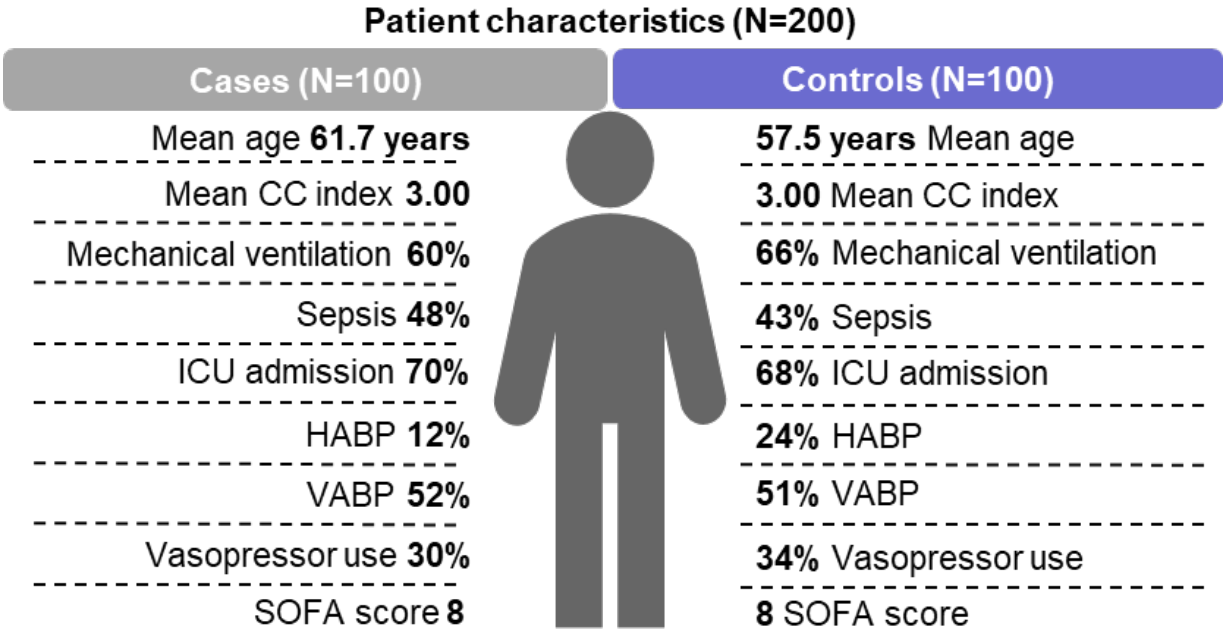
In a real-world setting, delayed initiation of C/T were associated with significantly worse outcomes. This was demonstrated by a retrospective, multi-site study conducted in the US which evaluated patients receiving ≥24 hours of C/T between December 2014 and February 2018.[68] Clinical success was reported in 73.7%, microbiological success was 70.7% and mortality in 19.0% of patients. A multivariate analysis showed that patients that started C/T ≤4 days after culture were associated with greater clinical success (OR=2.93, 95% CI 1.40–6.10), microbiological success (OR=2.59, 95% CI 1.24–5.38), and had 5.55 (95% CI 2.14–14.40) times higher odds of mortality if C/T was initiated after 4 days from culture.[68]

Moreover, C/T has demonstrated effectiveness against highly resistant infections. For example, Bassetti et al. conducted a multicenter, retrospective study at 22 hospitals in Italy.[67] One hundred and one patients who received ≥4 days of C/T for a *P. aeruginosa* infection from June 2016 to March 2018 were included. In this study, 17.8% of patients had MDR *Pseudomonas* and 52.5% had XDR/PDR, 23.8% were in the ICU due to the *Pseudomonas* infection, and over half were immunocompromised. However, clinical success was observed in 83.2% of the patients. The highest rate of clinical success was among patients with non-MDR *Pseudomonas* at 90.0%, yet the rates of success were still maintained for MDR (77.7%) and XDR/PDR (81.1%) infections. Predictive factors for clinical failure included sepsis (OR 3.02, p=0.05) and continuous renal replacement therapy (CRRT) (OR 4.50, p=0.02).[67]

Furthermore, evidence from real-world studies suggest that C/T is more effective than comparator antibacterials for *P. aeruginosa* infections. For example, a case-control study was conducted a teaching hospital in Madrid, Spain.[72] Fifty-seven patients with a hematologic malignancy and *P. aeruginosa* infection treated with C/T (cases) or alternative antibacterials (controls) between March 2016 and February 2018 were included.[72] The average age of C/T treated patients was 45.6 years vs. 57.6 years for alternative antibacterials, mean Charlson Comorbidity index was similar at 3.00 for C/T and 3.26 for controls, mean SOFA score was 5.42 for C/T and 4.50 for controls and ICU admission was 26.3% for C/T vs. 18.4% for controls. The rate of XDR was greater for patients treated with C/T at 47.4% vs. 21.1% of controls. Despite the higher rates of XDR *Pseudomonas* and underlying hematologic malignancies of these patients, the C/T treated patients had higher clinical success rates (89.5% vs. 71.1%, p>0.05) and lower mortality (5.3% vs. 28.9%, p<0.05) vs. the controls.[72]

Further evidence comes from a retrospective, multicenter study in the US which compared C/T treated patients with patients receiving an aminoglycoside or polymyxin based regimen for MDR and XDR *Pseudomonas*.[118] There were 100 patients in each arm and baseline characteristics were similar between the two groups (Figure 1)

Figure 1. Characteristics of patients recruited in Pogue et al.[118]



CC: Charlson comorbidity; HABP: hospital-acquired bacterial pneumonia; ICU: intensive care unit; SOFA: sequential organ failure assessment; VABP: ventilator-associated bacterial pneumonia.

More patients in the comparator group had combination therapy (72% vs. 15%) than in the C/T group.[118] There was a longer time from admission to time of treatment (C/T 55.5 hours vs. 43.5 hours comparator) and time to C/T or the aminoglycoside and/or polymyxin (63.5 hours vs. 53.3 hours). The duration of therapy was similar at 9.5 days for C/T and 9 days for comparator. All C/T patients and 92% of the aminoglycoside/polymyxin regimen had an ID consult. C/T was associated with a higher clinical cure rate and lower development of AKI vs. the aminoglycoside/polymyxin regimen even when adjusted for age, infectious diseases consult, baseline creatinine clearance, duration of therapy, and time to active therapy (Table 9). There was no difference in mortality between these two regimens, however the study was not powered to determine a difference and the complexity of the patient population makes it difficult to assess the impact of therapy for an infection on mortality amidst the other factors contributing to a mortality endpoint.118

Table 9. Outcomes of Pogue et al. 2019[118]

Outcome	Cases (ceftolozane/ tazobactam)	Controls (aminoglycoside/ polymyxin)	OR (95% CI)	aOR* (95% CI)
Clinical cure	81%	61%	2.72 (1.43, 5.17)	2.63 (1.31, 5.30)
In-hospital mortality	20%	25%	0.75 (0.38, 1.46)	0.62 (0.3, 1.28)
Development of AKI	6%	34%	0.12 (0.05, 0.31)	0.08 (0.03, 0.22)

*OR was adjusted for age, infectious diseases consult, baseline creatinine clearance, duration of therapy, and time to active therapy.
AKI: Acute kidney injury; aOR: Adjusted odds ratio; CI: Confidence interval; OR: Odds ratio.

