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Efficacy and Safety of Different Treatments for *Acinetobacter baumannii* Infection: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: This Network meta-analysis (NMA) aimed to assess antimicrobial treatments for *A. baumannii* infections (including pneumonia, bloodstream infections, and urinary tract infections), focusing on clinical cure, microbiological eradication, mortality, and adverse events.

Methods: Following PRISMA-NMA guidelines, we searched Medline, Scopus, Web of Science, Cochrane Library, and EMBASE (2000–2024) for interventional studies on MDR-, XDR-, or PDR-*A. baumannii* infections. Two independent reviewers screened studies for inclusion based on predefined criteria, extracted relevant data (e.g., patient demographics, APACHE II scores, treatment regimens), and assessed study quality using the Cochrane Risk of Bias 2 (RoB 2) tool. A pairwise meta-analysis was performed using random-effects models (DerSimonian-Laird method) to calculate risk ratios (RR) with 95% confidence intervals (CI). Node-splitting analysis was performed to assess the consistency of direct and indirect evidence in the network. Statistical heterogeneity was evaluated, and consistency between direct and indirect evidence was tested.

Results: From 4,941 records, 18 studies (2,750 patients) were included in the systematic review and 16 in the NMA. No RCTs on non-antimicrobial treatments (e.g., phages, monoclonal antibodies) met the inclusion criteria, limiting the analysis to antimicrobial regimens. Colistin with rifampin (RR = 0.27, 95% CI: 0.07–0.99) and sulbactam with durlobactam (RR = 0.22, 95% CI: 0.05–0.91) significantly reduced all-cause mortality compared to colistin alone. Colistin-meropenem dual therapy improved clinical cure (RR = 0.31, 95% CI: 0.11–0.84). No regimens significantly affected microbiological eradication or adverse events. Network consistency was confirmed, with no heterogeneity detected.

Conclusion: The combination of sulbactam-durlobactam significantly reduced mortality, while colistin-rifampin also showed efficacy but requires cautious interpretation given rifampin's role as a strategic antibiotic. These findings provide valuable evidence to guide treatment decisions for these challenging infections; however, the limited number of studies for certain interventions and the absence of RCTs on non-antimicrobial therapies warrant cautious interpretation and further research.

Keywords: *Acinetobacter baumannii*, Efficacy, Safety, Network meta-analysis, Randomized Controlled Trials

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Key Messages:

↑What is "already known" in this topic:

Previous network meta-analyses on *A. baumannii* treatments, including Kengkla et al. (2018), did not include newer RCTs on sulbactam-durlobactam or cefiderocol. Uncertainty persists regarding optimal combination therapy for mortality reduction and the safety profile of colistin-based regimens. The role of rifampin-containing regimens also remains debated.

→What this article adds:

By including 18 RCTs (2000–2024), this updated NMA identifies sulbactam-durlobactam as a mortality-reducing option (moderate certainty) while cautioning against routine rifampin use due to its strategic importance. Colistin-meropenem improves clinical cure but does not impact microbiological eradication. These findings inform evidence-based selection of antimicrobial regimens, particularly in settings with high MDR/XDR prevalence.

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Introduction

Acinetobacter baumannii infections, particularly pneumonia, pose a significant global health challenge due to their increasing resistance to antibiotic treatments. To evaluate the comparative effectiveness and safety of available treatments, various analytical methods are employed worldwide (1, 2). Among these, systematic reviews paired with network meta-analysis (NMA) are widely recognized as robust and precise approaches (2, 3). Unlike traditional pairwise meta-analyses, NMA integrates direct evidence and indirect evidence (derived from common comparators across studies), offering a comprehensive framework to assess multiple interventions simultaneously (4).

Network meta-analysis (NMA) integrates direct and indirect evidence from common comparators, offering a comprehensive framework to assess multiple interventions simultaneously (5). This approach surpasses conventional meta-analysis by resolving discrepancies across studies and enhancing statistical power through cross-validation (4, 6). However, the reliability of NMA hinges on the quality of included evidence and clinical homogeneity of trials (5). By synthesizing direct and indirect evidence, NMA provides a nuanced understanding of treatment effects, which is invaluable for informing clinical decision-making (2, 7, 8).

While previous NMAs, such as Kengkla et al. (2018), have evaluated treatments for *A. baumannii* infections, several important knowledge gaps remain (2, 7). First, newer RCTs evaluating novel therapies, including sulbactam-durlobactam and cefiderocol, have been published since these earlier analyses. Second, the optimal combination therapy for reducing mortality and improving clinical outcomes remains controversial. Third, the role of rifampin-containing regimens requires critical re-evaluation given rifampin's strategic importance for other infections. This study addresses these gaps by including the most recent RCTs up to 2024 and providing updated evidence to guide clinical decision-making (7, 8).

The primary objective of this NMA is to assess the efficacy and safety of antimicrobial treatments for *A. baumannii* infections, specifically evaluating all-cause mortality and clinical cure as primary outcomes. Secondary outcomes include microbiological eradication, nephrotoxicity, and non-nephrotoxic adverse events (neurotoxicity, hepatotoxicity, and skin rash). By utilizing NMA, this research aims to provide robust, evidence-based insights that will inform and guide therapeutic decision-making in the management of this critical infectious disease.

Methods

This systematic review and NMA was conducted in accordance with protocol CRD420250656044, registered with PROSPERO (9). The study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for NMA guidelines to ensure transparent and comprehensive reporting (10).

Eligibility Criteria

Eligible participants included patients diagnosed with infections caused by multidrug-resistant (MDR), extensively drug-resistant (XDR), or pandrug-resistant (PDR) Acinetobacter baumannii. The infections of interest encompassed hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), bloodstream infections (BSI), and urinary tract infections (UTIs). Diagnoses were defined according to criteria established by the Infectious Diseases Society of America (IDSA) (11) and the U.S. Centers for Disease Control and Prevention (CDC) (12).

Inclusion criteria were based on RCTs assessing MDR/XDR/PDR *A. baumannii* infections (HAP, VAP, BSI, UTI). Treatments included antimicrobial (e.g., colistin, sulbactam) therapies. Outcomes include all-cause mortality, clinical cure, or microbiological eradication. Published between 2000 and 2024. Eligible treatments included colistin, sulbactam, ampicillin-sulbactam, and other antibiotics administered as monotherapy, combination therapy, or triple therapy. Specific details regarding treatment regimens (e.g., dosage, duration) were extracted where reported in the original studies. Exclusion criteria encompassed studies involving studies with mixed Gram-negative infections. Single-arm studies, conference abstracts, editorials, reviews, or meta-analyses. Non-interventional studies. Observational studies were excluded to reduce confounding, minimize the risk of bias, and ensure high-quality evidence from RCTs, which provide the highest level of evidence for treatment comparisons. This approach aligns with the methodological standards for NMA, which require rigorously designed studies to maintain the validity of indirect comparisons.

Outcomes and Definitions

Eligible studies were those that evaluated at least one of three key outcomes: all-cause mortality, clinical cure, or microbiological eradication using clearly defined criteria. Clinical cure and microbiological eradication were considered secondary outcomes. Clinical cure was defined as the resolution of infection-related signs and symptoms, including fever, leukocytosis, and clinical improvement, by treatment completion. In the included clinical trials, comparison groups consisted of colistin monotherapy, other antibiotic regimens (e.g., meropenem, cefiderocol), or best available therapy, as detailed in Table 1. For this NMA, the primary outcomes of interest were all-cause mortality and clinical cure. Clinical cure was defined as the resolution of infection-related signs and symptoms by the end of treatment, while all-cause mortality was defined as death from any cause during the study period. Secondary outcomes included microbiological eradication (defined as a negative culture after completing therapy), nephrotoxicity, and non-nephrotoxic adverse events (including neurotoxicity, hepatotoxicity, and skin rash).

MDR is defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories. XDR describes isolates that are non-susceptible to at least one

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agent in all but two or fewer antimicrobial categories, with carbapenem resistance being a mandatory criterion. PDR refers to non-susceptibility to all agents in all antimicrobial categories.

Search Strategy and Selection Criteria

A comprehensive search strategy was developed to identify relevant studies. Initially, keywords were derived from the study title, including "Acinetobacter", "drug resistance", "treatment", "response", "mortality", "nephrotoxicity", and "adverse events". Synonyms and controlled vocabulary terms were identified using Medical Subject Headings (MeSH), Emtree, and Thesaurus to broaden the search scope. International databases including MEDLINE (via PubMed), Scopus, Web of Science, Cochrane Library, EMBASE, and CINAHL were searched for studies published between January 1, 2000, and December 30, 2024. Additionally, grey literature and ongoing trials were explored through ClinicalTrials. gov, the WHO International Clinical Trials Registry Platform (ICTRP), and the European Union Clinical Trials Register. Reference lists of relevant systematic reviews and included studies were handsearched to identify additional eligible studies (Appendix Table A1).

Study Selection and Data Extraction

Study selection was performed in two stages. First, two investigators (MAR and YM) independently screened titles and abstracts to identify potentially eligible studies. Discrepancies were resolved through discussion with the review team (MAR, YM, GM, and PM). Second, the same two investigators assessed full-text articles against predefined inclusion criteria. Data were extracted on study characteristics (design, sample size), intervention details (treatment regimens, dosages, durations), and patient demographics (mean age, sex, resistance profile, infection site, and mean Acute Physiology and Chronic Health Evaluation II [APACHE II] score). All extracted data were cross-verified by MAR and YM to ensure accuracy.

The primary aim was to evaluate the efficacy and safety of antimicrobial and non-antimicrobial treatments, both as monotherapies and in combination, for *A. baumannii* infections, with a particular focus on pneumonia (Appendix Table A1).

Quality Assessment

Following screening, the quality of the selected studies was evaluated by three investigators (MAR, YM, and PM) using Version 2 of the Cochrane Risk of Bias Tool for Randomized Trials (RoB 2) (13). This tool was applied to assess the risk of bias across the included randomized controlled trials.

Data Synthesis and Analysis

The study employed both pairwise meta-analysis and NMA, conducted using STATA 17.0 software. For the pairwise meta-analysis, a random-effects model, specifically the DerSimonian and Laird method, was used to calculate pooled risk ratios (RR) with 95% confidence intervals (CI) (14). Heterogeneity across pairwise comparisons was quantified using the I^2 statistic (15), with analysis restricted to data from clinical trials meeting the predefined inclusion criteria.

To assess inconsistencies between direct and indirect evidence, a loop-specific approach was implemented, evaluating triangular or quadratic loops for consistency. An inconsistency factor was calculated to detect discrepancies in treatment effect estimates within these loops (16). Additionally, node-splitting was employed to identify inconsistencies within the network by separating direct and indirect evidence for specific comparisons.

The Surface Under the Cumulative Ranking (SUCRA) method was utilized to estimate the probability of each treatment's ranking and to evaluate their relative effectiveness (17). The analysis adhered to key assumptions of network meta-analysis, including homogeneity, transitivity, and consistency.

Summary of Results Using the GRADE Approach

The certainty of evidence for each treatment comparison and outcome was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, as adapted for network meta-analysis. The assessment considered five domains: risk of bias (based on the RoB 2 tool), inconsistency (I^2 statistic and heterogeneity), indirectness (population, intervention, and outcome applicability), imprecision (confidence intervals and sample size), and publication bias (funnel plot asymmetry and small-study effects). Evidence certainty was rated as high, moderate, low, or very low.

Results

A total of 4,941 records were identified through database searches, with an additional 12 records obtained from other sources (Figure 1). Of the 64 potentially relevant articles, 18 studies were included in the systematic review, and 16 were incorporated into the NMA. No RCTs evaluating non-antimicrobial treatments (e.g., phages, monoclonal antibodies) met inclusion criteria, limiting the analysis to antimicrobial regimens.

Characteristics and Quality Assessment of Included Studies

The characteristics of studies included in the systematic review and NMA are summarized in Table 1. Across the 18 studies, encompassing 2,750 patients, the mean ± SD (Standard Deviation) age of participants was 64.8 ± 3.64 years, with 57.7% being male. The mean APACHE II score was 17.8 (IQR 14.2–20.4). Of the 18 included studies, 7 focused exclusively on ventilator-associated pneumonia (VAP), while 11 studies included patients with mixed infections, including VAP, hospital-acquired pneumonia (HAP), bloodstream infections (BSIs), and urinary tract infections (UTIs). The majority of patients across studies had pneumonia (approximately 85% of the total patient population), reflecting the predominance of pulmonary infections in the clinical trials. Most studies (11 studies, 61.2%) included patients with multidrug-resistant *A. baumannii*

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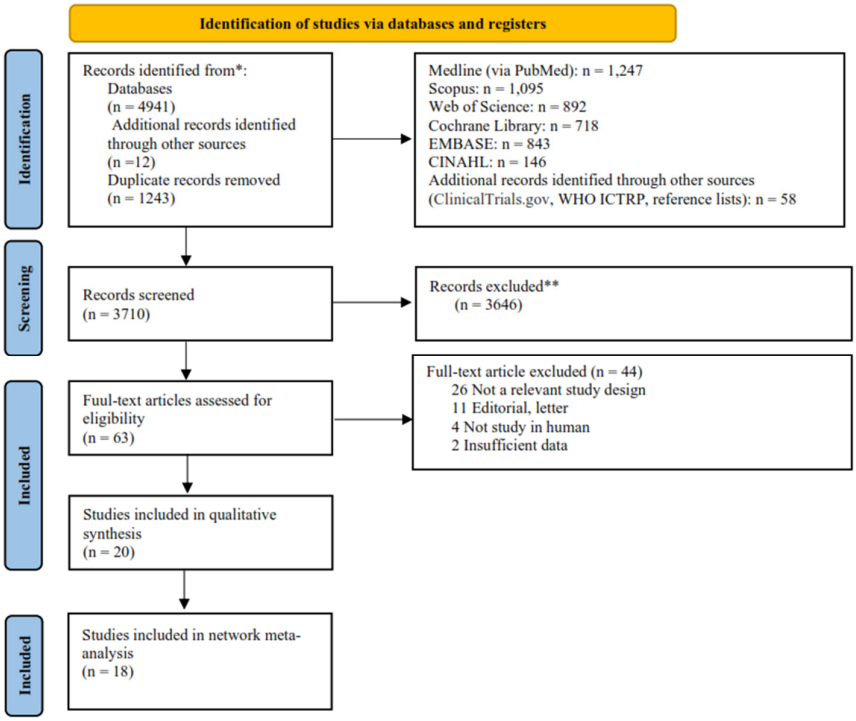


Figure 1. Flow diagram and references of included studies.

(MDR-AB), while the remaining seven (38.8%) involved patients with extensively drug-resistant *A. baumannii* (XDR-AB). Additional study characteristics are detailed in the Appendix Table A2-A5. The quality assessment of the included RCTs is presented in the Appendix Figure A1. The majority of studies (10/18) exhibit low overall risk of bias, indicating robust trial designs. The key node of colistin + rifampin, which significantly reduces all-cause mortality, is primarily driven by studies with low risk of bias (Aydemir, Durante-Mangoni), with only one study (Park et al.) having some concerns. This suggests high confidence in the finding, as the majority of the evidence comes from high-quality studies. In contrast, the Sulbactam + Durlobactam node relies on a study with some concerns (Kaye et al.), indicating a need for cautious interpretation. The Colistin + Meropenem node for clinical cure is supported by a low-risk study (Paul et al.), reinforcing its reliability. Overall, the NMA's key findings for Colistin + Rifampin are robust, as they are not heavily influenced by high-risk or concerning studies.

Network Consistency

The eligible comparison networks for each treatment outcome are shown in Figure 2 [Figure 2-a) all-cause mortality, 16 studies (2041 patients), Figure 2-b) clinical cure, 10 studies (1076 patients), Figure 2-c) microbiological cure, 11 studies (1082 patients), Figure 2-d) nephrotoxicity, 9 studies (1505 patients) and Figure 2-e), non-nephrotoxic adverse event (neurotoxicity, hepatotoxicity and skin rash), 7 studies (1323 patients)]**.** When data were pooled into treatment networks, no evidence of global inconsistency or heterogeneity was observed. The heterogeneity, as measured by I^2, varies across comparisons, with some showing low or negligible heterogeneity (e.g., Ampicillin + Sulbactam vs. Colistin for clinical cure, I^2= 13%), and others showing high heterogeneity (e.g., Colistin vs. Colistin + Rifampin for microbiological cure, I^2= 86%) (Appendix Table A6, Table A7, Figure A2).

Treatment Outcomes

Treatment effects were analyzed through pairwise meta-analysis of direct evidence (Appendix Table A6). No statistical heterogeneity was detected in pairwise comparisons for the primary outcomes, nor for nephrotoxicity and non-nephrotoxic adverse events.

