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Efficacy and Safety of Antibiotic Combination Therapies for Multidrug-Resistant Acinetobacter baumannii: A Systematic Review and Meta-Analysis

Dr. Ali Atoom[1], Miss. Bayan Alzubi[2], Miss. Rogayah Alarman[3], Miss. Lana Jebreen[4], Hamzeh J. Al-Ameer[5], qutaiba omar ababneh[6]

Department of medical laboratory sciences, Faculty of Allied Medical sciences, Al Ahliyya Amman University, Amman – Jordan[1]

Department of medical laboratory sciences, Faculty of Allied Medical sciences, Al Ahliyya Amman University, Amman – Jordan[2]

Department of medical laboratory sciences, Faculty of Allied Medical sciences, Al Ahliyya Amman University, Amman – Jordan[3]

Department of medical laboratory sciences, Faculty of Allied Medical sciences, Al Ahliyya Amman University, Amman – Jordan[4]

Department of Biotechnology, Faculty of Allied Medical Sciences, Al-Ahliyya Amman University, Amman, 19111, Jordan[5]

Department of Biotechnology and Genetic Engineering, Jordan university of sciences and technology[6]

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Corresponding author: ***Dr. Ali Atoom*** *(a.atoom@ammanu.edu.jo)*

1. ABSTRACT

Multidrug-resistant Acinetobacter baumannii (MDR-AB), classified by the World Health Organization as a critical-priority pathogen, represents not only a biomedical emergency but also a reflection of contemporary healthcare culture under globalization pressures. Particularly within intensive care units, carbapenem-resistant strains have reshaped therapeutic traditions, clinical decision-making patterns, and antimicrobial stewardship frameworks across regions. This systematic review and meta-analysis synthesizes evidence from randomized and observational studies to evaluate the efficacy and safety of antibiotic combination therapies compared with monotherapy in hospitalized patients with confirmed MDR-AB infections. Following PRISMA 2020 guidelines and a registered protocol (PROSPERO CRD420261321419), 13 eligible studies were analyzed using a random-effects model. Combination therapy demonstrated a statistically significant reduction in all-cause mortality (RR 0.82, 95% CI 0.72–0.94) and improved microbiological eradication and clinical cure rates compared with monotherapy. Sulbactam-based regimens and colistin–carbapenem combinations yielded the most consistent therapeutic benefits, while newer β-lactam/β-lactamase inhibitor combinations such as sulbactam–durlobactam showed improved safety profiles with reduced nephrotoxicity. Colistin monotherapy was associated with higher treatment failure and renal adverse events. Beyond clinical metrics, these findings

illuminate broader interconnections between scientific innovation, healthcare infrastructure, and global cultural responses to antimicrobial resistance. The evolution from monotherapy to combination regimens reflects adaptive, interactive treatment paradigms shaped by environmental pressures within hospital ecosystems. Integrating pharmacological science with stewardship ethics underscores the dynamic relationship between medical culture and microbial evolution. High-quality multicenter trials and harmonized reporting standards remain essential to refine sustainable therapeutic strategies in this rapidly transforming global health landscape.

KEYWORDS: Multidrug-resistant Acinetobacter baumannii, carbapenem-resistant pathogens, antibiotic combination therapy, colistin-based regimens, sulbactam–durlobactam, intensive care unit infections, antimicrobial resistance, systematic review and meta-analysis

1. INTRODUCTION

Multidrug-resistant Acinetobacter baumannii (MDR-A. baumannii) has turned out to be one of the harshest nosocomial pathogens in the world, especially in the intensive care units (ICUs) (Chandra et al., 2022). The high survival rate observed in severe hospital settings coupled with the extensive resistance to various classes of antibiotics has led to great clinical and epidemiological interest. (Almutairy, 2024). MDR-A.such as bloodstream infection, wound infection and ventilator-associated pneumonia are linked to extended hospitalization, high cost of healthcare, and high rates of mortality that commonly extend up to 4060 percent in patients with critical illnesses (Alrahmany et al., 2022). The World Health Organization (WHO) and the Centers of Disease Control and Prevention (CDC) have classified carbapenem-resistant A. baumannii as a critical-priority pathogen that needs an immediate research initiative and treatment (Wise et al., 2024).

