antibiotics

MDPI

Systematic Review

Ceftolozane/Tazobactam for Complex and Resistant Infections: Systematic Reviews of Comparative Efficacy Studies

Ignacio Martin-Loeches [1], Ryan K. Shields [2], Emre Yücel [3,*], Shalini Bagga [4], Maesumeh Korei [4], Hariprasad Esam [4], Nidhi Sharma [4] and Carolyn Cameron [5]

[1] Department of Intensive Care Medicine, Multidisciplinary Intensive Care Research Organization (MICRO), St. James's Hospital, D08 NHY1 Dublin, Ireland
[2] Department of Medicine, University of Pittsburgh, Pittsburgh, PA 15260, USA
[3] Merck & Co., Inc., 126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ 07065, USA
[4] CHEORS LLC, Chalfont, PA 18914, USA
[5] MSD, Sydney 2113, Australia
* Correspondence: emre.yucel@merck.com

Abstract

Introduction: The emergence and spread of multidrug-resistant infections has resulted in significant clinical and economic burdens. To address these infections, novel therapy combinations are needed. Ceftolozane/tazobactam is a treatment option that targets multidrug-resistant pathogens and may offer improved patient outcomes compared to traditional antibiotics that are now often ineffective. **Objectives:** Our objective was to collate findings from comparative efficacy studies to assess the efficacy of ceftolozane/tazobactam for the indications of complex intra-abdominal infection, complex urinary tract infection, ventilated hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. **Methods:** Two systematic literature reviews were conducted, including randomized controlled trials comparing ceftolozane/tazobactam with other interventions for complex intra-abdominal infection, complex urinary tract infection, ventilated hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia indications. The outcomes of interest were mortality, clinical cure and microbiological eradication. **Results:** Ceftolozane/tazobactam was determined to be non-inferior to comparators for all outcomes of interest. All-cause mortality for ceftolozane/tazobactam displayed non-inferiority to meropenem, with the largest numerical differences in all-cause mortality displayed in susceptible patients, such as those with severe renal impairment. Similarly, the clinical cure and microbiological eradication for ceftolozane/tazobactam demonstrated non-inferiority compared to meropenem or levofloxacin. **Conclusions:** These reviews support the role of ceftolozane/tazobactam as an alternative option, particularly when MDR pathogens are suspected or documented. Their findings may contribute to the standardization of treatment guidelines, ultimately helping to reduce the clinical and economic burdens associated with these infections.

Keywords: Ceftolozane/tazobactam; mortality; clinical cure; microbiological eradication; cUTI; cIAI; HABP/VABP

Check for updates

Academic Editor: Guido Granata

Received: 20 November 2025
Revised: 22 January 2026
Accepted: 2 February 2026
Published: 9 February 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

1. Introduction

Antimicrobial resistance (AMR) poses a significant global threat and impacts populations across every country regardless of region or income level [1]. Consequently, the World Health Organization (WHO) has reported AMR as a public health concern [1].

Common forms of healthcare-associated infections include complex intra-abdominal infection (cIAI), complex urinary tract infection (cUTI), ventilated hospital-acquired bacterial pneumonia (vHABP) and ventilator-associated bacterial pneumonia (VABP) [2]. These healthcare-associated infections, which are often associated with AMR, can be attributed to six main pathogens: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacterales* spp. [3]. In particular, *P. aeruginosa* was responsible for 10.3% of HABP and hospital-acquired lower respiratory tract infections and 7.9% of healthcare-acquired infections overall in the Point Prevalence Survey of European Hospitals 2022–2023 [4]. In the US in 2017, the CDC estimated that there were 32,600 cases of *P. aeruginosa* in hospitalized patients, leading to 2700 deaths [5]. A recent study found that approximately 10% of cUTI, cIAI and HABP/VABP pathogens tested were non-susceptible to carbapenem, the typical treatment for severe, complicated infections [3]. Of these isolates, *P. aeruginosa* and *A. baumannii* were found to have the highest levels of resistance (>20%) to carbapenems [3]. A growing number of infections are caused by pathogens that are resistant to multiple antibiotics. In 2021, 1.27 million deaths globally were attributable to infections caused by antimicrobial-resistant organisms, a figure projected to rise to 8.22 million by 2050 [6]. AMR has led to an increase in healthcare resource utilization, which contributes to direct and indirect costs. Healthcare costs directly related to AMR are approximately US $66 billion per year and are expected to rise to US $159 billion per year by 2050 [7].

Due to the rise in multidrug-resistant (MDR) infections, traditional antibiotics are becoming less effective, which complicates care, leading to clinical and economic burdens, necessitating novel treatment combinations. To deal with the rising burden of AMR infections, there is a need for new antimicrobial therapies with novel mechanisms that effectively treat otherwise resistant infections. Ceftolozane/tazobactam (C/T) is a treatment made up of an antipseudomonal cephalosporin and a β-lactamase inhibitor for use against MDR or extensively drug-resistant Gram-negative pathogens such as *P. aeruginosa* and *Enterobacterales* [8]. C/T has been approved for use in patients with cIAI, cUTI and HABP/VABP and has demonstrated decreased resistance development and increased lung penetration when compared to other antipseudomonal antibiotics [8,9].

The aim of this paper was to evaluate the comparative efficacy of C/T versus standard comparators in vHABP/VABP, cIAI and cUTI based on the findings of two systematic literature reviews (SLRs).

2. Results

2.1. Overview of Included Studies

2.1.1. Ventilated Hospital-Acquired Bacterial Pneumonia/Ventilator-Associated Bacterial Pneumonia

The original SLR and the SLR update yielded a total of 2592 publications from Medline, EMBASE, and Cochrane databases. After excluding 380 duplicates, a total of 2212 publications underwent title and abstract screening, with 142 publications found to be eligible for full-text review. After full-text reading, eight publications were included. Hand searches were also performed from other sources (e.g., conference proceedings, clinicaltrials.gov, and bibliographic searching), and one conference abstract was included.

In total, nine publications from one unique trial, ASPECT-NP, were included (Figure 1). Study characteristics are outlined in Table 1. ASPECT-NP included patients with VABP and vHABP, a subset of HABP which requires mechanical ventilation.

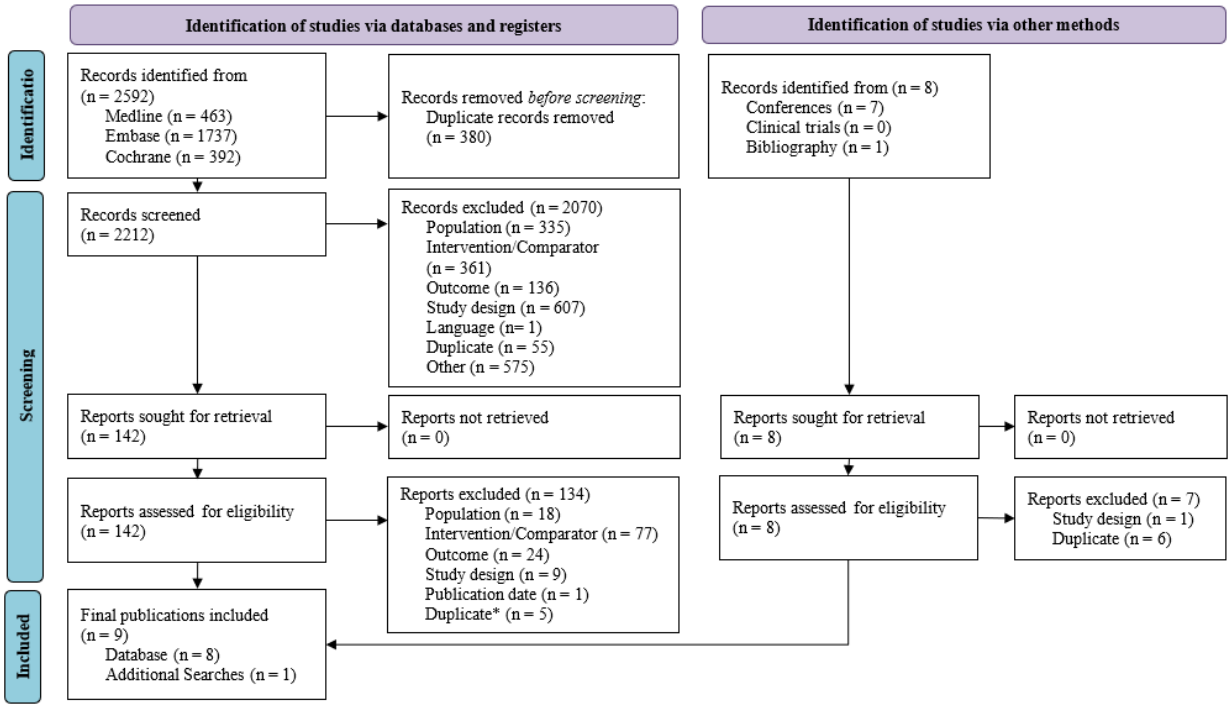

Figure 1. PRISMA study selection flow diagram from the SLR on ventilated hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia. * One record was included in the original SLR: a trial registry website. All the data published in the trial registry have been published in the publications included during the SLR update. The registry record has been excluded from the PRISMA as a duplicate.