All-Cause Mortality

A network meta-analysis of 16 studies, involving 2,041 patients, evaluated all-cause mortality (Figure 2-a). The combination of colistin and rifampin was associated with a significant reduction in all-cause mortality compared to colistin alone (RR = 0.27, 95% CI: 0.07–0.99). Similarly, the combination of sulbactam and durlobactam correlated with a reduced mortality risk compared to colistin (RR = 0.22, 95% CI: 0.05–0.91). No significant differences were observed in other treatment comparisons (Figure 3-a). Based on the GRADE framework, interventions were classified according to their relative effectiveness and certainty of evidence for all-cause mortality. GRADE certainty: moderate for sulbactam + durlobactam [SUCRA 85.2] and colistin + rifampin [SUCRA 82.7]; low for other comparisons (Table 2).

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Table 1. Characteristics of included studies

Study ID	First Author	Location	Study Design	Infection	Resistance	Participant	Treatment regiments	Treatment duration (Day)	Age	Male (%)	APACHE II
1	Aydemir (2013) (29)	Turkey	RCT	VAP	MDR	43	COL; COL + RIF	9.3±3.2	60.5	51	19
2	Durante-Mangoni (2013) (30)	Italy	RCT	Mixed (VAP 70%, BSI 20%, HAP 9%)	XDR	209	COL; COL + RIF	12.5 (8-17)	61.5	65	NA
3	Betrisian (2007) (31)	Greece	RCT	VAP (100%)	XDR	28	COL; AMP + SUL	9.2 ±1.5 vs 9.9 ±2.6	69.5	55.7	14.2
4	Sirijatuphat (2014) (32)	Thailand	RCT	Mixed (Pneumonia 75%, BSI 5%)	MDR	94	COL; COL + FOS	12 (3-15)	68	47	22
5	Aranzana-Climent (2024) (33)	Spain	RCT	HAP, VAP, BS, urosepsis,	MDR	207	COL; COL + MER	1	62	57	NA
6	Bassetti (2020) (34)	North America, South America, Europe, and Asia	RCT	Mixed (VAP, BSI, HAP, UTI)	MDR	152	BAT; CEF	7-14	63	67	15.3
7	Dickstein (2018) (35)	Italy, Greece, Israel	RCT	Mixed (VAP, BSI, HAP, UTI)	MDR	266	COL; COL + MER	10	70.5	66.1	NA
8	Hakamifard (2022) (36)	Iran	RCT	VAP	XDR	55	COL; TOB+FOS	13.7 vs 10.6	61.4	60.2	NA
9	Keith (2023) (37)	United States, Thailand, Taiwan, Israel, Greece, Italy, and Bulgaria	RCT	Pneumonia and/or BSI	XDR	423	COL; COL + MER	7-14	67.8	62.5	21.5
10	Nutman (2020) (38)	Italy, Greece and Israel	RCT	Mixed (VAP, BSI, HAP, UTI)	MDR	131	COL; COL + MER	14	69	72	NA
11	Jung Park (2019) (39)	South Korea	RCT	VAP	MDR	9	COL; COL + RIF	7-28	67	62.5	NA
12	Paul (2018) (40)	Israel, Greece, and Italy	RCT	Mixed (VAP, BSI, HAP, UTI)	XDR	406	COL; COL + MER	17	66	37.5	NA
13	Pourheidar (2019) (41)	Iran	RCT	VAP	MDR	28	COL + NEB; COL + AMP + SUL	8±3 vs 9±3	59.5	56.2	15.5
14	Rattanaumpawan (2010) (42)	Thailand	RCT	VAP	MDR	100	COL(CMS); NEB (NNS)	9.5 VS 11.8	68.1	64	18.5
15	Koomanachai (2007) (43)	Thailand	RCT	VAP	MDR	93	COL; Non-COL	11.9 vs 11.9	61.2	65.5	22.1
16	Wunderink (2020) (44)	Asia, Europe, and the USA	RCT	Mixed (VAP, HAP, or HCAP)	XDR	297	CEF; MER	10.4.1 vs 10.1	65	68.5	16.2
17	Khorvash (2019) (45)	Iran	RCT	Mixed (VAP, HAP, or HCAP)	MDR	60	COL + MER; COL + MER + TOB	14	60.5	65	15.3
18	Kaye (2023) (46)	16 countries	RCT	Mixed (VAP, BSI, HAP, UTI)	XDR	177	COL + SUL+ DUR; COL + OTH	7-14	64	74.5	16.5

Abbreviations: NA, not available; ICU, Intensive care unit; VAP, Ventilator-associated pneumonia; HAP, Hospital-acquired pneumonia, HCAP (Healthcare-Associated Pneumonia), NEB, nebulized sterile normal saline; CMS, Parenteral colistimethate sodium; NNS, nebulized sterile normal saline

Abbreviations: COL*, Colistin (Include COL and NEB, BAT (best available therapy), and OTH); SUL, Sulbactam; CEF, Cefiderocol; SUL, Sulbactam; DUR, AMP, Ampicillin; FOS, Fosfomycin, RIF, Rifampin; MER, Meropenem; TOB, Tobramycin; NEB, Nebulized; Non-Col, None Colistin; OTH, Other antibiotic

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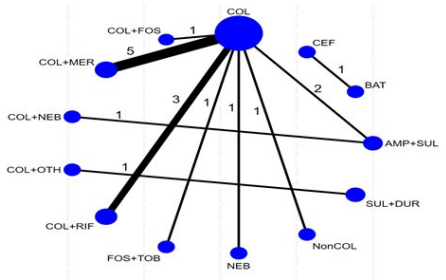


Figure 2-a. All-cause mortality, 16 studies (2041 patients).

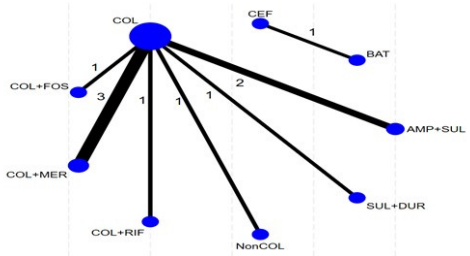


Figure 2-b. Clinical cure, 10 studies (1076 patients).

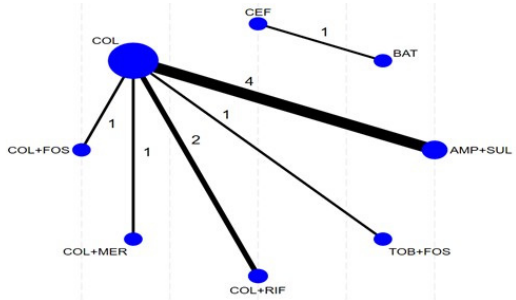


Figure 2-c. Microbiological cure, 11 studies (1082 patients).

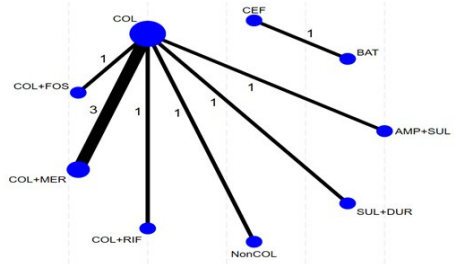


Figure 2-d. Nephrotoxicity, 9 studies (1505 patients).

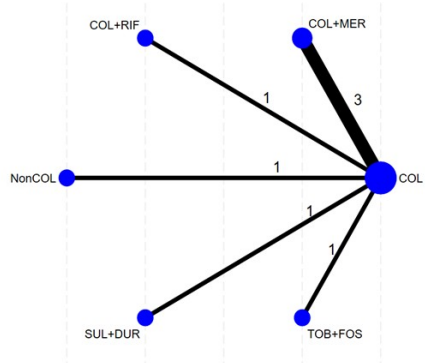


Figure 2-e. Non-nephrotoxic adverse event (neurotoxicity, hepatotoxicity and skin rash), 7 studies (1323 patients).

Figure 2. Networks of all treatment comparisons.

The size of the nodes corresponds to the number of trials that studied the treatments. The directly compared treatments are linked with a line, the thickness of which corresponds to the number of trials that assessed this comparison.
Abbreviations: COL*, Colistin (includes colistin monotherapy, nebulized colistin, best available therapy (47), and other antibiotics (48)); SUL, Sulbactam; CEF, Cefiderocol; DUR, Durlobactam; AMP, Ampicillin; FOS, Fosfomycin; RIF, Rifampin; MER, Meropenem; TOB, Tobramycin; Non-Col, Non-colistin-based regimens (includes regimens without colistin as a component); NEB, Nebulized therapy.

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Table 2. GRADE-Based Classification of Efficacy and Safety of Different Treatments for Acinetobacter baumannii Infection: Relative Effects, Rankings, and Certainty of Evidence

Certainty of Evidence (GRADE)	Classification	Treatment Comparison	SUCRA	RR (95% CI)
All-Cause Mortality				
Moderate	Among the most effective	Sulbactam + Durlobactam vs. Colistin	85.2	0.22 (0.05 to 0.91)
Moderate	Among the most effective	Colistin + Rifampin vs. Colistin	82.7	0.27 (0.07 to 0.99)
Low	Inferior to the most effective / Superior to the least effective	Colistin + Meropenem vs. Colistin	68.4	0.52 (0.24 to 1.13)
Low	Inferior to the most effective / Superior to the least effective	Colistin + Fosfomycin vs. Colistin	55.1	0.75 (0.38 to 1.48)
Low	Inferior to the most effective / Superior to the least effective	Cefiderocol vs. Colistin	43.6	0.94 (0.54 to 1.63)
Low	Inferior to the most effective / Superior to the least effective	Ampicillin + Sulbactam vs. Colistin	36.2	1.05 (0.43 to 2.57)
Low	May be among the least effective	Non-Colistin vs. Colistin	18.4	1.52 (0.58 to 3.98)
Clinical Cure				
Moderate	Among the most effective	Colistin + Meropenem vs. Colistin	89.7	3.23 (1.19 to 9.09)
Low	Inferior to the most effective / Superior to the least effective	Colistin + Rifampin vs. Colistin	72.3	1.95 (0.91 to 4.18)
Low	Inferior to the most effective / Superior to the least effective	Colistin + Fosfomycin vs. Colistin	64.8	1.60 (0.44 to 5.82)
Low	Inferior to the most effective / Superior to the least effective	Ampicillin + Sulbactam vs. Colistin	58.1	1.45 (0.53 to 3.97)
Low	Inferior to the most effective / Superior to the least effective	Cefiderocol vs. Colistin	41.5	1.12 (0.67 to 1.87)
Low	May be among the least effective	Non-Colistin vs. Colistin	24.6	0.85 (0.52 to 1.39)
Microbiological Eradication				
Very Low	Among the most effective	Colistin + Fosfomycin vs. Colistin	78.4	2.52 (0.93 to 6.83)
Low	Inferior to the most effective / Superior to the least effective	Colistin + Meropenem vs. Colistin	65.9	1.63 (0.67 to 3.94)
Low	Inferior to the most effective / Superior to the least effective	Ampicillin + Sulbactam vs. Colistin	52.7	1.21 (0.54 to 2.73)
Low	Inferior to the most effective / Superior to the least effective	Colistin + Rifampin vs. Colistin	44.8	1.07 (0.65 to 1.76)
Low	Inferior to the most effective / Superior to the least effective	Cefiderocol vs. Colistin	36.3	0.88 (0.44 to 1.76)
Very Low	May be among the least effective	Non-Colistin vs. Colistin	21.9	0.63 (0.20 to 1.98)
Nephrotoxicity				
Low	Among the most effective (lowest risk)	Cefiderocol vs. Colistin	72.6	0.58 (0.19 to 1.75)
Low	Inferior to the most effective / Superior to the least effective	Colistin + Meropenem vs. Colistin	63.4	0.73 (0.35 to 1.50)
Low	Inferior to the most effective / Superior to the least effective	Non-Colistin vs. Colistin	48.1	1.00 (0.58 to 1.73)
Low	Inferior to the most effective / Superior to the least effective	Colistin + Rifampin vs. Colistin	39.7	1.10 (0.64 to 1.89)
Very Low	May be among the least effective (highest risk)	Ampicillin + Sulbactam vs. Colistin	28.5	1.31 (0.34 to 5.08)
Very Low	May be among the least effective (highest risk)	Colistin + Fosfomycin vs. Colistin	22.3	1.56 (0.27 to 9.08)
Non-Nephrotoxic Adverse Events				
Low	Among the most effective (lowest risk)	Colistin + Meropenem vs. Colistin	58.7	1.00 (0.58 to 1.73)
Low	Among the most effective (lowest risk)	Cefiderocol vs. Colistin	56.2	1.02 (0.46 to 2.26)
Very Low	Inferior to the most effective / Superior to the least effective	Colistin + Fosfomycin vs. Colistin	52.4	1.06 (0.52 to 2.15)
Low	Inferior to the most effective / Superior to the least effective	Non-Colistin vs. Colistin	40.8	1.31 (0.54 to 3.18)
Very Low	May be among the least effective (highest risk)	Colistin + Rifampin vs. Colistin	28.9	1.77 (0.37 to 8.50)

Abbreviations: RR, Risk Ratio; CI, Confidence Interval; SUCRA, Surface Under the Cumulative Ranking Curve; GRADE, Grading of Recommendations Assessment, Development and Evaluation; COL, Colistin; RIF, Rifampin; MER, Meropenem; FOS, Fosfomycin; SUL, Sulbactam; DUR, Durlobactam; AMP, Ampicillin; CEF, Cefiderocol; Non-Col, Non-colistin-based regimens.
Bold values indicate statistically significant results (95% CI does not cross 1.0).
SUCRA Interpretation: Higher SUCRA values indicate better efficacy (for mortality, clinical cure, and microbiological eradication) or better safety (lower risk for nephrotoxicity and adverse events).
GRADE Interpretation:

- High: Very confident that the true effect lies close to the estimate
- Moderate: Moderately confident in the estimate; further research may change confidence
- Low: Limited confidence; further research is very likely to change the estimate
- Very Low: Very little confidence in the estimate; true effect is likely substantially different

Classification Definitions: 1) Among the most effective: Treatment ranked in the top tier for the outcome based on SUCRA values and statistical significance; 2) Inferior to the most effective / Superior to the least effective: Treatment with intermediate effectiveness; not significantly different from the best or worst, & 3) May be among the least effective: Treatment with lower SUCRA values; suggestive of inferiority, though not statistically significant

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Clinical Cure

A network meta-analysis of 10 studies, including 1,076 patients, assessed clinical cure (Figure 2-b). Non-colistin combination therapies significantly improved clinical cure rates compared to other antibiotics. The combination of colistin and meropenem significantly improved clinical cure compared to colistin monotherapy (RR = 3.23, 95% CI: 1.19–9.09) (Figure 3-b). These findings were consistent with data synthesized from randomized controlled trials. GRADE certainty: moderate for colistin + meropenem [SUCRA 89.7]; low for other comparisons (Table 2).

Microbiological Cure

Eleven studies, comprising 1,082 patients, evaluated microbiological cure (Figure 2-c). In the NMA, neither monotherapy nor combination therapies significantly improved microbiological eradication (Figure 3-c). GRADE certainty: low to very low for all comparisons (Table 2).