A full summary of non-randomized and non-controlled evidence for the use of C/T in clinical practice is presented in Table 10.

Table 1. C/T real-world evidence summary[67-125]

Citation Study type Location	N	Bacteria Type(s)	Infection Type(s)	Patient illness severity[a]	C/T therapy characteristics[b]	LOS (days)	Clinical (micro) cure (%)	30-day ACM (%)	Outcome by cUTI/cIAI/HABP/VABP indication (%)
Peer-reviewed literature – retrospective analyses, observational studies, case-control studies and case series									
Bassetti et al. 2018[67] Retrospective, multicenter Italy	101	Mixed PsA 50.5% XDR PsA 29.7% non-MDR PsA 17.8% MDR PsA 2.0% PDR PsA	31.7% NP 20.8% ABSSSI 13.9% cUTI 12.9% cIAI 8.9% bone infection 5.9% primary bacteremia 5.9% other	ICU N=24 IMC N=21 APACHE II=ND CCI mean=4.4 SOFA=ND	Initial C/T: ND Confirmed C/T: ND Duration: med.=14 days	ND	83.2 (ND)	5[c]	Clinical cure 75.0 NP 92.9 cUTI 76.9 cIAI
Gallagher et al. 2018[68] Retrospective, multicenter US	205[d]	MDR PsA	28.3% VABP 30.7% non-VABP 2.9% bloodstream 7.8% bone/joint 9.8% IAI 12.7% wound 13.7% UTI	ICU N=105 IMC=ND APACHE II med.=19 CCI med.=4 SOFA=ND	Initial C/T: ND Confirmed C/T: ND Duration: med.=10 days	Med.=31.5	73.7 (70.7)	19	Clinical (Micro) cure 50.0 (53.4) VABP 81.0 (60.3) non-VABP pneumonia 75.0 (90.0) IAI 89.3 (89.3) UTI Mortality rates 37.9 VABP 14.2 non-VABP pneumonia 10.0 IAI 14.3 UTI
Diaz-Cañestro et al. 2018[69] Prospective, single center Spain	58	96.6% MDR PsA 50% XDR PsA	60.3% RTI 17.2% UTI 6.9% IAI 5.2% Bacteremia 3.4% Osteoarticular 6.9% other 93.1% nosocomial	ICU N=16 IMC N=7 APACHE II=ND CCI med.=4 SOFA med.=3	Initial C/T: 1.7% Confirmed C/T: 91.4%[e] Duration: mean=11.4 days	ND	63.8 (ND)	27.6	Clinical cure 51.4 RTI 22.9 UTI 8.6 IAI
Dietl et al. 2018[70] Retrospective, single center Spain	7	Mixed XDR PsA	43% SSTI 57% osteomyelitis	ICU=ND IMC=ND APACHE II=ND CCI med.=6 SOFA=ND	Initial C/T: 0% Confirmed C/T: 71%[f] Duration: med.=13 (SSTI)/ 48 (osteo.) days	Med.=61	86 (100[g])	0	-

Citation Study type Location	N	Bacteria Type(s)	Infection Type(s)	Patient illness severity[a]	C/T therapy characteristics[b]	LOS (days)	Clinical (micro) cure (%)	30-day ACM (%)	Outcome by cUTI/cIAI/HABP/VABP indication (%)
Escolà-Vergé et al. 2018[71] Retrospective, single center Spain	38	Mixed XDR PsA	36.8% RTI 15.8% SSTI 15.8% UTI 10.5% bone 10.5% IAI 7.9% BSI 2.6% mediastinitis 28.9% bacteremic	ICU N=12 IMC=ND APACHE II=ND CCI med.=3.5 SOFA=ND	Initial C/T: ND Confirmed C/T: ND Duration: med.=15.5 days	ND	86.8 (68.4)	13.2[h]	Clinical cure[h] 79 RTI 83 UTI
Fernández-Cruz et al. 2018[72] Case-control[i], single center Spain	57[j]	Mixed PsA 47.4% cases 21.1% controls	Cases: 26.3% pneumonia 21.1% catheter-related BSI 21.1% primary BSI 15.7% perianal/ genital infection 10.5% UTI 5.3% SSTI	ICU N=12[k] IMC N=57 Cases: APACHE II=ND CCI mean=3 SOFA mean=5.42	Initial C/T:15.8% Confirmed C/T: 84.2% Duration: med.=14 days	Mean: 34.8[l]	Case vs. control 89.5 vs. 71.1, p=0.183	Case vs. control 5.3 vs. 28.9, p=0.05	ND
Hakki et al. 2018[73] Retrospective, single center US	6	7 episodes of MDR PsA	42.9% bacteremia 42.9% pneumonia 14.3% soft tissue	ICU=ND IMC N=6[m] APACHE II=ND CCI=ND SOFA=ND	Initial C/T: 33.3% Confirmed C/T: 66.7% Duration: mean=23 days	ND	83.3 (ND)	0	Clinical success[n] 66.6 pneumonia
Xipell et al. 2018[74] Retrospective, single center Spain	23	24 episodes of MDR PsA	33.3% RTI 25% SSTI 29.2% UTI 12.5% IAI	ICU N=4 IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial C/T: 13% Confirmed C/T: ND Duration: mean=14.3 days	ND	88 (75[o])	22[p]	Clinical (Micro[q]) success[n] 87.5 (60.0) RTI 85.7 (100.0) UTI 100.0 (100.0) IAI Mortality rates 37.0 RTI 14.3 UTI 0.0 IAI
Castón et al. 2017[75] Retrospective, multicenter Spain	12	Mixed MDR PsA	25% IAI 50% RTI 8.3% venous catheter 8.3% otitis + mastoiditis 8.3% biliary 83.3% had septic shock	ICU=ND IMC N=4 APACHE II=ND CCI=ND SOFA=ND	Initial C/T: 0% Confirmed C/T: 100% Duration: med.=12 days	ND	75 (58.3)	25	Clinical[r] (Micro) cure 66.6 IAI 66.6 RTI Mortality 33.3 IAI 33.3 RTI