Table 1. Study characteristics of included studies: Ventilated hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (ASPECT-NP).

Study (Year)	Primary or Secondary Publication	Patient Enrollment Time	No. of Sites/Centers	Study Design	Selection Criteria for Patients
Kollef (2019) [10]	Primary	16 January 2015 and 27 April 2018	263 hospitals across 34 countries	RCT, Phase 3, double-blind, non-inferiority, multicenter trial	Patients ≥18 years intubated and mechanically ventilated, and had vHABP/VABP
Martin-Loeches (2022) [11]	Secondary			Subgroup analysis of ASPECT-NP trial	Patients with LRT pathogens
Timsit (2021) [12]	Secondary			Subgroup analysis of ASPECT-NP trial	Patients with vHABP
Martin-Loeches (2023) [13]	Secondary			Post hoc analysis of ASPECT-NP trial	Patients with respiratory or cardiovascular dysfunction
Shorr (2021) [14]	Secondary			Post hoc analysis of ASPECT-NP trial	Patients with augmented renal clearance
Huntington (2020) [15]	Secondary			Subgroup analysis of ASPECT-NP trial	Patients with renal impairment
Kollef (2022) [16]	Secondary			Post hoc analysis of ASPECT-NP trial	Patients with failure of initial anti-bacterial therapy
Paterson (2022) [17]	Secondary			Retrospective post hoc analysis of the ASPECT-NP trial	Patients with ESBL-producing Enterobacterales
Martin-Loeches (2019) [18]	Secondary			Subgroup analysis of ASPECT-NP trial	Patients with confirmed baseline LRT pathogen status

Abbreviation: ESBL: extended spectrum beta-lactamase; LRT: lower respiratory tract pathogen; RCT: randomized control trial; VABP: ventilator-associated bacterial pneumonia; vHABP: ventilated hospital-acquired bacterial pneumonia.

2.1.2. Complex Intra-Abdominal Infection and Complex Urinary Tract Infection

A total of 1173 publications were identified from PubMed, EMBASE, and Cochrane databases. After excluding 226 duplicates, a total of 947 publications were included for title and abstract screening, resulting in the identification of 87 publications eligible for full-text review. After full-text reading, six publications were included. Hand searches were also performed from other sources (e.g., conference proceedings, clinicaltrials.gov, and bibliographic searching), and one conference abstract was included.

In total, seven publications from four unique trials (ASPECT-cIAI, ASPECT-cUTI, NCT01147640 and NCT03830333) were included (Figure 2). Study characteristics for the included studies can be found in Table 2.

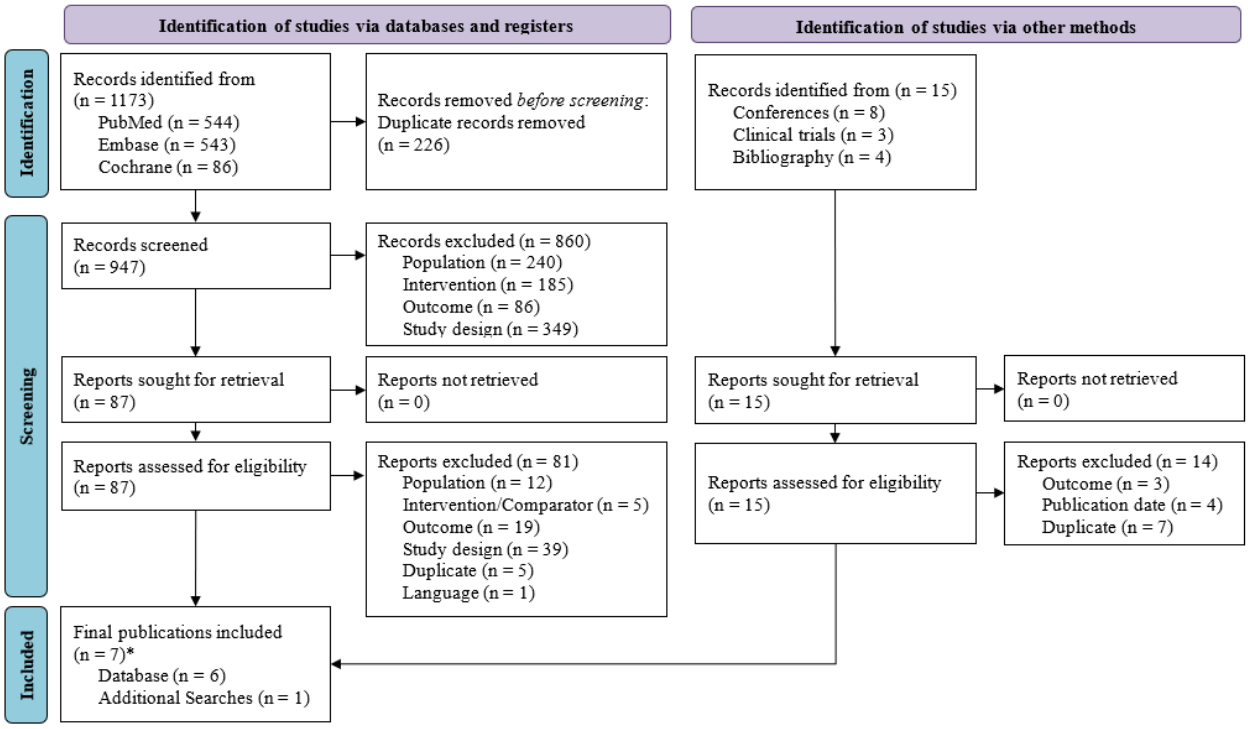

Figure 2. PRISMA study selection flow diagram from the SLR on complex intra-abdominal infection and complex urinary tract infection. * Seven studies included from four unique trials.

Table 2. Study characteristics of included studies: Complex intra-abdominal infection and complex urinary tract infection.

Study	Primary or Secondary	Patient Enrollment Time	No. Sites/Centers	Study Design	Selection Criteria for Patients
ASPECT-cIAI					
Solomkin (2015) [19]	Primary	December 2011–October 2013	15 countries across 61 locations	Phase 3, double-blind, RCT	Adults with clinical evidence of cIAI
Miller et al. 2016 [20]	Secondary		15 countries across 61 locations	Subgroup analysis: Patients with or without *P. aeruginosa*	
Miller et al. 2015 [19]	Secondary		Europe, number of sites NR	Subgroup analysis: European patients	European adults with cIAI
NCT01147640					
Lucasti (2014) [21]	Primary	June 2010–March 2011	5 countries across 35 sites	Phase 2, double-blind, RCT	Hospitalized male and female patients with evidence of cIAI requiring surgical intervention

Table 2. *Cont.*

Study	Primary or Secondary	Patient Enrollment Time	No. Sites/Centers	Study Design	Selection Criteria for Patients
NCT03830333					
Sun (2022) [22]	Primary	March 2019–October 2020	China in 21 sites across 14 provinces	Phase 3, double-blind, RCT	Chinese descents with a diagnosis of cIAI
ASPECT-cUTI					
Wagenlehner (2015) [23]	Primary	June 2011–September 2013	25 countries across 209 centers	Phase 3, double-blind, double-dummy, non-inferiority, RCT	Hospital inpatients who had pyuria and a diagnosis of a cUTI or pyelonephritis
Huntington (2016) [24]	Secondary		25 countries across 209 centers	Subgroup analysis: cUTIs caused by levofloxacin-resistant pathogens	Hospitalized adults with pyuria and clinical signs and/or symptoms of cUTI or pyelonephritis

Abbreviations: cIAI: complicated intra-abdominal infection; cUTI: complicated urinary tract infection; RCT: randomized control trial.