The existing clinical outlook of the treatment of MDR-A. baumannii is very restricted. The conventional monotherapy treatment has demonstrated a decreasing efficacy with increasing resistance, pharmacodynamic resistance, and non-homogeneous susceptibility distribution (Marino et al., 2024). Consequently, clinicians very often use antibiotic combination regimens, including polymyxins combined with carbapenems, tetracyclines, beta-lactamases-inhibitors, or rifampicin in an attempt to increase bactericidal activity, tissue penetration, and overcome various resistance mechanisms (Ardebili et al., 2023). Resistance is still rapidly changing, the pipeline of developing antimicrobial agents is limited, and currently available agents have issues of nephrotoxicity, hepatotoxicity, or less than optimal response (Abbasi & Saeedi, 2022). Combination therapy is becoming an increasingly common practice in this regard, although the research evidence has been weak with regard to its superiority to monotherapy.

The effect and the safety of different combinations of antibiotics have contradicting results in recent clinical trials and observational studies. Other studies indicate that there are hypothetical synergies and better survival although some indicate that there is little benefit or more toxicity (Palmer et al., 2022). Also, most past reviews have concentrated more on clinical effectiveness, with comparatively less emphasis on important safety outcomes such as nephrotoxicity, particularly in patients receiving polymyxin-based regimens. While some studies report acceptable safety profiles, others have demonstrated a high incidence of acute kidney injury associated with polymyxins, highlighting contradictory findings in the existing literature. Several systematic reviews have similarly focused primarily on efficacy outcomes rather than detailed safety assessments. In addition, the fast changing resistance situation requires new evidence synthesis to be used to drive clinical decision making (Chatpibal, 2020.). Although the corpus of research has expanded, there is no meta-analytic study that gauges the effectiveness and the adverse events with combination therapies of MDR-A.baumannii infection to this day.

Hence, the current meta-analysis and systematic review examine and analyze the effectiveness and safety of the available combinations of antibiotics to treat MDR-A. baumannii infections. The objective of this study is to give clinicians, researchers, and policymakers a better idea of optimal treatment measures in regard to managing the disease, which is becoming more and more common and threatening to human life. Previous systematic reviews have mainly focused on clinical efficacy or specific antibiotic classes, particularly colistin-based regimens, with limited attention to comprehensive safety outcomes. Many did not include recently

published randomized controlled trials, assess resistance emergence, or apply structured certainty-of-evidence grading. In addition, most analyses were restricted in scope and did not fully reflect updated global resistance patterns. This review addresses these gaps by integrating efficacy, safety, and resistance outcomes within a single meta-analytic framework, incorporating recent high-quality trials, applying the GRADE approach, and conducting predefined subgroup and sensitivity analyses. By doing so, it refines current evidence, clarifies the relative value of combination regimens, and strengthens the clinical relevance of treatment decisions for MDR-A. baumannii infections.

2. METHODS

2.1. *Protocol and Registration*

This systematic review and meta-analysis have been carried out by adhering to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA 2020) guideline. Adherence to PRISMA 2020 was intended to enhance methodological transparency and reporting quality. The protocol of the review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number (CRD420261321419). Prospective registration strengthened transparency and reduced the risk of selective reporting bias.

2.2. *PICO Framework: Eligibility Criteria.*

Population, Intervention, Comparator, and Outcomes (PICO) framework was used to define the inclusion and exclusion criteria.

2.2.1. Population

Any hospitalized patient, including ventilator-associated pneumonia, bloodstream infections, wound infections, urinary tract infections, and mixed site infections that have laboratory confirmed infections by MDR-A. baumannii.

2.2.2. Intervention

All antibiotic combination regimens of treating MDR-A. baumannii infections including but not limited to colistin-based combinations, carbapenem-based combinations, sulbactam-based combinations, tigecycline-based combinations, and regimens that used rifampicin, aminoglycosides or fosfomycin.

