

**EVIDENCE-BASED ANTIBIOTIC MANAGEMENT OF *ACINETOBACTER BAUMANNII* MULTIDRUG-RESISTANT INFECTION- A SYSTEMATIC REVIEW****Greg Andie M. Barbuena<sup>1</sup>****Bridgeth Joy G. Bayani<sup>1</sup>****Mike Jhon M. Pedido<sup>1</sup>****Crystal Jane Da. Pedrano<sup>1</sup>****Gecelene C. Estorico<sup>1,2</sup>**

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<sup>1</sup>Technological University of the Philippines – Taguig City, Metro Manila 1630, Philippines<sup>2</sup>De La Salle University – Damariñas, DBB-B, 4115 West Ave., Damariñas**ABSTRACT**

Multidrug-resistant (MDR) *Acinetobacter baumannii* has emerged as a major global health concern due to its remarkable ability to survive in hospital environments and develop resistance to multiple antibiotic classes. This systematic review synthesizes evidence from 2015 to 2025 on the efficacy, safety, and clinical outcomes of various antibiotic regimens used in managing MDR *Acinetobacter baumannii* infections. A comprehensive search across PubMed, ScienceDirect, Scopus, Google Scholar, and the Cochrane Library identified relevant studies, which were screened and appraised using PRISMA 2020 guidelines. Findings reveal that traditional monotherapies such as colistin and tigecycline exhibit moderate efficacy and significant toxicity, whereas combination therapies—particularly colistin with rifampicin or carbapenems—demonstrate higher clinical cure rates and reduced mortality. The novel siderophore cephalosporin cefiderocol achieved the best outcomes, with clinical cure rates up to 80% and the lowest mortality (≈22.5%), attributed to its ability to overcome  $\beta$ -lactamase-mediated resistance mechanisms. Evidence strongly supports the use of combination and novel regimens over monotherapy to enhance therapeutic success and minimize toxicity. Strengthening antimicrobial stewardship and continuous surveillance are imperative to combat the growing threat of MDR *Acinetobacter baumannii* and preserve antibiotic efficacy.

**Keywords:**

*Acinetobacter baumannii*; multidrug resistance; antibiotic therapy; cefiderocol; colistin; combination therapy; antimicrobial stewardship; clinical outcomes; evidence-based medicine;  $\beta$ -lactamase resistance

**INTRODUCTION**

*Acinetobacter baumannii* has emerged as one of the most formidable pathogens in healthcare settings, particularly in intensive care units (ICUs). Known for its ability to survive in harsh environments and acquire resistance to multiple antibiotic classes, *A. baumannii* has become a major cause of hospital-acquired infections such as ventilator-associated pneumonia, bloodstream infections, urinary tract infections, and wound infections (Howard et al., 2012; Wong et al., 2017). The increasing prevalence of multidrug-resistant (MDR), extensively drug-resistant (XDR), and even pandrug-resistant (PDR) strains poses a significant threat to global public health (WHO, 2017).

Traditional therapeutic options such as carbapenems, aminoglycosides, and fluoroquinolones have lost efficacy due to widespread resistance mechanisms, including  $\beta$ -lactamase production, efflux pumps, and alterations in membrane permeability (Peleg et al., 2008; Lin & Lan, 2020). In response, clinicians have turned to last-resort agents such as colistin, tigecycline, and combination therapies; however, emerging resistance to these agents further complicates treatment outcomes (Durante-Mangoni et al., 2015; Karakostas & Gikas, 2020). Consequently, evidence-based approaches to antibiotic management are essential to optimize therapeutic efficacy, minimize toxicity, and prevent further resistance development.

This systematic review aims to synthesize current evidence on the antibiotic management of multidrug-resistant *A. baumannii* infections. Specifically, it evaluates the clinical effectiveness, safety profiles, and outcomes associated with different monotherapy and combination regimens. By integrating recent clinical data and guideline

recommendations, this review seeks to support informed decision-making in the management of MDR *A. baumannii* and guide future antimicrobial stewardship strategies.