Citation Study type Location	N	Bacteria Type(s)	Infection Type(s)	Patient illness severity[a]	C/T therapy characteristics[b]	LOS (days)	Clinical (micro) cure (%)	30-day ACM (%)	Outcome by cUTI/cIAI/HABP/VABP indication (%)
Dinh et al. 2017[76] Retrospective France	15	Mixed XDR PsA	46.7% RTI 20.0% UTI 13.3% IAI 6.7% meningitis 6.7% vascular graft infection 6.7% BJI	ICU N=8 IMC N=10 APACHE II=ND CCI=ND SOFA mean=7.6	Initial C/T: ND Confirmed C/T: ND Duration: med.=15 days	Med.=12[s]	67 (75[t])	27[u]	ND
Haidar et al. 2017[77] Retrospective, case series US	21	Mixed MDR PsA	86% RTI 5% cUTI 5% cIAI 5% bacteremia	ICU=ND IMC N=9 APACHE II=ND CCI med.=5 SOFA med.=6	Initial C/T: ND Confirmed C/T: ND Duration: med.=14 days	ND	71 (ND)	10	Clinical (Micro) cure[n] 66.6 (ND) RTI 100 (ND) cUTI 100 (ND) cIAI Mortality[h,n] 50 RTI 0 cUTI 0 cIAI
Munita et al. 2017[78] Retrospective, multicenter US	35	Mixed CR PsA	51.0% pneumonia 17.1% secondary BSI	ICU=ND IMC=ND APACHE II=ND CCI med.=4 SOFA med.=ND	Initial C/T: ND Confirmed C/T: ND Duration: med.=16 days	ND	74 (100[v])	22.8[u]	ND
Álvarez Lerma et al. 2017[79] Case series Spain	2	PDR PsA	Ventilation-associated respiratory infections	ICU N=2 IMC=ND APACHE II=23, 28 CCI=ND SOFA=ND	Initial C/T: 0% Confirmed C/T: 100% Duration: mean=15.5 days	ND	100 (100)	50	ND
Sacha et al. 2017[80] Retrospective, single center US	60[w]	Mixed PsA 86.7% PsA 34.6% non-MDR PsA 40.4% MDR PsA 25% XDR PsA	56.7% NP 18.3% IAI 5% SSTI 6.7% primary bacteremia 3.3% BJI 3.3% pleural space infection	ICU N=37 IMC N=25 APACHE II=ND CCI=ND SOFA=ND	Initial C/T: 36.7% Confirmed C/T: 63.3% Duration: med.=1-8 days[x]	Med.=38	64.1 (38.5[y])	16.7[u]	ND
Xipell et al. 2017[81] Case series Spain	3	66.6% PsA[n] 33.3% XDR PsA 33.3% ESBL-producing *E. coli*	Mediastinitis Liver abscess Septic shock	ICU=ND IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial C/T: 0% Confirmed C/T: 100% Duration: mean=30.3 days[z]	ND	100 (ND)	0	-

Citation Study type Location	N	Bacteria Type(s)	Infection Type(s)	Patient illness severity[a]	C/T therapy characteristics[b]	LOS (days)	Clinical (micro) cure (%)	30-day ACM (%)	Outcome by cUTI/cIAI/HABP/VABP indication (%)
Gelfand et al. 2015[82] Case series US	3	MDR PsA	Pneumonia	ICU=ND IMC=3 APACHE II=ND CCI=ND SOFA=ND	Initial C/T: ND Confirmed C/T: ND Duration: mean=12.7 days[aa]	ND	100 (100)	0	Clinical (Micro) cure 100 pneumonia
Peer-reviewed literature - case reports									
Alessa et al. 2018[83] US	1	MDR PsA	NP	ICU=ND IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Confirmed Duration: 13 days	31	100 (100)	0	-
Frattari et al. 2018[84] Italy	1	XDR PsA	Otogenous meningitis	ICU N=1 IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: ND Duration: 14 days	ND	100 (ND)	ND	-
Hassan et al. 2018[85] US	1	XDR PsA	Osteomyelitis	ICU=0 IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Confirmed Duration: 8 weeks	ND	100 (100)	0	-
Lewis et al. 2018[86] US	1	MDR PsA	HCAP	ICU=ND IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: ND Duration: 11 days	ND	0 (0)	100	-
Monterrubio-Villar et al. 2018[87] Spain	1	MDR PsA	Soft tissue infection	ICU N=1 IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Confirmed Duration: 7 days	ICU LOS: 12	100 (100[bb])	ND	-
So et al. 2018[88] US	1	MDR PsA	Bacteremia	ICU=ND IMC N=1 APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Confirmed Duration: 37 days	ND	100[cc] (ND)	0	-

Citation Study type Location	N	Bacteria Type(s)	Infection Type(s)	Patient illness severity[a]	C/T therapy characteristics[b]	LOS (days)	Clinical (micro) cure (%)	30-day ACM (%)	Outcome by cUTI/cIAI/HABP/VABP indication (%)
Stewart et al. 2018[89] US	1	MDR PsA	Pulmonary infection	ICU N=1 IMC N=1 APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Confirmed Duration: 42 days	ND	100 (ND)	0	-
Stokem et al. 2018[90] US	1	MDR PsA	Pulmonary exacerbation of cystic fibrosis	ICU=ND IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: ND Duration: 14 days	ND	100 (ND)	0	-
Teleb et al. 2018[91] US	1	MDR PsA ESBL-producing *E. coli*	Liver abscess	ICU=ND IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Initial Duration: ND	ND	0 (0)	ND[dd]	-
Aye et al. 2017[92] Australia	1	MDR PsA	Mycotic pseudoaneurysm	ICU=ND IMC N=1 APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Initial Duration: 8 weeks	ND	100 (100)	0	-
Castaldo et al. 2017[93] Italy	1	MDR PsA	SSTI	ICU=ND IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Confirmed[ee] Duration: ND	ND	100 (ND)	0	-
Dinh et al. 2017[94] France	1	MDR PsA	Febrile UTI	ICU=ND IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Confirmed Duration: 7 days	ND	100 (100)	0	-
Dominguez et al. 2017[95] Spain	1	MDR PsA	cSSTI	ICU=ND IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Initial Duration: 14 days	ND	100 (ND)	0	-

Citation Study type Location	N	Bacteria Type(s)	Infection Type(s)	Patient illness severity[a]	C/T therapy characteristics[b]	LOS (days)	Clinical (micro) cure (%)	30-day ACM (%)	Outcome by cUTI/cIAI/HABP/VABP indication (%)
Gentile et al. 2017[96] Italy	1	XDR PsA	Osteomyelitis	ICU=ND IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Initial Duration: 8 weeks	ND	100[h] (ND)	0	-
Hernández-Tejedor et al. 2017[97] US	1	MDR PsA	Ventilator-associated tracheobronchitis	ICU N=1 IMC N=1 APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Confirmed Duration: 10 days	ND	100 (100)	0	-
Jones et al. 2017[98] US	1	MDR PsA	UTI	ICU N=0 IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Initial Duration: 2 weeks	ND	100 (100)	0	-
Kurtzhalts et al. 2017[99] US	1	MDR PsA	Osteomyelitis	ICU=ND IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Confirmed Duration: 6 weeks	ND	100 (100)	0	-
MacVane et al. 2017[100] US	1	MDR PsA	Wound infection	ICU=ND IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Confirmed Duration: 6 weeks	ND	0 (0)[ff]	0[gg]	-
Peghin et al. 2017[101] Italy	1	MDR PsA	LVAD related infection	ICU=ND IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Confirmed Duration: 6 weeks / 4.5 weeks[hh]	ND	100 (100)[hh]	0	-
Schwarz et al. 2017[102] US	1	XDR PsA	Facial cellulitis and extranodal natural killer T-cell lymphoma, septic shock	ICU N=1 IMC N=1 APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: ND Duration: ND	ND	100 (ND)	0	-