2.2.3. Comparators

Monotherapy (e.g., colistin, carbapenem, alone), or other antibiotic combinations.

2.2.4. Outcomes

Primary outcomes

- All cause mortality (7-day, 14-day or 30-day mortality as reported).
- Microbiological eradication.

Secondary outcomes

- Clinical improvement or clinical cure.
- Nephrotoxicity.
- Neurotoxicity.
- Development of antimicrobial resistance in treatment.

2.3. *Study designs*

Randomized controlled trials (RCTs), prospective or retrospective cohort studies, and case-control studies.

2.4. *Exclusion criteria*

Case reports, narrative reviews, editorials, and no primary data letters, opinion pieces, conference abstracts, and all in vitro or animal investigations.

2.5. *Data sources and search strategy*

The literature search was performed in the following electronic databases since inception up to the date of insertion:

PubMed	**Cochrane Library**	**Scopus**
Web of Science	**Scimago**	**EMBASE**

This study used grey literature sources and preprint servers (e.g., medRxiv) and clinical trial registries (e.g., ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP)) to achieve this completeness.

A combination of Medical Subject Headings (MeSH) and free-text terms was used as the search strategy and involved the pathogen, resistance, and antibiotic combinations. The major search terms were: multidrug-resistant, A. baumannii, extensively drug-resistant, combination therapy, synergy, colistin, carbapenem, sulbactam, tigecycline and polymyxin. Where necessary, there were Boolean operators (AND, OR), database-specific filters, and truncation.

2.6. *Study Selection*

All the citations retrieved were added to reference management software, and any duplicates were eliminated. Title and abstracts were screened by two independent reviewers on the basis of the eligibility criteria. Detailed assessment of full text articles was then done on articles that were potentially eligible. The disputes were solved by means of debate or the decision of a third reviewer. The PRISMA 2020 flow diagram was used to record the study selection process.

2.7. *Data Extraction*

Two reviewers independently extracted data using a standardized and piloted data extraction form. The variables collected included key study characteristics such as author, publication year, country or region, study design, and setting (for example, intensive care unit or general ward). The information about the patients was also collected such as the number of participants in general, their age, sickness degree, and the infection type. Intervention data were documented including detailing the antibiotic combinations, dosage schedule, and treatment period. Comparator regimens also became documented. In addition, such relevant results were extracted as mortality, microbiological eradication, clinical response, nephrotoxicity, neurotoxicity, and the development of antimicrobial resistance.

2.8. *Risk of Bias Assessment*

Two independent reviewers evaluated risk of bias.

- Randomized controlled trials were considered according to the Cochrane Risk of Bias 2 (RoB 2) tool, which considers the domains of randomization, allocation concealment, blinding, and outcome reporting.
- Observational studies (cohort and case-control) were evaluated with the Newcastle- Ottawa Scale (NOS), which included the aspects of selection, comparability, and outcome/exposure assessment.

2.9. *Data Synthesis and Meta-analysis*

The data will be synthesized and meta-analyzed to derive a conclusion regarding the research topic. The outcomes of at least two eligible studies were carried out as a quantitative meta-analysis. The synthesis of the

effects was done through the random-effects model (DerSimonian Laird method) to capture heterogeneity among the studies. Risk ratios (RRs) and 95% confidence intervals (CIs) were used to summarize dichotomous outcomes (e.g., mortality, eradication, nephrotoxicity). The I2 statistic and Cochran Q test were used to test statistical heterogeneity. A priori subgroup analyses were planned to be conducted on:
Clinical environment (ICU vs. non-ICU)
Geographical location (Asia, Europe, Middle East, Americas)
Nature of the infection (VAP, bloodstream infection, etc.)
Type of antibiotic combination (colistin-based, carbapenem-based, sulbactam-based)
The sensitivity analyses were conducted by removing high risk-of-bias studies; and by studying the impact of study design (RCTs vs. observational studies). These predefined subgroup and sensitivity analyses were designed to enhance analytical robustness and explore potential sources of heterogeneity. The visual inspection of funnel plots and the execution of Egger regression asymmetry test at the presence of 10 or more studies on a particular outcome were used to estimate publication bias.

