Journal of Global Antimicrobial Resistance 49 (2026) 117–127

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

Review

Efficacy and safety of antibiotics in the treatment of multidrug-resistant *Acinetobacter baumannii* infections: A systematic review and Bayesian network meta-analysis

Binh Van Tran[a,*], Phi Yen Huynh[a], Tu Tuan Tran[b], Bao Bui Hoang[c], Ka-Wai Tam[d]

[a] International Ph.D. Program in Medicine, College of Medicine, Taipei Medical University, Taipei City, Taiwan
[b] Department of Internal Medicine, Thai Nguyen University of Medicine and Pharmacy, Thai Nguyen, Vietnam
[c] Internal Medicine Department, University of Medicine and Pharmacy, Hue University, Hue City, Vietnam
[d] Cochrane Taiwan, Taipei Medical University, Taipei City, Taiwan

ARTICLE INFO

Article history:
Received 30 December 2025
Revised 25 March 2026
Accepted 25 April 2026
Available online 6 May 2026

Editor: Dr Huong Vu Thi Lan

Keywords:
Antimicrobial resistance
Multidrug-resistant
Acinetobacter baumannii
Network meta-analysis

ABSTRACT

Objectives: This study aims to compare the efficacy and safety of antimicrobial regimens for multidrug-resistant *Acinetobacter baumannii* (MDR *A. baumannii*) infections using a Bayesian network meta-analysis (NMA).

Methods: The PubMed, Embase, Web of Science, Scopus, and Cochrane Library databases were searched from inception through 6th January 2025, for randomized controlled trials (RCTs) and cohort studies. The primary outcome was all-cause mortality; secondary outcomes included clinical improvement, microbiological cure, and nephrotoxicity. A random-effects NMA estimated odds ratios (ORs) with 95% credible intervals (CrIs) and ranked regimens using the surface under the cumulative ranking curve (SUCRA).

Results: The Bayesian NMA included 10 RCTs and 38 cohort studies (14 regimens; 7 300 patients), with cohorts contributing 80.6% of the data. Compared with tigecycline, cefiderocol-based therapies (combination: OR = 0.41, 95% CrI: 0.22–0.77; monotherapy: OR = 0.44, 95% CrI: 0.27–0.76) and sulbactam–durlobactam (OR = 0.42, 95% CrI: 0.15–1.20) were associated with reduced mortality (very low certainty). Sulbactam–durlobactam also ranked highest for clinical improvement (OR = 5.79, 95% CrI: 1.62–21.46, SUCRA 91.0%) and microbiological cure (OR = 8.66, 95% CrI: 1.92–41.01, SUCRA 98.2%; very low certainty). Colistin-based regimens had the highest nephrotoxicity (combination: OR = 8.21, 95% CrI: 1.41–59.35; monotherapy: OR = 7.75, 95% CrI = 1.81–40.82; very low certainty).

Conclusions: Sulbactam–durlobactam ranked highest for clinical improvement and microbiological cure, while cefiderocol-based therapies scored highest for mortality reduction in our NMA. However, the evidence was largely derived from observational studies with very low certainty. Further *A. baumannii*-specific RCTs are needed to confirm these findings.

© 2026 The Author(s). Published by Elsevier Ltd on behalf of International Society for Antimicrobial Chemotherapy. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

1. Introduction

Multidrug-resistant *Acinetobacter baumannii* (MDR *A. baumannii*) is a challenging pathogen responsible for over 250 000 deaths

Abbreviations: A. baumannii, *Acinetobacter baumannii*; APACHE II, Acute Physiological Assessment and Chronic Health Evaluation II; BGR, Brooks–Gelman–Rubin; CLSI, Clinical and Laboratory Standards Institute; CR, Carbapenem-resistant; CrI, Credible interval; DIC, Deviance information criterion; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, U.S. Food and Drug Administration; GNB, Gram-negative bacteria; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HAP, Hospital-acquired pneumonia; IDSA, Infectious Diseases Society of America; KDIGO, Kidney Disease: Improving Global Outcomes; MCMC, Markov Chain Monte Carlo; MDR, Multidrug-resistant; MIC, Minimum inhibitory concentration; MIU, Million international units; NMA, Network metaanalysis; OR, Odds ratio; PBP, Penicillin-binding protein; PICOS, Population, intervention, comparison, outcomes and study design; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, Randomized controlled trial; RIFLE, Risk, injury, failure, loss, end-stage kidney disease; RoB, Risk of bias; ROBIN-I, Risk of bias in non-randomized studies of interventions; SUCRA, Surface under the cumulative ranking curve; TDM, Therapeutic drug monitoring; VAP, Ventilator-associated pneumonia; w_j, Weighting parameter; XDR, Extensively drug-resistant.

* Corresponding author. Mailing address: International Ph.D. Program in Medicine, College of Medicine, Taipei Medical University, Address: No. 250, Wuxing Street, Xinyi District, Taipei City 110, Taiwan.

E-mail address: d142113030@tmu.edu.tw (B.V. Tran).

https://doi.org/10.1016/j.jgar.2026.04.016
2213-7165/© 2026 The Author(s). Published by Elsevier Ltd on behalf of International Society for Antimicrobial Chemotherapy. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

annually, with mortality rates among critically ill patients often exceeding 40% worldwide [1,2]. Based on their patterns of antimicrobial nonsusceptibility, *A. baumannii* isolates are classified as multidrug-resistant, extensively drug-resistant (XDR), or pandrug-resistant (PDR) [3]. Among these, carbapenem-resistant (CR) *A. baumannii* strains typically exhibit minimum inhibitory concentrations (MICs) for meropenem >8 µg/mL [3,4]. The World Health Organization emphasizes CR *A. baumannii* as a critical-priority pathogen ("ESKAPE" pathogen) due to its capacity to cause severe infections, particularly hospital-acquired pneumonia and bloodstream infections [5]. Its persistence and extensive resistance mechanisms, including carbapenemase production, porin loss, efflux pump activity, and lipopolysaccharide modification, render MDR *A. baumannii* infections exceptionally difficult to treat [6].

Over the past two decades, conventional antibiotics such as carbapenems, tigecycline, amikacin, and fosfomycin have been widely used, yet their therapeutic windows have increasingly narrowed [7]. This phenomenon, characterized by increasing MIC, results in effective doses that progressively approach toxic thresholds [8]. Although colistin remains a vital agent in the treatment of CR *A. baumannii*, its clinical applicability is significantly limited due to nephrotoxicity, poor tissue penetration, and emerging resistance [9]. Achieving a plasma concentration of 2 mg/L often requires a daily dose of 9 MIU of colistin, which increases the risk of nephrotoxicity and appears insufficient for lower respiratory tract infections [10,11]. Sulbactam, a β-lactamase inhibitor with intrinsic antibacterial activity, has shown favorable outcomes at high doses ($\geq$6 g/day) [12,13]. For severe CR *A. baumannii* infections, ampicillin/sulbactam (total daily dose of 27 g) is recommended as a component of combination therapy with colistin and carbapenems [14]. Nevertheless, the nephrotoxic and neurotoxic risks of combining high-dose sulbactam with colistin and carbapenems have not been clearly evaluated [15]. Consequently, therapeutic drug monitoring (TDM) has become increasingly challenging, requiring greater precision in the selection of administration routes, dosing levels, and infusion strategies [16].

Advancements in genomic technologies have accelerated the discovery of novel resistance mechanisms [17]. Since around 2010, several novel antimicrobial agents have been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) based on resistant phenotypes, accompanied by global efforts to strengthen antibiotic stewardship [18]. Cefiderocol, a siderophore cephalosporin, was approved by the FDA in 2019 following clinical trials involving patients with infections caused by MDR Gram-negative bacteria (MDR GNB) [19]. In 2023, the ATTACK trial demonstrated that the sulbactam–durlobactam combination was noninferior to colistin while exhibiting reduced nephrotoxicity [20]. Accordingly, the 2024 Infectious Diseases Society of America (IDSA) guidelines recommend sulbactam–durlobactam as a preferred treatment option for CR *A. baumannii* infections, although the most recent European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines have yet to incorporate this regimen [14,21]. Despite these advances, the overall evidence supporting novel antibiotics and comprehensive comparisons among currently available regimens remains limited, resulting in inconsistencies across contemporary guideline recommendations.

Unlike traditional meta-analyses that restrict comparisons to only two treatments, network meta-analysis (NMA) permits the simultaneous assessment of multiple interventions by integrating both direct and indirect evidence [22]. The Bayesian method enhances NMA by providing precise rankings and robust estimates of relative treatment effects [23]. Accordingly, the current Bayesian NMA aimed to evaluate the comparative efficacy and safety of available antimicrobial regimens for the treatment of MDR *A. baumannii* infections, seeking to determine the most effective therapeutic option.