2.2. All-Cause Mortality

2.2.1. Ventilated Hospital-Acquired Bacterial Pneumonia/Ventilator-Associated Bacterial Pneumonia

All-cause mortality (ACM) was reported for all publications on the ASPECT-NP trial (Table 3). In the overall trial population at 28 days, ACM was similar in the C/T group (24%) compared to the meropenem group (25.3%) for the whole study population with vHABP/VABP [10]. Across the different subgroups analyzed within this population, C/T demonstrated numerically lower or similar mortality rates compared to meropenem (Table S14). The overall mortality was numerically lower in several subgroups treated with C/T compared to meropenem, including vulnerable patients such as those with severe renal impairment (RI) (30.8% versus 57.1%), extended spectrum beta-lactamase (ESBL) positive infections (8.0% versus 30.3%), or failure of initial therapy (22.6% versus 45.0%) [15–17]. C/T demonstrated a non-inferiority to meropenem across all subgroups.

Table 3. All-cause mortality with C/T versus meropenem in patients with ventilated hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (ASPECT-NP).

Study (Year)	Outcome	C/T (% [n/N])	Meropenem (% [n/N])	Percent Difference, % (95% CI)
Kollef (2019) [10]	**vHABP/VABP (ITT) [a]**			
	28-day ACM	24.0 (87/362)	25.3 (92/364)	1.1 (−5.1 to 7.4)
	VABP (ITT) [a]			
	28-day ACM	24.0 (63/263)	20.3 (52/256)	–3.6 (–10.7 to 3.5)
	HABP (ITT) [a]			
	28-day ACM	24.2 (24/99)	37.0 (40/108)	12.8 (0.2 to 24.8)
Timsit (2021) [12]	**vHABP (mITT) [b]**			
	28-day ACM	18.2 (10/55)	36.6 (26/71)	18.4 (2.5 to 32.5)

Abbreviations: CI: confidence interval; ITT: intention-to-treat; mITT: microbiological intention-to-treat population; VABP: ventilator-associated bacterial pneumonia; vHABP: ventilated hospital-associated bacterial pneumonia. [a] ITT was defined as all randomized participants, regardless of whether they received study drug. [b] mITT was defined as the ITT participants who received ≥1 dose of study treatment and with ≥1 Gram-negative or streptococcal respiratory pathogen from baseline lower respiratory tract (LRT) cultures confirmed to be susceptible to ≥1 study drug.

2.2.2. Complex Intra-Abdominal Infection and Complex Urinary Tract Infection

Three publications reported ACM in patient populations with cIAI from ASPECT-cIAI, NCT01147640 and NCT03830333. ACM was low across all three trials, and no statistically significant differences were identified between C/T plus metronidazole versus meropenem (Table 4) [19,21,22].

Table 4. All-cause mortality with C/T + metronidazole versus meropenem in patients with complex intra-abdominal infection.

Study (Year)	Outcome	C/T + Metronidazole (% [n/N])	Meropenem (% [n/N])	Percent Difference, % (95% CI)
ASPECT-cIAI				
Solomkin (2015) [19]	**cIAI (ITT) [a]**			
	All-cause mortality	2.3 (11/482)	1.6 (8/497)	NR
NCT01147640				
Lucasti (2014) [21]	**cIAI (mITT) [b]**			
	All-cause mortality	3.65 (3/82)	0	NR
NCT03830333				
Sun (2022) [22]	**cIAI (ITT) [a]**			
	All-cause mortality	0 (0/0)	0.7 (1/134)	−0.7 (−4.1 to 2.1)

Abbreviations: CI: confidence interval; cIAI: complicated intra-abdominal infection; ITT: intention-to-treat; mITT: modified intent-to-treat; NR: not reported. [a] ITT was defined as all randomized participants, regardless of whether they received study drug. [b] The modified intent-to-treat (mITT) population was defined as all randomized patients who received at least one dose of the study drug.

No publications reported ACM for patients with cUTI.

2.3. Clinical Cure

2.3.1. Ventilated Hospital-Acquired Bacterial Pneumonia/Ventilator-Associated Bacterial Pneumonia

Eight publications reported the clinical cure attributed to C/T compared to meropenem. Similar or favorable clinical results were presented across all publications. The rate of clinical cure was similar in the C/T group (54.4%) compared to the meropenem group (53.3%) for the whole study population with vHABP/VABP [10]. C/T demonstrated a non-inferiority to meropenem across all subgroups (Table 5).

Table 5. Rates of clinical cure with C/T versus meropenem for patients with ventilated hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (ASPECT-NP).

Study (Year)	Outcome	C/T (% [n/N])	Meropenem (% [n/N])	Percent Difference, % (95% CI)
Kollef (2019) [10]	**vHABP/VABP (ITT) [a]**			
	Clinical cure at TOC	54.4 (197/362)	53.3 (194/364)	1.1 (−6.2 to 8.3)
	VABP (ITT) [a]			
	Clinical cure at TOC	55.9 (147/263)	57.0 (146/256)	−1.1 (−9.6 to 7.4)
	vHABP (ITT) [a]			
	Clinical cure at TOC	50.5 (50/99)	44.4 (48/108)	6.1 (−7.4 to 19.3)

Table 5. *Cont.*

Study (Year)	Outcome	C/T (% [n/N])	Meropenem (% [n/N])	Percent Difference, % (95% CI)
Martin-Loeches (2019) [18]	**vHABP/VABP (ME) [b]**			
	Clinical cure: Overall	75.2 (85/113)	66.7 (78/117)	8.6 (−3.19 to 19.94)

Abbreviations: CI: confidence interval; C/T: ceftolozane/tazobactam; ITT: intention-to-treat; ME: microbiological evaluable; N: number; TOC: test-of-cure; VABP: ventilator-associated bacterial pneumonia; vHABP: ventilated hospital-associated bacterial pneumonia. [a] ITT was defined as all randomized participants, regardless of whether they received study drug. [b] Microbiologically evaluable (ME) population was defined as participants who received study drug, adhered to protocol requirements, and had ≥1 Gram-negative or streptococcal respiratory pathogen from baseline lower respiratory tract (LRT) cultures.

Subgroup analyses demonstrated that patients in the clinically evaluable populations with vHABP/VABP who had failed initial anti-bacterial therapy had numerically higher rates of clinical cure when C/T was utilized compared to meropenem (63.6% vs. 45.0%; Table S15) [16]. Additionally, use of C/T in patients with ESBL-positive infections and patients with Gram-negative infections resulted in numerically higher rates of clinical cure when compared to meropenem (72.0% vs. 66.7% and 75.2% vs. 66.7%, respectively) [11,17].

2.3.2. Complex Intra-Abdominal Infection and Complex Urinary Tract Infection

Three publications reported on clinical cure for cIAI from the ASPECT-cIAI trial. The rates of clinical cure were similar in the C/T plus metronidazole group compared to the meropenem group in all three publications investigating cIAI (Table 6) [19,21,22]. C/T plus metronidazole demonstrated a non-inferiority to meropenem across all subgroups (Table S16).

Table 6. Rates of clinical cure with C/T + metronidazole versus meropenem in patients with complex intra-abdominal infection (ASPECT-cIAI).