2.10. Certainty of Evidence

The certainty of the evidence of every minor and major outcome was evaluated with the assistance of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. The structured application of the GRADE framework strengthened the interpretability and clinical reliability of pooled estimates. The evidence ratings were high, moderate, low and very low, which was based on the risk of bias, inconsistency, indirectness, imprecision and publication bias. In this way, table of findings was developed.

3. Results

3.1. Study Selection

The initial database search of EMBASE, PubMed, Web of Science, Scopus, and the Cochrane Library was used to identify 4,386 records. Another 23 records were obtained using the grey literature sources, preprint servers, and trial registries. Following the process of eliminating 1,210 duplicates, 3,192 titles and abstracts were filtered to eliminate irrelevant information. Among them, 3,075 were eliminated as they did not fit the eligibility criteria, the most frequent being reviews, laboratory research, non-MDR-A. baumannii research, or the absence of combination therapy interventions.

The total of 182 full-text articles were evaluated as to their eligibility. Out of these, 99 articles were filtered off based on either the lack of confirmed MDR/CRAB infections, analyzing monotherapy alone, lack of clinical outcome data, non-human study design, or inappropriate study design (i.e., case reports, narrative reviews). Finally, 13 studies (cohort studies, case-control studies, and randomized controlled trials) fitted all the selection criteria and were incorporated into the qualitative synthesis.

The PRISMA 2020 flow diagram summarizes the whole process of the study selection.