2. Material and methods

This study conducted a systematic review with a Bayesian NMA, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24]. The protocol was prospectively registered in PROSPERO (CRD420251009925).

2.1. Database search

Two authors independently searched the Cochrane Library, PubMed, Embase, Web of Science, Scopus from database inception to 6th January 2025. The search utilized Medical Subject Headings (MeSH) terms and keywords related to *A. baumannii* or GNB, infection types, and antibiotic agents (Table S2). Studies reporting mortality in adult MDR *A. baumannii* patients, published in English, were included. All records were imported into EndNote, where duplicates were removed, and titles and abstracts were independently screened by two reviewers. Subsequently, full texts of potentially eligible studies were then assessed in accordance with the PRISMA 2020 guidelines, with any disagreements resolved by a third author.

2.2. Study selection

The inclusion and exclusion criteria were developed following the PICOS (population, intervention, comparison, outcome, and study design) framework [25] (Table S3). The definition of MDR *A. baumannii* followed the clinical breakpoints established by the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [3]. Accordingly, studies reporting MDR GNB with subgroups for MDR *A. baumannii* and pathogen-specific trials examining MDR, XDR, and CR *A. baumannii* were included.

2.3. Definition of outcomes

The primary outcome of interest was all-cause mortality, particularly 28-day mortality. If unavailable, 14-day, 30-day, or in-hospital mortality was used instead. Secondary outcomes included clinical improvement, microbiological cure, and nephrotoxicity. Clinical improvement was defined as the resolution of or substantial recovery from infection signs, symptoms, or radiographic findings at the end of therapy. Microbiological cure was defined as the eradication or presumed eradication of MDR *A. baumannii* from culture specimens. Nephrotoxicity was characterized as acute kidney injury according to the RIFLE or KDIGO criteria [26,27]. The definitions of the outcomes varied slightly across the included studies (Table S4).

2.4. Data extraction

We abbreviated antibiotic names and classified the regimens as either monotherapy or combination therapy (Table S5). The details of the antibiotic regimens, including dosage, duration, and number of patients, were collected. We also extracted data on study location, research design, infection site, resistance type, patient demographics, and APACHE II score [28]. Mortality, clinical improvement, and microbiological cure rates were extracted for each antimicrobial treatment arm.

2.5. Quality assessment

Two investigators independently assessed the risk of bias using the Cochrane risk of bias (RoB 2) tool for RCTs, and the risk of bias in nonrandomized studies of interventions (ROBINS-I) tool for cohort studies, with findings visualized using the *robvis* package [29–31]. The overall quality rating was determined by the highest risk

of bias in any single domain. Disagreements were resolved through consensus.

2.6. Statistical analysis

The Bayesian NMA was conducted using a random-effects model to assess the relative effects of different interventions, incorporating both direct and indirect evidence [32]. The initial data were integrated into a network setup, and the plot function was used to create a visual representation of the network, presenting direct comparisons between the antibiotic regimens. For each outcome, we ran Markov chain Monte Carlo (MCMC) simulations with four parallel chains. Following 50 000 burn-in iterations per chain, 20 000 iterations were retained with a thinning interval of 5, resulting in 4 000 posterior samples per chain and 16 000 samples overall. Convergence was assessed using trace plots and the Brooks–Gelman–Rubin (BGR) diagnostic test [33]. Treatment effects were estimated from the posterior distributions and expressed as odds ratios (ORs) with 95% credible intervals (CrIs) [34]. Forest plots and league tables were employed to present effect sizes and all pairwise comparisons, respectively. Ranking probabilities were estimated using the surface under the cumulative ranking curve (SUCRA) values [35].

Model fit and complexity were evaluated using the deviance information criterion (DIC), lower DIC values indicate better model fit after accounting for complexity. The difference in DIC values between the inconsistency and consistency models was also calculated, with higher values denoting greater model differences [32]. Inconsistency was further assessed using the node-splitting method, with comparisons considered inconsistent when direct and indirect estimates differed significantly ($P < 0.05$) [33].

Sensitivity analyses were conducted to assess the robustness of the Bayesian NMA results. Given the inherent differences in study design, risk of bias, and effect estimate heterogeneity between RCTs and cohort studies, a separate analysis including only RCTs was performed to determine whether the overall findings were influenced by observational data. To synthesize the evidence from RCTs and cohort studies in a single NMA, we used the design-adjusted method proposed by Efthimiou et al. [36]. The level of confidence in cohort evidence was downrated by the weighting parameter (w_j). Setting larger w_j values places more confidence in cohort estimates. Additional analyses were restricted to (1) CR *A. baumannii* phenotypes, (2) respiratory infections (VAP/HAP), (3) studies reporting 28-day mortality, (4) studies without critical risk of bias according to the ROBINS-I tool, and (5) meta-regression using the APACHE II score as a covariate.

Analyses were performed in R (v4.4.2) with the “gemtc” and “rjags” packages [37]. The “coda” package was used to assess convergence and generate BGR plots, and the “netmeta” and “ggplot2” packages were applied to create network and forest plots.

2.7. Certainty of evidence

Certainty of evidence for key findings was rated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [38], following guidance from the Cochrane Handbook for Systematic Reviews of Interventions [39]. For indirect comparisons, the certainty of evidence was assessed using the method proposed by Puhan et al. [40]. This approach assesses the most influential loop connecting two interventions via a single common comparator, with the indirect estimate rated according to the lower of the two direct comparisons.

3. Results

3.1. Characteristics of included trials

The literature search identified 5 227 records, of which 4 580 were screened at the title and abstract level. Full texts of 391 articles were assessed for eligibility, the excluded studies and the reasons for their exclusion are summarized (Table S6). Ultimately, 48 studies met the inclusion criteria, involving 7 300 patients with MDR *A. baumannii* infections. The studies included 10 RCTs, 4 prospective cohort studies, and 34 retrospective cohort studies. The study selection process is illustrated in the PRISMA diagram (Fig. 1). A PRISMA extension checklist for reporting systematic reviews comparing multiple treatments involving NMA was provided (Table S1).

Across the included studies, the mean age of participants was 64.3 years, and 48.8% were male. APACHE II scores were recorded for 4 770 patients, with a mean of 19.97. Infection sites were reported as ventilator-associated pneumonia (VAP)/hospital-acquired pneumonia (HAP) (22 studies), mixed sites (19 studies), and primary bloodstream infections (7 studies). CR *A. baumannii* was the most common resistant isolate (31 studies), followed by MDR *A. baumannii* (10 studies) and XDR *A. baumannii* (7 studies). Antibiotic dosages and treatment durations varied across studies (Table S7). Clinical improvement was assessed in 29 studies including a total of 4 514 patients (61.8%), microbiological cure in 27 studies with 3 840 patients (52.6%), and nephrotoxicity in 27 studies comprising 4 265 patients (58.4%) (Table S8).

3.2. Assessment of risk of bias

Ten RCTs were evaluated using the Cochrane RoB 2 tool. Five RCTs reported methods for randomization, two were single-blinded, and three were open-label. One RCT was rated as having a high risk of bias for outcome measurement. Overall, four RCTs (40%) were assessed as having a low risk of bias, five RCTs (50%) as having moderate risk, and one RCT (10%) as having high risk (Fig. S1). A total of 38 cohort studies were assessed using the ROBINS-I tool, with detailed risk of bias across domains. In general, the overall risk of bias was determined to be moderate in 15 studies (39.5%), serious in 17 studies (44.7%), and critical in 6 studies (15.8%) (Fig. S2).

3.3. Network setup

The mortality network comprised 14 treatment nodes connected by 63 direct comparisons. Intravenous colistin monotherapy was the most frequently studied regimen, including 2 098 patients (Fig. 2A). For secondary outcomes, the networks consisted of 11 nodes with 35 direct comparisons for clinical improvement, 12 nodes with 33 direct comparisons for microbiological cure, and 11 nodes with 29 direct comparisons for nephrotoxicity (Fig. 2B–D).

3.4. Assessment of convergence, model fit, and consistency

All models demonstrated good convergence, as confirmed by trace plots and the BGR diagnostic, with all values approaching 1 (Fig. S3–6). Significant ΔDIC values for all-cause mortality (8.22) and microbiological cure (5.39) indicated meaningful differences between the consistency and inconsistency models (Table S9). Nodesplitting analysis detected no significant inconsistency among the networks for 28-day mortality, microbiological cure, and nephrotoxicity, whereas significant *P*-values in the clinical improvement network indicated local inconsistency; however, direct and indirect estimates remained directionally concordant (Table S10).