(a) Network estimated risk ratios (95% confidence intervals) of colistin combination based regimens on all-cause mortality

SUL+DUR								
0.80 [0.31, 2.09]	COL+RIF							
0.74 [0.26, 2.05]	0.92 [0.40, 2.08]	COL+FOS						
0.66 [0.29, 1.54]	0.83 [0.46, 1.48]	0.90 [0.45, 1.79]	COL+MER					
0.65 [0.19, 2.28]	0.81 [0.27, 2.42]	0.89 [0.28, 2.80]	0.99 [0.37, 2.66]	NEB				
0.61 [0.20, 1.89]	0.76 [0.29, 1.97]	0.83 [0.30, 2.30]	0.92 [0.40, 2.13]	0.93 [0.27, 3.24]	AMP+SUL			
0.60 [0.27, 1.34]	0.75 [0.45, 1.25]	0.81 [0.43, 1.54]	0.90 [0.70, 1.18]	0.92 [0.35, 2.39]	0.98 [0.44, 2.19]	COL*		
0.48 [0.16, 1.42]	0.60 [0.24, 1.47]	0.65 [0.25, 1.72]	0.72 [0.33, 1.58]	0.73 [0.22, 2.45]	0.78 [0.26, 2.32]	0.80 [0.38, 1.66]	Non COL	
0.39 [0.05, 2.72]	0.48 [0.08, 3.07]	0.52 [0.08, 3.47]	0.58 [0.10, 3.52]	0.59 [0.08, 4.46]	0.63 [0.09, 4.45]	0.64 [0.11, 3.82]	0.81 [0.12, 5.55]	TOB+FOS
0.22 [0.05, 0.91]	**0.27 [0.07, 0.99]**	0.30 [0.08, 1.14]	0.33 [0.10, 1.11]	0.33 [0.07, 1.53]	0.36 [0.09, 1.49]	0.36 [0.11, 1.19]	0.45 [0.11, 1.84]	0.56 [0.07, 4.79]

*Comparisons between treatments should be read from column to row for each outcome (row treatment is reference)

Abbreviations: COL, Colistin [(Include COL and NEB, Nebulized; BAT, best available therapy; and OTH, Other antibiotic)]; SUL, Sulbactam; CEF, Cefiderocol; DUR, Durlobactam; AMP, Ampicillin; FOS, Fosfomycin, RIF, Rifampin; MER, Meropenem; TOB, Tobramycin; Non-Col, None Colistin

(b) Network estimated risk ratios (95% confidence intervals) of colistin combination based regimens on clinical cure

Non COL						
0.15 [0.03, 0.68]	COL+MER					
0.11 [0.03, 0.47]	0.75 [0.47, 1.21]	COL*				
0.09 [0.02, 0.53]	0.63 [0.22, 1.86]	0.84 [0.32, 2.21]	COL+FOS			
0.09 [0.01, 0.56]	0.58 [0.16, 2.08]	0.78 [0.24, 2.52]	0.92 [0.20, 4.24]	AMP+SUL		
0.05 [0.01, 0.25]	**0.31 [0.11, 0.84]****	0.41 [0.17, 0.99]	0.49 [0.13, 1.80]	0.53 [0.12, 2.30]	SUL+DUR	
0.02 [0.00, 0.69]	0.12 [0.00, 3.56]	0.16 [0.01, 4.58]	0.19 [0.01, 6.24]	0.20 [0.01, 7.19]	0.38 [0.01, 12.45]	COL+RIF

*Comparisons between treatments should be read from column to row for each outcome (row treatment is reference)

** Invert the comparator to report RR > 1 (e.g., colistin + meropenem vs. colistin: RR = 3.23, 95% CI: 1.19–9.09, calculated as 1/0.31).

Abbreviations: COL, Colistin [(Include COL and NEB, Nebulized; BAT, best available therapy; and OTH, Other antibiotic)]; SUL, Sulbactam; CEF, Cefiderocol; DUR, Durlobactam; AMP, Ampicillin; FOS, Fosfomycin, RIF, Rifampin; MER, Meropenem; TOB, Tobramycin; Non-Col, None Colistin

(c) Network estimated risk ratios (95% confidence intervals) of colistin combination based regimens on microbiological cure

TOB+FOS						
0.37 [0.03, 4.96]	COL*					
0.38 [0.01, 12.49]	1.04 [0.10, 10.57]	COL+MER				
0.23 [0.01, 8.90]	0.63 [0.05, 8.12]	0.61 [0.02, 19.15]	CEF			
0.21 [0.01, 3.97]	0.58 [0.15, 2.20]	0.56 [0.04, 8.12]	0.92 [0.05, 16.45]	AMP+SUL		
0.16 [0.01, 4.22]	0.42 [0.06, 3.22]	0.41 [0.02, 8.90]	0.67 [0.03, 17.57]	0.73 [0.06, 8.26]	COL+RIF	
0.02 [0.00, 1.41]	0.04 [0.00, 1.67]	0.04 [0.00, 3.16]	0.07 [0.00, 5.93]	0.07 [0.00, 3.64]	0.10 [0.00, 6.67]	COL+FOS

*Comparisons between treatments should be read from column to row for each outcome (row treatment is reference)

Abbreviations: COL, Colistin [(Include COL and NEB, Nebulized; BAT, best available therapy; and OTH, Other antibiotic)]; SUL, Sulbactam; CEF, Cefiderocol; DUR, Durlobactam; AMP, Ampicillin; FOS, Fosfomycin, RIF, Rifampin; MER, Meropenem; TOB, Tobramycin; Non-Col, None Colistin

Figure 3. Network estimated risk ratios (95% CIs) of treatment options for (3-a) all-cause mortality, (3-b) clinical cure, (3-c) microbiological cure, (d) nephrotoxicity, and (e) no nephrotoxicity adverse event.

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(d) Network estimated risk ratios (95% confidence intervals) of colistin combination based regimens on Nephrotoxicity

AMP+SUL				
0.96 [0.27, 3.42]	COL+RIF			
0.83 [0.36, 1.92]	0.86 [0.33, 2.24]	COL*		
0.73 [0.15, 3.62]	0.76 [0.15, 4.01]	0.88 [0.23, 3.44]	CEF	
0.65 [0.16, 2.67]	0.67 [0.15, 2.97]	0.78 [0.25, 2.44]	0.88 [0.15, 5.20]	COL+MER

*Comparisons between treatments should be read from column to row for each outcome (row treatment is reference)

Abbreviations: COL, Colistin [(Include COL and NEB, Nebulized; BAT, best available therapy; and OTH, Other antibiotic)]; SUL, Sulbactam; CEF, Cefiderocol; DUR, Durlobactam; AMP, Ampicillin; FOS, Fosfomycin, RIF, Rifampin; MER, Meropenem; TOB, Tobramycin; Non-Col, None Colistin

(e) Network estimated risk ratios (95% confidence intervals) of colistin combination based regimens on Non-Nephrotoxicity adverse event (neurotoxicity, hepatotoxicity and skin rash)

TUB+FOS				
0.69 [0.14, 3.43]	COL+MER			
0.35 [0.10, 1.20]	0.51 [0.18, 1.43]	COL		
0.23 [0.03, 2.08]	0.33 [0.04, 2.72]	0.66 [0.11, 4.06]	AMP+SUL	
0.11 [0.00, 3.58]	0.17 [0.01, 4.86]	0.33 [0.01, 8.12]	0.50 [0.01, 20.04]	COL+MER

*Comparisons between treatments should be read from column to row for each outcome (row treatment is reference)

Abbreviations: COL, Colistin [(Include COL and NEB, Nebulized; BAT, best available therapy; and OTH, Other antibiotic)]; SUL, Sulbactam; CEF, Cefiderocol; DUR, Durlobactam; AMP, Ampicillin; FOS, Fosfomycin, RIF, Rifampin; MER, Meropenem; TOB, Tobramycin; Non-Col, None Colistin

Treatments are reported in order of efficacy ranking according to SUCRA. Comparisons should be read from left to right. The estimate is located at the intersection of the column-defining treatment and the row-defining treatment. For clinical cure and microbiological cure, an RR value >1 favours the column-defining treatment. Significant results are in bold.

Nephrotoxicity and Non-Nephrotoxic Adverse Events

Nine studies, involving 1,505 patients, assessed nephrotoxicity, while seven studies, including 1,323 patients, evaluated non-nephrotoxic adverse events (neurotoxicity, hepatotoxicity, and skin rash) (Figures 2-d and 2-e). No significant differences in the risk of non-nephrotoxic adverse events were observed across the antibiotic treatments (Figures 3-d and 3-e).

The ranking of treatments based on SUCRAs is shown in (Appendix Figure A3). GRADE certainty: low to very low for all comparisons (Table 2). Comparison-adjusted funnel plots showed no sign of asymmetry (Appendix Figure A4).

Discussion

This systematic review and network meta-analysis evaluated the efficacy and safety of treatment options for patients with MDR and XDR *A. baumannii* infections, yielding several key findings. Combination therapies, notably sulbactam with durlobactam, were associated with significantly lower all-cause mortality compared to colistin monotherapy. Colistin with rifampin also showed significant mortality reduction, although this regimen should be interpreted with caution given rifampin's status as a strategic antibiotic for other infections. Additionally, dual therapy with colistin and meropenem improved clinical cure rates relative to colistin alone. However, neither monotherapy nor combination therapies significantly reduced microbiological burden, and no notable differences in nephrotoxic or non-nephrotoxic adverse events were observed across treatments.

The findings indicate that colistin combined with rifampin significantly reduced all-cause mortality in patients with MDR- and XDR-AB compared to colistin alone (RR = 0.27, 95% CI: 0.07–0.99). Similarly, the sulbactam-durlobactam combination was linked to a lower mortality risk (RR = 0.22, 95% CI: 0.05–0.91). The present study adds important new evidence to the existing literature by identifying sulbactam-durlobactam as a mortality-reducing option, which was not featured in older NMAs such as Kengkla et al. (2018) (2), This is a particularly significant finding given the recent approval of sulbactam-durlobactam and its potential role as a preferred treatment option for MDR- and XDR-AB infections. Unlike previous

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analyses that were limited to older therapies, our study incorporates the most recent RCTs, providing updated evidence that can directly inform clinical practice. However, other meta-analyses (18, 19) reported contrasting results, suggesting that colistin-based combination therapies did not enhance clinical success or survival. For instance, a study of carbapenem-resistant *A. baumannii* infections, particularly bloodstream infections (BSIs), favored cefiderocol-based regimens over colistin-based ones (30). Another Bayesian NMA identified sulbactam as the most effective option for reducing mortality in critically ill patients with MDR/XDR-AB pneumonia, though its retrospective design and small sample sizes limit its generalizability (1). In contrast, the present study leveraged high-quality RCTs with sufficient statistical power to detect significant effects.

Regarding clinical cure, dual therapy with colistin and meropenem significantly outperformed colistin monotherapy (RR = 0.31, 95% CI: 0.11–0.84). Other studies reported different findings: triple therapy with colistin, sulbactam, and tigecycline ranked highest for clinical success but lacked statistical significance (2), while high-dose sulbactam combined with levofloxacin or tigecycline excelled in clinical improvement (20). Huang et al. (21) noted that colistin-meropenem reduced microbiological cure, contrasting with this study's focus on clinical outcomes. These discrepancies may stem from variations in study design, patient populations, or outcome definitions.

Microbiological eradication showed no significant improvement with either monotherapy or combination therapies, consistent with some prior reports (22). However, Jung et al. (1) found that sulbactam enhanced microbiological clearance, and another study indicated that tigecycline monotherapy yielded lower microbiological cure rates, even in combination (23). However, individual studies, such as Sirijatuphat et al. (24), reported significant eradication with colistin + fosfomycin, suggesting potential benefits not detected in the pooled analysis. These conflicting results may reflect retrospective biases, small sample sizes, or unaccounted confounders in earlier studies, warranting cautious interpretation.

Adverse events, including nephrotoxicity, neurotoxicity, and other toxicities (e.g., hepatotoxicity, skin rash), showed no significant association with any treatment regimen in this study. This aligns with findings from multiple studies (2, 18, 25, 26) reporting no notable differences in nephrotoxicity across antibiotics. However, a meta-analysis estimated a 28.2% incidence of nephrotoxicity with colistin (27), and another study found cefiderocol associated with a lower, though not statistically significant, rate of acute kidney injury (AKI) compared to colistin (22). Colistin's well-documented nephro- and neurotoxicity are dose-dependent, as is its therapeutic efficacy, suggesting a need for further dose-response studies in colistin-based regimens.

Currently, no evidence-based guidelines specify optimal treatments for MDR- and XDR-AB infections. Clinicians should weigh clinical factors such as infection site, renal/hepatic function, and comorbidities alongside local resistance patterns when selecting therapies, particularly those combining colistin with other agents. This study's robust inclusion of RCTs and its network meta-analysis framework strengthen its findings, offering a comprehensive, up-to-date evaluation of efficacy and safety across multiple regimens. By incorporating real-world clinical trial data, it enhances the generalizability of results compared to prior reviews.

A key strength of this study is its inclusion of a larger number of high-quality RCTs than previous analyses, providing greater statistical power and contemporary insights into treatment outcomes. The network meta-analysis enabled comparisons across diverse regimens, even with limited direct evidence. Since Kengkla et al. (2), new RCTs have emerged (e.g., Kaye et al.) (28), necessitating an updated NMA. We focused on RCTs to minimize bias from observational studies, providing robust evidence for MDR/XDR *A. baumannii* pneumonia.

However, limitations include variability in MDR- and XDR-AB definitions across studies, particularly pre-2010 publications. To harmonize this issue, the definitions of drug resistance of all available studies were classified according to the standard reference. Future studies should explore dose optimization and long-term outcomes. Other limitations of this study include the small number of studies investigating non-nephrotoxic adverse events and the lack of consistency in calculations. It is suggested that a larger number of trial studies be examined in future studies.

Conclusion

This RCTs NMA demonstrates that sulbactam-durlobactam significantly reduces all-cause mortality in MDR- and XDR-AB infections compared to colistin alone. Colistin-rifampin also showed significant mortality reduction; however, given rifampin's critical role in treating tuberculosis and other infections, this combination is not recommended as a first-line treatment for *A. baumannii* infections. Dual therapy with colistin and meropenem enhances clinical cure rates. No regimens demonstrated statistically significant effects on microbiological eradication in the NMA. However, individual studies evaluating colistin + fosfomycin suggested potential microbiological benefits that did not achieve statistical significance in the pooled NMA analysis. This discrepancy highlights the need for larger, well-powered studies to definitively assess microbiological outcomes. Adverse events showed no significant differences across regimens. These findings provide critical evidence to guide treatment decisions for resistant *A. baumannii* infections, though large-scale RCTs may be needed to confirm and expand these results. The development of evidence-based guidelines is recommended to assist clinicians in selecting optimal treatments for MDR- and XDR-AB infections, integrating efficacy, safety, and local resistance data.

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Conflict of Interests

The authors declare that they have no competing interests.

Authors' Contributions

G.M., Y.M., M.A.R. contributed to the conception and design of the study. Y.M., M.A.R., P.M. conducted the data collection. G.M., Y.M., M.A.R. performed the analysis. G.M., Y.M., M.A.R., and P.M. contributed to drafting and revising the manuscript and approved the final version.

Ethical Considerations

As this study is a systematic review and network meta-analysis based on previously published data, it did not involve direct interaction with human participants or access to identifiable personal data. Therefore, ethical approval and informed consent were not required. All included studies were conducted in accordance with relevant ethical standards, and the present study adhered to established guidelines for conducting and reporting systematic reviews.

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Data Availability

All data analyzed in this study are derived from previously published articles, which are cited within the manuscript. Additional details are available from the corresponding author upon reasonable request.

AI Use Statement

Artificial intelligence tools were used to assist in language editing and improving the clarity of the manuscript. No AI tools were used for data analysis or generation of scientific results. All content was critically reviewed and approved by the authors, who take full responsibility for the integrity and accuracy of the work.