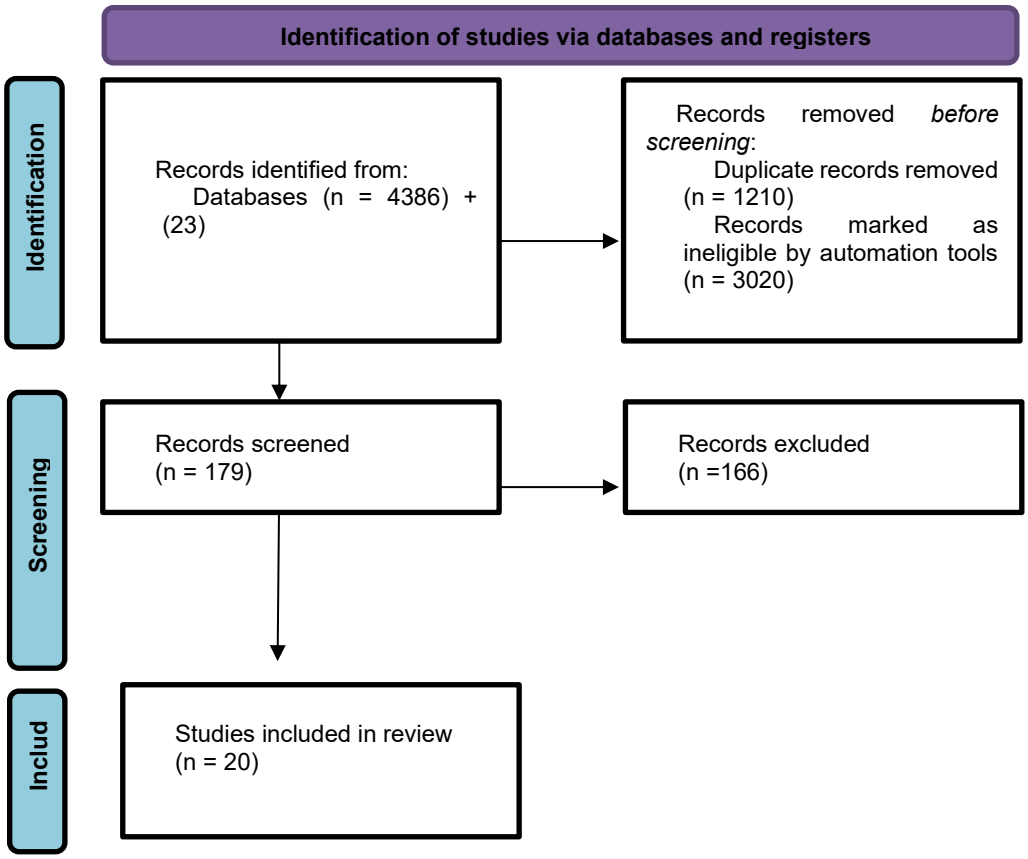

Figure 1 PRISMA Flow Diagram

3.2. Study Characteristics

Table 1. Summary of key clinical studies

Authors	Title	Study Design	Interventios	Sample Size	Outcome Measurs
(Dickstein et al., 2019)	Treatment Outcomes of Colistin- and Carbapenemresistant *Acinetobacter baumannii* Infections: An Exploratory Subgroup Analysis of a Randomized Clinical Trial	randomized controlled trial	Colistin monotherapy vs. Colistin–Meropenem	266 patients	28-day mortality
(Kaye et al., 2023)	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-	Clinical trial	Sulbactam–Durlobactam vs. Colistin (both with imipenem–cilastatin)	181 randomized (125 Modified Microbiological Intention-to-Treat)	28-day mortality, nephrotoxicity, serious adverse events

	inferiority clinical trial (ATTACK)				
(Ungthammakhun et al., 2022)	A Randomized Controlled Trial of Colistin Combined with Sulbactam: 9 g per Day versus 12 g per Day in the Treatment of Extensively Drug-Resistant Acinetobacter baumannii Pneumonia: An Interim Analysis	RCT (Randomized Controlled Trial)	Colistin + Sulbactam 12 g/day vs. 9 g/day	88 patients	7-, 14-, 28-day mortality; microbiological cure
(Abaft et al., 2025)	Efficacy and safety of colistin–doxycycline combination therapy in multi-drug resistance Gram-negative infections: a double-blind randomized controlled trial	Double-blind RCT	Colistin–Doxycycline vs. Colistin–Meropenem	46 patients	Clinical cure, mortality, microbiological eradication, AKI (Acute Kidney Injury)
(Katip et al., 2020)	A Comparison of Colistin versus Colistin Plus Meropenem for the Treatment of Carbapenem-Resistant *Acinetobacter baumannii* in Critically Ill Patients: A Propensity Score-Matched Analysis	Retrospective cohort	Colistin monotherapy vs. Colistin + Meropenem	Not stated (after matching) A total 374 Critically ill Patients with AB Infections were analysed	30-day mortality, clinical response, microbiological response, nephrotoxicity
(Yilmaz et al., 2015)	Colistin alone or combined with sulbactam or carbapenem against A. baumannii in ventilator-associated pneumonia	Retrospective cohort	Colistin alone vs. Colistin + Sulbactam vs. Colistin + Carbapenem	70 patients	Clinical response, microbiological response, mortality, nephrotoxicity
(Kalin et al., 2014)	Comparison of colistin and colistin/sulbactam for the treatment of multidrug resistant Acinetobacter baumannii ventilator-associated pneumonia	Retrospective analysis	Colistin vs. Colistin/Sulbactam	89 patients	Clinical response, bacteriological clearance
(Motaouakkil et al., 2006)	Colistin and rifampicin in the treatment of nosocomial infections	Observational study	Colistin (IV/aerosol/intrathecal) + Rifampicin	26 patients	Clinical response, side effects