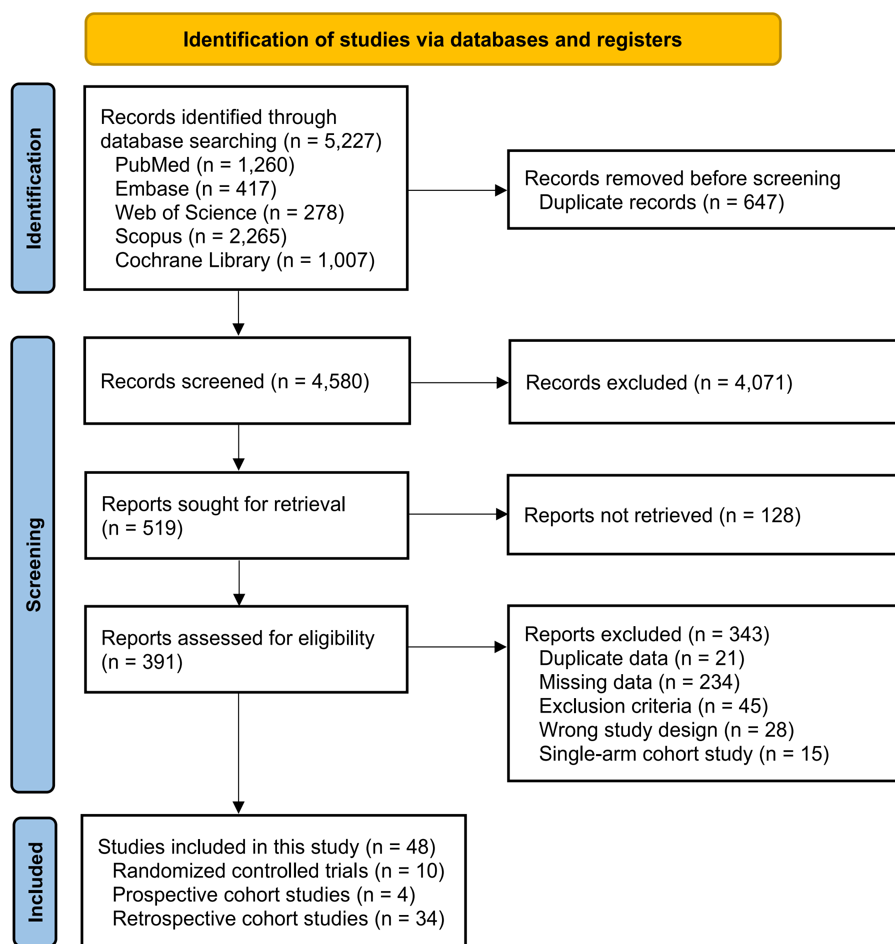

Fig. 1. PRISMA 2020 flow diagram of the study selection process.

3.5. Efficacy and safety outcomes

3.5.1. All-cause mortality

Among the included studies, 28-day, 30-day, in-hospital, and 14-day mortalities were assessed in 19, 18, 9, and 2 studies, respectively (Table S4). The overall mortality rate was 44.8% (3 264/7 300). The NMA showed that cefiderocol combination therapy (OR = 0.41, 95% CrI: 0.22–0.77) and monotherapy (OR = 0.44, 95% CrI: 0.26–0.76) had the highest probabilities of reducing mortality, compared with tigecycline monotherapy. These were followed by sulbactam–durlobactam (OR = 0.42, 95% CrI: 0.15–1.20), sulbactam–intravenous colistin (OR = 0.55, 95% CrI: 0.32–0.95) and another sulbactam combination therapy (OR = 0.56, 95% CrI: 0.38–0.85). Using tigecycline monotherapy as a comparator, the mortality rates are illustrated in the forest plot (Fig. 3).

Direct comparisons and network estimates from the league table showed that cefiderocol-based regimens and sulbactam–intravenous colistin combination were associated with lower mortality than intravenous colistin (either as monotherapy or in combination), meropenem combination therapy, and tigecycline monotherapy (Fig. 4). Cefiderocol combination therapy ranked first in reducing all-cause mortality, with the highest SUCRA (88.1%), followed by cefiderocol monotherapy (85.2%), sulbactam–durlobactam (79.9%), sulbactam–intravenous colistin (72.4%), and sulbactam combination therapy (68.3%). In contrast, aerosolized colistin combination therapy exhibited a lower probability of reducing mortality, and tigecycline monotherapy showed the lowest probability, with SUCRA of 46.8% and 9.8%, respectively (Table S11, Fig. 5).

Sensitivity analysis including only RCTs, as depicted in the separated network plots (Fig. S7) and the league table (Table S12), indicated that sulbactam–durlobactam ranked highest for survival probability (SUCRA = 84.9%), whereas colistin monotherapy (SUCRA = 37.9%) and combination therapy (SUCRA = 37.7%) ranked lowest (Table S13). Cohort studies accounted for 5 909 (80.9%) of the total 7 300 patients (Fig. S7). When the weighting of cohort evidence was reduced, its contribution was 80.6% in the naïve analysis ($w_j = 1$) and it decreased to 76.9% for $w_j = 0.8$, 67.5% for $w_j = 0.5$, and 45.4% for $w_j = 0.2$. Across these weights, the treatment effects and rankings remained largely unchanged (Table S14). The incorporation of cohort studies in the network helped corroborated the findings based on RCTs alone and improved the precision of the estimates (Fig. S8).

Additionally, sensitivity analyses supported the robustness of the primary findings. Analyses restricted to CR *A. baumannii* phenotypes included 31 studies with 4 568 patients; respiratory infections included 22 studies with 3 253 patients; 28-day mortality was reported in 19 studies with 2 736 patients; and 42 studies with 6 155 patients were included after excluding those with critical risk of bias (Fig S9–12). Across these analyses, cefiderocol-based therapies, sulbactam–durlobactam, and sulbactam-based therapies remained among the treatments with the highest probability of mortality reduction (Table S15–18). Finally, meta-regression including 29 studies reporting APACHE II scores (4 770 patients) showed