Study (Year)	Efficacy	C/T + Metronidazole (% [n/N])	Meropenem (% [n/N])	Percent Difference, % (95% CI)
ASPECT-cIAI				
Solomkin (2015) [19]	**cIAI (ITT) [a]**			
	Clinical cure at TOC visit	83.6 (NR)	86.2 (NR)	−2.6 (−7.08 to 1.87)
NCT01147640				
Lucasti. (2014) [21]	**cIAI (CE) [b]**			
	Clinical cure	91.4 (64/70)	94.3 (33/35)	−2.9 (−23.5 to 18.0)
NCT03830333				
Sun (2022) [22]	**cIAI (CE) [b]**			
	Clinical response at the TOC visit	95.2 (NR)	93.1 (NR)	2.1 (−4.7 to 8.8)

Abbreviations: CE: clinical evaluable; CI: confidence interval; cIAI: complicated intra-abdominal infection; C/T: ceftolozane/tazobactam; NR: not reported; TOC: test-of-cure. [a] ITT was defined as all randomized participants, regardless of whether they received study drug. [b] Clinically evaluable (CE) population was defined as the participants who received study drug, adhered to the study protocol through the TOC visit, and had an evaluable clinical outcome at the TOC visit or clinical failure prior to the TOC visit.

Two studies reported on clinical cure in patients with cUTI based on ASPECT-cUTI. The rate of clinical cure was numerically higher in the C/T group (92%) compared to the levofloxacin group (88.6%) [23]. C/T demonstrated non-inferiority to levofloxacin across all subgroups (Table 7). In the post hoc analysis of ASPECT-cUTI by Huntington (2016) differentiating patients with cUTI and pyelonephritis, C/T was identified as non-inferior when compared to levofloxacin [24].

Table 7. Clinical response rates of C/T versus levofloxacin in patients with complex urinary tract infection and pyelonephritis (ASPECT-cUTI).

Study (Year)	Outcome	C/T (% [n/N])	Levofloxacin (% [n/N])	Percent Difference, % (95% CI)
Wagenlehner (2015) [23]	**cUTI + Pyelonephritis (mMITT) [a]**			
	Clinical cure (Overall population)	92.0 (366/398)	88.6 (356/402)	3.4 (−0.7 to 7.6)
	cUTI + Pyelonephritis (Per-Protocol)			
	Clinical cure (overall population)	95.9 (327/341)	93.2 (329/353)	2.7 (−0.8 to 6.2)
Huntington (2016) [24]	**cUTI + Pyelonephritis caused by levofloxacin-resistant pathogens (mMITT) [a]**			
	Clinical response at the TOC visit (Overall population)	90.0 (90/100)	76.8 (86/112)	13.2 (3.1 to 22.9)
	Clinical response at the TOC visit (cUTI only)	82.8 (24/29)	68.6 (24/35)	14.2 (−7.4 to 33.3)
	Clinical response at the TOC visit (Pyelonephritis only)	93.0 (66/71)	80.5 (62/77)	12.4 (1.3 to 23.4)

Abbreviations: CI: confidence interval; cUTI: complicated urinary tract infection; mMITT: microbiological modified intention-to-treat population; TOC: test-of-cure. [a] The microbiological modified intention-to-treat population (mMITT) included all randomized patients who received the study drug and had growth of one or two uropathogens of at least 105 cfu/mL in a pretreatment baseline urine culture.

2.4. Microbiological Eradication

2.4.1. Ventilated Hospital-Acquired Bacterial Pneumonia/Ventilator-Associated Bacterial Pneumonia

Eight publications reported on microbiological eradication in patients with vHABP/VABP based on ASPECT-NP. The rate of microbiological eradication was numerically higher in the C/T group (73.1%) compared to the meropenem group (68.0%) for the whole study population with vHABP/VABP (Table 8) [10]. C/T demonstrated a non-inferiority to meropenem across all subgroups (Table S17). Notably, subgroup analyses of vulnerable patient populations such as those with severe RI or patients requiring mechanical ventilation treated with C/T displayed numerically higher microbiological eradication when compared to meropenem (69.2% vs. 57.1% and 78.2% vs. 62.0%, respectively) [12,15].

Table 8. Rates of microbiological eradication with C/T versus meropenem for ventilated hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (ASPECT-NP).

Study (Year)	Outcome	C/T (% [n/N])	Meropenem (% [n/N])	Percent Difference, % (95% CI)
Timsit (2021) [12]	**vHABP (mITT) [a]**			
	Microbiological eradication at TOC	78.2 (43/55)	62.0 (44/71)	16.2 (−0.1 to 30.8)
	vHABP (ME) [b]			
	Microbiological eradication at TOC	71.4 (15/21)	64.0 (16/25)	7.4 (−19.1 to 31.9)

Abbreviations: CI: confidence interval; C/T: ceftolozane/tazobactam; ME: microbiological evaluable; mITT: microbiological intention-to-treat population; N: number; TOC: test-of-cure; vHABP: ventilated hospital-acquired bacterial pneumonia. [a] mITT was defined as the ITT participants who received ≥1 dose of study treatment and with ≥1 Gram-negative or streptococcal respiratory pathogen from baseline lower respiratory tract (LRT) cultures confirmed to be susceptible to ≥1 study drug. [b] Microbiologically evaluable (ME) population was defined as participants who received study drug, adhered to protocol requirements, had ≥1 Gram-negative or streptococcal respiratory pathogen from baseline lower respiratory tract (LRT) cultures.

2.4.2. Complex Intra-Abdominal Infection and Complex Urinary Tract Infection

Two publications reported on microbiological eradication in patients with cUTI. The rate of microbiological eradication was numerically higher in the C/T group (80.4%) compared to the levofloxacin group (72.1%) for the whole study population [23]. This

8.3% difference is statistically significant (95% confidence interval 2.4–14.1%) [23]. C/T demonstrated a non-inferiority to levofloxacin in patients with cUTI (Table 9) [23,24]. Microbiological eradication was not reported in patients with cIAI.

Table 9. Microbiological eradication rates with C/T versus levofloxacin in patients with complex urinary tract infection and pyelonephritis (ASPECT-cUTI).

Study (Year)	Outcome	C/T (% [n/N])	Levofloxacin (% [n/N])	Percent Difference, % (95% CI)
Wagenlehner (2015) [23]	**cUTI + Pyelonephritis (mMITT) [a]**			
	Microbiological eradication (Overall population)	80.4 (320/398)	72.1 (290/402)	8.3 (2.4 to 14.1)
	cUTI + Pyelonephritis (Per-Protocol)			
	Microbiological eradication (Overall population)	86.2 (294/341)	77.6 (274/353)	8.6 (2.9 to 14.3)
Huntington (2016) [24]	**cUTI + Pyelonephritis (mMITT) [a]**			
	Microbiological response at the TOC visit (Overall population)	63.0 (63/100)	43.8 (49/112)	19.3 (5.8 to 31.7)
	Microbiological response at the TOC visit (cUTI only)	62.1 (18/29)	17.1 (6/35)	44.9 (21.1 to 62.6)
	Microbiological response at the TOC visit (Pyelonephritis only)	63.4 (45/71)	55.8 (43/77)	7.5 (−8.2 to 22.6)

Abbreviations: CI: confidence interval; cUTI: complicated urinary tract infection; mMITT: microbiological modified intention-to-treat population; TOC: test-of-cure. [a] The microbiological modified intention-to-treat population (mMITT) included all randomized patients who received the study drug and had growth of one or two uropathogens of at least 105 cfu/mL in a pretreatment baseline urine culture.

2.5. Risk of Bias

2.5.1. Ventilated Hospital-Acquired Bacterial Pneumonia/Ventilator-Associated Bacterial Pneumonia Systematic Literature Review

The ASPECT-NP trial had low risk of bias across all domains, including risk of bias arising from the randomization process, risk of bias due to deviations from the intended interventions (effect of assignment to intervention), risk of bias due to deviations from the intended interventions (effect of adhering to intervention), risk of bias due to missing outcome data, risk of bias in the measurement of the outcome, and risk of bias in the selection of the reported result (Figure 3) [10].