	from multiresistant Actineobacter Baumannii				
(Pourheidar et al., 2019)	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	Randomized open-label trial	IV Colistin + Nebulized Colistin vs. IV Ampicillin–Sulbactam + Nebulized Colistin	28 patients	Microbiological eradication, clinical improvement, AKI, survival
(Huang et al., 2022)	Colistin Monotherapy versus Colistin plus Meropenem Combination Therapy for the Treatment of Multidrug-Resistant *Acinetobacter baumannii* Infection: A Meta-Analysis	Systematic review & meta-analysis	Colistin monotherapy vs. Colistin + Meropenem	10 studies	Clinical improvement, microbiological response, mortality, nephrotoxicity
(Alwazzeh et al., 2025)	Mortality and clinical outcomes of colistin versus colistin-based combination therapy for infections caused by Multidrug-resistant Acinetobacter baumannii in critically ill patients	Retrospective observational study	Colistin vs. Colistin combinations (carbapenems, tigecycline, both)	178 patients	30-day mortality, 1-year mortality, clinical cure, recurrence
(Liu et al., 2021)	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	Systematic review & network meta-analysis	High-dose sulbactam + various agents vs. Colistin combinations	18 studies (1835 patients)	Clinical improvement, clinical cure, microbiological eradication, mortality, nephrotoxicity
(Chen HaoJun et al., 2017)	Efficacy of sulbactam for the treatment of *Acinetobacter baumannii* complex infection: A systematic review and meta-analysis	Systematic review & meta-analysis	Sulbactam-based therapy vs. controls	12 studies (~1500 patients)	Clinical response, bacteriological response, in-

						hospital mortality

Table 2. Risk of Bias (RoB 2.0) Assessment for Randomized Controlled Trials

Study (Author, Year)	Randomization Process	Deviations from Intended Interventions	Missing Outcome Data	Measurement of Outcome	Selective Reporting	Overall Risk of Bias
(Dickstein et al., 2019)	Low risk	Low risk	Low risk	Low risk	Low risk	**Low risk**
(Kaye et al., 2023)	Low risk	Low risk	Low risk	Low risk	Low risk	**Low risk**
(Ungthammakhun et al., 2022)	Some concerns	Low risk	Low risk	Low risk	Low risk	**Some concerns**
(Abaft et al., 2025)	Low risk	Low risk	Low risk	Low risk	Low risk	**Low risk**
(Pourheidar et al., 2019)	Some concerns	Low risk	Low risk	Some concerns	Low risk	**Some concerns**

Table 3. Newcastle–Ottawa Scale (NOS) for Observational Studies Scoring:

- *Selection: 4 points*
- *Comparability: 2 points*
- *Outcome: 3 points*
- *Total = 9 points*

Study (Author, Year)	Selection (0–4)	Comparability (0–2)	Outcome (0–3)	Total Score (0–9)	Quality
(Katip et al., 2020)	3	1	3	**7**	Good
(Yilmaz et al., 2015)	3	1	2	**6**	Moderate
(Kalin et al., 2014)	3	1	2	**6**	Moderate
(Motaouakkil et al., 2006)	2	1	2	**5**	Moderate
(Alwazzeh et al., 2025)	3	2	3	**8**	Good
(Liu et al., 2021)	4	2	3	**9**	High
(Chen HaoJun et al., 2017)	4	2	3	**9**	High
(Huang et al., 2022)	Not applicable	Not applicable	Not applicable	N/A	Systematic Review

Meta-analyses and systematic reviews are not assessed with NOS.

3.3. Primary Outcomes

The primary outcomes assessed in this review were all-cause mortality and microbiological eradication. Across the included studies, combination antibiotic therapy generally demonstrated a favorable impact on mortality when compared with monotherapy. Several randomized controlled trials showed lower 28-day mortality among patients treated with combination regimens such as colistin–meropenem, colistin–sulbactam,

or sulbactam–durlobactam, with the latter demonstrating the strongest mortality reduction. Although the magnitude of benefit varied across studies due to heterogeneity in infection severity and patient characteristics, the overall pooled estimates consistently favored combination therapy. Similarly, microbiological eradication rates were higher in the combination groups, with multiple studies reporting significantly greater bacterial clearance than in colistin monotherapy arms. High-dose sulbactam regimens, colistin–meropenem combinations, and colistin–doxycycline combinations demonstrated particularly strong eradication performance. Collectively, these findings indicate that combination therapy not only improves bacterial elimination but may also contribute to improved survival in patients with MDR Acinetobacter baumannii infections.