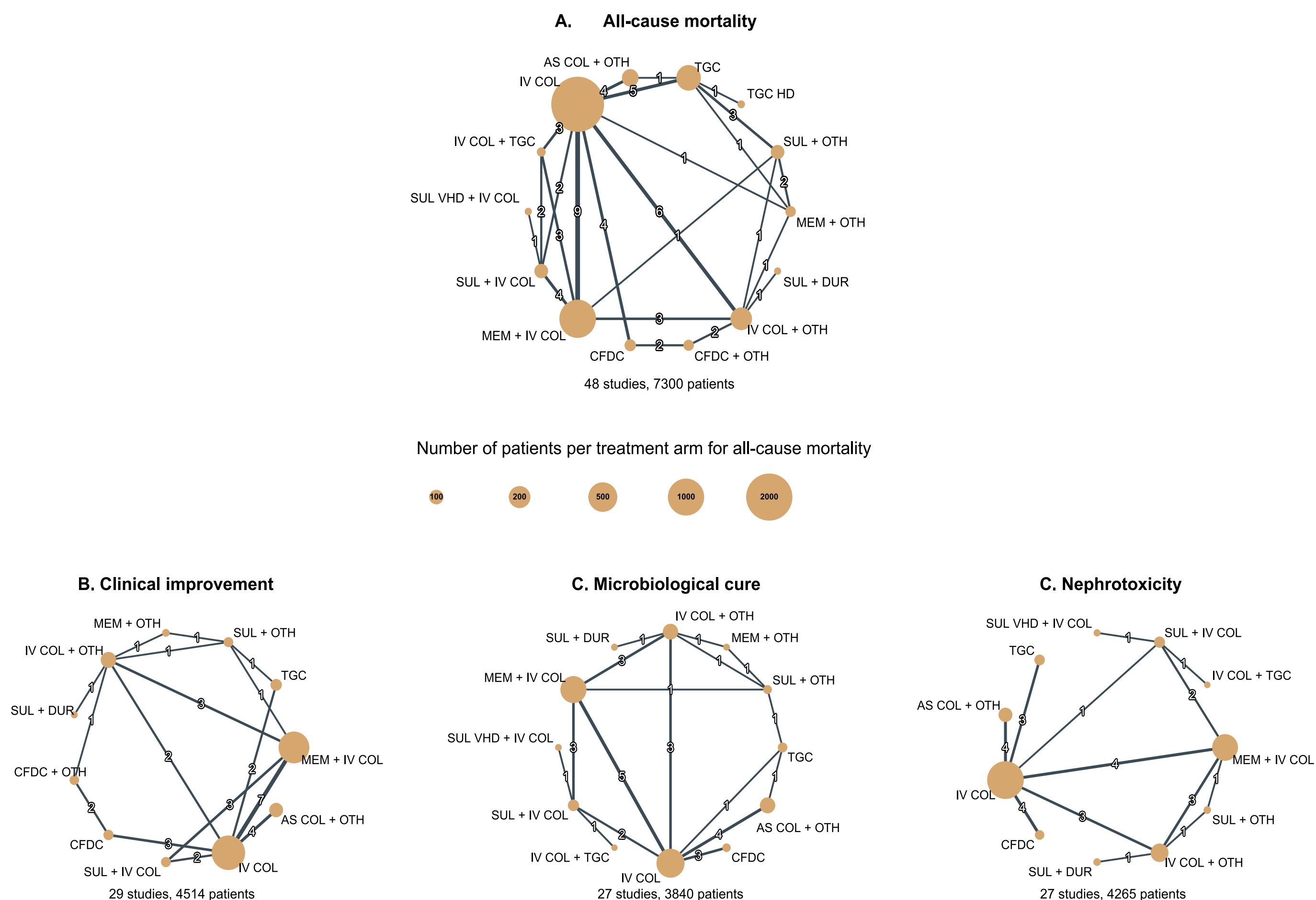

Fig. 2. Network plots of antimicrobial regimens for all outcomes.
Notes: The size of the yellow nodes represents the number of patients who received the corresponding antibiotic regimen. The thickness of the dark bluish-gray edges corresponds to the number of trials for each specific comparison. (A) All-cause mortality, (B) Clinical improvement, (C) Microbiological cure, (D) Nephrotoxicity. Abbreviations: TGC, tigecycline monotherapy; TGC HD, high-dose tigecycline; IV COL, intravenous colistin; SUL + IV COL, sulbactam–intravenous colistin; CFDC, cefiderocol monotherapy; IV COL + OTH, intravenous colistin combination therapy; CFDC + OTH, cefiderocol combination therapy; MEM + IV COL, meropenem–intravenous colistin; SUL + OTH, sulbactam combination therapy; AS COL + OTH, aerosolized colistin combination therapy; SUL + DUR, sulbactam–durlobactam; MEM + OTH, meropenem combination therapy; IV COL + TGC, intravenous colistin–tigecycline; SUL VHD + IV COL, very high-dose sulbactam–intravenous colistin.

no significant association with mortality (OR = 1.02, 95% CrI: 0.43–2.38, per 1-point increase) (Table S19).

3.5.2. Clinical improvement

Clinical outcome data were reported in 8 RCTs and 21 cohort studies, encompassing 11 antibiotic regimens. The pooled rate of clinical improvement was 50.1% (2 260 of 4 514 patients). Compared with tigecycline, sulbactam–durlobactam (OR = 5.79, 95% CrI: 1.62–21.46, SUCRA = 91.0%), cefiderocol combination therapy (OR = 4.98, 95% CrI: 1.87–13.33, SUCRA = 88.6%), and cefiderocol monotherapy (OR = 4.90, 95% CrI: 2.08–11.41, SUCRA = 88.4%) ranked highest for clinical improvement (Table S19). In contrast, tigecycline monotherapy (SUCRA = 12.5%) was the lowest-ranked treatment among the 11 evaluated therapies (Table S11, Fig. 5).

3.5.3. Microbiological cure

The analysis included 27 studies (9 RCTs and 18 cohort studies) covering 12 antimicrobial regimens. The pooled microbiological cure rate was 58.8% (2 256 of 3 840 patients). According to the league table, sulbactam–durlobactam (OR = 8.66, 95% CrI: 1.92–41.01, SUCRA = 98.2%) and sulbactam–intravenous colistin (OR = 2.39, 95% CrI: 1.01–5.60, SUCRA = 81.7%) ranked highest for microbiological cure, whereas tigecycline ranked lowest (SUCRA = 23.6%) (Table S20, Fig. 5).

3.5.4. Nephrotoxicity

Nephrotoxicity data were reported in 27 studies (9 RCTs and 18 cohort studies), including 11 antibiotic regimens. The overall pooled incidence was 32.9% (1 403 of 4 265 patients). Among regimens including intravenous colistin, the nephrotoxicity rate was 36.7% (1 205 of 3 287 patients), with all patients receiving high-dose colistin (≥9 MIU/day). Compared with tigecycline, intravenous colistin monotherapy (OR = 7.75, 95% CrI: 1.81–40.82, SUCRA = 73.9%) and combination therapy (OR = 8.21, 95% CrI: 1.41–59.35, SUCRA = 79.6%) ranked highest for nephrotoxicity (Table S21). In contrast, cefiderocol monotherapy (SUCRA = 13.5%) and tigecycline monotherapy (SUCRA = 15.5%) had the lowest probabilities of nephrotoxicity (Table S11, Fig. 5). Meanwhile, aerosolized colistin did not lead to significant differences in nephrotoxicity compared with other regimens, as all 95% CrIs included 1 (Table S21). Sensitivity analysis restricted to studies using standard criteria (RIFLE/KDIGO) confirmed that intravenous colistin-based regimens had the highest nephrotoxicity (Table S22).

3.6. The certainty of evidence

Using tigecycline as a comparator, comparisons with cefiderocol-based therapies, sulbactam–durlobactam, sulbactam–intravenous colistin, and colistin combination therapy in this

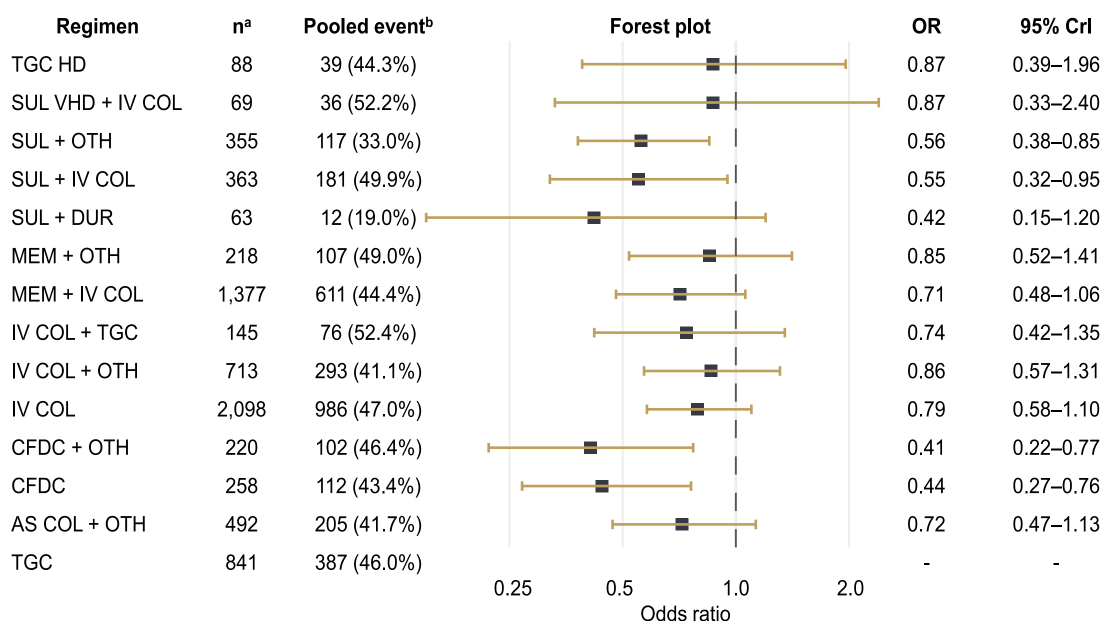

Fig. 3. Forest plots for all-cause mortality, using tigecycline as comparator.
Notes: The vertical dashed black line indicates no effect (OR = 1). Dark bluish-gray squares represent estimated ORs, and yellow lines show 95% credible intervals (CrIs). OR (95% CrI) <1 indicates reduced mortality compared with tigecycline. Abbreviations: TGC, tigecycline monotherapy; TGC HD, high-dose tigecycline; IV COL, intravenous colistin; SUL + IV COL, sulbactam–intravenous colistin; CFDC, cefiderocol monotherapy; IV COL + OTH, intravenous colistin combination therapy; CFDC + OTH, cefiderocol combination therapy; MEM + IV COL, meropenem–intravenous colistin; SUL + OTH, sulbactam combination therapy; AS COL + OTH, aerosolized colistin combination therapy; SUL + DUR, sulbactam–durlobactam; MEM + OTH, meropenem combination therapy; IV COL + TGC, intravenous colistin–tigecycline; SUL VHD + IV COL, very high-dose sulbactam–intravenous colistin; OR, odds ratio; CrI, credible interval.