References

1. Jung SY, Lee SH, Lee SY, Yang S, Noh H, Chung EK, et al. Antimicrobials for the treatment of drug-resistant Acinetobacter baumannii pneumonia in critically ill patients: a systemic review and Bayesian network meta-analysis. Crit Care. 2017;21(1):1-15.
2. Kengkla K, Kongpakwattana K, Saokaew S, Apisarnthanarak A, Chaiyakunapruk N. Comparative efficacy and safety of treatment options for MDR and XDR Acinetobacter baumannii infections: a systematic review and network meta-analysis. J Antimicrob hemother. 2018;73(1):22-32.
3. Li T, Puhan MA, Vedula SS, Singh S, Dickersin K, Group AHNM-aMMW. Network meta-analysis-highly attractive but more methodological research is needed. BMC Med. 2011;9:1-5.
4. Tonin FS, Rotta I, Mendes AM, Pontarolo R. Network meta-analysis: a technique to gather evidence from direct and indirect comparisons. Pharm Pract (Granada). 2017;15(1).
5. Ghasemi K, Mansourian M, Vaseghi G. Network Meta-analysis Application in Comparison of Clinical Trial Studies. Studies. 2020;16(2):143-50.
6. Mei H, Yang T, Wang J, Wang R, Cai Y. Efficacy and safety of tigecycline in treatment of pneumonia caused by MDR Acinetobacter baumannii: a systematic review and meta-analysis. J Antimicrob Chemother. 2019;74(12):3423-31.
7. Chen L, Liang X, Jiang J, Li X, Li Y. Carbapenems vs tigecycline for the treatment of complicated intra-abdominal infections: a Bayesian network meta-analysis of randomized clinical trials. Medicine. 2019;98(40):e17436.
8. Muteeb G. Network meta-analysis of antibiotic resistance patterns in gram-negative bacterial infections: a comparative study of carbapenems, fluoroquinolones, and aminoglycosides. Front Microbiol.. 2023;14:1304011.
9. Rasouli MA MG, Moradi Y, Mohamadi P. Efficacy and safety of different treatments for Acinetobacter baumannii infection: a systematic review and network meta-analysis. PROSPERO 2025 CRD420250656044 Available from https://wwwcrdyorkacuk/PROSPERO2/view/CRD420250656044. 2025.
10. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med.. 2015;162(11):777-84.
11. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63(5):e61-e111.
12. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care–associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008;36(5):309-32.
13. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366.
14. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled clinical trials. 1986;7(3):177-88.
15. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.
16. Higgins JPT, Jackson D, Barrett J, Lu G, Ades A, White I. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synth Methods. 2012;3(2):98-110.
17. Salanti G, Ades A, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011;64(2):163-71.
18. Chen Z, Chen Y, Fang Y, Wang X, Chen Y, Qi Q, et al. Meta-analysis of colistin for the treatment of Acinetobacter baumannii infection. Sci Rep. 2015;5(1):17091.
19. Liu Q, Li W, Feng Y, Tao C. Efficacy and safety of polymyxins for the treatment of Acinectobacter baumannii infection: a systematic review and meta-analysis. PLoS One. 2014;9(6):e98091.
20. Liu J, Shu Y, Zhu F, Feng B, Zhang Z, Liu L, et al. Comparative efficacy and safety of combination therapy with high-dose sulbactam or colistin with additional antibacterial agents for multiple drug-resistant and extensively drug-resistant Acinetobacter baumannii infections: A systematic review and network meta-analysis. J Glob Antimicrob Resist. 2021;24:136-47.
21. Huang C, Chen I, Tang T. Colistin monotherapy versus colistin plus meropenem combination therapy for the treatment of multidrug-resistant Acinetobacter baumannii infection: a meta-analysis. J Clin Med. 2022;11(11):3239.
22. Zhan Y, Mao W, Zhao C, Lu D, Chen C, Hu W, et al. Comparison of cefiderocol and colistin-based regimens for the treatment of severe infections caused by carbapenem-resistant Acinetobacter baumannii: A systematic review with meta-analysis and trial sequential analysis. BMC Infect. 2024;24(1):967.
23. Ni W, Han Y, Zhao J, Wei C, Cui J, Wang R, et al. Tigecycline treatment experience against multidrug-resistant

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[DOI: 10.47176/mjiri.40.108]

Acinetobacter baumannii infections: a systematic review and meta-analysis. Int J Antimicrob Agents. 2016;47(2):107-16.
24. Sirijatuphat R, Thamlikitkul V. Preliminary study of colistin versus colistin plus fosfomycin for treatment of carbapenem-resistant Acinetobacter baumannii infections. Antimicrob Agents Chemother. 2014;58(9):5598-601.
25. Cheng IL, Chen YH, Lai CC, Tang HJ. Intravenous colistin monotherapy versus combination therapy against carbapenem-resistant gram-negative bacteria infections: meta-analysis of randomized controlled trials. J Clin Med. 2018;7(8):208.
26. Vardakas KZ, Mavroudis AD, Georgiou M, Falagas ME. Intravenous colistin combination antimicrobial treatment vs. monotherapy: a systematic review and meta-analysis. Int J Antimicrob Agents. 2018;51(4):535-47.
27. Wagenlehner F, Lucenteforte E, Pea F, Soriano A, Tavoschi L, Steele VR, et al. Systematic review on estimated rates of nephrotoxicity and neurotoxicity in patients treated with polymyxins. Clin Microbiol Infect. 2021;27(5):671-86.
28. Kaye KS, Shorr AF, Wunderink RG, Du B, Poirier GE, Rana K, et al. Efficacy and safety of sulbactam–durlobactam versus colistin for the treatment of patients with serious infections caused by Acinetobacter baumannii–calcoaceticus complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK). Lancet Infect Dis. 2023;23(9):1072-84.
29. Aydemir H, Akduman D, Piskin N, Comert F, Horuz E, Terzi A, et al. Colistin vs. the combination of colistin and rifampicin for the treatment of carbapenem-resistant Acinetobacter baumannii ventilator-associated pneumonia. Epidemiol Infect. 2013;141(6):1214-22.
30. Durante-Mangoni E, Signoriello G, Andini R, Mattei A, De Cristoforo M, Murino P, Bassetti M, Malacarne P, Petrosillo N, Galdieri N, Mocavero P. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant Acinetobacter baumannii: a multicenter, randomized clinical trial. Clin Infect Dis. 2013;57(3):349-58.
31. Betrosian AP, Frantzeskaki F, Xanthaki A, Georgiadis G. High-dose ampicillin-sulbactam as an alternative treatment of late-onset VAP from multidrug-resistant Acinetobacter baumannii. Scand J Infect Dis. 2007;39(1):38-43.
32. Sirijatuphat R, Thamlikitkul V. Preliminary study of colistin versus colistin plus fosfomycin for treatment of carbapenem-resistant Acinetobacter baumannii infections. Antimicrob Agents Chemother. 2014;58(9):5598-601.
33. Aranzana-Climent V, van Os W, Nutman A, Lellouche J, Dishon-Benattar Y, Rakovitsky N, et al. Integration of individual preclinical and clinical anti-infective PKPD data to predict clinical study outcomes. Sci Transl Med. 2024;17(7):e13870.
34. Bassetti M, Echols R, Matsunaga Y, Ariyasu M, Doi Y, Ferrer R, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. Lancet Infect Dis. 2021;21(2):226-40.
35. Dickstein Y, Lellouche J, Ben Dalak Amar M, Schwartz D, Nutman A, Daitch V, Yahav D, Leibovici L, Skiada A, Antoniadou A, Daikos GL. Treatment outcomes of colistin-and carbapenem-resistant Acinetobacter baumannii infections: an exploratory subgroup analysis of a randomized clinical trial. Clin Infect Dis. 2019;69(5):769-76.
36. Hakamifard A, Torfeh Esfahani AA, Homayouni A, Khorvash F, Ataei B, Abbasi S. Comparing inhaled colistin with inhaled fosfomycin/tobramycin as an adjunctive treatment for ventilator-associated pneumonia: An open-label randomized controlled trial. Eur Clin Respir J. 2023;17(4):295-302.
37. Kaye KS, Marchaim D, Thamlikitkul V, Carmeli Y, Chiu CH, Daikos G, et al. Colistin Monotherapy versus Combination Therapy for Carbapenem-Resistant Organisms. NEJM Evid. 2023;2(1).
38. Nutman A, Carmeli Y. Re: 'Colistin plus meropenem for carbapenem-resistant gram-negative infections: in vitro synergism is not associated with better clinical outcomes'-Author's reply. Clin Microbiol Infect. 2020;26(9):1275.
39. Park HJ, Cho JH, Kim HJ, Han SH, Jeong SH, Byun MK. Colistin monotherapy versus colistin/rifampicin combination therapy in pneumonia caused by colistin-resistant Acinetobacter baumannii: A randomised controlled trial. J Glob Antimicrob Resist. 2019;17:66-71.
40. Paul M, Daikos GL, Durante-Mangoni E, Yahav D, Carmeli Y, Benattar YD, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. Lancet Infect Dis. 2018;18(4):391-400.
41. Pourheidar E, Haghighi M, Kouchek M, Miri MM, Shojaei S, Salarian S, et al. Comparison of Intravenous Ampicillin-sulbactam Plus Nebulized Colistin with Intravenous Colistin Plus Nebulized Colistin in Treatment of Ventilator Associated Pneumonia Caused by Multi Drug Resistant Acinetobacter Baumannii: Randomized Open Label Trial. Iran J Pharm Res. IJPR. 2019;18(Suppl1):269-81.
42. Rattanaumpawan P, Lorsutthitham J, Ungprasert P, Angkasekwinai N, Thamlikitkul V. Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by Gram-negative bacteria. J Antimicrob Chemother. 2010;65(12):2645-9.
43. Koomanachai P, Tiengrim S, Kiratisin P, Thamlikitkul V. Efficacy and safety of colistin (colistimethate sodium) for therapy of infections caused by multidrug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii in Siriraj Hospital, Bangkok, Thailand. J Infect Dis. 2007;11(5):402-6.
44. Wunderink RG, Matsunaga Y, Ariyasu M, Clevenbergh P, Echols R, Kaye KS, et al. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis. 2021;21(2):213-25.
45. Khorvash F, Yaghoubi S, Farsaei S, Ataei B, Hakamifard A, Mohajeri F, et al. Comparison of two therapeutic approaches for the management of ventilator-associated pneumonia due to multidrug-resistant Acinetobacter: a randomized clinical trial study. J Immunoass Immunochem. 2020;41(1):97-105.
46. Kaye KS, Shorr AF, Wunderink RG, Du B, Poirier GE, Rana K, et al. Efficacy and safety of sulbactam-durlobactam versus colistin for the treatment of patients with serious infections caused by Acinetobacter baumannii-calcoaceticus complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK). Lancet Infect Dis. 2023;23(9):1072-84.
47. Batirel A, Balkan I, Karabay O, Agalar C, Akalin S, Alici O, et al. Comparison of colistin–carbapenem, colistin–sulbactam, and colistin plus other antibacterial agents for the treatment of extremely drug-resistant Acinetobacter baumannii bloodstream infections. Eur J Clin Microbiol. 2014;33:1311-22.
48. Chan JD, Graves JA, Dellit TH. Antimicrobial treatment and clinical outcomes of carbapenem-resistant Acinetobacter baumannii ventilator-associated pneumonia. J Intensive Care Med. 2010;25(6):343-8.

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Appendix Table A1. Search Terms, Databases, and Search Deadline

Category	Details	
Search Terms	"Acinetobacter", "Acinetobacter baumannii", "multidrug-resistant", "extensively drug resistant", "extremely drug resistant", "pan-drug resistant", "carbapenem-resistant", "drug resistant", "clinical", "microbiological", "cure", "response", "death", "mortality", "nephrotoxicity", "adverse event"	
Databases Searched	Medline (via PubMed), Scopus, Web of Science, Cochrane Library, EMBASE, and CINAHL,	
Search Terms and Boolean Logic		
PubMed (Medline)	("Acinetobacter baumannii"[MeSH Terms] OR "Acinetobacter baumannii"[All Fields] OR "A. baumannii"[All Fields]) AND ("Drug Resistance, Multiple"[MeSH Terms] OR "multidrug resistant"[All Fields] OR MDR[All Fields] OR XDR[All Fields] OR PDR[All Fields]) AND (treatment[All Fields] OR therapy[All Fields] OR antibiotics[All Fields]) AND (mortality[Title/Abstract] OR "clinical cure"[Title/Abstract] OR "microbiological eradication"[Title/Abstract]) NOT (review[Publication Type] OR meta-analysis[Publication Type]) Filters: 2000/01/01-2024/12/30	
EMBASE	('acinetobacter baumannii'/exp OR 'acinetobacter baumannii':ti,ab OR 'a. baumannii':ti,ab) AND ('multidrug resistant'/exp OR 'multidrug resistant':ti,ab OR mdr:ti,ab OR xdr:ti,ab OR pdr:ti,ab) AND (treatment:ti,ab OR therapy:ti,ab OR antibiotics:ti,ab) AND (mortality:ti,ab OR 'clinical cure':ti,ab OR 'microbiological eradication':ti,ab) NOT ('review'/it OR 'meta analysis'/it) DATE: 2000-2024	
Scopus	(TITLE-ABS-KEY("Acinetobacter baumannii" OR "A. baumannii") AND TITLE-ABS-KEY("multidrug resistant" OR MDR OR XDR OR PDR) AND TITLE-ABS-KEY(treatment OR therapy OR antibiotics) AND TITLE-ABS-KEY(mortality OR "clinical cure" OR "microbiological eradication")) AND NOT (DOCTYPE("re") OR DOCTYPE("sr")) AND PUBYEAR > 1999 AND PUBYEAR < 2025	
Web of Science	TS=("Acinetobacter baumannii" OR "A. baumannii") AND TS=("multidrug resistant" OR MDR OR XDR OR PDR) AND TS=(treatment OR therapy OR antibiotics) AND TS=(mortality OR "clinical cure" OR "microbiological eradication") NOT (DT="review" OR DT="systematic review") AND PY=2000-2024	
Cochrane Library	("Acinetobacter baumannii" OR "A. baumannii"):ti,ab,kw AND ("multidrug resistant" OR MDR OR XDR OR PDR):ti,ab,kw AND (treatment OR therapy OR antibiotics):ti,ab,kw AND (mortality OR "clinical cure" OR "microbiological eradication"):ti,ab,kw NOT (review OR meta-analysis) Filters: 2000-2024	
CINAHL	(MH "Acinetobacter baumannii" OR "Acinetobacter baumannii" OR "A. baumannii") AND (MH "Drug Resistance, Multiple" OR "multidrug resistant" OR MDR OR XDR OR PDR) AND (treatment OR therapy OR antibiotics) AND (mortality OR "clinical cure" OR "microbiological eradication") NOT (PT review OR PT meta-analysis) Filters: 2000-2024	
Grey Literature Search Results	ClinicalTrials.gov: Four ongoing trials were identified, but none had published results by the search deadline (December 30, 2024) and were thus ineligible for inclusion. Hand-Searching Reference Lists: Eight records were identified from reference lists of relevant systematic reviews, but none met inclusion criteria.	
Search Deadline	From January 1, 2000, to December 30, 2024	
Inclusion criteria	Overall	- Study types include interventional trials that compare antibiotic treatments and other non-antibiotic treatments (herbal remedies or other antiseptics) for the treatment of patients with Acinetobacter baumannii pneumonia. -Studies reporting outcomes such as frequency, odds ratios (OR), or risk ratios (RR) with 95% confidence intervals (CIs) -Published in English -Accessible and full-text studies
	Population (P)	- Patients with Acinetobacter baumannii pneumonia
	Intervention (I)	- Antibiotic treatments and other non-antibiotic treatments (such as herbal remedies or antiseptics)
	Comparison (C)	- Comparison of these treatments with each other or with other standard treatments
	Outcome (O)	- Outcomes of all-cause mortality, clinical cure, microbiological cure, and adverse events
	Type of Studies (T)	- All randomized clinical trials and clinical trials

Abbreviations: NA, Not available; VAP, Ventilator-associated pneumonia; BSI, blood-stream infection/bacteremia; ICU, Intensive care unit;; HAP, Hospital-acquired pneumonia; UTIs, Urinary tract infections; HCAP, Health care–associated pneumonia; CR, Carbapenem-resistant; MDR, Multidrug resistant; XDR, Extensively drug resistant, IV, Intravenous; NG, Nasogastric; NB, Nebulizer, COL, Colistin [(Include COL and NEB, Nebulized; BAT, best available therapy; and OTH, Other antibiotic)]; SUL, Sulbactam; CEF, Cefiderocol; DUR, Durlobactam; AMP, Ampicillin; FOS, Fosfomycin, RIF, Rifampin; MER, Meropenem; TOB, Tobramycin; Non-Col, None Colistin

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Appendix Table A2. Description of included studies.