Citation Study type Location	N	Bacteria Type(s)	Infection Type(s)	Patient illness severity[a]	C/T therapy characteristics[b]	LOS (days)	Clinical (micro) cure (%)	30-day ACM (%)	Outcome by cUTI/cIAI/HABP/VABP indication (%)
Jolliff et al. 2016[103] US	1	MDR *S. maltophilia*	Polymicrobial osteomyelitis	ICU=ND IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Confirmed Duration: 6 weeks	ND	100 (100)	0	-
Kuti et al. 2016[104] US	1	MDR PsA	VABP	ICU N=1 IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Confirmed Duration: 10 days	~30	100 (100)	0[ii]	-
Patel et al. 2016[105] US	1	MDR PsA *P. mirabilis* *K. pneumoniae*	BSI	ICU=ND IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Confirmed Duration: 25 days	ND	100 (100)	0	-
Vickery et al. 2016[106] US	1	MDR PsA	Pulmonary exacerbation of cystic fibrosis	ICU=ND IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Confirmed Duration: 12 days	16	100 (ND)	0	-
Soliman et al. 2015[107] UK	1	PDR PsA	Exacerbation of chronic pulmonary infection (bronchiectasis)	ICU=ND IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Confirmed Duration: 14 days	73[n]	100 (100)	0	-
Conference proceedings									
Gioia et al. 2018[108] Retrospective, single center Spain	15	MDR PsA	53% RTI 27% IAI 13% Wound 7% BSI	ICU N=8 IMC N=9 APACHE II=ND CCI med.=4 SOFA=ND	Initial C/T: ND Confirmed C/T: ND Duration: med.=23 days	ND	60 (60)	27	ND
Jayakumar et al. 2018[109] Retrospective, multicenter US	22	Mixed 95% PsA 90% MDR PsA	Sepsis and/or bacteremia	ICU=ND IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial C/T: 18% Confirmed C/T: ND Duration: med.=10±6 days	ND	77 (ND)	23	ND

Citation Study type Location	N	Bacteria Type(s)	Infection Type(s)	Patient illness severity[a]	C/T therapy characteristics[b]	LOS (days)	Clinical (micro) cure (%)	30-day ACM (%)	Outcome by cUTI/cIAI/HABP/VABP indication (%)
Jorgensen et al. 2018[110] Retrospective, multicenter US	116	MDR PsA	65% RTI 10.3% UTI 9.4% SSTI 6% Bone/joint 3.4% IAI 1.7% BSI 4.3% Other	ICU N=72 IMC N=22 APACHE II med.=21 CCI med.=3.5 SOFA=ND	Initial C/T: ND Confirmed C/T: ND Duration: ND	ND	61.2[jj] (ND)	17.2	ND
Pogue et al. 2018[111] Retrospective, database US	113	PsA	64% cUTI 36% cIAI	ICU=ND IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial C/T: 31% Confirmed C/T: early definite 28% and late definite 41% Duration: ND	11	ND (ND)	12[c]	Mortality 8 cUTI 20 cIAI
Tordato et al. 2018[112] Retrospective, single center Italy	11	Mixed 73% XDR PsA	54% RTI 27% BSI 18% IAI	ICU N=6 IMC N=3[kk] APACHE II=ND CCI med.=4 SOFA=ND	Initial C/T: ND Confirmed C/T: ND Duration: med.=16 days	ND	100 (ND)	36	ND
Elabor et al. 2018[113] Retrospective, multicenter US	65	MDR PsA	Pneumonia Wound/bone/ joint UTI IAI BSI[ll]	ICU N=65 IMC N=37 APACHE II med.=20 CCI med.=6 SOFA=ND	Initial C/T: ND Confirmed C/T: ND Duration: ND	ND	78.4 (75.3)	13.9	30-d ACM: 9.1 Pneumonia 22.3 UTI 0.0 IAI Clinical (Micro) cure: 84.8 (72.7) Pneumonia 88.8 (77.7) UTI 57.1 (100.0) IAI
Henry et al. 2018[114] Retrospective, single center US	29	86% PsA 7% *Klebsiella* 7% *E. coli*	26% Pneumonia 21% IAI 21% UTI 17% BSI 14% SSTI	ICU N=15 IMC=ND[mm] APACHE II=ND CCI=ND SOFA=ND	Initial C/T: 36% Confirmed C/T: ND Duration: med.=10 days	ND	76 (ND)	38	ND
Hirsch et al. 2018[115] Retrospective, multicenter US	35	79% PsA	33% RTI 21% BSI 18% Bone/joint 15% Wound 9% Other 3% Urine	ICU N=26 IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial C/T: 20% Confirmed C/T: ND Duration: ND	53 ± 57	77.4 (74.2)	14.3	ND

Citation Study type Location	N	Bacteria Type(s)	Infection Type(s)	Patient illness severity[a]	C/T therapy characteristics[b]	LOS (days)	Clinical (micro) cure (%)	30-day ACM (%)	Outcome by cUTI/cIAI/HABP/VABP indication (%)
Hooper et al. 2018[116] Case report Canada	1	MDR PsA *S. anginosus*	Chronic Spinal Osteomyelitis	ICU=ND IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial/confirmed C/T: Confirmed Duration: 6 weeks	ND	100 (100)	0	-
Jorgensen et al. 2018[117] Retrospective, multicenter US	137	MDR PsA	ND	ICU N=87 IMC N=11 APACHE II=ND CCI=ND SOFA=ND	Initial C/T: ND Confirmed C/T: ND Duration: ND	ND	ND	18.2	ND
Pogue et al. 2019[118] Retrospective, multicenter, cohort US	200[nn]	MDR or XDR PsA	Cases/controls 52/51% VABP 12/24% HABP 16/11% cUTI 13/8% Wound 7/6% Other	ICU N=138[oo] IMC N=ND APACHE II=ND CCI mean=3[pp] SOFA=ND	Initial C/T: ND Confirmed C/T: ND Duration: med.=9.5 hours	ND	Cases 81 (ND) Controls 61 (ND)	Cases 20[u] Controls 25[u]	ND
Puzniak et al. 2018[119] Retrospective, database US	1,490	Mixed 78% PsA[qq]	ND	ICU N=824 IMC=ND APACHE II=ND CCI mean=3 SOFA=ND	Initial C/T: ND Confirmed C/T: ND Duration: med.=8 days	Med.=18 (hospital LOS)	ND	9.1	ND
Puzniak et al. 2018[120] Retrospective, database US	199	PsA	57% RTI 17% Urine 26% Other	ICU N=107 IMC N=ND APACHE II=ND CCI mean=2.9 SOFA=ND	Initial C/T: 34% Confirmed C/T: early direct 50% and late direct 16% Duration: med.=8 days	Med.=18 (hospital LOS)	ND	14	ND
Davis et al. 2017[121] Case report US	1	Mixed MDR PsA ESBL-*E. coli*	Pulmonary exacerbation of cystic fibrosis	ICU=ND IMC N=ND APACHE II=ND CCI mean=2.9 SOFA=ND	Initial/confirmed C/T: Confirmed Duration: ND	ND	100 (ND)	0	-
Leuthner et al. 2017[122] Retrospective, single center US	30	Mixed 93% PsA (87% MDR) 3% *E. coli* 3% *P. stuartii*	67% RTI 27% cUTI 20% BSI 7% cIAI	ICU N=8 IMC N=4 APACHE II=ND CCI=ND SOFA=ND	Initial C/T: 23% Confirmed C/T: ND Duration: med.=10 days	ND	80 (92[ss])	20[tt]	ND