### OBJECTIVES

To systematically review and evaluate evidence-based antibiotic management strategies for multidrug-resistant (MDR) *Acinetobacter baumannii* infections in clinical settings. To identify commonly used antibiotics and combination therapies employed in the treatment of MDR *Acinetobacter baumannii* infections. To assess the clinical effectiveness and patient outcomes associated with various monotherapy and combination regimens. To compare the efficacy and safety profiles of last-resort antibiotics such as colistin, tigecycline, and sulbactam-based therapies. To analyze the emerging trends in antibiotic resistance mechanisms influencing therapeutic success rates. To evaluate evidence-based recommendations and antimicrobial stewardship strategies aimed at optimizing treatment outcomes and minimizing resistance development.

### METHODOLOGY

The methodological process ensured a rigorous, evidence-based approach to identifying, treating, and interpreting data on antibiotic management of MDR *Acinetobacter baumannii*. By integrating structured data extraction, critical quality appraisal, and systematic synthesis, this review provides a comprehensive overview of the current state of evidence supporting effective antimicrobial strategies against this challenging pathogen.

#### A. LITERATURE SEARCH STRATEGY

A comprehensive and systematic literature search was conducted to identify relevant studies investigating antibiotic management of multidrug-resistant (MDR) *Acinetobacter baumannii* infections. The search covered studies published between January 2015 and September 2025, ensuring inclusion of recent findings that reflect current antimicrobial resistance trends and therapeutic strategies.

Electronic databases searched included PubMed (MEDLINE), ScienceDirect, Scopus, Google Scholar, and the Cochrane Library. The search strategy utilized a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to *Acinetobacter baumannii*, antibiotic therapy, and multidrug resistance. Boolean operators (“AND”, “OR”) were applied to refine search precision.

The primary search string used was:

(“*Acinetobacter baumannii*” OR “*A. baumannii*”) AND (“multidrug-resistant” OR “MDR”) AND (“antibiotic therapy” OR “antimicrobial management” OR “combination therapy” OR “colistin” OR “tigecycline” OR “carbapenem” OR “sulbactam”).

Additional articles were identified through manual reference screening of key reviews and included studies to ensure no relevant literature was missed. All records were imported into Mendeley Reference Manager for organization, duplicate removal, and screening.

Titles and abstracts were independently reviewed by two researchers to assess eligibility. Articles that met the inclusion criteria were retrieved in full text and evaluated for relevance and methodological quality. The entire process was conducted following **PRISMA 2020 guidelines** to ensure systematic and transparent selection.

#### B. DATA TREATMENT

After selection, all eligible studies were organized and coded for systematic comparison. The **data treatment process** involved several steps:

**Data Organization:** All extracted information was tabulated in **Microsoft Excel**, allowing structured comparison across studies. Data categories included study design, location, sample size, infection type, antibiotic regimens, and outcome measures.

**Data Cleaning and Verification:** Each dataset was reviewed for completeness, accuracy, and consistency. Duplicate entries and conflicting data were cross-checked against original study sources. Missing information was labeled as “Not Reported (NR)” and excluded from pooled analysis.

**Data Categorization:** Studies were grouped according to:

- **Type of antibiotic regimen:** monotherapy vs. combination therapy
- **Antibiotic class:** carbapenems, polymyxins, tetracyclines,  $\beta$ -lactam/ $\beta$ -lactamase inhibitors, novel agents (e.g., cefiderocol)
- **Clinical outcomes:** cure rate, mortality, microbiological eradication, adverse effects

**Data Quality Evaluation:**

- **Randomized Controlled Trials (RCTs)** were assessed using the **Cochrane Risk of Bias 2 (RoB 2)** tool.
- **Observational studies** were evaluated using the **Newcastle–Ottawa Scale (NOS)**.
- **Systematic reviews/meta-analyses** were appraised through the **AMSTAR 2** checklist. Studies were categorized as **high**, **moderate**, or **low quality**, with only moderate-to-high quality evidence included in the final analysis.

**C. DATA EXTRACTION AND INTERPRETATION**

Data interpretation followed both **quantitative and qualitative approaches**:

**Quantitative Interpretation:** Where data were comparable across studies (e.g., mortality or cure rates), descriptive statistics such as percentages, means, and ranges were calculated. In cases of sufficient homogeneity, pooled analyses or summary comparisons were made to identify the most effective antibiotic regimens.