TGC	1.15 [0.60–2.17]	1.25 [0.83–1.82]						1.61 [0.97–2.63]	1.79 [0.81–4.00]		1.45 [0.56–3.70]		
1.15 [0.51–2.58]	**TGC HD**												
1.26 [0.91–1.71]	1.10 [0.46–2.59]	**IV COL**	**2.22 [1.08–5.00]**	1.32 [0.60–2.94]	1.06 [0.71–1.64]		1.08 [0.79–1.45]		1.03 [0.67–1.56]	2.04 [0.90–4.55]	0.90 [0.44–1.86]	1.07 [0.65–1.75]	
1.84 [1.07–3.13]	1.60 [0.60–4.19]	1.45 [0.93–2.27]	**SUL + IV COL**									0.66 [0.33–1.34]	0.63 [0.32–1.23]
2.24 [1.33–3.72]	1.96 [0.74–5.06]	**1.78 [1.18–2.71]**	1.22 [0.67–2.24]	**CFDC**		0.93 [0.47–1.89]							
1.15 [0.77–1.74]	1.01 [0.41–2.49]	0.92 [0.68–1.26]	0.63 [0.38–1.06]	**0.52 [0.32–0.84]**	**IV COL + OTH**	**2.44 [1.25–5.00]**	1.27 [0.70–2.27]	1.69 [0.76–3.70]			1.22 [0.58–2.56]		
2.44 [1.31–4.55]	2.13 [0.77–5.95]	**1.94 [1.12–3.42]**	1.33 [0.67–2.71]	1.09 [0.65–1.90]	**2.11 [1.24–3.64]**	**CFDC + OTH**							
1.40 [0.95–2.06]	1.23 [0.50–2.99]	1.11 [0.87–1.44]	0.76 [0.51–1.16]	0.63 [0.39–1.01]	1.21 [0.86–1.71]	0.58 [0.32–1.03]	**MEM + IV COL**	1.11 [0.30–4.00]				0.96 [0.51–1.78]	
1.77 [1.19–2.65]	1.55 [0.63–3.84]	1.41 [0.91–2.21]	0.97 [0.53–1.79]	0.79 [0.44–1.44]	1.54 [0.95–2.46]	0.73 [0.37–1.41]	1.27 [0.79–2.06]	**SUL + OTH**			0.58 [0.30–1.14]		
1.40 [0.89–2.14]	1.22 [0.48–3.03]	1.11 [0.77–1.60]	0.76 [0.43–1.35]	0.63 [0.36–1.08]	1.21 [0.74–1.93]	0.57 [0.29–1.10]	1.00 [0.63–1.54]	0.79 [0.45–1.35]	**AS COL + OTH**				
2.37 [0.84–6.86]	2.07 [0.55–7.80]	1.88 [0.70–5.28]	1.29 [0.44–3.96]	1.06 [0.37–3.17]	2.05 [0.80–5.48]	0.97 [0.32–2.96]	1.69 [0.61–4.81]	1.33 [0.47–3.99]	1.69 [0.59–5.07]	**SUL + DUR**			
1.18 [0.71–1.92]	1.04 [0.39–2.64]	0.94 [0.59–1.49]	0.64 [0.34–1.21]	**0.53 [0.28–0.97]**	1.02 [0.62–1.65]	**0.48 [0.24–0.95]**	0.84 [0.50–1.39]	0.67 [0.39–1.10]	0.85 [0.48–1.52]	0.50 [0.17–1.44]	**MEM + OTH**		
1.33 [0.74–2.34]	1.16 [0.43–3.12]	1.05 [0.65–1.72]	0.72 [0.42–1.24]	0.59 [0.31–1.12]	1.15 [0.65–2.00]	0.54 [0.26–1.11]	0.95 [0.58–1.53]	0.75 [0.39–1.42]	0.95 [0.52–1.75]	0.56 [0.18–1.69]	1.12 [0.58–2.21]	**IV COL + TGC**	
1.14 [0.42–3.03]	1.00 [0.28–3.54]	0.91 [0.35–2.31]	0.62 [0.27–1.42]	0.51 [0.18–1.41]	0.99 [0.37–2.60]	0.47 [0.16–1.37]	0.81 [0.32–2.03]	0.64 [0.23–1.80]	0.82 [0.30–2.25]	0.48 [0.12–1.89]	0.96 [0.34–2.73]	0.86 [0.32–2.34]	**SUL VHD + IV COL**

Fig. 4. League table of all-cause mortality in MDR *A. baumannii* infections.
Notes: Direct evidence meta-analysis (upper-right part) and overall NMA estimates (lower-left part). In the upper-right part (yellow), OR (95% CrI) <1 indicates that the row treatment is associated with lower mortality compared with the column treatment. In the lower-left part (light grayish blue), OR (95% CrI) <1 indicates that the column treatment is associated with lower mortality compared with the row treatment. Abbreviations: TGC, tigecycline monotherapy; TGC HD, high-dose tigecycline, IV COL, intravenous colistin; SUL + IV COL, sulbactam–intravenous colistin; CFDC, cefiderocol monotherapy; IV COL + OTH, intravenous colistin combination therapy; CFDC + OTH, cefiderocol combination therapy; MEM + IV COL, meropenem–intravenous colistin; SUL + OTH, sulbactam combination therapy; AS COL + OTH, aerosolized colistin combination therapy; SUL + DUR, sulbactam–durlobactam; MEM + OTH, meropenem combination therapy; IV COL + TGC, intravenous colistin–tigecycline; SUL VHD + IV COL, very high-dose sulbactam–intravenous colistin; OR, odds ratio; CrI, credible interval.

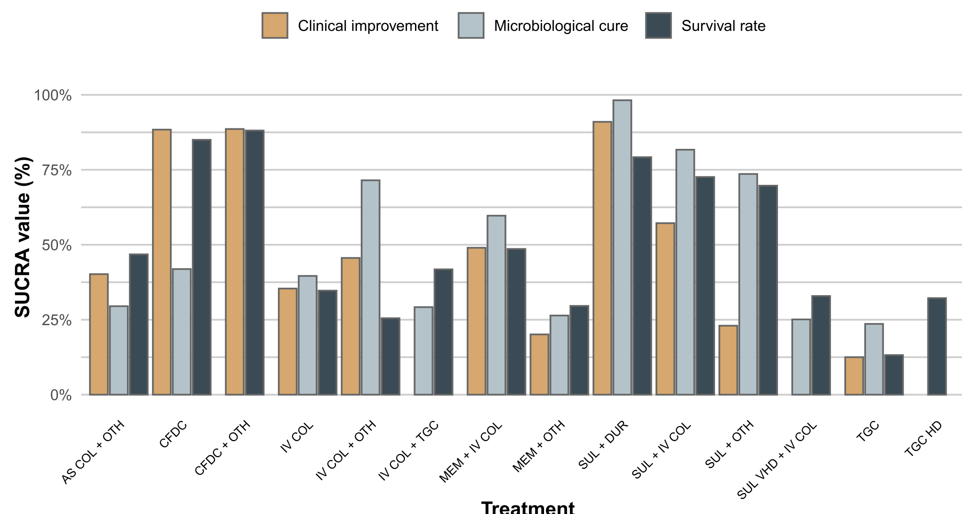

Fig. 5. Surface under the cumulative ranking curve of antimicrobial regimens.
Abbreviations: TGC, tigecycline monotherapy; TGC HD, high-dose tigecycline; IV COL, intravenous colistin; SUL + IV COL, sulbactam–intravenous colistin; CFDC, cefiderocol monotherapy; IV COL + OTH, intravenous colistin combination therapy; CFDC + OTH, cefiderocol combination therapy; MEM + IV COL, meropenem–intravenous colistin; SUL + OTH, sulbactam combination therapy; AS COL + OTH, aerosolized colistin combination therapy; SUL + DUR, sulbactam–durlobactam; MEM + OTH, meropenem combination therapy; IV COL + TGC, intravenous colistin–tigecycline; SUL VHD + IV COL, very high-dose sulbactam–intravenous colistin; SUCRA, surface under the cumulative ranking curve; higher SUCRA indicates a better ranking.

NMA were derived from indirect evidence. The certainty of these indirect comparisons was rated as very low, based on the lowest certainty of the direct comparisons forming the most influential loop. The comparison between tigecycline and intravenous colistin in the nephrotoxicity NMA was informed by direct evidence from three cohort studies with serious risk of bias, resulting in very low certainty of evidence (Table 1).

4. Discussion

The current NMA showed that sulbactam–durlobactam ranked highest for clinical improvement and microbiological cure, and third for mortality reduction in the treatment of MDR *A. baumannii* infections. Cefiderocol-based therapies and sulbactam–intravenous colistin combinations also scored highest for survival probability. In contrast, intravenous colistin-based therapies were associated with nephrotoxicity. The evidence was largely derived from cohort studies with high risk of bias and low certainty.