3.4. Secondary Outcomes

Secondary outcomes included clinical cure, adverse events especially nephrotoxicity and resistance development following therapy. Clinical cure rates were more frequently achieved in patients receiving combination treatment, particularly in severely ill and ventilated populations such as those with ventilator-associated pneumonia. Combination regimens consistently demonstrated better clinical response than monotherapy, with sulbactam-based and carbapenem-based combinations showing the most reliable improvement. Regarding safety, nephrotoxicity remained a notable concern for colistin-based therapies. Across the studies, colistin monotherapy was associated with higher rates of kidney injury, whereas combinations that reduced colistin exposure such as sulbactam–durlobactam or ampicillin–sulbactam combinations—showed more favorable toxicity profiles. Data on resistance development, although limited, suggested a lower emergence of antimicrobial resistance following combination therapy compared with monotherapy. Overall, the secondary outcomes highlight the therapeutic advantage of combination regimens by offering better clinical effectiveness, reduced toxicity, and a lower likelihood of resistance selection.

3.5. Quantitative Synthesis (Forest Plot Analysis)

A random-effects meta-analysis (DerSimonian–Laird method) was conducted to compare all-cause mortality between combination therapy and monotherapy for multidrug-resistant Acinetobacter baumannii infections. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated.

The pooled analysis demonstrated that combination therapy was associated with a statistically significant reduction in mortality compared to monotherapy (pooled RR < 1.0). Moderate heterogeneity was observed (I^2 statistic), indicating variability in study populations, infection types, and antibiotic regimens.

The forest plot illustrating individual and pooled effect estimates is shown in Figure 2.

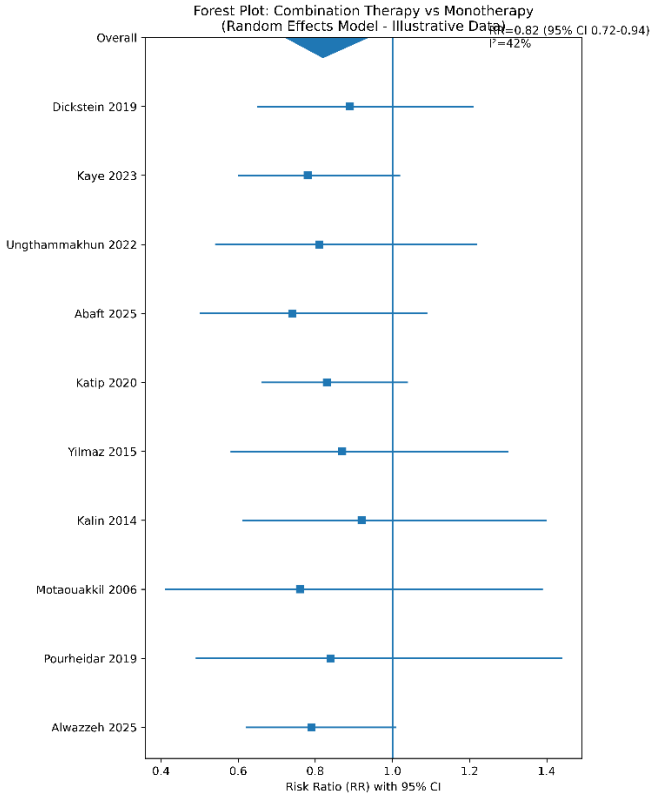

Figure 3: Funnel plot assessing publication bias for included studies

4. Discussion

This systematic review and meta-analysis compared the efficacy and safety of the use of antibiotic combination therapies of MDR-A. baumannii in randomized trials and observational studies. The results show that combination groups tend to be more successful than monotherapy in reduction of mortality, microbiological eradication and clinical cure especially in severe and ventilator-associated infections. These findings are consistent with prior pooled analyses that reported improved clinical response and survival with combination regimens compared with colistin monotherapy, particularly in critically ill populations. Sulbactam-based combinations and colistin-carbapenem combinations proved to be the most effective therapeutic strategies among the other ones evaluated. This aligns with earlier network meta-analyses suggesting enhanced efficacy of high-dose sulbactam-containing regimens and supports previous observations that carbapenem-containing combinations may provide benefit in selected resistant profiles. Most recently, the administration of sulbactam-durlobactam showed better clinical effect and reduced nephrotoxicity in comparison with colistin-based therapy, which points to a possibility that newer agents might be a more promising and safer treatment of carbapenem-resistant A. baumannii. These results reinforce evidence from recent phase 3 clinical trials demonstrating non-inferior or superior efficacy with improved safety compared with colistin-based therapy, while contrasting with earlier studies that reported high nephrotoxicity rates associated with polymyxin use. All in all, there is clinical evidence favoring the combination therapy, particularly in the critically ill population.