Primary Publication and Trial Name	D1	D2a	D2b	D3	D4	D5	Overall
Kollef et al. 2019 ASPECT-NP (NCT02070757)	⊕	⊕	⊕	⊕	⊕	⊕	⊕

Figure 3. Risk of bias summary assessment for the systematic literature review on ventilated hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia [10]. Abbreviations: D1: Domain 1; D2a: Domain 2a; D2b: Domain 2b; D3: Domain 3; D4: Domain 4; D5: Domain 5. Note: Meaning of results: ⊕ Low risk of bias. D1: Risk of bias arising from the randomization process. D2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention). D2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention). D3: Risk of bias due to missing outcome data. D4: Risk of bias in measurement of the outcome. D5: Risk of bias in selection of the reported result.

2.5.2. Complex Intra-Abdominal Infection and Complex Urinary Tract Infection Systematic Literature Review

Overall, the ASPECT-cIAI trial, ASPECT-cUTI trial and NCT03830333 trail had a low risk of bias for all domains, including risk of bias arising from the randomization process, risk of bias due to deviations from the intended interventions (effect of assignment to intervention), risk of bias due to deviations from the intended interventions (effect of adhering to intervention), risk of bias due to missing outcome data, risk of bias in the measurement of the outcome, and risk of bias in the selection of the reported result [22–24]. The NCT01147640 trial had an unclear risk of bias arising from the randomization process and risk of bias in the selection of the reported result (Figure 4) [21].

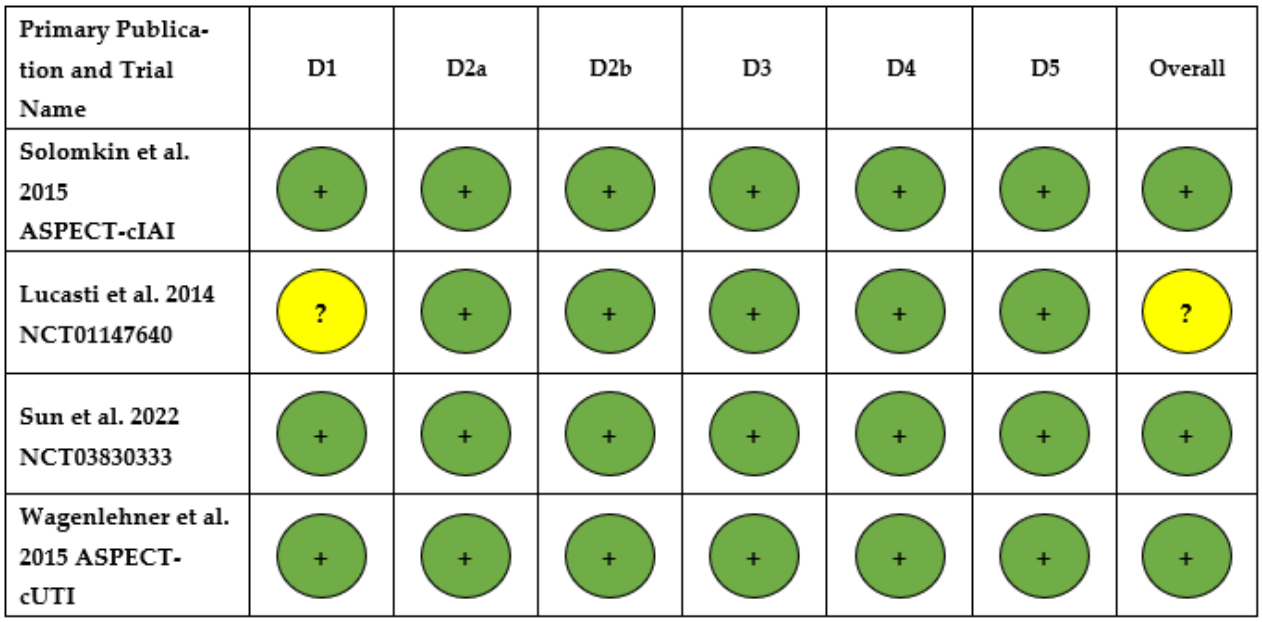

Figure 4. Risk of bias summary assessment for the systematic literature review on complex intra-abdominal infection and complex urinary tract infection [19,21–23]. Abbreviations: D1: Domain 1; D2a: Domain 2a; D2b: Domain 2b; D3: Domain 3; D4: Domain 4; D5: Domain 5. Note: Meaning of results: Low risk of bias. : Unclear risk of bias. D1: Risk of bias arising from the randomization process. D2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention). D2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention). D3: Risk of bias due to missing outcome data. D4: Risk of bias in measurement of the outcome. D5: Risk of bias in selection of the reported result.

3. Discussion

These SLRs evaluated the efficacy of C/T for the treatment of HABP/VABP and cIAI and cUTI based on data from RCTs. Most studies demonstrated the non-inferiority of C/T to standard comparators, supporting its role as an effective treatment option for these indications.

Nine publications were included for HABP/VABP, all of which were based on ASPECT-NP reporting on at least two of the outcomes of interest; ACM, clinical cure and microbiological eradication. Seven publications from four unique trials were included for cIAI and cUTI (ASPECT-cIAI, ASPECT-cUTI, NCT01147640 and NCT03830333). Three trials reported on ACM (ASPECT-cIAI, NCT01147640 and NCT03830333) and two trials reported on clinical cure (ASPECT-cIAI, ASPECT-cUTI), while only one trial reported on microbiological eradication (ASPECT-cUTI).

Overall, ACM at 28 days was non-inferior with C/T when compared to meropenem (24.0% versus 25.3%) in patients with vHABP/VABP [16]. Notably, this review reported ev-

idence that C/T demonstrated numerically lower mortality, consistent with non-inferiority but not powered to detect superiority, when compared to meropenem in patients with severe RI (30.8% vs. 57.1%), who are known to have worse infection outcomes than the general population. Furthermore, C/T was associated with numerically lower ACM versus meropenem in patients with ESBL-producing *Enterobacterales* (13.0% vs. 29.4%) and patients who failed initial therapy (22.6% vs. 45.0%), indicating that C/T may provide an alternative treatment option in vulnerable/high-risk patient populations [11,15,16,25]. Similarly, ACM was low across all three trials investigating C/T for the treatment of cIAI, displaying a non-inferiority to meropenem. No studies including cUTI reported on ACM. These results are similar to those found in studies external to these SLRs. For example, SPECTRA was a large, multinational, multicenter trial which found that C/T was associated with low ACM in patients with Gram-negative infections in the real world. Similarly, a 2024 retrospective, observational study compared the outcomes of non-COVID-19 hospitalized patients with pneumonia caused by MDR *P. aeruginosa* and demonstrated non-inferior rates of mortality of C/T when compared to ceftazidime/avibactam (C/A) [26,27].

Within this SLR, in ASPECT-NP, C/T was non-inferior to meropenem when considering clinical cure in patients with vHABP/VABP. Similarly, C/T was found to be non-inferior to levofloxacin in patients with cUTI, while C/T plus metronidazole was non-inferior to meropenem for the treatment of cIAI when considering clinical cure. These results suggest that C/T plus metronidazole or C/T alone may be considered an effective treatment choice in patients with vHABP/VABP, cIAI and cUTI. These results are further externally validated by CACTUS, a multicenter, retrospective study which demonstrated the non-inferiority of C/T to ceftazidime/avibactam (C/A) in patients with MDR *P. aeruginosa*. C/T displayed non-inferiority in clinical cure when compared with C/A [28]. Notably, in this study, patients who had previously failed initial therapies displayed higher rates of clinical cure when C/T was administered compared with meropenem (63.6% vs. 45.0%) [16]. These findings highlight the potential efficacy of C/T in treating patients for whom other antimicrobials are no longer effective.

Microbiological eradication was investigated in ASPECT-NP, displaying non-inferiority when C/T was compared to meropenem. Within this trial, vulnerable patient populations such as patients with severe RI or patients requiring mechanical ventilation showed numerically higher microbiological eradication with C/T versus meropenem (69.2% vs. 57.1% and 78.2% vs. 62.0%, respectively) [12,15]. Additionally, within the ASPECT-cUTI trial, C/T demonstrated a non-inferiority to levofloxacin when considering microbiological eradication. These findings are similar to the results from an external review conducted by Lizza (2021) investigating the safety and efficacy of C/T for Gram-negative infections, which found that C/T was associated with similar levels of microbiological eradication (81%) [29].