Study ID	First Author	Year	Location	Study Design	Department	Pathogen	Type of Resistance (Original)	Type of Infection	Intervention (N)	Study size (N)	Age per group (mean±S)	Male vs Female (%)	APACHE II score per group (mean±SD)
1	Aydemir	2012	Turkey	Randomized control trial	ICU	A. baumannii	Carbapenem resistant	VAP	Colistin (n=22) Colistin + rifampin (n=21)	43	63±17 vs 58±23	73 vs 67	18±4.9 vs 20±6.8
2	Durante-Mangoni	2013	Italy	Randomized control trial	ICU and General med	A. baumannii	Extensively drug resistant	Mixed (VAP 70%, BSI 20%, HAP 9%)	Colistin (n=105) Colistin + rifampin (n=104)	209	61±16 vs 62±15	67 vs 64	NA
3	Betrosian	2007	Greece	Randomized control trial	ICU	A. baumannii	Multidrug resistant	VAP (100%)	Colistin (n=15) Ampicillin/sulbactam (n=13)	28	67±4 vs 72±5	50 vs 61.5	14±2 vs 14±5
4	Sirijatuphat	2014	Thailand	Randomized control trial	ICU	A. baumannii	Carbapenem resistant	Mixed (Pneumonia 75%, BSI 5%)	Colistin (n=47) Colistin + fosfomycin (n=47)	94	69±16 vs 67±17	51 vs 43	21.9±7.9 vs 23.0±6.4
5	Aranzana-Climent	2024	Spain	Randomized control trial	ICU	A. Baumannii	Multidrug resistant	HAP, VAP, BS, urosepsis,	Colistin (n=115) Colistin + meropenem (n=92)	207	NA	NA	NA
6	Bassetti	2020	Japan, China, Croatia, United Kingdom, Brazil, Thailand, United state, Turkey, Taiwan, Greece, Taiwan, Belarus, Hungary, Israel, India, Lithuania, Peru, Mexico, South Korea, Russia and others	Randomized control trial	ICU	A. Baumannii, Klebsiella pneumoniae, Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Acinetobacter nosocomialis, E coli	Colistin- and Carbapenem-resistant	Mixed (VAP, BSI, HAP, UTI)	Cefiderocol (n=101) Best available therapy (n=51)	152	63±19 vs 63±16.7	63 vs 71	15.3±6.5 vs 15.4±6.2

Abbreviations: NA, Not available; VAP, Ventilator-associated pneumonia; BSI, blood-stream infection/bacteremia; ICU, Intensive care unit;; HAP, Hospital-acquired pneumonia; UTIs, Urinary tract infections; HCAP, Health care–associated pneumonia; CR, Carbapenem-resistant; MDR, Multidrug resistant; XDR, Extensively drug resistant, IV, Intravenous; NG, Nasogastric; NB, Nebulizer, COL, Colistin [(Include COL and NEB, Nebulized; BAT, best available therapy; and OTH, Other antibiotic)]; SUL, Sulbactam; CEF, Cefiderocol; DUR, Durlobactam; AMP, Ampicillin; FOS, Fosfomycin, RIF, Rifampin; MER, Meropenem; TOB, Tobramycin; Non-Col, None Colistin

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Appendix Table A2. Cont

Study ID	First Author	Year	Location	Study Design	Department	Pathogen	Type of Resistance (Original)	Type of Infection	Intervention (N)	Study size (N)	Age per group (mean±S)	Male vs Female (%)	APACHE II score per group (mean±SD)
7	Dickstein	2018	Italy, Greece, Israel	Randomized control trial	ICU, Medical Ward, Surgical Ward	A. Baumannii	Carbapenem resistant	Mixed (VAP, BSI, HAP, UTI)	Colistin (n=214) Colistin+meropenem (n=52)	266	69 vs 72.5	63.1 vs 69.2	NA
8	Hakamifard	2022	Iran	open-label randomized controlled trial	ICU	A. Baumannii	Extensively drug-resistant	VAP	Meropenem + colistin (IV) + Inhaled colistin (n=28) Meropenem + colistin (IV) + Inhaled tobramycin/ fosfomycin (n=27)	55	63.6±14.9 vs 59.3±15.2	53.6 vs 66.8	NA
9	Keith	2023	United States, Thailand, Taiwan, Israel, Greece, Italy, and Bulgaria	Randomized control trial	ICU	A. Baumannii, Enterobacterales, Pseudomonas aeruginosa, CRE	Extensively drug-resistant	Pneumonia and/or BSI	Colistin (n=213) Colistin + Meropenem (n=210)	423	67.6±16.6 vs 68.5±15.5	61 vs 64	22 vs 21
10	Nutman	2020	Italy, Greece and Israel	Randomized control trial	ICU	A. baumannii, Enterobacteriaceae and Pseudomonas aeruginosa.	Carbapenem-resistant	Mixed (VAP, BSI, HAP, UTI)	Colistin (n=61) Colistin + Meropenem (n=70)	131	69±14.6 vs 69±15.3	70 vs 74	NA
11	Jung Park	2019	South Korea	Randomized control trial	ICU	A. baumannii	Carbapenem-resistant	VAP	Colistin (n=5) Colistin + rifampin (n=4)	9	58±39 vs 76±43	100 vs 25	NA
12	Paul	2018	Israel, Greece, and Italy	Randomized control trial	ICU	A. baumannii	Colistin-resistant	Mixed (VAP, BSI, HAP, UTI)	Colistin (n=198) Colistin + Meropenem (n=208)	406	66±16 vs 66±18	38 vs 37	NA
13	Pourheidar	2019	Iran	Randomized control trial	ICU	A. baumannii	Multidrug resistant	VAP	Colistin IV + Colistin Nebulizer (n=16) Ampicillin-Sulbactam IV + Colistin Nebulizer (n=12)	28	60±19 vs 59±16	62.5 vs 50	15±4 vs 16±5

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Appendix Table A2. Cont

Study ID	First Author	Year	Location	Study Design	Department	Pathogen	Type of Resistance (Original)	Type of Infection	Intervention (N)	Study size (N)	Age per group (mean±S)	Male vs Female (%)	APACHE II score per group (mean±SD)
14	Ratta-naumpawan	2010	Thailand	Randomized control trial	ICU	A. baumannii and/or P. aeruginosa, Klebsiella pneumoniae, E.coli	Multidrug resistant	VAP	Colistimethate sodium (n= 49) Nebulized sterile normal saline (N-51)	100	70.2±18.5 vs 66.2±15.8	67.3vs 60.7	19.1±5.8 vs 18.5±4.7
15	Koo-manachai	2007	Thailand	Randomized control trial	ICU	A. baumannii and/or P. aeruginosa,	Multidrug resistant	VAP	Colistin (n=78) Non-Colistin (n=15)	93	63.5 vs 58.9	57.7 va 73.3	21.9 vs 22.3
16	Wunderink	2020	Asia, Europe, and the USA	Randomized control trial	ICU	A. baumannii and/or P. aeruginosa, Klebsiella pneumoniae, E.coli and Other	Multidrug resistant	Mixed (VAP, HAP, or HCAP)	Cefiderocol (n=145) Meropenem (n=147)	297	64.6±14.6 vs 65.5±15.1	68 va 69	16±6.1 vs 16.4±6.9
17	Khorvash	2019	Iran	Randomized control trial	ICU	A. Baumannii	carbapenem-resistant	VAP	(IV) meropenem + injectable colistin + nebulized colistin (n=30)	60	60.13±13.7 vs 61.1±10	63.3 vs 66.7	None
18	Kaye	2023	China, Brazil, Thailand, United state, Turkey, Taiwan, Greece, Taiwan, Belarus, Hungary, Israel, India, Lithuania, Peru, Mexico, South Korea, Russia	Randomized control trial	ICU	A. Baumannii	carbapenem-resistant	Mixed (VAP, BSI, HAP, UTI)	(IV) meropenem + injectable colistin + nebulized tobramycin (n=30) Part (A) Colistin (n= 64) Sulbactam+ durlobactam (n= 64) Part (B): Sulbactam+ durlobactam (n= 28) Background for two groups: Imipenem + Cilastatin	177	62 vs 66	72 vs 77	16±5 vs 17±5

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Appendix Table A3. Description of participants of included studies

Study ID	First Author (year)	Type of Infection	Details of criteria for diagnosis	Type of Resistance (Original data)	Details of drug resistance	Type of Resistance (Classified according to standard reference)
1	Aydemir (2013)	VAP	A diagnosis of pneumonia required a new or persistent infiltrate on chest radiography plus two or more of the following: abnormal temperature (>38 ºC or <35.5 ºC), leukocytosis (leukocyte count >12 000 cells/mm3) or leukopenia (leukocyte count <4000 cells/mm3), and purulent bronchial secretion. Pneumonia was considered to be ventilator associated when the onset occurred 48 h after the initiation of mechanical ventilation	Carbapenem-resistant	Resistant to all carbapenems (imipenem and meropenem)	MDR
2	Durante-Mangoni (2013)	Mixed (VAP 70%, BSI 20%, HAP 9%)	HAP/VAP was diagnosed as an evolving infiltrate on chest radiograph with either fever or leukocytosis/leukopenia or purulent respiratory secretions with positive quantitative culture from tracheal aspirate (at least 10^6 colony-forming units [CFU]/mL) or bronchoalveolar lavage (at least 10^4 CFU/mL). BSI was defined as positive blood cultures for Acb in the presence of systemic inflammatory signs. Complicated intra-abdominal infections were diagnosed as a positive Acb culture of purulent exudate from abdominal collections, associated with a systemic inflammation.	Extensive drug-resistant	"Extensively drug resistant" was defined as resistance to carbapenems (MIC ≥16 mg/L) and to all other antimicrobial drug classes, except colistin	XDR
3	Betrisian (2007)	VAP (100%)	Diagnosis of ventilator-associated pneumonia was established when the bronchoscopic bronchoalveolar lavage (BAL) quantitative culture grew the microorganism at a concentration of at least 10^4 colony-forming units (CFU)/mL. The clinical indicators for VAP included abnormal temperature (>38 C or <36 C), leukocytosis (white blood cell count > 10,000) or leukopenia (white blood cell count < 4000), macroscopically purulent sputum, and new or changing infiltrate on chest radiograph	Multidrug-resistant	Resistant to all antibiotic agents routinely tested, including penicillins, aminoglycosides, ampicillin/sulbactam, cephalosporins, aztreonam, carbapenems, fluoroquinolones, tetracyclines, excluding polymyxin E (colistin).	XDR
4	Sirijatuphat (2014)	Mixed (Pneumonia 75%, BSI 5%)	Carbapenem-resistant A. baumannii infection is defined as having clinical signs and symptoms of infection in the presence of CR A. baumannii isolated from the relevant clinical specimens.	Carbapenem-resistant	NA	MDR
5	Aranzana-Climent (2024)	HAP, VAP, BS, urosepsis	Briefly, patients with hospital- acquired pneumonia, ventilator-associated pneumonia, bloodstream infections, or urosepsis, caused by Gram- negative bacteria non-susceptible to carbapenems (MIC >2 mg/L) and susceptible to colistin (MIC ≤2 mg/L for Acinetobacter spp. and Enterobacteriaceae and MIC ≤4 mg/L foe Pseudomonas spp), were randomly assigned to rither colistin momotherapy or colistin- meropenem combinationvtreatment. Patients in both treatment arms received 9 million units (MU) loading dose of colistimethate sodium (CMS), followed by 4.5 MU maintenance doses q12h, administered as intravenous infusions over 30 min. Maintenance doses were reduced in patients with creatinine clearance (CrCl) <50 mL/min according to a previously propossed formula. CMS dosing before randomization was allowed, but no loading dose was administered to patients treated with colistin for >48 h before randomization. Patients in the combination treatment arm additionally received 2 g meropenem q8h as intravenous infusions over 3 h, with dose reductions for patients with renal impairment. The primary outcome, clinical failure on day 14, was defined as a failure to meet a composite of success criteria: patient alive, hemodynamic stability, and improved or stable Sequential Organ Failure Assessment (SOFA) score. In addition, patients with pneumonia should have had stable or improved ratio of partial pressure of arterial oxygen to fraction of expired oxygen, and patients with bacteremia should have had no microbiological failure on day 14 or later. Microbiological failure, a secondary outcome, was defined as repeat isolation on or after day 7 of bacteria phenotypically identical to the index isolate.	Multidrug-resistant	colistin monotherapy and colistin–meropenem combination therapy for carbapenem- resistant Gram-negative infections	MDR

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Appendix Table A3. Cont

Study ID	First Author (year)	Type of Infection	Details of criteria for diagnosis	Type of Resistance (Original data)	Details of drug resistance	Type of Resistance (Classified according to standard reference)
6	Bassetti 2020	Mixed (VAP, BSI, HAP, UTI)	Eligible participants were adult patients (≥18 years) with a diagnosis of hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), health care- associated pneumonia (HCAP), bloodstream infection or sepsis (in whom the primary source of infection was not pneumonia or complicated UTIs), or complicated UTIs, with evidence of carbapenem-resistant Gram-negative infection.	Carbapenem resistant	The pathogen was confirmed as S maltophilia, which has intrinsic resistance to carbapenems.	MDR
7	Dickstein 2018	Mixed (VAP, BSI, HAP, UTI)	Patient recruitment occurs only after microbiological documentation, susceptibility testing and signed informed consent. Carbapenem nonsusceptibility is defined using the EUCAST breakpoint of minimal inhibitory concentration (MIC) >2 mg/L and colistin susceptibility as MIC ≤2 mg/L for Acinetobacter spp. and Enterobacteriaceae and ≤4 mg/L for Pseudomonas spp. We include patients with infections caused by bacteria susceptible to sulbactam, tetracyclines, tigecycline, cotrimoxazole or aminoglycosides as we consider that these are not established treatments for severe Gram-negative infections and nor has their superiority to colistin been established. We permit the inclusion of patients with polymicrobial infections where all Gram-negative isolates are carbapenem non-susceptible, or mixed with Gram-positive bacteria or anaerobes.	Carbapenem resistant and colistin resistance	Carbapenem resistance was defined as minimum inhibitory concentration (MIC) >2 mg/L; colistin resistance was defined as MIC >2 mg/L	MDR
8	Hakamifard 2022	VAP	Clinical criteria for the suspicious of VAP include a new or pro- gressive radiographic infiltrate and at least two of three following clinical characteristics: fever above 38 C, leukopenia or leukocytosis, and purulent secretions. kopenia or leukocytosis, and purulent secretions. These represent the most accurate criteria for starting empiric antibiotic therapy.20 The trend of Clinical Pulmonary Infection Score (CPIS) was evaluated,21 and chest X-ray, ETA secretions and cultures, temperature, and leukocyte and PaO2/FiO2 percentage were also recorded at specified time intervals: at the initiation of treatment, after 72 h and 7 days, and at the treatment termination.	Extensively drug-resistant	XDR was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories) and PDR was defined as non-susceptibility to all agents in all antimicrobial categories.	XDR
9	Keith 2023	Pneumonia and/or BSI	A patient with a positive culture with a study pathogen from a respiratory specimen (e.g., sputum, bronchoalveolar lavage, pleural effusion) at the time of study enrollment and either Chest imaging consistent with pneumonia within 72 hours before enrollment to 48 hours after enrollment and the presence of at least two signs and symptoms of pneumonia within 72 hours before enrollment or The site principal investigator and treating physician both believe that the patient has pneumonia and needs to be treated with an intravenous polymyxin	Extensively drug-resistant	XDR was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories) and PDR was defined as non-susceptibility to all agents in all antimicrobial categories.	XDR
10	Nutman 2020		all isolates were shipped to a central laboratory after sub- culturing and storage at e80 C. Isolates were subcultured twice in 5 mL of braineheart infusion broth (BHI) at 35 ± 2 C before testing. All isolates were re-identified in the central laboratory to the spe- cies level using VITEK-2 or VITEK-MS systems (bioMe rieux SA, Marcy l'Etoile, France). Meropenem minimal inhibitory concen- tration (MIC) was determined by broth microdilution. Colistin MIC was determined by broth microdilution according to the recommendations of the CLSI-EUCAST Polymyxin Breakpoints Working Group.	carbapenem-resistant	Resistant to colistin	MDR
11	Jung Park 2019	VAP	subjects who were diagnosed as having active pneumonia caused by CoRAB based on the following criteria: (a) new-onset respiratory symptoms (such as cough, sputum and dyspnoea) or rales or desaturation; (b) new-onset or progressive infiltrative lesion on chest radiography suggestive of pneumonia; (c) fever (38.0 C) or hypothermia (35.0 C) for >48 h or abnormal white blood cell count (10 000/mm3 or 4500/mm3); and (d) CoRAB documented by a culture study of sputum samples (>106 CFU/mL), airway aspirates (>105 CFU/mL) or bronchoalveolar fluid (>104 CFU/mL); (iii) non-pregnant women agreeing to avoid pregnancy during the study; and (iv) subjects who fully understand the provided explanation regarding the study and agreed to participate in the study.	Colistin-resistant	Resistant to colistin	MDR