Our findings are supported by studies with heterogeneous evidence quality. The ATTACK trial demonstrated that sulbactam–durlobactam was noninferior to colistin for 28-day mortality (19% versus 32%) and showed higher clinical response (62% versus 40%) and microbiological cure (68% versus 42%), with lower nephrotoxicity (13% versus 38%) [20]. Integrating these data into our Bayesian NMA confirmed the greater efficacy of sulbactam–durlobactam across outcomes. The sulbactam–intravenous colistin combination, although supported primarily by cohort studies, also showed favorable outcomes, consistent with findings from smaller RCTs and previous meta-analyses [13,41–45]. Regarding cefiderocol, the two existing RCTs primarily targeted MDR GNB rather than MDR *A. baumannii* specifically [46,47]. In the APEKS-NP trial, 28-day all-cause mortality in patients with CR *A. baumannii* infection was 6/18 (33%) with cefiderocol and 7/18 (39%) with meropenem [47]. In CREDIBLE-CR, all-cause mortality at the end of the study was 19/39 (49%) in the cefiderocol group versus 3/17 (18%) in the best available therapy group; however, baseline severity was higher in the cefiderocol group, with ongoing shock in 19% versus 6% of the patients [46]. Due to their small sample sizes (<20 patients per arm), neither of these RCTs was incorporated into the Bayesian NMA. Consequently, evidence for cefiderocol was derived mainly from cohort studies conducted in Italy, all of which reported favorable outcomes in patients receiving cefiderocol [48–55]. The benefits of cefiderocol identified in our NMA were consistent with those reported in another meta-analysis [56].

Sulbactam, a classic β-lactamase inhibitor, has intrinsic activity against MDR *A. baumannii* by binding to penicillin-binding proteins (PBPs), specifically PBP1 and PBP3; at high doses (>9 g/day), it achieves complete PBP3 saturation [12]. In addition, durlobactam inhibits class A, C, and D beta-lactamases [57]. In vitro, more than 95% of *A. baumannii* isolates were susceptible to the sulbactam–durlobactam combination (MIC $\leq$4 µg/mL) [58]. Sulbactam combined with intravenous colistin has consistently demonstrated synergistic activity across multiple studies, particularly in severe MDR *A. baumannii* infections [59,60]. Cefiderocol, by exploiting ferric iron transport systems to enter GNB, exhibits potent in vitro activity against MDR *A. baumannii* strains producing class A, B, and D carbapenemases [61,62]. From a safety perspective, oxidative stress and apoptosis are key mechanisms underlying the nephrotoxicity of intravenous colistin regimens [63]. The incidence of nephrotoxicity strongly correlated with higher colistin doses, and consistently, all patients involved in the included studies received 9 MIU/day [64]. Unlike intravenous colistin, aerosolized colistin was not associated with increased nephrotoxicity. However, its clinical efficacy remained suboptimal, as its distribution in the lower respiratory tract appears inadequate and it poses a potential risk of bronchospasm [11,65–67].

This study provides a comprehensive synthesis by integrating evidence from both RCTs and cohort studies. The constructed network included multiple treatment arms, reflecting current clinical applications. Combining evidence from RCTs and cohort studies is essential, considering the limited number of pathogen-specific RCTs examining MDR *A. baumannii* infections. The Bayesian framework with MCMC simulations provided robust estimates, enabling simultaneous comparisons across multiple regimens, a feature lacking in conventional pairwise analyses [34].

This study has several limitations. First, the predominance of cohort evidence increased the risk of bias and lowered the certainty of these findings. Second, minor inconsistencies were observed in the clinical improvement network, but they did not materially affect the treatment hierarchy. Third, variations in antibi-

Table 1
Summary of key findings and GRADE certainty of evidence across outcomes.

Comparison	Study design[a]		n[b]	OR[c] [95% CrI]	Absolute effect[d] (per 1 000)	Certainty assessment					Overall certainty of evidence
	RCT	Cohort				Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias[e]	
A. All-cause mortality (Treatment versus TGC)											
CFDC[f]	0	6	258	0.44 [0.27–0.76]	187 fewer	Very serious	Not serious	Serious	Serious	No downgrade	⊕◯◯◯ Very low
CFDC + OTH[f]	0	4	220	0.41 [0.22–0.77]	201 fewer	Very serious	Not serious	Serious	Serious	No downgrade	⊕◯◯◯ Very low
SUL + DUR[f]	1	0	63	0.42 [0.15–1.20]	197 fewer	Very serious	Not serious	Serious	Serious	No downgrade	⊕◯◯◯ Very low
B. Clinical improvement (Treatment versus TGC)											
SUL + DUR[f]	1	0	63	5.79 [1.62–21.5]	387 more	Serious	Not serious	Not serious	Serious	No downgrade	⊕◯◯◯ Very low
CFDC + OTH[f]	0	3	188	4.98 [1.87–13.3]	363 more	Serious	Not serious	Not serious	Serious	No downgrade	⊕◯◯◯ Very low
CFDC[f]	0	5	211	4.90 [2.08–11.4]	360 more	Serious	Not serious	Not serious	Serious	No downgrade	⊕◯◯◯ Very low
C. Microbiological cure (Treatment versus TGC)											
SUL + DUR[f]	1	0	63	8.66 [1.92–41.0]	425 more	Serious	Not serious	Not serious	Serious	No downgrade	⊕◯◯◯ Very low
SUL + IV COL[f]	1	4	260	2.39 [1.01–5.60]	211 more	Serious	Not serious	Not serious	Serious	No downgrade	⊕◯◯◯ Very low
D. Nephrotoxicity (Treatment versus TGC)											
IV COL	4	14	1 425	7.75 [1.81–40.8]	201 more	Serious	Not serious	Not serious	Not serious	No downgrade	⊕◯◯◯ Very low
IV COL + OTH[f]	4	4	567	8.21 [1.41–59.4]	211 more	Very serious	Not serious	Not serious	Not serious	No downgrade	⊕◯◯◯ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial; OR, odds ratio; CrI, credible interval; TGC, tigecycline monotherapy; CFDC + OTH, cefiderocol combination therapy; CFDC, cefiderocol monotherapy; SUL + DUR, sulbactam–durlobactam; SUL + IV COL, sulbactam–intravenous colistin; IV COL, intravenous colistin.

[a] Direct evidence contributing to each treatment arm in the network.

[b] Number of patients in each treatment arm.

[c] Estimated effects are reported as odds ratios with 95% credible intervals derived from the network meta-analysis.

[d] Absolute effects (per 1 000) were calculated by applying the estimated effect to the pooled baseline risk of the comparison group across included trials.

[e] Publication bias could not be formally assessed due to the limited number of studies per comparison (<10 studies).

[f] Indirect comparisons were rated following Puhan et al., using the most influential loop, and confidence was assigned as the lower certainty of the contributing direct comparisons.

otic dosage, administration route, or treatment duration, which may influence outcomes, were not considered. In addition, the search was limited to English publications, and trial registries or conference abstracts were not included. Finally, the NMA analysis cannot substitute for randomized comparisons, and treatment rankings are intended to generate hypotheses rather than guide definitive clinical decisions.

Given the very low certainty of evidence, these NMA findings should be applied cautiously, recognizing the need for further robust studies. Moreover, in the complex clinical context, they should not be used to guide treatment decisions. Notably, in light of the ATTACK trial, the 2024 IDSA guidelines recommend sulbactam–durlobactam as first-line therapy for HAP/VAP caused by MDR *A. baumannii* [14]. Sulbactam–intravenous colistin remains an alternative when sulbactam–durlobactam is unavailable [14,68]. However, guidance on cefiderocol is inconsistent, being listed as an alternative by the IDSA but discouraged by the 2022 ESCMID guidelines [14,21]. These conflicting recommendations reflect the paucity and low quality of the evidence currently available. Therefore, high-quality and pathogen-specific RCTs are needed to confirm these findings. Pending additional evidence, conventional strategies incorporate TDM principles to optimize efficacy is preferred.

5. Conclusions

This Bayesian NMA suggested that sulbactam–durlobactam ranked third for mortality reduction and scored first for clinical improvement and microbiological cure in the treatment of MDR *A. baumannii* infections. Cefiderocol-based therapies also ranked highest for survival probability, whereas intravenous colistin-based regimens were associated with the greatest nephrotoxicity. Given very low certainty of evidence, further *A. baumannii*-specific clinical trials are needed to validate these findings.

Author contributions: Conceptualization: B. V. Tran, B. B. Hoang, K. W. Tam. Methodology: B. V. Tran, P. Y. Huynh, T. T. Tran. Formal analysis and investigation: B. V. Tran, P. Y. Huynh, T. T. Tran. Writing–original draft: B. V. Tran, K. W. Tam. Writing–review and editing: B. B. Hoang, K. W. Tam. Supervision: K. W. Tam.