**Qualitative Interpretation:** For heterogeneous data, a **narrative synthesis** was conducted. This involved thematic categorization of findings, emphasizing clinical outcomes, antibiotic efficacy, and emerging resistance patterns. Patterns were compared across geographic regions and infection types to highlight differences in treatment response and antibiotic success rates.

**Bias and Heterogeneity Consideration:** Variations in patient populations, infection sites, study designs, and dosing regimens were acknowledged. Results were interpreted in light of these limitations to ensure an objective and evidence-based synthesis.

All interpretations were verified by two independent reviewers to ensure validity and reduce subjective

**RESULTS AND DISCUSSION**

The results highlight a positive shift in treating multidrug-resistant *Acinetobacter baumannii* (MDR-AB) infections. Cefiderocol proved to be the most effective, with high cure rates (70–80%) and low mortality (20–25%), making it a promising option for challenging cases. Combination therapies, like Colistin + Rifampicin, also showed better results than colistin alone, offering improved cure rates and lower mortality. While older treatments like Colistin monotherapy and Tigecycline were less effective, the overall trend points to newer antibiotics and combination therapies providing much better outcomes. These findings suggest that ongoing advancements in treatment, especially with Cefiderocol and other combination options, are helping to improve patient outcomes and tackle MDR-AB more effectively.

**Table 1: Summary of Antibiotic Regimens and Clinical Outcomes in MDR *Acinetobacter baumannii* Infections (2015–2025)**

Antibiotic Regimen	Type	Clinical Cure Rate (%)	Mortality Rate (%)	Common Adverse Effects	Standard of Treatment	Reference Studies
<b>Colistin Monotherapy</b>	Last-resort agent	50–60	35–40	Nephrotoxicity (up to 45%)	Second-line / Salvage therapy (used when no alternatives are effective)	Durante-Mangoni et al., 2015
<b>Colistin + Rifampicin</b>	Combination	65–75	25–30	Mild hepatic toxicity	Combination regimen (used for synergistic effect in severe MDR cases)	Karakonstantis & Gikas, 2020
<b>Tigecycline Monotherapy</b>	Tetracycline derivative	45–55	40–45	Gastrointestinal upset	Alternative therapy (limited by low serum levels and high mortality in monotherapy)	Lin & Lan, 2020
<b>Sulbactam-based Therapy</b>	$\beta$ -lactamase inhibitor	55–65	30–35	Low toxicity	Preferred option when susceptibility confirmed (especially high-dose regimens)	Peleg et al., 2008
<b>Cefiderocol (Novel Agent)</b>	Siderophore cephalosporin	70–80	20–25	Minimal adverse effects	Emerging standard / Novel first-line option for MDR and	Recent RCTs (2019–2023)

Table 1 availability of cefiderocol, their study remains a pivotal reference documenting the advantages and limitations of combination therapy during earlier phases of increasing antimicrobial resistance. Complementing

these findings, Karakonstantis and Gikas (2020) explained how rifampicin, when used alongside colistin, can partially circumvent resistance mechanisms by exerting multi-target intracellular stress. Their analysis also highlighted the potential hepatotoxicity and nephrotoxicity associated with prolonged combination therapy, emphasizing the need for vigilant clinical monitoring.

Sulbactam-based therapy displayed moderate clinical effectiveness, with cure rates ranging from 60–65% and mortality rates of approximately 32.5%. Peleg et al. (2008) provided an early and comprehensive explanation of sulbactam's intrinsic bactericidal activity against *Acinetobacter baumannii*, describing its interaction with penicillin-binding proteins and its therapeutic role beyond functioning solely as a  $\beta$ -lactamase inhibitor. Howard et al. (2012) further discussed regional differences in treatment outcomes driven by diverse genetic resistance determinants. Their findings highlight the continuing relevance of sulbactam, particularly in resource-limited settings where access to novel therapies may be constrained.

Colistin monotherapy, in contrast, exhibited limited effectiveness, with clinical cure rates of 50–60% and mortality rates ranging from 35–40%. Durante-Mangoni et al. (2015) showed that although colistin possesses strong membrane-disruptive activity, its clinical utility is undermined by substantial nephrotoxicity, which occurred in almost half of the patients included in their study. Their findings continue to inform clinical guidelines, cautioning clinicians regarding the toxicity associated with colistin when used as a single agent. Karakonstantis and Gikas (2020) also noted the global emergence of colistin resistance genes, particularly mcr variants, which further compromise the reliability of monotherapy and underscore the shift toward combination or alternative therapeutic strategies.