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Appendix Table A3. Cont

Study ID	First Author (year)	Type of Infection	Details of criteria for diagnosis	Type of Resistance (Original data)	Details of drug resistance	Type of Resistance (Classified according to standard reference)
12	Paul 2018	Mixed (VAP, BSI, HAP, UTI)	Included adults with severe infections caused by carbapenem-non-susceptible Gram-negative bacteria (MIC >2 mg/L) that are susceptible to colistin (MIC ≤2 mg/L for A baumannii and Enterobacteriaceae and ≤4 mg/L for P aeruginosa), according to EUCAST 2012 recommendations and criteria. Infections included bacteraemia, definite ventilator- associated or hospital-acquired pneumonia, probable ventilator-associated pneumonia, and urosepsis, defined in the study protocol.	Colistin--resistant	Resistant to all antibiotics other than colistin, aminoglycosides, sulbactam, tetracyclines, tigecycline, and cotrimoxazole.	XDR
13	Pourheidar 2019	VAP	clinical and radiological signs and positive sputum culture of MDR Acinetobacter Baumannii with sensitivity to colistin or colistin and ampicillin–sulbactam only, which is defined by disk diffusion in our setting, with concentration > 105 CFU/mL in patients who mechanically ventilated for >48 h.	Multidrug-resistant	Resistant to three or more antimicrobial classes normally used for the treatment of infections	MDR
14	Rattanaumpawan 2010	VAP	Diagnosis of Gram-negative VAP was made if a patient who had received mechanical venti- lation for ≥48 h developed fever, leucocytosis, purulent tracheal secretions and new or progressive pulmonary infiltrates, and if Gram- negative bacilli were isolated from an endotracheal tube aspirate specimen.	Multidrug-resistant	Resistant to three or more antimicrobial classes normally used for the treatment of infections	MDR
15	Koomanachai 2007	VAP	The eligible subjects were hospitalized patients over the age of 18 years who were infected with A. baumannii or P. aeruginosa resistant to beta-lactams, fluoroquinolones and aminoglycosides.	Multidrug-resistant	Resistant to three or more antimicrobial classes normally used for the treatment of infections	MDR
16	Wunderink 2020	Mixed (VAP, HAP, or HCAP)	Eligible patients were adults (≥18 years old) admitted to hospital with acute bacterial pneumonia in the form of HAP, VAP, or HCAP. HCAP was included as a subset clinical diagnosis to enrich the patient population for Gram-negative pathogens. Inclusion criteria for HAP and VAP were in accordance with the US Food and Drug Administration (FDA) guidelines. Eligibility required Gram-negative bacterial infection of the lower respiratory tract suspected on the basis of Gram stain or microbiological culture of respiratory secretions within 72 h before randomisation, or both. Eligibility included patients with pneumonia that was highly suspected to be due to Gram-negative bacteria on the basis of previous antibiotic use or local epide- miological evidence of a Gram-negative outbreak and those who did not respond to empirical antibiotic therapy within 2 calendar days for pneumonia caused by a Gram- negative pathogen. Key exclusion criteria included.	Extensively drug-resistant	Extreme drug resistance is defined by susceptibility to only one or two categories	XDR
17	Khorvash	VAP	definitive diagnosis of VAP was performed based on the eligible criteria that mentioned in previous papers including: manifestation of chest infiltration based on radiography report, leukocyte count more than 11.103 per milliliter, body temperature more than 38.4°C or less than 36.5°C, and above all, purulent bronchial secretions. Acinetobacter was settled in specimens that sampled from lower respiratory tract by fiberoptic bronchoscopy. The numbers of colony-forming units per milliliter (at least 104 in our study) play an important role for definitive diagnosis of VAP caused by Acinetobacter.	Multidrug-resistant	MDR was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories, and XDR was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories	None

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Appendix Table A4. Description of treatment interventions of included studies

ID	First Author (year)	Intervention (N)	Route of administration	Treatment details	Treatment duration (days)	Co-interventions
1	Aydemir (2013)	Colistin (n=22) Colistin + rifampin (n=21)	IV NG tube	Colistin 300 mg per day Colistin 300 mg per day + rifampin 600 mg per day	9.3±3.2	None
2	Durante-Mangoni (2013)	Colistin (n=105) Colistin + rifampin (n=104)	IV IV	Colistin 2 MIU mg every 8 hours Colistin 2 MIU mg every 8 hours + rifampin 600 mg every 12 hours	12.5 (8-17)	None
3	Betrosian (2007)	Colistin (n=15) Ampicillin/sulbactam (n=13)	IV IV	Colistin 3 MIU every 8 hours Ampicillin/sulbactam (2:1) 9 g every 8 hours	9.2 ±1.5 vs 9.9 ±2.6	None
4	Sirijatuphat (2014)	Colistin (n=47) Colistin + fosfomycin (n=47)	IV IV	Colistin 5mg/kg per day Colistin 5-10 mg/kg per day + fosfomycin 4g every 12 hours	12 (3-15)	Carbapenems (17% vs 8.5%)
5	Aranzana-Climent (2024)	Colistin (n=115) Colistin + meropenem (n=92)	IV	Patients in both treatment arms received 9 million units (MU) loading dose of colistimethate sodium (CMS), followed by 4.5 MU maintenance doses q12h, administered as intravenous infusions over 30 min. Patients in the combination treatment arm additionally received 2 g meropenem q8h as intravenous infusions over 3 h	24 Hours	None
6	Bassetti 2020	Cefiderocol (n=101) Best available therapy (n=51)	IV	Cefiderocol (n=101) cefiderocol 2 g every 8 h as a 3-h intravenous infusion Best available therapy (n=51)	7-14 days	None
7	Dickstein 2018	Colistin (n=214) Colistin+meropenem (n=52)	IV	Colistin arm: Patients receive a loading dose of 9 MIU, regardless of renal function. For patients with normal renal function (CrCl ≥50 mL/min), the loading dose is followed by 4.5 MIU q12 h32 35 beginning 12 h after the loading dose. Colistin + meropenem: 2 g q8 h for patients with normal renal function (CrCl >50 mL/min). Meropenem is administered as a prolonged infusion over 3 h.	10 Day	None
8	Hakamifard 2022	Meropenem + colistin (IV) + Inhaled colistin= (n=28) Meropenem + colistin (IV) + Inhaled tobramycin/ fosfomycin= (n=27)	IV + Inhaleed	Meropenem (2 g as a 3-h extended infusion every 8 h) + intravenous colistin (a loading dose of 9 million IU and then 4.5 million IU every 12 h). The control group + inhaled colistin (1 million IU per 8 h) Meropenem (2 g as a 3-h extended infusion every 8 h) + intravenous colistin (a loading dose of 9 million IU and then 4.5 million IU every 12 h). The control group inhaled tobramycin/Fosfomycin (300 mg every 12 h/80 mg every 12 h).	13.73 ±3.22 vs 10.58 ±2.84	None
9	Keith 2023	Colistin (n=213) Colistin + Meropenem (n=210)	IV	colistin (5 mg/kg once followed by 1.67 mg/kg every 8 hours) in combination with either meropenem (1000 mg every 8 hours) or matching placebo for the treatment of pneumonia and/or BSI caused by XDR A. baumannii, XDR P. aeruginosa, or CRE.	7-14 Day	None
10	Nutman 2020	Colistin (n=61) Colistin + Meropenem (n=70)	IV	Concentration matrix was 0.125e1 mg/L for colistin and 0.5-64 mg/L for meropenem containing antibiotic combinations of colistinemeropenem were inoculated with 5 105 CFU/mL of 5*10^5 CFU/mL	14 Day	None

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Appendix Table A4. Cont

ID	First Author (year)	Intervention (N)	Route of administration	Treatment details	Treatment duration (days)	Co-interventions
11	Jung Park 2019	Colistin (n=5) Colistin + rifampin (n=4)	IV	a ratio of 1:1. Colistin (100 mg colistin sodium methanesulfonate; SCD Pharm, Seoul, South Korea) was administered intravenously with 100 mL of normal saline every 8 h. Rifampicin (600 mg; Yuhan, Seoul, South Korea) was administered orally daily. Treatment was administered daily for 7 days and up to 28 days.	7-28 Day	None
12	Paul 2018	Colistin (n=5) Colistin + rifampin (n=4)	IV	Colistin methanesulfonate was administered as a 9-million unit (MIU) loading dose, followed by 4·5-MIU. Meropenem was given as a 2 g extended-infusion (3 h) every 8 h.	17 Day	Nne
13	Pourheidar 2019	Colistin IV + Colistin Nebulizer (n=16) Ampicillin-Sulbactam IV + Colistin Nebulizer (n=12)	IV	The patients were allocated in intravenous (IV) colistin or intravenous high dose ampicillin–sulbactam group of the study using block randomization. The patients in the IV olistin group received 9 × 109 units loading dose followed by the 4.5 * 10^9 units twice daily colistin (Ronak dariu, Iran). Subjects in IV ampicillin–sulbactam group received continuous infusion of high dose ampicillin– sulbacatam (Dana Pharmaceutical, Iran) 24 g daily (6 g (at a ratio 2:1) four times a day, each dose infused over 6 h). Both groups received nebulized colistin 2*10^9 units every 8 h with mesh nebulizer.	8±3 vs 9±3	None
14	Rattanaumpawan 2010	Colistimethate sodium (n= 49) Nebulized sterile normal saline (N-51)	IV	To receive systemic antibiotic(s) plus nebulized sterile normal saline (NSS) or systemic antibiotic(s) plus nebulized CMS. Every 12 h, 4 mL of NSS or CMS equivalent to 75 mg of colistin base reconstituted in 4 mL of NSS was delivered immediately on reconstitution via a jet or ultrasonic nebulizer for 10 min or until the nebulized solution container was empty.	9.5±4.6 11.8±3.2	None
15	Koomanachai 2007	Colistin (n=78) Non-Colistin (n=15)	IV	The patients received intravenous colistin (colistimethate sodium) of 5 mg/kg/day in two divided doses. The dosage of colistin was adjusted according to the patients' renal function. If the patients or their responsible physicians did not wish to join the study, they received other antibiotics according to their physicians' decisions and these patients were defined as the 'non-colistin group'.	11.9	None
16	Wunderink 2020	Cefiderocol (n=145) Meropenem (n=147)	IV	Patients received 3-h intravenous infusions of either cefiderocol 2 g or meropenem 2 g (each in at least 100 mL saline solution) every 8 h for 7–14 days. Treatment could be extended to 21 days based on the investigator's clinical assessment of the patient. The meropenem dosing regimen was selected in consultation with clinical and medical experts and agreed with the FDA because it is not included in the product label. EUCAST has designed breakpoints for this meropenem regimen (susceptible: MIC ≤8 µg/mL).	10.4±4.1 10.1±4	None
17	Khorvash	(IV) meropenem + injectable colistin + nebulized colistin (n=30) (IV) meropenem + injectable colistin + nebulized tobramycin (n=30)	IV and NG	Patients were randomly divided into two groups (n = 30/each): Group 1 – patients with VAP that received IV meropenem (with a dose of 2 g every 8 h for 14 days), injectable colistin plus nebulized colistin (with a dose of 9 million international units (IU) and then 4.5 million IU every 12 h for 14 days), as a routine treatment, and Group 2 – patients with VAP that received IV meropenem (with a dose of 2 g every 8 h for 14 days), injectable colistin (with a dose of 9 million IU and then 4.5 million IU every 12 h for 14 days) plus nebulized tobramycin (with a dose of 300 mg every 12 h for 14 days).	14 Day	None
18	Kaye 2023	Part (A) Colistin (n= 64) Sulbactam+ durlobactam (n= 64)	IV	Patients allocated to sulbactam–durlobactam (1·0 g of each drug in combination) received an intravenous infusion over 3 h every 6 h; Patients allocated to colistin received an initial loading dose of 2·5–5·0 mg/kg (75 000–150 000 IU/kg), and then 2·5 mg/kg (75 000 IU/kg) via intravenous infusion over 30 min every 12 h.	7-14 Days	All patients also received imipenem– cilastatin (1·0 g of each drug in combination) via intravenous infusion over 1 h every 6 h.

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Appendix Table A5. Description of outcomes in studies included in network meta-analyses.

ID	First author, year	Outcome
Clinical cure		
1	Aydemir, 2013	The clinical response, laboratory response, radiological response, microbiological response, time to microbiological clearance (day), in-hospital mortality and VAP-related mortality
2	Durante-Mangoni, 2013	Infection was considered to have been cured if there was remission of pneumonia-related symptoms
3	Betrosian, 2007	The clinical response was rated as *(i)* success, if symptoms and signs of VAP resolved at the end of therapy, *(ii)* failure, if symptoms and signs persisted for >3 days, which required an additional antibiotic treatment, and *(iii)* improvement, if resolution of some, but not all, signs and symptoms of infection at the end of treatment.
4	Sirijatuphat, 2014	Clinical cure was defined as improvement of all attributable signs and symptoms.
5	Aranzana-Climent, 2024	Increase in odds of clinical failure when the increase in predicted bacterial burden at 24 h exceeded 2 log10 CFU/mL. Inclusion of ≥2-log10 bacterial growth as a predictive factor improved the model fit significantly.
6	Bassetti 2020	The primary endpoint in patients with nosocomial pneumonia, or a bloodstream infection or sepsis was the proportion achieving a clinical cure at test of cure. In patients with complicated UTIs, the primary endpoint was the proportion achieving microbiological eradication at test of cure. Secondary endpoints included assessments of clinical and microbiological outcomes at end of treatment, test of cure, and follow-up visits, including changes in SOFA scores for all indications and CPIS scores for patients with pneumonia.
7	Dickstein 2018	Clinical success was a composite of patient alive, hemodynamic stability, stable or improved Sequential Organ Failure Assessment (SOFA) score, stable or improved oxygen- ation for patients with pneumonia.
8	Hakamifard 2022	Clinical criteria for the suspicious of VAP include a new or progressive radiographic infiltrate and at least two of three following clinical characteristics: fever above 38 C, leukopenia or leukocytosis, and purulent secretions. These represent the most accurate criteria for starting empiric antibiotic therapy.
9	Keith 2023	For clinical failure, patients who were indeterminant in terms of the improvement in oxygenation criteria were assessed based on the other components of the composite outcome. Those who met another component of clinical failure were considered clinical failures, whereas those who did not meet any other failure criteria were considered not to be failures.
10	Nutman 2020	outcome was clinical failure at 14 days from randomization, defined as failure to meet all of the following criteria: patient alive; haemodynamically stable (systolic blood pressure >90 mmHg without vasopressor support); improved or stable Sequential Organ Failure Assessment (SOFA) score; improved or stable oxygenation (defined by PaO2/FiO2 ratio) for patients with pneumonia.
11	Jung Park 2019	Microbiological response (MR), defined as a negative conversion of culture study (eradication) of A. baumannii on Day 14.
12	Paul 2018	Clinical response (CR), defined as clinical resolution of fever, symptoms and infectious signs on Day 14 and mortality on Day 30.
13	Pourheidar 2019	Clinical response was defined as resolution of pneumonia related to signs and symptoms, including fever and bronchial secretions, for at least 48 h, Presence of one of the following signs considered as clinical failure: fever (T ≥ 38 °C) or hypothermia (T < 35.5 °C), copious and purulent pulmonary secretion, more than 50% increase in pulmonary infiltrate on CXR, lack of recovery in P O2/ F O2, septic shock or a multiorgan failure.
14	Rattanaumpawan 2010	Clinical outcomes on day 28 after receiving nebulized therapy were classified as favourable outcome (complete resolution of all signs and symptoms of pneumonia, and improvement or lack of progression of all abnormalities on the chest radiograph), death related to VAP, death due to other causes or indeterminate.
15	Koomanachai 2007	Clinical cure was defined as a disappearance of symptoms and signs of infection and clinical improvement was defined as a partial resolution of the symptoms and signs of infection.
16	Wunderink 2020	Key secondary endpoints included clinical and micro- biological outcomes per treatment group at test of cure (7 days [plus or minus 2 days] after the end of treatment). Other secondary endpoints consisted of clinical and microbiological outcomes per patient or per baseline athogen at early assessment (days 3–4 of treatment), end of treatment (last day of treatment), and follow-up (14 days [plus or minus 3 days] after the end of treatment.
17	Khorvash 2019	The clinical pulmonary infection score (CPIS) was determined on the basis of points assigned for various clinically manifestations of VAP.
18	Kaye 2023	clinical cure and microbiological favourable assessment at the end of therapy, test of cure (7 ±2 days after end of therapy), and late follow-up (14 ±2 days after end of therapy) visits in all populations.
Microbiological cure		
1	Aydemir, 2013	A microbiological response was considered to be achieved if subsequent cultures were negative for A. baumannii.
2	Durante-Mangoni, 2013	Microbiologic eradication was defined as disappearance of A. baumannii in all follow-up cultures from the primary source of infection (ie, blood, bronchoalveolar lavage, or bronchial aspirate, drainage fluids) during treatment.
3	Betrosian, 2007	Bacteriologic success was defined by the eradication of A. baumannii isolates
4	Sirijatuphat, 2014	Microbiological responses were classified as eradication (no target organisms found).
5	Aranzana-Climent, 2024	Microbiological failure on day 14 or later. Microbiological failure, a secondary outcome, was defined as repeat isolation on or after day 7 of bacteria phenotypically identical to the index isolate.
6	Bassetti, 2020	In patients with complicated UTIs, the primary endpoint was the proportion achieving microbiological eradication at test of cure. Secondary endpoints included assessments of clinical and microbiological outcomes at end of treatment, test of cure, and follow-up visits, including changes in SOFA scores for all indications and CPIS scores for patients with pneumonia.