Citation Study type Location	N	Bacteria Type(s)	Infection Type(s)	Patient illness severity[a]	C/T therapy characteristics[b]	LOS (days)	Clinical (micro) cure (%)	30-day ACM (%)	Outcome by cUTI/cIAI/HABP/VABP indication (%)
Sandoe et al. 2017[123] Case report UK	1	XDR PsA	Infective Endocarditis	ICU=ND IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial C/T: ND Confirmed C/T: ND Duration: ND	ND	100 (N/A)	0	-
Iovleva et al. 2016[124] Retrospective, single center US	2	PsA-imipenem-resistant	HCAP	ICU=ND IMC=ND APACHE II mean=13 CCI mean=2 SOFA=ND	Initial C/T: ND Confirmed C/T: ND Duration: ND	ND	100 (100)	0	-
Nathan et al. 2016[125] Retrospective, multicenter US	28	68% resistant pathogens[uu] 36.4% MDR PsA[n] 15.2% ESBL-producing *E. coli*	28.6% RTI 25% cIAI 25% cUTI 21.4% cSSTI	ICU N=0 IMC=ND APACHE II=ND CCI=ND SOFA=ND	Initial C/T: ND Confirmed C/T: ND Duration: med.=12 days for RTI, 12 days for cIAI and 15 days for cUTI	ND	89 (ND)	0	Clinical (cure) success[vv]: 100.0 (75.0) RTI 71.0 (43.0) cIAI 100.0 (71.0) cUTI
Chaftari et al. OFID 2022. Prospective randomized open label, US single center NCT03485950[126]	100	Gram negative blood stream isolates from febrile neutropenic cancer patients		100% febrile neutropenic cancer patients; prospective randomized open label study of C/T vs. SOC GN coverage	Following randomization to either C/T or SOC, subjects were immediately started on assigned GN coverage with febrile neutropenia as defined in the protocol	ND	86%	0% infection related; ACM 4%	
Bergas et al. Microbiol Spectr 2022. Multicenter international matched cohort study[127]	44 cases 88 controls	Pseudomonas aeruginosa	100% BSI; 91% MDR PSA	Neutropenic hematologic patients	C/T given empirically to 11 patients; definitive therapy to 41			C/T receipt associated with lower mortality, aOR 0.19 95% CI 0.07-0.55, P=0.002	Those receiving C/T experienced less mechanical ventilation need (13.6% v 33.3%); reduced 7-day and 30-day mortality (6.8 v 34.1, P=001; 22.7% v 48.9% P-0.005)

[a]Included measures on how ill the patients were: number of patients in the ICU, number of IMC patients, APACHE II score, CCI, and SOFA score. [b]Initial therapy, confirmed therapy and duration of therapy were included. Initial therapy was defined as therapy begun on the basis of a clinical "educated guess" in the absence of complete infection information. [c]No timeframe given. [d]Some patients had *Pseudomonas* isolated from multiple sites with multiple types of infection diagnosed; therefore, the total is greater than 205. [e]In 6.9% of patient's C/T treatment was classed as 'semi-initial'. [f]C/T used as salvage therapy in 2 (19%) of patients, no indication as to whether initial or confirmed. [g]Microbiological cure is not reported for three out of seven patients. [h]Timeframe: 90-day. [i]Controls were treated initially and targeted therapy was adjusted with piperacillin-tazobactam, cefepime, ceftazidime, meropenem, ciprofloxacin, colistin, or amikacin as per *in vitro* susceptibility results. Cases were treated with C/T. [j]19 cases treated with C/T and 38 controls. [k]5 cases, 7 controls. [l]LOS prior to infection. [m]6 patients had a hematologic malignancy or had undergone a hematopoietic stem cell transplant. [n]Calculated using data from the publication. [o]Microbiological cure is not reported for eight patients. [p]Timeframe for ACM was six weeks. [q]Microbiological cure is not reported for three patients with a RTI, 1 patient with a UTI and two patients with an IAI; percentages are given for those with data. [r]Clinical cure at 30 days. [s]LOS prior to treatment. [t]Microbiological cultures were obtained in only eight patients. [u]In-hospital mortality. [v]Microbiological cultures were collected for only 25 patients. [w]49 patients receiving 60 total courses of C/T therapy. [x]Median duration of therapy in patients who received pathogen-directed therapy was 8 days; initial-turned-pathogen-directed therapy, 8 days; initial-remained-initial therapy, 7.5 days; and initial therapy that was subsequently changed or discontinued, 1 day. [y]Microbiological cultures were collected in only 13 patients. [z]One patient was treated for 3 weeks, one for 4 weeks, and one for 6 weeks.
[aa]Two patients were treated for 14 days and one was treated for 10 days. [bb]Microbiological response reported as favorable. [cc]Susceptibility tests showed that the isolates developed resistance to C/T; success may have been due to use of combination tobramycin. [dd]Care was withdrawn due to poor prognosis and lack of response to treatment. [ee]C/T was the first antibacterial given but following susceptibility testing. [ff]Following 6 weeks of treatment, cultures grew PsA resistant to C/T. [gg]Patient died 8 months after transition to palliative care. [hh]Patient experienced a recurrent infection after the first course of C/T which was cured by a second course of C/T. [ii]Despite clinical and microbiological cure, the patient eventually died of acute myocardial infarction (timeframe not specified); [jj]Reported as composite clinical failure (30-day mortality, 30-day recurrence, failure to resolve signs and symptoms). [kk]Three patients had hematopoietic stem cell transplants and were "severely immunosuppressed". [ll]Percentages not reported. [mm]11 patients (38%) were SOT recipients. [nn]100 cases were treated with C/T and 100 controls were treated with a polymyxin- or aminoglycoside-based regimen. [oo]70 cases and 68 controls had an ICU admission. [pp]CCI was the same for both cases and controls. [qq]202 of 259 patients with microbiology results. [rr]This study reports on a subset of patients with PsA infections that were identified in the Puzniak *et al*. 2018 study displayed directly above. [ss]12 out of 13 assessed patients had microbiological eradication. [tt]Mortality within 60 days of last C/T dose. [uu]23 patients reported 33 isolates. [vv]Clinical success was defined as clinical cure (resolution of signs/symptoms and no further treatment needed) combined with clinical improvement (partial resolution of signs/symptoms or continued oral antibacterials).