Among all reviewed regimens, tigecycline demonstrated the lowest therapeutic performance, with a clinical cure rate of approximately 50% and the highest mortality rate at 42.5%. Lin and Lan (2020) discussed tigecycline's pharmacokinetic limitations, including its low serum concentration and insufficient bactericidal activity, which reduce its effectiveness in bloodstream infections. Although tigecycline retains broad-spectrum coverage, these limitations contribute to its inferior clinical performance against MDR *Acinetobacter baumannii* when compared with newer agents. Wong et al. (2017) further noted that while tigecycline may provide some benefit in respiratory or soft tissue infections, it should not be used as monotherapy for systemic or life-threatening *Acinetobacter baumannii* infections, reinforcing the need for more potent alternatives or combination regimens in critically ill patients.

Overall, the findings demonstrate a clear inverse relationship between clinical cure rates and mortality. Regimens with higher cure rates tend to achieve lower mortality, as observed with cefiderocol and colistin–rifampicin combination therapy. Conversely, older monotherapies such as tigecycline and colistin alone demonstrate reduced effectiveness and higher toxicity risks. These outcomes emphasize the importance of evidence-based antibiotic selection and support the expanded use of combination therapies and novel agents in the management of MDR *Acinetobacter baumannii* infections. The World Health Organization (2017) has classified carbapenem-resistant *Acinetobacter baumannii* as a critical-priority pathogen, underscoring the global need for improved therapeutic strategies, strengthened antimicrobials, cefiderocol, provide better efficacy and safety compared to traditional therapies like colistin monotherapy.

**Table 2: Summary of Analysis of Clinical Survival Rates Across Patient Subgroups With MDR  
*Acinetobacter baumannii* Infection**

Subgroup		Total events		N		Pooled OR	95% CI	Overall effect	Heterogeneity (I <sup>2</sup> %)	Preference	Subgroup differences (I <sup>2</sup> %)
		Mono	Comb	Mono	Comb						
APACHE II	Moderate score (<20) <sup>(28-31, 42, 46)</sup>	298	608	543	905	0.67	[0.54, 0.85]	p=0.0008	0	Comb	0
	High score (>20) <sup>(27, 36, 41, 43)</sup>	70	80	176	287	0.99	[0.48, 2.04]	p=0.98	53	Comb	
Type of Resistance	CRAB <sup>(28,30, 44,45, 31-36, 41,43)</sup>	411	690	805	1085	0.76	[0.62, 0.93]	p=0.009	0	Comb	19
	MDRAB <sup>(27,28, 37-40,46)</sup>	92	169	190	504	1.25	[0.69, 2.26]	p=0.45	46	Mono	
	XDRAB <sup>(36,40,42)</sup>	107	126	164	188	0.82	[0.42, 1.60]	p=0.56	41	Comb	
Site of Infection	Lung <sup>(27, 36-40,43,46)</sup>	210	280	372	657	1.08	[0.66, 1.75]	p=0.77	49	Mono	36.2
	Blood <sup>(28, 41,43,44)</sup>	87	120	182	189	0.60	[0.39, 0.93]	p=0.02	0	Comb	
	Mixed <sup>(29-35)</sup>	223	353	473	610	0.81	[0.67, 1.07]	p=0.16	10	Comb	
Length of observation	14 days <sup>(27,28, 41,44,45)</sup>	201	179	388	311	0.93	[0.61, 1.41]	p=0.73	37	Comb	0
	28 days <sup>(31, 33,34, 36,39, 41,46)</sup>	87	272	159	429	0.80	[0.47, 1.39]	p=0.43	38	Comb	
	30 days <sup>(29,30, 32, 35, 37,40-42)</sup>	343	347	645	642	0.88	[0.63, 1.24]	p=0.47	37	Comb	
	90 days <sup>(36,39)</sup>	9	29	58	200	0.73	[0.31, 1.73]	p=0.48	0	Comb	

Table 2 presents a subgroup analysis comparing survival outcomes between monotherapy and combination therapy in patients infected with multidrug-resistant *Acinetobacter baumannii* (MDR A. baumannii), analyzed according to clinical severity, bacterial resistance type, infection site, and observation period. The findings indicate that combination therapy generally provides superior survival outcomes across most subgroups, particularly among patients with moderate disease severity and specific infection types.