Outside of these SLRs, the appropriateness of C/T as an alternative treatment option has been demonstrated by the higher rates of susceptibility in *P. aeruginosa* isolates (97.5%) when compared with meropenem (76.0%) [30]. In addition, C/T has been suggested to provide a good activity against AmpC-producing *P. aeruginosa* and may be less affected by efflux-related resistance mechanisms [31,32]. When considered alongside the suggested non-inferiority to other antimicrobials in this study, the use of C/T may result in better coverage in high-risk patients. However in order to mitigate the risk of C/T resistance, stewardship programs, including the development of treatment guidelines, the education of clinicians, and antimicrobial cycling are key [33].

These findings indicate that C/T may be an effective alternative treatment to meropenem and levofloxacin and may be appropriate to consider when alternative treatments are limited by AMR or other factors, such as allergy or intolerance.

Given the demonstrated non-inferiority of C/T versus meropenem for cIAI and HABP/VABP and versus levofloxacin for cUTI, C/T should be positioned as a targeted reserve agent rather than as a first-line therapy. Antimicrobial stewardship principles support the use of C/T, assuming it is guided by local susceptibility patterns and institutional antibiogram, particularly in settings with a high prevalence of MDR *P. aeruginosa* or ESBL-producing Enterobacterales, or following the failure of prior therapy, alongside robust microbiology support such as rapid diagnostics and timely susceptibility testing to confirm pathogens, characterize resistance mechanisms, and enable de-escalation when feasible. Where available, indication-specific dosing with renal adjustment and therapeutic drug monitoring is recommended, particularly in vulnerable patient populations. Furthermore, clear criteria for escalation, such as documented or strongly suspected resistance to standard antipseudomonal agents or intolerance to comparators, and reassessment at 48–72 h for step-down or discontinuation are essential. The sensible, protocolized use of C/T may reduce the selective pressure relative to broad empiric carbapenem use and help to preserve carbapenem activity; however, it should be noted that resistance can still emerge. Mitigation strategies for resistance development include preauthorization or prospective audit and feedback, the use of shortest effective treatment durations, the avoidance of unnecessary combination therapy, and the ongoing local surveillance of C/T susceptibility trends.

4. Materials and Methods

Two SLRs were conducted. One SLR included RCTs evaluating the relative efficacy of C/T in adult patients with HABP/VABP, while the second SLR focused on the literature where C/T was utilized in patients with cIAI and cUTI. Both SLRs were conducted in line with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. The PRISMA checklist can be seen in Table S18.

4.1. Study Eligibility and Data Sources

Study eligibility criteria were defined in the population, interventions, comparisons, outcomes, time, and study design (PICOTS) structure outlined in Tables S1 and S2. The data sources are outlined in Table S3. Systematic searches were conducted in PubMed/Medline (Ovid), Embase (Ovid), and Cochrane databases from inception up to July 2024. Relevant conference proceedings from 2018 to 2024, clinicaltrials.gov and bibliographies of identified systematic reviews were also hand-searched (Tables S4–S13).

4.2. Literature Search and Screening Process

Searches for the SLR looking at HABP/VABP were conducted on 27 September 2018, and an update to the SLR was carried out with searches conducted on 18 July 2024. Searches for the SLR on cIAI and cUTI were carried out on 18 July 2024.

The studies identified by the searches were screened using a two-stage process. In the first stage, titles and abstracts were independently screened by two researchers to determine eligibility. Disagreements were resolved by a third reviewer. In the second stage, full-text articles of potentially relevant studies were reviewed by two independent researchers to confirm eligibility. Conflicts were resolved by a third reviewer. In this manuscript, we will report the following outcomes: all-cause mortality (ACM), clinical cure, and microbiological eradication. Additional outcomes were specified in the PICOTS for the SLRs (Tables S1 and S2).

The quality of individual trials included was assessed using the revised Cochrane risk of bias assessment tool [34].

4.3. Outcomes and Definitions

The definition of clinical cure was similar across all RCTs included in the SLRs, defined as the alleviation of signs and symptoms from baseline. Comparably, a favorable microbiological response was defined as the eradication of baseline pathogens across all RCTs. Each definition included slight variations in these based on infection type. For example, a microbiological eradication in HABP/VABP was defined as a $\geq$1 log reduction in baseline LRT pathogen bacterial burden, with a resulting per-pathogen count of $\leq$104 cfu/mL for endotracheal aspirate or sputum, $\leq$103 cfu/mL for bronchoalveolar lavage, or $\leq$102 cfu/mL for protected brush specimen.

5. Conclusions

The evidence identified by these SLRs highlights the potential for C/T to be used in patients with cIAI, cUTI and HABP/VABP to treat a range of Gram-negative infections, including those caused by MDR *P. aeruginosa*. This evidence was strongest in non-inferiority RCTs, with a descriptive analysis on RWE offering more limited support and lower-quality data on the use of C/T in MDR infections specifically. These SLRs may inform guideline discussions and local stewardship decisions, which could facilitate the more effective treatment of complex MDR infections, therefore reducing the clinical and economic impacts associated with these infections.

6. Limitations

The SLR for HABP/VABP relies solely on data from the ASPECT-NP trial which reduces the generalizability of the findings and introduces potential biases related to participant selection and outcome reporting. Due to the low numbers, a meta-analysis could not be performed, and heterogeneity could not be quantified, limiting the confidence in the findings.

Additionally, the SLR for cUTI and cIAI included trials which were designed to test noninferiority, so the sample size was calculated accordingly and was not adequately powered to test comparative effectiveness. For instance, in the publication by Lucasti et al. (2014), a small number of patients is included, and the patients are not equally randomized [21]. Furthermore, within the publication by Sun et al. (2022), differences in the clinical response rates in the ITT population were influenced by missing or intermediate responses in the C/T plus metronidazole arm compared to the meropenem arm [22].

A notable proportion of the results included in these SLRs came from post hoc or subgroup analyses (e.g., renal impairment, ESBL-positive infections), which are exploratory and not pre-specified in the original trial designs. These analyses may be prone to type I errors, so the results should be interpreted with caution.

The outcomes of interest in these SLRs focused on efficacy endpoints only, and the analysis did not include safety and tolerability. While this SLR suggests that C/T may be an effective treatment alternative, conclusions cannot be drawn on safety and tolerability, which are important factors when considering treatment guidelines.

The RCTs included in these SLRs largely include susceptible or non-carbapenem-resistant isolates. These results therefore may have limited generalizability to settings and infections where treatment choices or patient characteristics differ markedly from the included studies. The true MDR data included in the discussion come mainly from observational studies, which should be interpreted with caution due to possible confounding and bias.

SLRs may also introduce a potential bias from the included studies. The limitations of the SLRs highlight the need for further research, including head-to-head trials, to better understand the comparative effectiveness of C/T across diverse patient populations.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/antibiotics15020190/s1. Table S1: PICOTS criteria for the SLR on vHABP/VABP; Table S2: PICOTS criteria for the SLR on cIAI and cUTI; Table S3: List of data sources; Table S4: cIAI/cUTI search strategy for EMBASE in Ovid, 1974 to 17 July 2024; search executed 18 July 2024; Table S5: cIAI/cUTI search strategy for PubMed, 1992 to 18 July 2024, search executed 18 July 2024; Table S6: cIAI/cUTI search strategy for Cochrane Database of Systematic Reviews; search executed 18 July 2024; Table S7: cIAI/cUTI search strategy for Cochrane Central Register of Controlled Trials; search executed 18 July 2024; Table S8: HABP/VABP search strategy for EMBASE in Ovid, 1974 to 2018; search executed 27 September 2018; Table S9: HABP/VABP search strategy for MEDLINE in Ovid, 1946 to 2018; search executed 27 September 2018; Table S10: Search strategy for Cochrane Database of Systematic Reviews; search executed 27 September 2018; Table S11: HABP/VABP search strategy for EMBASE in Ovid, 1974 to 18 July 2024; search executed 18 July 2024; Table S12: HABP/VABP search strategy for MEDLINE in Ovid, 1946 to 16 July 2024; search executed 18 July 2024; Table S13: HABP/VABP search strategy for Cochrane Database of Systematic Reviews; search executed 18 July 2024; Table S14: All-cause mortality with C/T versus meropenem in patient subgroups with ventilated hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (ASPECT-NP); Table S15: Rates of clinical cure with C/T versus meropenem for patients subgroups with ventilated hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (ASPECT-NP); Table S16: Rates of clinical cure with C/T + metronidazole versus meropenem in patient subgroups with complex intra-abdominal infection (ASPECT-cIAI); Table S17: Rates of microbiological eradication with C/T versus meropenem for patient subgroups with ventilated hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (ASPECT-NP); Table S18: PRISMA Checklist.