ABSSSI: Acute bacterial skin and skin structure infection; ACM: All-cause mortality; APACHE: Acute Physiology and Chronic Health Evaluation; BJI: Bone and joint infection; BSI: Bloodstream infection; CCI: Charlson Comorbidity index; cIAI: complicated intra-abdominal infection; CR: carbapenem resistant; cSSTI: complicated skin and soft tissue infection; C/T: ceftolozane/tazobactam; cUTI: complicated urinary tract infection; ESBL: extended-spectrum β-lactamase; HABP: hospital-acquired bacterial pneumonia; HCAP: healthcare-associated pneumonia; IAI: intra-abdominal infection; ICU: intensive care unit; IMC: immunocompromised; LOS: length of stay; LVAD: left-ventricular assist device; MDR: multi-drug-resistant; N/A: not available; ND: not disclosed; NP: nosocomial pneumonia; osteo.: osteomyelitis; PDR: pan-drug-resistant; PsA: *Pseudomonas aeruginosa*; RTI: respiratory tract infection; SOFA: sequential organ failure assessment; SSTI: skin and soft tissue infection; UK: United Kingdom; US: United States; UTI: urinary tract infection; VABP: ventilator-associated bacterial pneumonia; XDR: extensively-drug-resistant

Review of Harms and Toxicity: Summary of Evidence of Safety

Safety Profile of C/T in Adults

Among patients in the trials, C/T was generally well tolerated and the overall safety profile and tolerability were similar to the comparator in the ASPECT-cUTI, ASPECT-cIAI and ASPECT-NP trials.

In ASPECT-cUTI, C/T demonstrated an overall safety profile and tolerability similar to levofloxacin. Incidence rates of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), drug-related TEAEs, discontinuations due to adverse events (AEs), and drug-related discontinuations due to AEs were comparable across the treatment groups. Most AEs were mild or moderate in severity; the most common TEAEs were headache, constipation and hypertension in the C/T treatment group, and headache, diarrhea, and constipation in levofloxacin treatment group, all commonly reported AEs in this indication.[53]

In ASPECT-cIAI, C/T demonstrated an overall safety profile and tolerability similar to meropenem. The incidence of TEAEs, SAEs, drug-related TEAEs, discontinuations due to AEs, drug- related discontinuations due to AEs, and deaths were comparable between the treatment arms.[56] Most AEs were mild or moderate in severity; the most common TEAEs were gastrointestinal (GI) disorders.

In ASPECT-NP, C/T demonstrated an overall safety profile and tolerability similar to meropenem and typical of critically ill, ventilated subjects with HABP/VABP receiving antibacterial therapy. The incidence of TEAEs, SAEs, discontinuation due to AEs, drug-related discontinuations due to AEs and deaths were comparable between the treatment arms. The proportion of subjects in each category of severity was similar between the treatment groups; the most common TEAEs were anemia, urinary tract infections (UTIs), diarrhea and decubitus ulcers.[61]

Safety/Tolerability of C/T in cUTI in Pediatric Patients

The safety and efficacy of C/T vs. meropenem was investigated in a phase II randomized, active comparator-controlled, multicenter, double-blind trial of 133 pediatric subjects from birth to <18 years of age with cUTI, including pyelonephritis. The primary objective of the trial was to evaluate that the safety of C/T was comparable to that of meropenem. This was confirmed by the similar percentage of AEs (59.0% vs. 60.6%) and DR-AEs (14.0% vs. 15.2%) between C/T and meropenem, combined with a lack of DR-SAEs for both C/T and meropenem treatment groups throughout the study.[38]

The efficacy rates of C/T were comparable to that of meropenem, and consistent with that of the adult population.[38] These data indicate that C/T may be efficacious in the pediatric population.

Safety/Tolerability of C/T in cIAI in Pediatric Patients

A phase II, randomized, active comparator-controlled, multicenter, double-blind study in 91 pediatric participants from birth to <18 years of age with cIAI was conducted in order to establish the safety and efficacy of C/T plus metronidazole (MTZ) compared to meropenem plus placebo.[39]

The primary objectives of this study were to evaluate the safety and tolerability of C/T plus metronidazole. There was a higher incidence of AEs in the C/T plus metronidazole group compared to the meropenem group (80.0% vs. 61.9%), further elucidated by the increased rate of DR-AEs (18.6% vs. 14.3%). It is worth noting however that none of these DR-AEs were considered to be serious. These AE rates were comparable to the C/T safety profile in adults.[38,39]

Clinical efficacy was the secondary objective of this Phase II clinical trial. Clinical success rates of IV C/T were high in treatment of cIAIs, although numerically lower than that of meropenem. The efficacy rates of C/T were consistent with that of the adult population.[39] These data indicate that C/T may be efficacious in the pediatric population.

Summary of Available Data on Comparative Cost and Cost-Effectiveness

Cost effectiveness models have been developed for C/T's HAP/VAP, cUTI and cIAI indications that demonstrate the economic value of C/T. Summaries of some of these models are provided below. Although these models were developed from the perspective of high-income countries, we anticipate these data support that C/T would also be cost-effective in LMICs.

HAP/VAP

Italian healthcare sector perspective

Mennini et al. (2022) evaluated the cost-effectiveness of C/T compared to meropenem for the treatment of patients with hospital-acquired pneumonia (HABP) or ventilator-associated pneumonia (VABP) from the Italian National Health Service (NHS) and social perspective. A decision tree and a Markov model were developed in order to forecast long-term and short-term disease effects respectively. A hypothetical target population of 1,000 HABP/VABP patients was followed for a lifetime time horizon. In the short-term decision tree, two different settings were developed in order to evaluate the value of empirical therapy compared with the start of treatment after confirmation of the antibiogram. Treated and cured patients enter the long-term Markov model following the mortality of the general population. Direct and indirect costs were considered accordingly with the analysis perspective.[128]

The analysis showed that C/T, in both treatment settings (empirical and confirmed), may be a cost-effective option compared to meropenem from the NHS and social perspective (ICER equal to € 1,913 and € 2,203 in the empirical treatment setting and € 6,163 and € 6,597 in the confirmed treatment setting for NHS and social perspective respectively). Based on study findings, the introduction of C/T within the Italian healthcare context represents a valid therapeutic solution both from an economic and an efficacy profile point of view.[128]

US healthcare sector perspective

Naik et al. (2021) assessed the cost-effectiveness of C/T compared with meropenem for the treatment of vHABP/VABP in a US hospital setting. A short-term decision tree followed by a long-term Markov model was developed to estimate lifetime costs and quality-adjusted life-years associated with C/T and meropenem in the treatment of patients with vHABP/VABP. Pathogen susceptibility and clinical efficacy were informed by the Program to Assess C/T Susceptibility (PACTS) database and ASPECT-NP, respectively. A US healthcare sector perspective was adopted, capturing direct costs borne by third-party payers or integrated health systems, and direct health effects for patients.[129]