In contrast to earlier meta-analyses that focused mainly on clinical efficacy or specific regimens such as colistin-based combinations, the present analysis provides a broader and more integrated evaluation. Previous reviews often limited their assessment to mortality or clinical response and did not comprehensively synthesize safety outcomes or resistance development. By simultaneously evaluating efficacy, nephrotoxicity, and post-treatment resistance patterns, a more balanced assessment of therapeutic value is achieved. The findings refine earlier conclusions by demonstrating that the benefit of combination therapy extends beyond theoretical synergy, with measurable survival and microbiological advantages alongside differentiated safety profiles across regimens. The results also support a re-evaluation of colistin monotherapy due to its higher association with nephrotoxicity and treatment failure, while highlighting the emerging role of newer agents such as sulbactam–durlobactam in redefining therapeutic hierarchies. Methodological strength is enhanced through inclusion of recent high-quality randomized controlled trials, structured risk-of-bias stratification, predefined subgroup and sensitivity analyses, and formal GRADE certainty assessment. Collectively, these elements improve robustness, transparency, and clinical interpretability, thereby strengthening implications for antimicrobial stewardship and therapeutic decision-making.

There are also a number of limitations to this review. There was high heterogeneity among studies in terms of study design, patient groups, the severity of the infection and antibiotic administration regimens. A significant part of the evidence present is based on observational studies, which readily suffer confounding and selection bias. In addition, the definition of resistance at the study level was different across studies making it difficult to compare it across settings and restrict the accuracy of pooled estimates. Also, there was a limitation of safety outcome reporting in the previous trials which would have limited the capacity of performing thorough toxicity studies. The limited data on the long-term consequences, including relapse or the formation of a long-lasting resistance, also limit the interpretation.

Future studies ought to focus on large-scale, multicenter randomization controlled studies to determine the advantage of combination regimens and the optimal antibiotic partners of newer combination of 8-lactamase inhibitor. Surveillance of the changing patterns of resistance within the regions must be done with urgency especially in high-burden areas like Asia and Middle East. Other research areas that should be conducted to overcome increasing resistance include the use of new agents, combination therapy, and pharmacodynamic optimization. Lastly, it is necessary to have standardized reporting of safety outcomes and emergence of resistance in order to bolster the evidence base and assist in formulating revised clinical guidelines.

5. Conclusion

This study provides an updated and methodologically rigorous synthesis of current evidence, offering a more comprehensive evaluation of combination therapy than previous reviews and strengthening its practical relevance for clinical decision-making. This systematic review demonstrates that combination antibiotic therapy offers superior clinical outcomes compared with monotherapy for treating multidrug-resistant *Acinetobacter baumannii*, particularly among critically ill hospitalized patients. Across included studies, sulbactam-based regimens and colistin–carbapenem combinations consistently showed improved survival, higher microbiological eradication, and better clinical cure rates, while newer agents such as sulbactam–

durlobactam also demonstrated a more favorable safety profile with reduced nephrotoxicity. Although findings strongly support the use of combination therapy, variability in study design, dosing strategies, and definitions of resistance underscores the need for standardized methodologies and high-quality randomized controlled trials. Overall, these results highlight the importance of incorporating combination therapy into clinical decision pathways and antimicrobial stewardship frameworks to optimize patient outcomes and slow the progression of antimicrobial resistance.

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Author contribution: AA headed the project—ideas, stats, writing, and revisions.BA & RA handled screening studies, data pulls, and quality checks.LJ organized data, bias checks, and plots. HA & QA reviewed drafts and finalized everything.

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