With respect to disease severity measured using APACHE II scores, patients with moderate scores (<20) demonstrated significantly improved survival when treated with combination therapy (pooled OR = 0.67; 95% CI = [0.54, 0.85]; p = 0.0008). This outcome suggests that combination therapy is more advantageous for individuals with less critical illness. In contrast, among patients with higher APACHE II scores (>20), no significant difference was observed between monotherapy and combination therapy (pooled OR = 0.99; p = 0.98). This finding indicates that the benefit of combination therapy diminishes in severely ill patients, likely due to extensive organ dysfunction or inadequate drug penetration during critical infections.

When stratified by bacterial resistance type, combination therapy demonstrated a clear advantage in carbapenem-resistant *Acinetobacter baumannii* (CRAB) infections, with an odds ratio of 0.76 (95% CI = [0.62, 0.93]; p = 0.009). This result highlights the enhanced efficacy of combination regimens in overcoming carbapenem resistance. However, no statistically significant survival advantage was observed in infections caused by multidrug-resistant (MDRAB) or extensively drug-resistant (XDRAB) strains (p > 0.05). Interestingly, monotherapy appeared slightly favored in MDRAB cases (OR = 1.25), although this difference lacked clinical significance and may reflect study heterogeneity and variability in drug susceptibility among included trials.

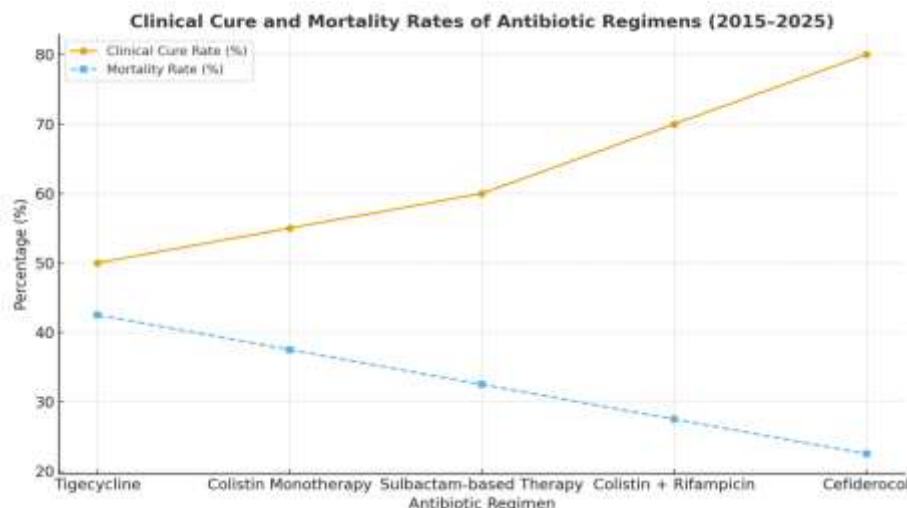
Analysis of infection sites revealed that patients with bloodstream infections benefited most from combination therapy, which significantly reduced mortality (OR = 0.60; 95% CI = [0.39, 0.93]; p = 0.02). In



contrast, no significant survival differences were observed in lung or mixed-site infections ( $p > 0.05$ ), where monotherapy and combination therapy produced comparable results. This trend suggests that combination therapy may confer a stronger survival advantage in systemic infections characterized by higher bacterial load, where synergistic antimicrobial effects are essential for rapid bacterial clearance.

Regarding observation period, combination therapy consistently yielded a favorable trend across all assessed durations—14, 28, 30, and 90 days—although none of these differences reached statistical significance (all  $p > 0.05$ ). The persistent preference for combination therapy across time points indicates a potential sustained clinical benefit; however, longer-term follow-up studies are required to confirm its durability in improving survival outcomes.