The analysis showed that in the confirmed treatment setting (post-susceptibility results), the incremental cost-effectiveness ratio for C/T compared to meropenem was US$12,126 per quality-adjusted life-year (QALY); this reduced when used in the early treatment setting (before susceptibility results) at $4775/QALY. Based on study findings, C/T represents a highly cost-effective treatment option for patients with vHABP/VABP vs. meropenem when used in either the confirmed or early treatment setting; with increased cost-effectiveness shown in the early setting.[129]

cUTI

Taiwan healthcare sector perspective

Chen et al. (2019) used a cost-utility model to compare the empiric use of C/T with piperacillin/tazobactam in patients with cUTI. The analysis was conducted using a decision tree and patient-level simulation approach. Patients in the model received empiric antibiotic treatment with C/T or piperacillin/tazobactam. Outcomes included mortality, medical costs and quality-adjusted life years (QALYs). Parameters related to pathogen distribution, length of hospital stay and medical costs, were estimated based on a cohort of patients with cUTI admitted during July 1, 2015 to August 31, 2016 to the National Taiwan University Hospital, a teaching hospital in Taiwan. Isolates used for the patient-level simulation to determine susceptibility to either drug were taken from the Study for Monitoring Antimicrobial Resistance Trend database.[130]

The analysis was performed on a simulation of 1,000 patients. Empiric use of C/T leads to higher total medical costs (US $4,199.01 per patient vs. US $3,594.76, respectively) but also more discounted QALYs (4.80 vs. 4.78, respectively). The additional cost per discounted

QALY gained associated with empiric C/T was US $32,521.08 (956,282 NTD). Findings suggest that empiric use of C/T for the treatment of cUTI could be a cost-effective choice in Taiwan.[130]

US healthcare sector perspective
Kauf et al. (2017) evaluated the cost-effectiveness of C/T compared with piperacillin/tazobactam for the treatment of hospitalized patients with cUTI. A decision-analytic Monte Carlo simulation model was developed to compare the costs and effectiveness of empiric treatment with either C/T or piperacillin/tazobactam in hospitalized adult patients with cUTI infected with Gram-negative pathogens in the US. The model applies the baseline prevalence of resistance as reported by national in-vitro surveillance data.[131]

The analysis showed that in a cohort of 1,000 patients, treatment with C/T resulted in higher total costs compared with piperacillin/tazobactam ($36,413 /patient vs. $36,028/patient, respectively), greater quality-adjusted life years (QALYs) (9.19/patient vs. 9.13/patient, respectively) and an incremental cost-effectiveness ratio (ICER) of $6,128/QALY. C/T remained cost-effective at a willingness to pay of $100,000 per QALY compared to piperacillin/tazobactam over a range of input parameter values during one-way and probabilistic sensitivity analysis. Based on study findings, C/T is likely to be cost-effective compared with piperacillin/tazobactam for the empiric treatment of hospitalized cUTI patients in the United States.[131]

cIAI

US healthcare sector perspective
Background: Prabhu et al. (2017) assessed the cost-effectiveness of C/T plus metronidazole compared with piperacillin/tazobactam in the treatment of hospitalized US patients with cIAI at risk of infection with resistant pathogens. A decision-analytic Monte Carlo simulation model was used to compare the costs and quality-adjusted life years (QALYs) of persons infected with nosocomial gram-negative cIAI treated empirically with either C/T + metronidazole or piperacillin/tazobactam. Pathogen isolates were randomly drawn from the Program to Assess C/T Susceptibility (PACTS) database, a surveillance database of non-duplicate bacterial isolates collected from patients with cIAIs in medical centers in the USA from 2011 to 2013. Susceptibility to initial therapy was based on the measured susceptibilities reported in the PACTS database determined using standard broth micro-dilution methods as described by the Clinical and Laboratory Standards Institute (CLSI).[132]

Model results, with baseline resistance levels from the PACTS database, indicated that C/T + metronidazole dominated piperacillin/tazobactam, with lower costs ($44,226/patient vs. $44,811/patient respectively) and higher QALYs (12.85/patient vs. 12.70/patient, respectively). C/T+ metronidazole remained the dominant choice in one-way and probabilistic sensitivity analyses. Based on surveillance data, C/T is more likely to be an appropriate empiric therapy for cIAI in the US. Results from a decision-analytic simulation model indicate that use

of C/T + metronidazole would result in cost savings and improves QALYs, compared with piperacillin/tazobactam.[132]

UK healthcare sector perspective

Prabhu et al. (2017) assessed the cost-effectiveness of C/T + metronidazole compared with piperacillin/tazobactam in the treatment of patients with cIAI in UK hospitals. A decision-analytic Monte Carlo simulation model was used to compare costs (antibiotic and hospitalization costs) and quality-adjusted life years (QALYs) of patients infected with gram-negative cIAI and treated empirically with either C/T + metronidazole or piperacillin/tazobactam. Bacterial isolates were randomly drawn from the Program to Assess C/T Susceptibility (PACTS) database, a surveillance database of non-duplicate bacterial isolates collected from patients in the UK infected with gram-negative pathogens. Susceptibility to initial empiric therapy was based on the measured susceptibilities reported in the PACTS database.[133]

C/T plus metronidazole was cost-effective when compared with piperacillin/tazobactam, with an incremental cost-effectiveness ratio (ICER) of £4,350/QALY and 0.36 hospitalization days/patient saved. Costs in the C/T+ metronidazole arm were £2,576/patient, compared with £2,168/patient in the piperacillin/tazobactam arm. The C/T + metronidazole arm experienced a greater number of QALYs than the piperacillin/tazobactam arm (14.31/patient vs. 14.21/patient, respectively). C/T+ metronidazole remained cost-effective in one-way sensitivity and probabilistic sensitivity analyses. Results indicated that empiric use of C/T+ metronidazole is cost-effective vs. piperacillin/tazobactam in UK patients with cIAI at risk of resistant infection.[133]

Summary of Regulatory Status and Market Availability

Country	Original regulatory approval date	Regulatory approval of HAP/VAP	Market availability
Algeria		Pending	Pending
Argentina	3/16/2017	10/21/2019	Yes
Australia	11/4/2015	3/31/2020	Yes
Austria	9/18/2015	8/23/2019	Yes
Bahrain	5/22/2019	9/14/2020	Yes
Belgium	9/18/2015	8/23/2019	Yes
Brazil	1/8/2018	2/10/2020	Yes
Bulgaria	9/18/2015	8/23/2019	Yes
Canada	9/30/2015	8/30/2019	Yes
Chile	1/26/2017	11/14/2019	Yes
Colombia	4/26/2018	6/17/2020	Yes
Costa Rica	10/5/2017	1/13/2020	No
Croatia	9/18/2015	8/23/2019	Yes
Cyprus	9/18/2015	8/23/2019	Yes
Czech Republic	9/18/2015	8/23/2019	Yes
Denmark	9/18/2015	8/23/2019	Yes
Dominican Republic	3/8/2017	10/1/2019	No
Ecuador	4/18/2017	9/3/2020	No
Egypt	2/28/2019	11/4/2019	Yes
Estonia	9/18/2015	8/23/2019	Yes
Finland	9/18/2015	8/23/2019	Yes
France	9/18/2015	8/23/2019	Yes
Germany	9/18/2015	8/23/2019	Yes
Greece	9/18/2015	8/23/2019	Yes
Guatemala	5/9/2017	11/20/2019	No
Honduras	12/28/2017	6/10/2020	No
Hong Kong	5/23/2017	4/28/2020	Yes
Hungary	9/18/2015	8/23/2019	Yes
Iceland	9/18/2015	8/23/2019	No
Indonesia	5/10/2019	4/20/2020	Yes
Ireland	9/18/2015	8/23/2019	Yes
Israel	2/7/2018	Pending	Yes
Italy	9/18/2015	8/23/2019	Yes
Jamaica		Pending	Pending
Japan	1/8/2019	12/20/2019	Yes
Jordan	11/29/2017	11/10/2019	Yes