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Appendix Table A5. Cont

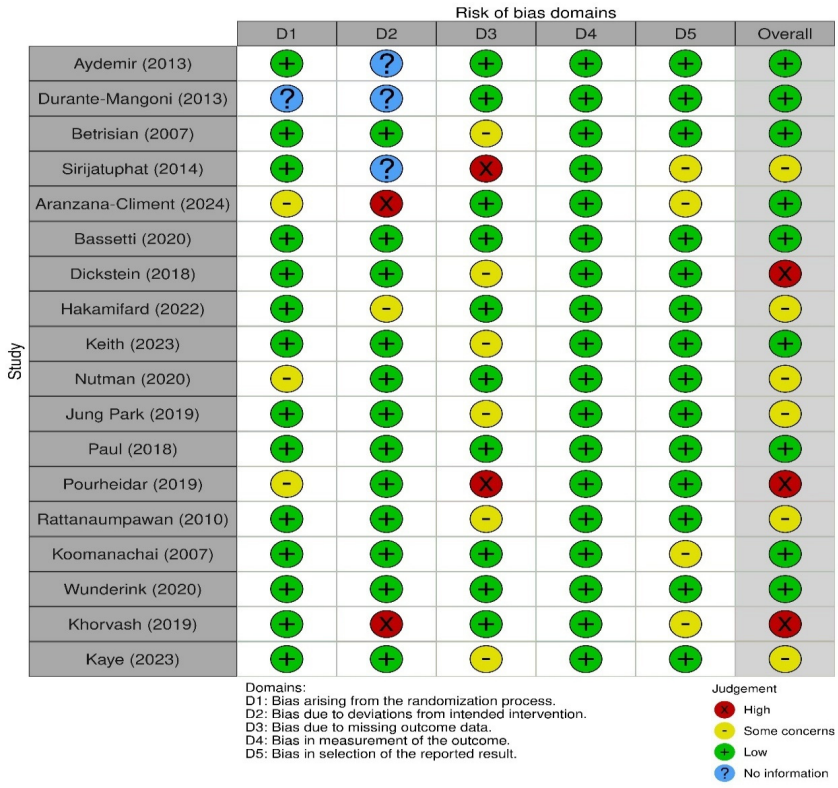
ID	First author (year)	Outcome
7	Dickstein 2018	Microbiological cure for patients with bacteremia; clinical failure was failure to meet all of the success criteria (a composite of patient alive, hemodynamic stability, stable or improved Sequential Organ Failure Assessment (SOFA) score, stable or improved oxygen- ation for patients with pneumonia.)
8	Hakamifard 2022	NA
9	Keith 2023	Microbiologic cure was only assessed for patients in whom repeat specimens were obtained and was defined as eradication of pathogen from the infection site (i.e., negative cultures) bythe end of treatment.
10	Nutman 2020	Microbio- logical cure (defined as no growth of the index isolate in blood cultures taken on day 14) for patients with BSI.
11	Jung Park 2019	Microbiological response (MR), defined as a negative conversion of culture study (eradication) of A. baumannii on Day 14.
12	Paul 2018	NA
13	Pourheidar 2019	Microbiological eradication.
14	Rattanaumpawan 2010	Microbiological outcomes were classified as favourable outcome (eradication, presumed eradica- tion) presumed persistence or indeterminate. Bronchospasm was present if respiratory wheezes were observed within 1 h after receiving nebulized solution.
15	Koomanachai 2007	Successful microbiological response was defined as an eradication of the causative organisms at the end of treatment.
16	Wunderink 2020	Key secondary endpoints included clinical and micro- biological outcomes per treatment group at test of cure (7 days [plus or minus 2 days] after the end of treatment). Other secondary endpoints consisted of clinical and microbiological outcomes per patient or per baseline athogen at early assessment (days 3–4 of treatment), end of treatment (last day of treatment), and follow-up (14 days [plus or minus 3 days] after the end of treatment.
17	Khorvash 2019	NA
18	Kaye 2023	Microbiologically modified ITT, and carbapenem-resistant ABC microbiologically evaluable populations; 14-day all-cause mortality in the carbapenem- resistant ABC microbiologically modified ITT and microbiologically modified ITT populations
All-cause mortality		
1	Aydemir (2013)	NA
2	Durante-Mangoni (2013)	30-day mortality defined as death for any cause occurring within 30 days from randomization.
3	Betrosian (2007)	28-day all-cause mortality
4	Sirijatuphat (2014)	28-day all-cause mortality
5	Aranzana-Climent (2024)	14-day mortality
6	Bassetti 2020	14 and 28-day all-cause mortality
7	Dickstein 2018	28-day all-cause mortality, 14-day mortality
8	Hakamifard 2022	Overall (crude) mortality
9	Keith 2023	28-day all-cause mortality
10	Nutman 2020	14-day and 28-day all-cause mortality
11	Jung Park 2019	14 and 28-day mortality
12	Paul 2018	30-day mortality
13	Pourheidar 2019	30-day mortality
14	Rattanaumpawan 2010	Overall (crude) mortality
15	Koomanachai 2007	30-day mortality
16	Wunderink 2020	14-day all-cause mortality, 28-day all-cause mortality
17	Khorvash 2019	14-day mortality
18	Kaye 2023	14-day all-cause mortality, 28-day all-cause mortality
Nephrotoxicity		
1	Aydemir (2013)	Nephrotoxicity was defined as a serum creatinine value of >2 mg/dl, which represented a reduction in the calculated creatinine clearance of 50% relative to the value at the initiation of antibiotic therapy.
2	Durante-Mangoni (2013)	Renal toxicity was defined according to the RIFLE (risk, injury, failure, loss, end-stage renal disease) criteria in terms of changes of serum creatinine levels relative to baseline.
3	Betrosian (2007)	Nephrotoxicity was defined as an increase in serum creatinine (SCr) of 0.5 mg/dL or more over the baseline value, an increase in SCr of 50% or greater over the baseline value, or a reduction in the calculated creatinine clearance of 50% or greater using the Cockcroft–Gault formula.
4	Sirijatuphat (2014)	Acute kidney injury was defined as at least the injury category (decreasing glomerular filtration rate, >50%, doubling of serum creatinine, or urine production of <0.5 ml/kg/h for 12 h) of the risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) classification
5	Aranzana-Climent (2024)	NA
6	Bassetti 2020	NA
7	Dickstein 2018	NA
8	Hakamifard 2022	Nephrotoxicity was defined as a serum creatinine >2 mg/dL, a reduction in the calculated creatinine clearance of 50% compared with the value at the start of therapy, or initiation of renal replacement therapy.
9	Keith 2023	NA
10	Nutman 2020	NA
11	Jung Park 2019	creatinine clearance (CLCr) <15 mL/min
12	Paul 2018	NA
13	Pourheidar 2019	NA
14	Rattanaumpawan 2010	Renal impairment was defined as a rise of 2 mg/dL in the serum creatinine level of patients with previously normal renal function or a doubling of the baseline serum creatinine level in patients with pre-existing renal insufficiency

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Appendix Table A5. Cont

ID	First author (year)	Outcome
15	Koomanachai 2007	Nephrotoxicity was defined as an increase in serum creatinine of at least two-fold of the baseline value or a 30% decrease of creatinine clearance from the baseline value.
16	Wunderink 2020	The initial dose of study drugs was modified based on estimated creatinine clearance, and was adjusted to 2 g every 6 h for cefiderocol in patients with a creatinine clearance of more than 120 mL/min
17	Khorvash 2019	mean of creatinine levels of patients was determined in five times.
18	Kaye 2023	Nephrotoxicity was defined as meeting RIFLE criteria at any visit after baseline; patients with multiple RIFLE events were counted only once at the highest severity. Patients with chronic haemodialysis at baseline were excluded from the analysis of nephrotoxicity.
Non-Nephrotoxicity adverse event (neurotoxicity, hepatotoxicity and skin rash)		
1	Aydemir (2013)	NA
2	Durante-Mangoni (2013)	NA
3	Betrosian (2007)	NA
4	Sirijatuphat (2014)	NA
5	Aranzana-Climent (2024)	NA
6	Bassetti 2020	NA
7	Dickstein 2018	NA
8	Hakamifard 2022	NA
9	Keith 2023	Acute kidney injury (AKI) was defined according to the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) criteria.15 All patients who received a trial drug for 48 hours or more with a baseline creatinine clearance of 30 ml/min or higher were eligible for AKI assessment, regardless of whether they remained in the mITT population.
10	Nutman 2020	NA
11	Jung Park 2019	NA
12	Paul 2018	NA
13	Pourheidar 2019	NA
14	Rattanaumpawan 2010	NA
15	Koomanachai 2007	NA
16	Wunderink 2020	NA
17	Khorvash 2019	NA
18	Kaye 2023	NA



Appendix Figure A1. Summarized Risk of bias of included randomized controlled trials studies using ROB2.
This report followed the recommended approach for assessing risk of bias in 18 randomized controlled trials included in Cochrane reviews. This tool addresses specific bias domains including bias arising from the randomization process, bias due to deviation from intended intervention, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result. Each item is adjudicated within each study and the results are represented in a risk of bias table. The adjudication of the risk of bias is achieved by answering pre-specified questions about the methods reported by each study in relation to the risk domain, such that the conclusion is either low risk of bias, unclear risk of bias or high risk of bias.

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Appendix Table A6. Pairwise meta-analysis risk ratio *(*and 95*%* CI*)* for all dichotomous outcomes.

		No. studies	Pairwise meta-analysis risk ratio *(95% CI)*
Clinical cure			
AMP + SUL	CEF	0	2.78 (0.38, 26.69)
	COL	2	0.88 (0.25, 3.44)
	COL + FOS	0	0.75 (0.13, 4.75)
	COL + MER	0	0.77 (0.19, 3.46)
	COL + RIF	0	0.57 (0.12, 2.59)
	NEB	0	0.97 (0.16, 6.5)
	Non_COL	0	0.98 (0.16, 6.42)
	SUL + DUR	0	0.64 (0.12, 3.94)
	TOB + FOS	0	1.61 (0.14, 23.78)
CEF	COL	1	0.32 (0.05, 1.52)
	COL + FOS	0	0.27 (0.03, 2.07)
	COL + MER	0	0.28 (0.04, 1.47)
	COL + RIF	0	0.35 (0.03, 3.16)
	NEB	0	0.23 (0.02, 1.93)
	Non_COL	0	0.35 (0.04, 2.82)
	SUL + DUR	0	0.23 (0.02, 1.93)
	TOB + FOS	1	0.57 (0.03, 10.3)
COL	COL + FOS	1	0.81 (0.22, 2.94)
	COL+ MER	3	0.83 (0.45, 1.5)
	COL + RIF	1	0.62 (0.22, 1.39)
	NEB	0	1.04 (0.23, 4.55)
	Non_COL	1	1.06 (0.26, 4.01)
	SUL + DUR	1	0.69 (0.17, 2.75)
	TOB + FOS	0	1.71 (0.19, 18.61)
COL+ FOS	COL+ MER	0	1.03 (0.25, 4.35)
	COL + RIF	0	0.77 (0.14, 3.39)
	NEB	0	1.29 (0.17, 9.35)
	Non_COL	0	1.31 (0.19, 8.58)
	SUL + DUR	0	0.85 (0.12, 5.72)
	TOB + FOS	0	2.14 (0.17, 32.08)
COL+ MER	COL + RIF	0	0.75 (0.23, 2.01)
	NEB	0	1.25 (0.24, 6.46)
	Non_COL	0	1.28 (0.28, 5.49)
	SUL + DUR	0	0.83 (0.17, 3.92)
	TOB + FOS	0	2.08 (0.21, 24.31)
COL + RIF	NEB	0	1.69 (0.32, 10.53)
	Non_COL	0	1.71 (0.36, 9.39)
	SUL + DUR	0	1.11 (0.23, 6.53)
	TOB + FOS	0	2.83 (0.28, 37.29)
NEB	Non_COL	0	1.01 (0.13, 7.73)
	SUL + DUR	0	0.66 (0.09, 4.96)
	TOB + FOS	0	1.66 (0.12, 26.63)
Non_COL	SUL + DUR	0	0.65 (0.09, 4.69)
	TOB + FOS	0	1.64 (0.13, 24.71)
SUL + DUR	TOB + FOS	0	2.52 (0.19, 38.75)
Microbiological cure			
AMP + SUL	CEF	0	2.78 (0.38, 26.69)
	COL	4	0.88 (0.25, 3.44)
	COL + FOS	0	0.75 (0.13, 4.75)
	COL + MER	0	0.77 (0.19, 3.46)
	COL + RIF	0	0.57 (0.12, 2.59)
	NEB	0	0.97 (0.16, 6.5)
	Non_COL	0	0.98 (0.16, 6.42)
	SUL + DUR	0	0.64 (0.12, 3.94)
	TOB + FOS	0	1.64 (0.14, 23.78)
CEF	COL	1	0.32 (0.05, 1.52)
	COL + FOS	0	0.27 (0.03, 2.07)
	COL + MER	0	0.28 (0.04, 1.47)
	COL + RIF	0	0.35 (0.03, 3.16)
	NEB	0	0.23 (0.02, 1.93)
	Non_COL	0	0.35 (0.04, 2.82)
	SUL + DUR	0	0.23 (0.02, 1.93)
	TOB + FOS	0	0.57 (0.03, 10.3)
COL	COL + FOS	1	0.81 (0.22, 2.94)
	COL+ MER	1	0.83 (0.45, 1.5)
	COL + RIF	2	0.62 (0.22, 1.39)
	NEB	0	1.04 (0.23, 4.55)
	Non_COL	0	1.06 (0.26, 4.01)
	SUL + DUR	0	0.69 (0.17, 2.75)
	TOB + FOS	1	1.71 (0.19, 18.61)
COL+ FOS	COL+ MER	0	1.03 (0.25, 4.35)
	COL + RIF	0	0.77 (0.14, 3.39)
	NEB	0	1.29 (0.17, 9.35)
	Non_COL	0	1.31 (0.19, 8.58)
	SUL + DUR	0	0.85 (0.12, 5.72)
	TOB + FOS	0	2.14 (0.17, 32.08)

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Appendix Table A6. Cont

Clinical cure			
		No. studies	Pairwise meta-analysis risk ratio (95% CI)
COL+ MER	COL + RIF	0	0.75 (0.23, 2.01)
	NEB	0	1.25 (0.24, 6.46)
	Non_COL	0	1.28 (0.28, 5.49)
	SUL + DUR	0	0.83 (0.17, 3.92)
	TOB + FOS	0	2.08 (0.21, 24.31)
COL + RIF	NEB	0	1.69 (0.32, 10.53)
	Non_COL	0	1.71 (0.36, 9.39)
	SUL + DUR	0	1.11 (0.23, 6.53)
	TOB + FOS	0	2.83 (0.28, 37.29)
NEB	Non_COL	0	1.01 (0.13, 7.73)
	SUL + DUR	0	0.66 (0.09, 4.96)
	TOB + FOS	0	1.66 (0.12, 26.63)
Non_COL	SUL + DUR	0	0.65 (0.09, 4.69)
	TOB + FOS	0	1.64 (0.13, 24.71)
All-cause mortality			
AMP + SUL	CEF	0	2.43 (0.06, 102.77)
	COL	2	0.61 (0.04, 7.41)
	COL + FOS	0	0.38 (0.01, 9.89)
	COL + MER	0	0.45 (0.03, 6.69)
	COL + RIF	0	0.26 (0.01, 4.13)
	NEB	0	0.76 (0.02, 21.03)
	Non_COL	0	0.8 (0.03, 24.13)
	SUL + DUR	0	0.43 (0.02, 11.21)
	TOB + FOS	0	1.24 (0.03, 51.73)
CEF	COL	1	0.25 (0.02, 2.63)
	COL + FOS	0	0.16 (0.01, 3.42)
	COL + MER	0	0.19 (0.01, 2.18)
	COL + RIF	0	0.11 (0, 1.43)
	NEB	0	0.32 (0.01, 10.17)
	Non_COL	0	0.33 (0.01, 8.56)
	SUL + DUR	0	0.18 (0, 5.51)
	TOB + FOS	0	0.52 (0.01, 20.76)
COL	COL + FOS	1	0.63 (0.08, 5.02)
	COL+ MER	5	0.75 (0.28, 1.84)
	COL + RIF	3	0.44 (0.09, 1.46)
	NEB	1	1.28 (0.1, 15.12)
	Non_COL	1	1.34 (0.15, 12.76)
	SUL + DUR	1	0.73 (0.07, 7.74)
	TOB + FOS	1	2.09 (0.13, 36.7)
COL+ FOS	COL+ MER	0	1.19 (0.12, 10.92)
	COL + RIF	0	0.71 (0.04, 6.65)
	NEB	0	2.05 (0.08, 49.14)
	Non_COL	0	2.13 (0.1, 44.87)
	SUL + DUR	0	1.17 (0.05, 25.89)
	TOB + FOS	0	3.34 (0.1, 110.69)
COL+ MER	COL + RIF	0	0.59 (0.09, 2.62)
	NEB	0	1.73 (0.12, 23.97)
	Non_COL	0	1.79 (0.17, 21.25)
	SUL + DUR	0	0.99 (0.08, 13.1)
	TOB + FOS	0	2.81 (0.15, 60.37)
COL + RIF	NEB	0	2.99 (0.19, 58.7)
	Non_COL	0	3.07 (0.27, 55.61)
	SUL + DUR	0	1.73 (0.13, 31.33)
	TOB + FOS	0	4.87 (0.25, 136.76)
NEB	Non_COL	0	1.03 (0.04, 31.73)
	SUL + DUR	0	0.57 (0.02, 15.35)
	TOB + FOS	0	1.63 (0.04, 68.35)
Non_COL	SUL + DUR	0	0.55 (0.02, 13.88)
	TOB + FOS	0	1.59 (0.04, 57.45)
SUL + DUR	TOB + FOS	0	2.87 (0.08, 114.48)
Nephrotoxicity			
AMP + SUL	CEF	0	1.16 (0.15, 10.21)
	COL	3	1.13 (0.39, 3.49)
	COL + MER	0	1.49 (0.29, 7.82)
	COL + RIF	0	0.91 (0.19, 5.03)
CEF	COL	1	0.97 (0.17, 4.86)
	COL + MER	0	1.27 (0.14, 10.47)
	COL + RIF	0	0.79 (0.11, 5.49)
COL	COL + MER	3	1.32 (0.35, 4.84)
	COL + RIF	2	0.81 (0.26, 2.63)
COL + MER	COL + RIF	0	0.61 (0.11, 3.75)
Non-Nephrotoxicity adverse event (neurotoxicity, hepatotoxicity and skin rash)			
AMP + SUL	COL	1	1.16 (0.15, 10.21)
	COL + MER	0	1.05 (0.33, 3.69)
	COL + RIF	0	1.49 (0.29, 7.82)
	TOB + FOS	0	0.91 (0.19, 5.03)
CEF	COL + MER	3	0.92 (0.17, 4.42)
	COL + RIF	1	1.27 (0.14, 10.47)
	TOB + FOS	1	0.79 (0.11, 5.49)
COL	COL + MER	0	1.41 (0.35, 5.48)
	COL + RIF	0	0.87 (0.28, 2.71)
COL + MER	COL + RIF	0	0.61 (0.11, 3.75)