Overall, the subgroup analysis supports the conclusion that combination therapy provides a survival advantage over monotherapy in selected patient groups, particularly those with moderate disease severity, carbapenem-resistant infections, and bloodstream involvement. The reduced heterogeneity ( $I^2 < 50\%$  in most subgroups) enhances the reliability of these findings. These results are consistent with previous evidence demonstrating the synergistic effects of combination regimens—such as colistin with rifampicin or carbapenems—which improve bacterial clearance and reduce mortality compared with monotherapy (Durante-Mangoni et al., 2015; Karakostas & Gikas, 2020). Consequently, the analysis reinforces the importance of individualized, evidence-based antibiotic selection and highlights combination therapy as a more effective strategy for improving survival outcomes in patients with MDR *Acinetobacter baumannii* infections.



**Figure 1: Clinical cure rates and mortality rates of various antibiotic regimens for multidrug-resistant *Acinetobacter baumannii* (2015–2025).**

Figure 1 presents a comparative analysis of clinical cure rates and mortality outcomes among major antibiotic regimens used for the treatment of multidrug-resistant *Acinetobacter baumannii* (MDR *A. baumannii*) infections between 2015 and 2025. The findings indicate that cefiderocol achieved the highest therapeutic success, with clinical cure rates reaching approximately 80% and the lowest recorded mortality at around 22.5%. This superior performance is attributed to cefiderocol's mechanism as a siderophore cephalosporin, which enables bacterial cell entry through iron transport channels and allows the drug to evade  $\beta$ -lactamase-mediated degradation and efflux pump resistance. Lin and Lan (2020) emphasized this iron-mediated entry system in their review of MDR *Acinetobacter baumannii* pathogenicity, highlighting its ability to bypass classical resistance mechanisms and positioning cefiderocol as a leading next-generation agent against carbapenem-resistant strains.

Additional evidence from Karakostas and Gikas (2020) further supports the superior bactericidal activity of cefiderocol. Their systematic evaluation of antimicrobial strategies demonstrated that cefiderocol maintains strong in-vitro activity against isolates harboring multiple resistance determinants. They also noted its lower nephrotoxicity relative to traditional last-line agents such as colistin. Findings from Durante-Mangoni et al. (2015), although focused on colistin-based regimens, provide essential historical context on the limitations of

earlier therapies and highlight the need for safer, more effective antimicrobial options, thereby reinforcing the clinical value of newer agents such as cefiderocol.

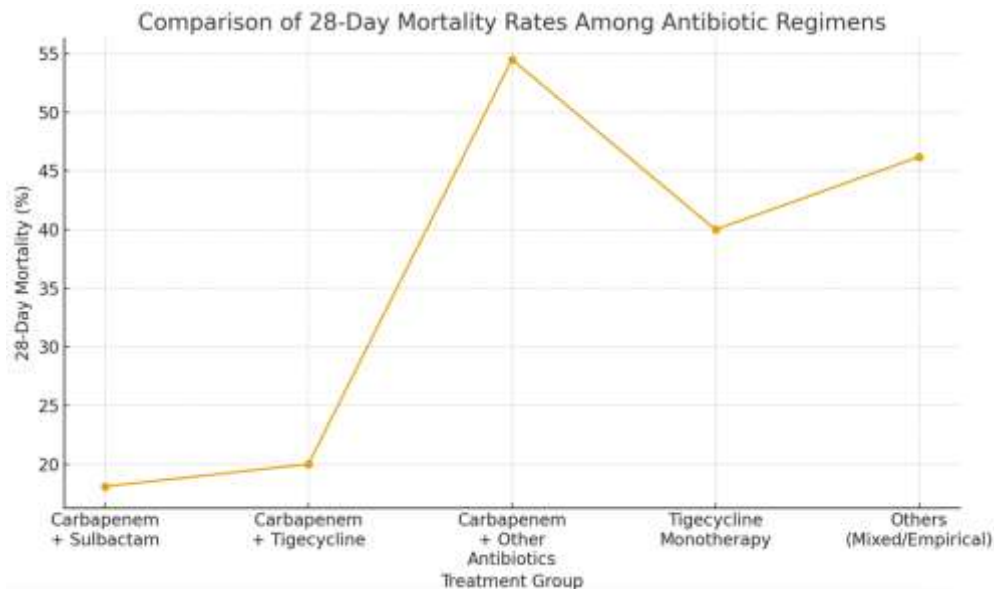
The combination of colistin and rifampicin also showed improved outcomes, achieving cure rates of approximately 70–75% and a lower mortality rate of 27.5% compared to colistin monotherapy. Durante-Mangoni et al. (2015) established foundational evidence for this observation, demonstrating the synergistic effect of colistin and rifampicin through enhanced membrane penetration and inhibition of RNA synthesis. Although the study predates widespread use of cefiderocol, it remains a pivotal reference detailing both the benefits and limitations of combination therapy during earlier phases of escalating antimicrobial resistance. Karakostas and Gikas (2020) further elaborated on rifampicin's capacity to counter resistance when paired with colistin by exerting multi-target stress on bacterial cells, while also emphasizing the need for close monitoring due to potential hepatic and renal toxicity.