Data availability statement: All extracted data and R code used for this Bayesian NMA are publicly available in the GitHub repository: https://github.com/d142113030-lgtm/NMA_Acinetobacter/releases/tag/v1.0. A DOI for this repository is also available at: https://doi.org/10.5281/zenodo.18883845.

Consent for publication: All authors have approved the manuscript and agree with its submission and publication.

Funding: None.

Ethics approval and consent to participate: No patient consent or ethical approval was required because analyses were based on the previously published studies.

Declaration of competing interest: The authors declare no competing interests.

Acknowledgements: The authors would like to thank the people who participated in this study. This manuscript was edited by PaperTrue Editing and Proofreading Services.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jgar.2026.04.016.

References

[1] Murray CJL, Ikuta KS, Sharara F, Swetschinski L, Aguilar GR, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 2022;399(10325):629–55. doi:10.1016/S0140-6736(21)02724-0.

[2] Mohd Sazlly Lim S, Zainal Abidin A, Liew SM, Roberts JA, Sime FB. The global prevalence of multidrug-resistance among *Acinetobacter baumannii* causing hospital-acquired and ventilator-associated pneumonia and its associated mortality: a systematic review and meta-analysis. J Infect 2019;79(6):593–600. doi:10.1016/j.jinf.2019.09.012.

[3] Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18(3):268–81. doi:10.1111/j.1469-0691.2011.03570.x.

[4] Humphries R, Bobenchik AM, Hindler JA, Schuetz AN. Overview of changes to the clinical and laboratory standards institute performance standards for antimicrobial susceptibility testing, M100, 31st edition. J Clin Microbiol 2021;59(12):e0021321. doi:10.1128/jcm.00213-21.

[5] Sati H, Carrara E, Savoldi A, Hansen P, Garlasco J, Campagnaro E, et al. The WHO Bacterial Priority Pathogens List 2024: a prioritisation study to guide research, development, and public health strategies against antimicrobial resistance. Lancet Infect Dis 2025;25(9):1033–43. doi:10.1016/S1473-3099(25)00118-5.

[6] Mancuso G, Midiri A, Gerace E, Biondo C. Bacterial antibiotic resistance: the most critical pathogens. Pathogens 2021;10(10). doi:10.3390/pathogens10101310.

[7] Viehman JA, Nguyen MH, Doi Y. Treatment options for carbapenem-resistant and extensively drug-resistant *Acinetobacter baumannii* infections. Drugs 2014;74(12):1315–33. doi:10.1007/s40265-014-0267-8.

[8] Gales AC, Seifert H, Gur D, Castanheira M, Jones RN, Sader HS. Antimicrobial susceptibility of Acinetobacter calcoaceticus-*Acinetobacter baumannii* complex and Stenotrophomonas maltophilia clinical isolates: results from the SENTRY antimicrobial surveillance program (1997-2016). Open Forum Infect Dis 2019;6(Suppl 1):S34–46. doi:10.1093/ofid/ofy293.

[9] Tsuji BT, Pogue JM, Zavascki AP, Paul M, Daikos GL, Forrest A, et al. International consensus guidelines for the optimal use of the polymyxins: endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). Pharmacotherapy 2019;39(1):10–39. doi:10.1002/phar.2209.

[10] Horcajada JP, Sorlí L, Luque S, Benito N, Segura C, Campillo N, et al. Validation of a colistin plasma concentration breakpoint as a predictor of nephrotoxicity in patients treated with colistin methanesulfonate. Int J Antimicrob Agents 2016;48(6):725–7. doi:10.1016/j.ijantimicag.2016.08.020.

[11] Boisson M, Jacobs M, Grégoire N, Gobin P, Marchand S, Couet W, et al. Comparison of intrapulmonary and systemic pharmacokinetics of colistin methanesulfonate (CMS) and colistin after aerosol delivery and intravenous administration of CMS in critically ill patients. Antimicrob Agents Chemother 2014;58(12):7331–9. doi:10.1128/aac.03510-14.

[12] Penwell WF, Shapiro AB, Giacobbe RA, Gu RF, Gao N, Thresher J, et al. Molecular mechanisms of sulbactam antibacterial activity and resistance determinants in *Acinetobacter baumannii*. Antimicrob Agents Chemother 2015;59(3):1680–9. doi:10.1128/aac.04808-14.

[13] Liu J, Shu Y, Zhu F, Feng B, Zhang J, 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. doi:10.1016/j.jgar.2020.08.021.

[14] Tamma PD, Heil EL, Justo JA, Mathers AJ, Satlin MJ, Bonomo RA. Infectious Diseases Society of America 2024 guidance on the treatment of antimicrobial-resistant gram-negative infections. Clin Infect Dis 2024. doi:10.1093/cid/ciae403.

[15] Zerbib Y, Gaulin C, Bodeau S, Batteux B, Lemaire-Hurtel AS, Maizel J, et al. Neurological burden and outcomes of excessive β-lactam serum concentrations of critically ill septic patients: a prospective cohort study. J Antimicrob Chemother 2023;78(11):2691–5. doi:10.1093/jac/dkad284.

[16] Abdul-Aziz MH, Alffenaar JC, Bassetti M, Bracht H, Dimopoulos G, Marriott D, et al. Antimicrobial therapeutic drug monitoring in critically ill adult patients: a position paper(. Intensive Care Med 2020;46(6):1127–53. doi:10.1007/s00134-020-06050-1.

[17] Kakoullis L, Papachristodoulou E, Chra P, Panos G. Mechanisms of antibiotic resistance in important gram-positive and gram-negative pathogens and novel antibiotic solutions. Antibiotics (Basel) 2021;10(4). doi:10.3390/antibiotics10040415.

[18] García-Castro M, Sarabia F, Díaz-Morilla A, JM López-romero. Approved antibacterial drugs in the last 10 years: from the bench to the clinic. Explor Drug Sci 2023;1(3):180–209. doi:10.37349/eds.2023.00013.

[19] Parsels KA, Mastro KA, Steele JM, Thomas SJ, Kufel WD. Cefiderocol: a novel siderophore cephalosporin for multidrug-resistant gram-negative bacterial infections. J Antimicrob Chemother 2021;76(6):1379–91. doi:10.1093/jac/dkab015.

[20] 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. doi:10.1016/s1473-3099(23)00184-6.

[21] Paul M, Carrara E, Retamar P, Tängdén T, Bitterman R, Bonomo RA, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant gram-negative bacilli (endorsed by European society of intensive care medicine). Clin Microbiol Infect 2022;28(4):521–47. doi:10.1016/j.cmi.2021.11.025.

[22] Higgins JPT, López-López JA, Becker BJ, Davies SR, Dawson S, Grimshaw JM, et al. Synthesising quantitative evidence in systematic reviews of complex health interventions. BMJ Glob Health 2019;4(Suppl 1):e000858. doi:10.1136/bmjgh-2018-000858.

[23] 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):943. doi:10.18549/PharmPract.2017.01.943.

[24] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi:10.1136/bmj.n71.

[25] Amir-Behghadami M, Janati A. Population, intervention, comparison, outcomes and study (PICOS) design as a framework to formulate eligibility criteria in systematic reviews. Emerg Med J 2020;37(6):387. doi:10.1136/emermed-2020-209567.

[26] Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs. In: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care, 8; 2004. p. R204–12. doi:10.1186/cc2872.

[27] Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120(4):c179–84. doi:10.1159/000339789.

[28] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13(10):818–29. doi:10.1097/00003246-198510000-00009.

[29] McGuinness LA, Higgins JPT. Risk-of-bias visualization (robvis): an R package and shiny web app for visualizing risk-of-bias assessments. Res Synth Methods 2021;12(1):55–61. doi:10.1002/jrsm.1411.

[30] Higgins JPT, Savovic J, Page MJ, Elbers RG, Sterne JAC. Assessing risk of bias in a randomized trial. In: Cochrane handbook for systematic reviews of interventions; 2019. p. 205–28. doi:10.1002/9781119536604.ch8.

[31] Sterne JAC, Hernán MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919. doi:10.1136/bmj.i4919.

[32] Spiegelhalter DJ, Best NG, Carlin BP, Van Der Linde A. Bayesian measures of model complexity and fit. J Royal Statistical Soc: Series B (Statistic Methodol) 2002;64(4):583–639. doi:10.1111/1467-9868.00353.

[33] Van Valkenhoef G, Dias S, Ades AE, Welton NJ. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. Res Synth Methods 2016;7(1):80–93. doi:10.1002/jrsm.1167.

[34] Shim SR, Kim SJ, Lee J, Rücker G. Network meta-analysis: application and practice using R software. Epidemiol Health 2019;41:e2019013. doi:10.4178/epih.e2019013.