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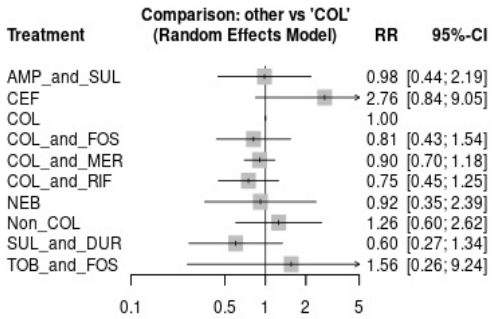
Appendix Table A7. Assessment of inconsistency for all studies

Comparison	No.Studies	NMA	Direct	Indirect	Difference	95 % CI	P value	Loop heterogeneity tau^2
Clinical cure								
AMP + SUL: COL	2	0.12	0.12	NA	NA	NA	NA	0.331
CEF: COL	1	-0.08	-0.08	NA	NA	NA	NA	0.331
COL + FOS: COL	1	0.07	0.07	NA	NA	NA	NA	0.331
COL + MER: COL	3	-0.21	-0.21	NA	NA	NA	NA	0.331
COL + RIF: COL	1	0.45	0.45	NA	NA	NA	NA	0.331
NonCOL: COL	1	-0.89	-0.89	NA	NA	NA	NA	0.331
SUL + DUR: COL	1	0.44	0.44	NA	NA	NA	NA	0.331
Microbiological cure								
AMP + SUL: COL	5	0.02	0.02	NA	NA	NA	NA	2.55
CEF: COL	1	0.19	0.19	NA	NA	NA	NA	2.55
COL + FOS: COL	1	0.21	0.21	NA	NA	NA	NA	2.55
COL + MER: COL	1	-0.02	-0.02	NA	NA	NA	NA	2.55
COL + RIF: COL	2	0.40	0.40	NA	NA	NA	NA	2.55
TOB + FOS: COL	1	-0.26	-0.26	NA	NA	NA	NA	2.55
All-cause mortality								
AMP + SUL: COL	2	-0.15	-0.15	NA	NA	NA	NA	0.652
CEF: COL	1	1.48	1.48	NA	NA	NA	NA	0.651
COL + FOS: COL	1	-0.42	-0.42	NA	NA	NA	NA	0.651
COL + MER: COL	5	-0.19	-0.19	NA	NA	NA	NA	0.651
COL + RIF: COL	3	-0.68	-0.68	NA	NA	NA	NA	0.651
NEB: COL	1	-0.11	-0.11	NA	NA	NA	NA	0.651
NonCOL: COL	1	0.29	0.29	NA	NA	NA	NA	0.651
SUL + DUR: COL	1	-0.65	-0.65	NA	NA	NA	NA	0.651
TOB + FOS: COL	1	0.48	0.48	NA	NA	NA	NA	0.651
Nephrotoxicity								
AMP + SUL: COL	3	-0.18	-0.18	NA	NA	NA	NA	0.778
CEF: COL	1	0.12	0.12	NA	NA	NA	NA	0.778
COL + MER: COL	3	0.25	0.25	NA	NA	NA	NA	0.778
COL + RIF: COL	2	-0.14	-0.14	NA	NA	NA	NA	0.778
Non-Nephrotoxicity adverse event (neurotoxicity, hepatotoxicity and skin rash)								
AMP + SUL: COL	1	0.40	0.40	NA	NA	NA	NA	-
COL + MER: COL	3	-0.65	-0.65	NA	NA	NA	NA	-
COL + RIF: COL	1	1.10	1.10	NA	NA	NA	NA	-
TOB + FOS: COL	1	-0.75	-0.75	NA	NA	NA	NA	-

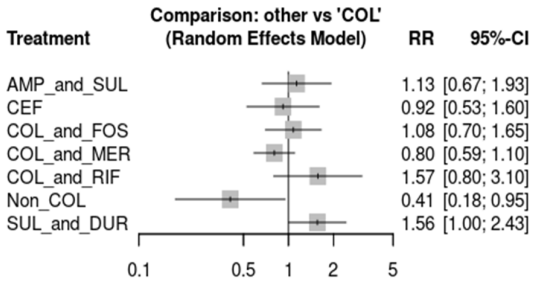
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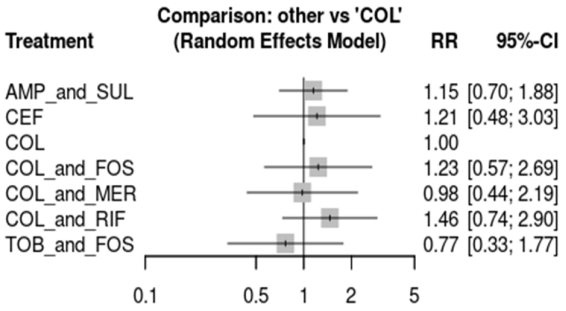
(a) All-cause mortality



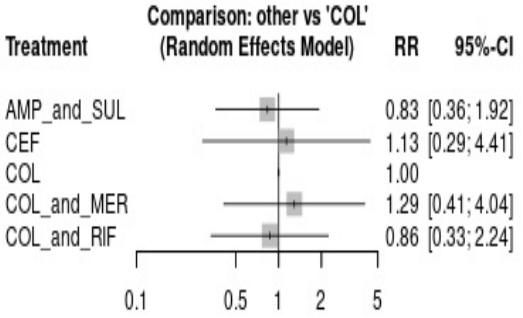
(b) Clinical cure



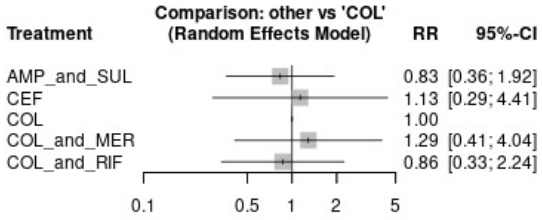
(c) Microbiological cure



(d) Nephrotoxicity



(e) Non-Nephrotoxicity adverse event (neurotoxicity, hepatotoxicity and skin rash)

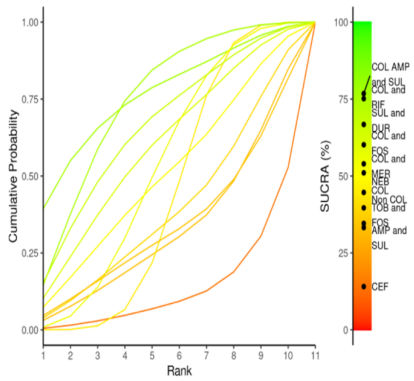


Appendix Figure A2. Results of network meta-analysis of treatment options using randomized control trials

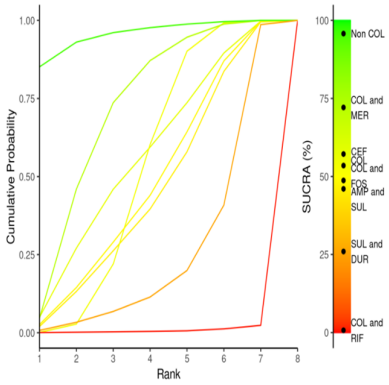
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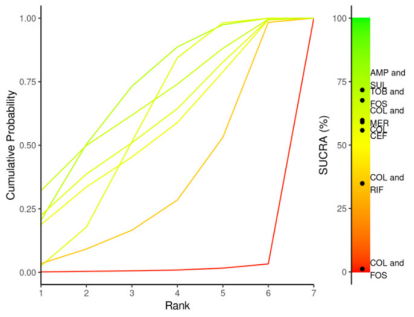
(a) All-cause mortality



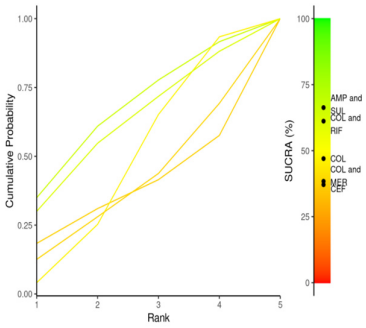
(b) Clinical cure



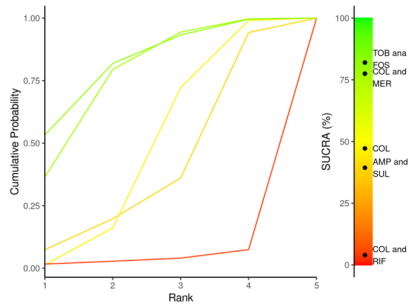
(c) Microbiological cure



(d) Nephrotoxicity



(e) Non-Nephrotoxicity adverse event (neurotoxicity, hepatotoxicity and skin rash)



Key Elements of the Graph

1. X-Axis (Rank): Represents the possible ranks (1 to 11) that treatments can achieve. A rank of 1 indicates the best-performing treatment, while a rank of 11 indicates the worst-performing treatment for the given outcome.
2. Y-Axis (Cumulative Probability): Represents the cumulative probability that a treatment ranks at or better than a specific rank. This ranges from 0 to 1 (or 0% to 100%).
3. Curves: Each colored line represents a different treatment or intervention. The position and shape of the curve indicate how likely that treatment is to rank highly (closer to rank 1) or poorly (closer to rank 11).
4. Color Legend (SUCRA Values): The right-hand side shows a color gradient corresponding to SUCRA values (0% to 100%). Higher SUCRA values (closer to 100%, shown in green) indicate better performance, while lower SUCRA values (closer to 0%, shown in red) indicate poorer performance.
5. Treatment Labels: The legend lists treatments or combinations, such as:
    - COL and SUL (likely colistin and sulbactam)
    - AMP and SUL (likely ampicillin and sulbactam)
    - CEF (likely cefepime or another cephalosporin)
    - And others like FOS, NEB, etc.

Interpreting the Graph

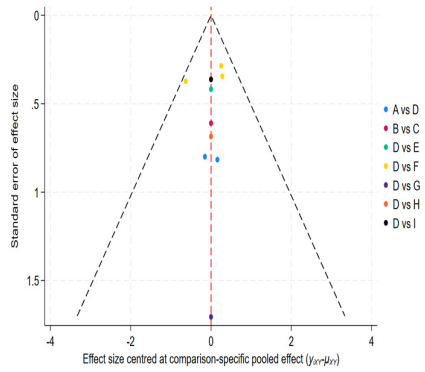
- Higher Curves (Nearer the Top Left): Treatments with curves that start higher on the Y-axis and peak earlier (closer to rank 1) are more likely to be among the best-performing for the outcome. These correspond to higher SUCRA values (greener colors in the legend).
- Lower Curves (Nearer the Bottom Right): Treatments with curves that start lower on the Y-axis and peak later (closer to rank 11) are more likely to perform poorly, corresponding to lower SUCRA values (redder colors).
- SUCRA Values: The color of each curve corresponds to its SUCRA value, as shown in the legend. For example:
    - A curve in green (e.g., 75%–100% SUCRA) indicates a treatment with high probability of being among the best.
    - A curve in red (e.g., 0%–25% SUCRA) indicates a treatment with a high probability of being among the worst.

Appendix Figure A3. SUCRA ranking curve for *(a)* all-cause mortality, *(b)* clinical cure, *(c)* microbiological cure *(d)* nephrotoxic adverse events, *(e)* non-nephrotoxic adverse events. Litmus Rank-O-Gram: Higher SUCRA (Surface Under the Cumulative Ranking Curve) values and cumulative ranking curves nearer the top left indicate better performance

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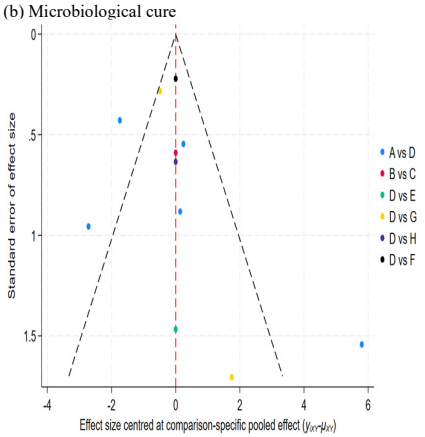
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(a) Clinical cure



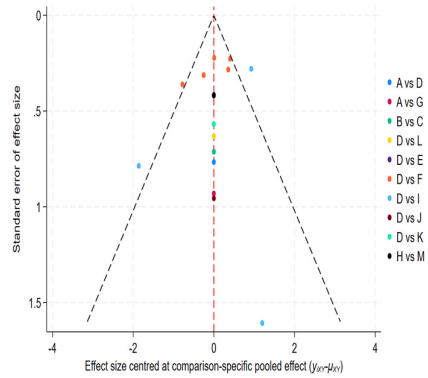
A=AMP+SUL, B=BAT, C=CEF, D=COL, E=COL+FOS, F=COL+MER, G= COL+RIF, H= NonCOL, I=SUL+DUR

(b) Microbiological cure



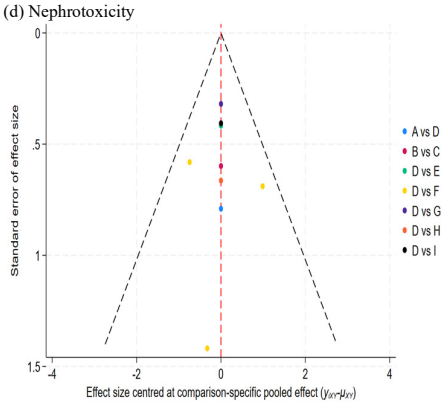
A=AMP+SUL, B=BAT, C=CEF, D=COL, E=COL+FOS, F=COL+MER, G= COL+RIF, H=TOB+FOS

(c) All-cause mortality



A=AMP+SUL, B=BAT, C=CEF, D=COL, E=COL+FOS, F=COL+MER, G= COL+NEB, H=COL+OTH, I=COL+RIF, J=FOS+TOB, K=NEB, L=NonCOL, M=SUL+DUR

(d) Nephrotoxicity



A=AMP+SUL, B=BAT, C=CEF, D=COL, E=COL+FOS, F=COL+MER, G= COL+RIF, H=NonCol, I=SUL+DUR

Appendix Figure A4. Comparison-adjusted funnel plot for the network.

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