Kazakhstan	11/16/2017	6/19/2020	No
Korea, Republic of	4/7/2017	10/29/2019	Yes
Kuwait	12/7/2016	6/10/2020	Yes
Latvia	9/18/2015	8/23/2019	No
Lebanon	3/23/2017	9/17/2019	No
Liechtenstein	9/18/2015	8/23/2019	No
Lithuania	9/18/2015	8/23/2019	No
Luxembourg	9/18/2015	8/23/2019	No
Malaysia	12/22/2016	2/13/2020	Yes
Malta	9/18/2015	8/23/2019	No
Mexico	2/2/2017	8/2/2021	Yes
Morocco	11/5/2018	5/11/2020	No
Netherlands	9/18/2015	8/23/2019	Yes
New Zealand	10/8/2015	11/18/2021	Yes
Northern Ireland	9/18/2015	8/23/2019	Yes
Norway	9/18/2015	8/23/2019	Yes
Oman	11/4/2019	6/20/2020	Yes
Pakistan		Pending	Pending
Panama	9/21/2017	8/10/2020	Yes
Paraguay		Pending	Pending
Peru	8/31/2017	8/16/2019	Yes
Philippines	12/19/2016	10/24/2019	Yes
Poland	9/18/2015	8/23/2019	Yes
Portugal	9/18/2015	8/23/2019	Yes
Qatar	1/31/2018	2/17/2020	Yes
Romania	9/18/2015	8/23/2019	Yes
Russian Federation	9/28/2018	10/31/2019	Yes
Saudi Arabia	11/29/2017	3/26/2020	Yes
Serbia	3/28/2017	5/5/2020	Yes
Singapore	8/14/2017	7/17/2020	Yes
Slovakia	9/18/2015	8/23/2019	Yes
Slovenia	9/18/2015	8/23/2019	Yes
South Africa	10/27/2020	Pending	Yes
Spain	9/18/2015	8/23/2019	Yes
Sweden	9/18/2015	8/23/2019	Yes
Switzerland	3/3/2016	3/4/2020	Yes
Taiwan	6/30/2017	11/11/2019	Yes
Thailand	6/16/2017	6/12/2020	Yes
Trinidad and Tobago		Pending	Pending
Turkey	5/18/2017	12/16/2020	No
United Arab Emirates	9/29/2016	10/17/2019	Yes
UK	9/18/2015	8/23/2019	Yes

Ukraine	10/11/2017	7/2/2020	No
United States	12/19/2014	6/3/2019	Yes
Uruguay	8/5/2020	8/7/2020	No
Vietnam	10/23/2019	Pending	Yes

Availability of Pharmacopoeia Standards

C/T is not currently available in any pharmacopoeia standards.

Appendix A – Abbreviations

ABSSSI	Acute bacterial skin and skin structure infection
ACM	All-cause mortality
AE	Adverse event
AKI	Acute kidney injury
AmpC	Ampicillin class C
AMR	Antimicrobial resistance
aOR	Adjusted odds ratio
APACHE	Acute Physiology and Chronic Health Evaluation
ASPECT	Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam
AST	Antimicrobial susceptibility testing
BJI	Bone and joint infection
BSI	Bloodstream infection
CCI	Charlson Comorbidity index
CDC	The Centers for Disease Control and Prevention
CDDEP	Center for Disease Dynamics, Economics and Policy
CE	Clinically evaluable
CI	Confidence interval
cIAI	Complicated intra-abdominal infection
CL	Clearance
CLSI	Clinical and Laboratory Standards Institute
C_{max}	Maximum (peak) plasma drug concentration
CrCL	Creatinine clearance
CRE	Carbapenem resistant *Enterobacterales*
CRRT	Continuous renal replacement therapy
cSSTI	Complicated skin and soft tissue infection
CT	Computed tomography
C/T	Ceftolozane/tazobactam
CTX-M	Active on cefotaxime
CUA	Cost-utility analysis
cUTI	Complicated urinary tract infection
eGFR	Estimated glomerular filtration rate
EMA	European Medicine Agency

EML	Model List of Essential Medicines
ERS	European Respiratory Society
ESBL	Extended-spectrum β-lactamase
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
ESRD	End-stage renal disease
EU	European Union
FDA	Food and Drug Administration
g	Gram
GI	Gastrointestinal
GN	Gram-negative
HAP	Hospital-acquired pneumonia
HABP	Hospital-acquired bacterial pneumonia
HAP	Hospital-acquired pneumonia
HCAP	Healthcare-associated pneumonia
HD	Hemodialysis
IAI	Intra-abdominal infection
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
IIAT	Initial inappropriate antibacterial therapy
IMC	Immunocompromised
ITT	Intent-to-treat
IV	Intravenous
Kg	Kilogram
KPC	*Klebsiella pneumoniae* carbapenemase
L	Liter
LIMIC	Low- and middle-income countries
LOS	Length of stay
LVAD	Left-ventricular assist device
M	Meter
MDR	Multi-drug-resistant
ME	Microbiologically evaluable
Mg	Milligram
MIC	Minimum inhibitory concentration
Micro.	Microbiological success
Min	Minute
mITT	Microbiological intent-to-treat
mL	Milliliter
mmHg	Millimeter of mercury
mMITT	Microbiological modified intent-to-treat
MTZ	Metronidazole
N	Number of patients in population
N/A	Not applicable
NHS	National Health Service
NP	Nosocomial pneumonia
OprD	Outer membrane porin

OR	Odds ratio
OXA	Oxacillin β-lactamase
PACTS	Program to Assess Ceftolozane/Tazobactam Susceptibility
PBP	Penicillin-binding protein
PDR	Pan-drug-resistant
PK	Pharmacokinetics
PK/PD	Pharmacokinetic/pharmacodynamic
PSA	Probabilistic sensitivity analysis
PsA	*Pseudomonas aeruginosa*
QALY	Quality-adjusted life year
q8h	Every 8 hours
RTI	Respiratory tract infection
SAE	Serious adverse event
SD	Standard deviation
SHV	SHV β-lactamase
SIS	Surgical Infection Society
SMART	Study for Monitoring Antimicrobial Resistance Trends
SOFA	Sequential organ failure assessment
SSTI	Skin and soft tissue infection
TEAE	Treatment-emergent adverse events
TEM	β-lactamase first found in patient “Temoniera”
TOC	Test-of-cure
UK	United Kingdom
US	United States
USD	United States Dollar
UTI	Urinary tract infection
VAP	Ventilator-associated pneumonia
VABP	Ventilator-associated bacterial pneumonia
WHO	World Health Organization
WSES	World Society of Emergency Surgery
XDR	Extensively drug-resistant

Appendix B: Regulatory Documents

ZERBAXA PI 2019.pdf

ZERBAXA SmPC 2019.pdf

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