[35] Mbuagbaw L, Rochwerg B, Jaeschke R, Heels-Andsell D, Alhazzani W, Thabane L, et al. Approaches to interpreting and choosing the best treatments in network meta-analyses. Syst Rev 2017;6(1):79. doi:10.1186/s13643-017-0473-z.

[36] Efthimiou O, Mavridis D, Debray TP, Samara M, Belger M, Siontis GC, et al. Combining randomized and non-randomized evidence in network meta-analysis. Stat Med 2017;36(8):1210–26. doi:10.1002/sim.7223.

[37] Van Valkenhoef G, Kuiper J. gemtc: network meta-analysis using Bayesian methods (version 1.1-0). CRAN R package; 2025. doi:1032614/CRANpackagegemtc.

[38] Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328(7454):1490. doi:10.1136/bmj.328.7454.1490.

[39] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions version 6.5. Cochrane; 2024 https://www.cochrane.org/handbook.

[40] Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ 2014;349:g5630. doi:10.1136/bmj.g5630.

[41] Makris D, Petinaki E, Tsolaki V, Manoulakas E, Mantzarlis K, Apostolopoulou O, et al. Colistin versus colistin combined with ampicillin-sulbactam for multiresistant Acinetobacter baumannii ventilator-associated pneumonia treatment: an open-label prospective study. Indian J Crit Care Med 2018;22(2):67–77. doi:10.4103/ijccm.IJCCM_302_17.

[42] Betrosian AP, Frantzeskaki F, Xanthaki A, Douzinas EE. Efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. J Infect 2008;56(6):432–6. doi:10.1016/j.jinf.2008.04.002.

[43] 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):319. doi:10.1186/s13054-017-1916-6.

[44] Chen H, Liu Q, Chen Z, Li C. Efficacy of sulbactam for the treatment of Acinetobacter baumannii complex infection: a systematic review and meta-analysis. J Infect Chemother 2017;23(5):278–85. doi:10.1016/j.jiac.2017.01.005.

[45] 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 Chemother 2018;73(1):22–32. doi:10.1093/jac/dkx368.

[46] 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. doi:10.1016/s1473-3099(20)30796-9.

[47] 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. doi:10.1016/s1473-3099(20)30731-3.

[48] Russo A, Gullì SP, D'Avino A, Borrazzo C, Carannante N, Dezza FC, et al. Intravenous fosfomycin for treatment of severe infections caused by carbapenem-resistant Acinetobacter baumannii: a multi-centre clinical experience. Int J Antimicrob Agents 2024;64(1):107190. doi:10.1016/j.ijantimicag.2024.107190.

[49] Oliva A, Liguori L, Covino S, Petrucci F, Cogliati-Dezza F, Curtolo A, et al. Clinical effectiveness of cefiderocol for the treatment of bloodstream infections due to carbapenem-resistant Acinetobacter baumannii during the COVID-19 era: a single center, observational study. Eur J Clin Microbiol Infect Dis 2024;43(6):1149–60. doi:10.1007/s10096-024-04833-8.

[50] Dalfino L, Stufano M, Bavaro DF, Diella L, Belati A, Stolfa S, et al. Effectiveness of first-line therapy with old and novel antibiotics in ventilator-associated pneumonia caused by carbapenem-resistant Acinetobacter baumannii: a real life, prospective, observational, single-center study. Antibiotics (Basel) 2023;12(6). doi:10.3390/antibiotics12061048.

[51] Giacobbe DR, Labate L, Russo Artimagnella C, Marelli C, Signori A, Di Pilato V, et al. Use of cefiderocol in adult patients: descriptive analysis from a prospective, multicenter, cohort study. Infect Dis Ther 2024;13(9):1929–48. doi:10.1007/s40121-024-01016-y.

[52] Giannella M, Verardi S, Karas A, Abdel Hadi H, Dupont H, Soriano A, et al. Carbapenem-resistant Acinetobacter spp infection in critically ill patients with limited treatment options: a descriptive study of cefiderocol therapy during the COVID-19 pandemic. Open Forum Infect Dis 2023;10(7):ofad329. doi:10.1093/ofid/ofad329.

[53] Bavaro DF, Papagni R, Belati A, Diella L, De Luca A, Brindicci G, et al. Cefiderocol versus colistin for the treatment of carbapenem-resistant Acinetobacter baumannii complex bloodstream infections: a retrospective, propensity-score adjusted, monocentric cohort study. Infect Dis Ther 2023;12(8):2147–63. doi:10.1007/s40121-023-00854-6.

[54] Falcone M, Tiseo G, Leonildi A, Della Sala L, Vecchione A, Barnini S, et al. Cefiderocol- compared to colistin-based regimens for the treatment of severe infections caused by carbapenem-resistant Acinetobacter baumannii. Antimicrob Agents Chemother 2022;66(5):e0214221. doi:10.1128/aac.02142-21.

[55] Pascale R, Pasquini Z, Bartoletti M, Caiazzo L, Fornaro G, Bussini L, et al. Cefiderocol treatment for carbapenem-resistant Acinetobacter baumannii infection in the ICU during the COVID-19 pandemic: a multicentre cohort study. JAC Antimicrob Resist 2021;3(4):dlab174. doi:10.1093/jacamr/dlab174.

[56] 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 Dis 2024;24(1):967. doi:10.1186/s12879-024-09899-5.

[57] Karruli A, Migliaccio A, Pournaras S, Durante-Mangoni E, Zarrilli R. Cefiderocol and sulbactam-durlobactam against carbapenem-resistant Acinetobacter baumannii. Antibiotics (Basel) 2023;12(12). doi:10.3390/antibiotics12121729.

[58] Karlowsky JA, Hackel MA, McLeod SM, Miller AA. In vitro activity of sulbactam-durlobactam against global isolates of Acinetobacter baumannii-calcoaceticus complex collected from 2016 to 2021. Antimicrob Agents Chemother 2022;66(9):e0078122. doi:10.1128/aac.00781-22.

[59] Bian X, Liu X, Feng M, Bergen PJ, Li J, Chen Y, et al. Enhanced bacterial killing with colistin/sulbactam combination against carbapenem-resistant Acinetobacter baumannii. Int J Antimicrob Agents 2021;57(2):106271. doi:10.1016/j.ijantimicag.2020.106271.

[60] Qu J, Yu R, Wang Q, Feng C, Lv X. Synergistic antibacterial activity of combined antimicrobials and the clinical outcome of patients with carbapenemase-producing Acinetobacter baumannii infection. Front Microbiol 2020;11-2020. doi:10.3389/fmicb.2020.541423.

[61] Abdul-Mutakabbir JC, Nguyen L, Maassen PT, Stamper KC, Kebriaei R, Kaye KS, et al. In vitro antibacterial activity of cefiderocol against multidrug-resistant Acinetobacter baumannii. Antimicrob Agents Chemother 2021;65(9):e0264620. doi:10.1128/aac.02646-20.

[62] Kayama S, Kawakami S, Kondo K, Kitamura N, Yu L, Hayashi W, et al. In vitro activity of cefiderocol against carbapenemase-producing and meropenem-non-susceptible gram-negative bacteria collected in the Japan Antimicrobial Resistant Bacterial Surveillance. J Glob Antimicrob Resist 2024;38:12–20. doi:10.1016/j.jgar.2024.05.009.

[63] Dai C, Li J, Tang S, Li J, Xiao X. Colistin-induced nephrotoxicity in mice involves the mitochondrial, death receptor, and endoplasmic reticulum pathways. Antimicrob Agents Chemother 2014;58(7):4075–85. doi:10.1128/aac.00070-14.

[64] Lee YJ, Wi YM, Kwon YJ, Kim SR, Chang SH, Cho S. Association between colistin dose and development of nephrotoxicity. Crit Care Med 2015;43(6):1187–93. doi:10.1097/ccm.0000000000000931.

[65] 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. doi:10.1093/jac/dkq360.

[66] Yapa SWS, Li J, Patel K, Wilson JW, Dooley MJ, George J, et al. Pulmonary and systemic pharmacokinetics of inhaled and intravenous colistin methanesulfonate in cystic fibrosis patients: targeting advantage of inhalational administration. Antimicrob Agents Chemother 2014;58(5):2570–9. doi:10.1128/aac.01705-13.

[67] Choe J, Sohn YM, Jeong SH, Park HJ, Na SJ, Huh K, et al. Inhalation with intravenous loading dose of colistin in critically ill patients with pneumonia caused by carbapenem-resistant gram-negative bacteria. Ther Adv Respir Dis 2019;13:1753466619885529. doi:10.1177/1753466619885529.

[68] Choi SJ, Kim ES. Optimizing treatment for carbapenem-resistant Acinetobacter baumannii complex infections: a review of current evidence. Infect Chemother 2024;56(2):171–87. doi:10.3947/ic.2024.0055.