Author Contributions: Conceptualization, E.Y., R.K.S., I.M.-L., S.B., M.K., H.E., N.S. and C.C.; methodology, E.Y., I.M.-L., S.B., M.K., H.E., N.S. and C.C.; software, S.B., M.K., H.E. and N.S.; validation, S.B., M.K., H.E. and N.S.; formal analysis, S.B., M.K., H.E. and N.S.; investigation, S.B., M.K., H.E. and N.S.; resources, E.Y. and C.C.; data curation, S.B., M.K., H.E. and N.S.; writing—original draft preparation, E.Y., R.K.S., I.M.-L., S.B., M.K., H.E., N.S. and C.C.; writing—review and editing, E.Y., R.K.S., I.M.-L., S.B., M.K., H.E., N.S. and C.C.; visualization, S.B., M.K., H.E. and N.S.; supervision, E.Y. and C.C.; project administration, E.Y. and C.C.; funding acquisition, E.Y. and C.C. All authors have read and agreed to the published version of the manuscript.

Funding: Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Although the sponsors formally reviewed a penultimate draft, the opinions expressed are those of the authors and may not necessarily reflect those of the sponsors. All co-authors approved the final version of the manuscript.

Institutional Review Board Statement: No ethical approval or informed consent was needed because the work is based on existing published literature.

Informed Consent Statement: Not applicable.

Data Availability Statement: The full datasets generated and analyzed to inform the conclusions drawn within this manuscript during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest: Emre Yücel is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Authors Shalini Bagga, Maesumeh Korei, Hariprasad Esam and Nidhi Sharma were employed by the company CHEORS LLC. Author Carolyn Cameron was employed by the company MSD. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The authors declare that this study received funding from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

References

1. WHO. Antimicrobial Resistance. 2023. Available online: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance (accessed on 1 February 2026).
2. Weiner-Lastinger, L.M.; Abner, S.; Edwards, J.R.; Kallen, A.J.; Karlsson, M.; Magill, S.S.; Pollock, D.; See, I.; Soe, M.M.; Walters, M.S. Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: Summary of data reported to the National Healthcare Safety Network, 2015–2017. *Infect. Control Hosp. Epidemiol.* **2020**, *41*, 1–18. [CrossRef]
3. Ferrer, R.; Fariñas, M.C.; Maseda, E.; Salavert, M.; Bou, G.; Diaz-Reganon, J.; López, D.; Lozano, V.; Gómez-Ulloa, D.; Fenoll, R. Clinical management of cUTI, cIAI, and HABP/VABP attributable to carbapenem-resistant Gram-negative infections in Spain. *Rev. Española Quimioter.* **2021**, *34*, 639. [CrossRef]
4. European Centre for Disease Prevention and Control. Point Prevalence Survey of Healthcareassociated Infections and Antimicrobial Use in European Acute Care Hospitals, 2022–2023. 2024. Available online: https://www.ecdc.europa.eu/en/publications-data/PPS-HAI-AMR-acute-care-europe-2022-2023 (accessed on 9 January 2026).
5. Centers for Disease Control and Prevention (U.S.); National Center for Emerging and Zoonotic Infectious Diseases, Division of Healthcare Quality Promotion, Antibiotic Resistance Coordination and Strategy Unit. *Antibiotic Resistance Threats in the United States, 2019*; U.S. Department of Health and Human Services, CDC: Atlanta, GA, USA, 2019.
6. Naghavi, M.; Vollset, S.E.; Ikuta, K.S.; Swetschinski, L.R.; Gray, A.P.; Wool, E.E.; Aguilar, G.R.; Mestrovic, T.; Smith, G.; Han, C. Global burden of bacterial antimicrobial resistance 1990–2021: A systematic analysis with forecasts to 2050. *Lancet* **2024**, *404*, 1199–1226. [CrossRef]
7. McDonnell, A.; Countryman, A.; Laurence, T.; Gulliver, S.; Drake, T.; Edwards, S.; Kenny, C.; Lamberti, O.; Morton, A.; Shafira, A.; et al. *Forecasting the Fallout from AMR: Economic Impacts of Antimicrobial Resistance in Humans*; Center for Global Development: Washington, DC, USA, 2024.
8. López, I.; Montero, M.; Sorlí, L.; Horcajada, J.P. Ceftolozane-tazobactam: When, how and why using it? *Rev. Española Quimioter.* **2021**, *34*, 35. [CrossRef]
9. Sorbera, M.; Chung, E.; Ho, C.W.; Marzella, N. Ceftolozane/Tazobactam: A new option in the treatment of complicated gram-negative infections. *Pharm. Ther.* **2014**, *39*, 825.
10. Kollef, M.H.; Nováček, M.; Kivistik, Ü.; Réa-Neto, Á.; Shime, N.; Martin-Loeches, I.; Timsit, J.-F.; Wunderink, R.G.; Bruno, C.J.; Huntington, J.A. Ceftolozane–tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): A randomised, controlled, double-blind, phase 3, non-inferiority trial. *Lancet Infect. Dis.* **2019**, *19*, 1299–1311. [CrossRef]
11. Martin-Loeches, I.; Timsit, J.-F.; Kollef, M.H.; Wunderink, R.G.; Shime, N.; Nováček, M.; Kivistik, Ü.; Réa-Neto, Á.; Bruno, C.J.; Huntington, J.A. Clinical and microbiological outcomes, by causative pathogen, in the ASPECT-NP randomized, controlled, Phase 3 trial comparing ceftolozane/tazobactam and meropenem for treatment of hospital-acquired/ventilator-associated bacterial pneumonia. *J. Antimicrob. Chemother.* **2022**, *77*, 1166–1177. [CrossRef]
12. Timsit, J.-F.; Huntington, J.A.; Wunderink, R.G.; Shime, N.; Kollef, M.H.; Kivistik, Ü.; Nováček, M.; Réa-Neto, Á.; Martin-Loeches, I.; Yu, B. Ceftolozane/tazobactam versus meropenem in patients with ventilated hospital-acquired bacterial pneumonia: Subset analysis of the ASPECT-NP randomized, controlled phase 3 trial. *Crit. Care* **2021**, *25*, 290. [CrossRef] [PubMed]
13. Martin-Loeches, I.; Shorr, A.F.; Wunderink, R.G.; Kollef, M.H.; Timsit, J.F.; Yu, B.; Huntington, J.A.; Jensen, E.; Bruno, C.J. Outcomes in participants with ventilated nosocomial pneumonia and organ failure treated with ceftolozane/tazobactam versus meropenem: A subset analysis of the phase 3, randomized, controlled ASPECT-NP trial. *Ann. Intensive Care* **2023**, *13*, 8. [CrossRef] [PubMed]
14. Shorr, A.F.; Bruno, C.J.; Zhang, Z.; Jensen, E.; Gao, W.; Feng, H.-P.; Huntington, J.A.; Yu, B.; Rhee, E.G.; De Anda, C. Ceftolozane/tazobactam probability of target attainment and outcomes in participants with augmented renal clearance from the randomized phase 3 ASPECT-NP trial. *Crit. Care* **2021**, *25*, 354. [CrossRef] [PubMed]
15. Huntington, J.A.; Yu, B.; Li, L.; Jensen, E.; Bruno, C.; Boakye, M.; Zhang, Z.; Gao, W.; Feng, H.-P.; Rhee, E. Outcomes in participants with renal impairment from a phase 3 clinical trial for ceftolozane/tazobactam treatment of nosocomial pneumonia (ASPECT-NP). *Antimicrob. Agents Chemother.* **2020**, *64*, e00731-20. [CrossRef]
16. Kollef, M.H.; Timsit, J.-F.; Martin-Loeches, I.; Wunderink, R.G.; Huntington, J.A.; Jensen, E.H.; Yu, B.; Bruno, C.J. Outcomes in participants with failure of initial antibacterial therapy for hospital-acquired/ventilator-associated bacterial pneumonia prior to enrollment in the randomized, controlled phase 3 ASPECT-NP trial of ceftolozane/tazobactam versus meropenem. *Crit. Care* **2022**, *26*, 373. [CrossRef]
17. Paterson, D.L.; Bassetti, M.; Motyl, M.; Johnson, M.G.; Castanheira, M.; Jensen, E.H.; Huntington, J.A.; Yu, B.; Wolf, D.J.; Bruno, C.J. Ceftolozane/tazobactam for hospital-acquired/ventilator-associated bacterial pneumonia due to ESBL-producing Enterobacterales: A subgroup analysis of the ASPECT-NP clinical trial. *J. Antimicrob. Chemother.* **2022**, *77*, 2522–2531. [CrossRef]
18. Martin-Loeches, I.; Kivistik, U.; Novácek, M.; Réa-Neto, A.; Timsit François, J.; Shime, N.; Wunderink, R.G.; Kollef, M.H. *Clinical and Microbiologic Outcomes by Causative Pathogen in the ASPECTNP Randomised, Controlled, Phase III Trial Evaluating Ceftolozane/Tazobactam for Treatment of Ventilator-Associated Pneumonia*; ESCMID: Basel, Switzerland, 2019.

19. Solomkin, J.; Hershberger, E.; Miller, B.; Popejoy, M.; Friedland, I.; Steenbergen, J.; Yoon, M.; Collins, S.; Yuan, G.; Barie, P.S.; et al. Ceftolozane/tazobactam plus metronidazole for complicated intra-abdominal infections in an era of multidrug resistance: Results from a randomized, double-blind, phase 3 trial (ASPECT-cIAI). *Clin. Infect. Dis.* **2015**, *60*, 1462–1471. [CrossRef]
20. Miller, B.; Popejoy, M.W.; Hershberger, E.; Steenbergen, J.N.; Alverdy, J. Characteristics and outcomes of complicated intra-abdominal infections involving Pseudomonas aeruginosa from a randomized, double-blind, phase 3 ceftolozane-tazobactam study. *Antimicrob. Agents Chemother.* **2016**, *60*, 4387–4390. [CrossRef]
21. Lucasti, C.; Hershberger, E.; Miller, B.; Yankelev, S.; Steenbergen, J.; Friedland, I.; Solomkin, J. Multicenter, double-blind, randomized, phase II trial to assess the safety and efficacy of ceftolozane-tazobactam plus metronidazole compared with meropenem in adult patients with complicated intra-abdominal infections. *Antimicrob. Agents Chemother.* **2014**, *58*, 5350–5357. [CrossRef]
22. Sun, Y.; Fan, J.; Chen, G.; Chen, X.; Du, X.; Wang, Y.; Wang, H.; Sun, F.; Johnson, M.G.; Bensaci, M.; et al. A phase III, multicenter, double-blind, randomized clinical trial to evaluate the efficacy and safety of ceftolozane/tazobactam plus metronidazole versus meropenem in Chinese participants with complicated intra-abdominal infections. *Int. J. Infect. Dis.* **2022**, *123*, 157–165. [CrossRef] [PubMed]
23. Wagenlehner, F.M.; Umeh, O.; Steenbergen, J.; Yuan, G.; Darouiche, R.O. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: A randomised, double-blind, phase 3 trial (ASPECT-cUTI). *Lancet* **2015**, *385*, 1949–1956. [CrossRef]
24. Huntington, J.A.; Sakoulas, G.; Umeh, O.; Cloutier, D.J.; Steenbergen, J.N.; Bliss, C.; Goldstein, E.J. Efficacy of ceftolozane/tazobactam versus levofloxacin in the treatment of complicated urinary tract infections (cUTIs) caused by levofloxacinresistant pathogens: Results from the ASPECT-cUTI trial. *J. Antimicrob. Chemother.* **2016**, *71*, 2014–2021. [CrossRef] [PubMed]
25. Chang, C.-H.; Fan, P.-C.; Kuo, G.; Lin, Y.-S.; Tsai, T.-Y.; Chang, S.-W.; Tian, Y.-C.; Lee, C.-C. Infection in advanced chronic kidney disease and subsequent adverse outcomes after dialysis initiation: A nationwide cohort study. *Sci. Rep.* **2020**, *10*, 2938. [CrossRef] [PubMed]
26. Soriano, A.; Puzniak, L.; Paterson, D.; Thalhalmmer, F.; Kluge, S.; Viale, P.; Kaul, S. 2279. Study of Prescribing patterns and Effectiveness of Ceftolozane–tazobactam (C/T): Real-world Analysis (SPECTRA): A multi-national, multicenter observational study. In *Open Forum Infectious Diseases*; Oxford University Press: Oxford, UK, 2019.
27. Lodise, T.P.; Obi, E.N.; Watanabe, A.H.; Yucel, E.; Min, J.; Nathanson, B.H. Comparative evaluation of early treatment with ceftolozane/tazobactam versus ceftazidime/avibactam for non-COVID-19 patients with pneumonia due to multidrug-resistant Pseudomonas aeruginosa. *J. Antimicrob. Chemother.* **2024**, *79*, 2954–2964. [CrossRef] [PubMed]
28. Shields, R.K.; Abbo, L.M.; Ackley, R.; Aitken, S.L.; Albrecht, B.; Babiker, A.; Burgoon, R.; Cifuentes, R.; Claeys, K.C.; Curry, B.N. Effectiveness of ceftazidime–avibactam versus ceftolozane–tazobactam for multidrug-resistant Pseudomonas aeruginosa infections in the USA (CACTUS): A multicentre, retrospective, observational study. *Lancet Infect. Dis.* **2025**, *25*, 574–584. [CrossRef] [PubMed]
29. Lizza, B.D.; Betthauser, K.D.; Ritchie, D.J.; Micek, S.T.; Kollef, M.H. New perspectives on antimicrobial agents: Ceftolozane-tazobactam. *Antimicrob. Agents Chemother.* **2021**, *65*, e02318-20. [CrossRef]
30. Sader, H.S.; Flamm, R.K.; Carvalhaes, C.G.; Castanheira, M. Antimicrobial Susceptibility of Pseudomonas aeruginosa to Ceftazidime-Avibactam, Ceftolozane-Tazobactam, Piperacillin-Tazobactam, and Meropenem Stratified by U.S. Census Divisions: Results from the 2017 INFORM Program. *Antimicrob. Agents Chemother.* **2018**, *62*, e01587-18. [CrossRef]
31. Li, X.-Z.; Plésiat, P.; Nikaido, H. The Challenge of Efflux-Mediated Antibiotic Resistance in Gram-Negative Bacteria. *Clin. Microbiol. Rev.* **2015**, *28*, 337–418. [CrossRef]
32. Tebano, G.; Zaghi, I.; Cricca, M.; Cristini, F. Antibiotic Treatment of Infections Caused by AmpC-Producing Enterobacterales. *Pharmacy* **2024**, *12*, 142. [CrossRef] [PubMed]
33. MacDougall, C.; Polk, R.E. Antimicrobial stewardship programs in health care systems. *Clin. Microbiol. Rev.* **2005**, *18*, 638–656. [CrossRef]
34. Sterne, J.A.C.; Savović, J.; Page, M.J.; Elbers, R.G.; Blencowe, N.S.; Boutron, I.; Cates, C.J.; Cheng, H.-Y.; Corbett, M.S.; Eldridge, S.M.; et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ* **2019**, *366*, l4898. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.