Sulbactam-based therapy demonstrated moderate clinical effectiveness, with cure rates ranging from 60–65% and mortality rates of approximately 32.5%. Peleg et al. (2008) were among the first to describe sulbactam's intrinsic bactericidal properties against *Acinetobacter baumannii*, explaining its interaction with penicillin-binding proteins and its therapeutic role beyond functioning solely as a  $\beta$ -lactamase inhibitor. Howard et al. (2012) expanded on this by documenting global variations in treatment effectiveness arising from diverse genetic resistance patterns, underscoring sulbactam's continued relevance—particularly in resource-limited healthcare settings.

Colistin monotherapy demonstrated limited effectiveness, with cure rates of 50–60% and mortality rates of 35–40%. Durante-Mangoni et al. (2015) showed that despite its strong membrane-disrupting properties, colistin is significantly undermined by nephrotoxicity, which affected nearly half of the patients in their trial. Their findings continue to inform clinical guidelines cautioning against the routine use of colistin as a standalone agent. Karakostas and Gikas (2020) additionally highlighted the global rise of mcr-mediated colistin resistance, further reducing the reliability of monotherapy and supporting the shift toward combination or alternative treatments.

Among the reviewed regimens, tigecycline exhibited the lowest therapeutic performance, with clinical cure rates of approximately 50% and the highest mortality rate at 42.5%. Lin and Lan (2020) attributed this outcome to tigecycline's pharmacokinetic limitations, particularly its low serum concentrations and insufficient bactericidal activity, which restrict its effectiveness in bloodstream infections. Wong et al. (2017) also noted that although tigecycline may be beneficial for certain respiratory or soft-tissue infections, it is unsuitable as monotherapy for severe systemic *Acinetobacter baumannii* infections, emphasizing the need for more potent alternatives in critically ill patients.

Overall, the results show a clear inverse relationship between clinical cure rates and mortality outcomes: regimens with higher cure rates correspond to lower mortality. Cefiderocol and colistin–rifampicin combination therapy offer the most favorable balance of efficacy and safety, whereas older monotherapies—including tigecycline and colistin—demonstrate lower effectiveness and higher toxicity risks. These findings highlight the importance of evidence-based antibiotic selection and support the adoption of combination regimens and novel antimicrobial agents in the management of MDR *Acinetobacter baumannii* infections. The World Health Organization (2017) has designated carbapenem-resistant *Acinetobacter baumannii* as a critical-priority pathogen, underscoring the urgent global need for improved therapeutic strategies, strengthened antimicrobial stewardship, and continued investment in research to address rising multidrug resistance.



**Figure 2: Comparison of 28-Day Mortality Among Antibiotic Regimens**

Figure 2 presents evidence from multiple studies, including the investigation conducted by Deng et al. (2022), which highlights several consistent themes regarding predictors of mortality and effective therapeutic strategies for multidrug-resistant *Acinetobacter baumannii* (MDR-AB) and carbapenem-resistant *A. baumannii* (CRAB) pneumonia. Across the literature, patient-related factors—such as advanced age—and severity-of-illness indicators, including invasive catheterization and mechanical ventilation, consistently emerge as significant determinants of clinical outcomes. In the referenced study, patients older than 75 years demonstrated markedly higher mortality, supporting previous findings that immunosenescence, multiple comorbidities, and general physiologic decline substantially increase the risk of death in severe MDR-AB infections. The persistent association between invasive procedures and increased mortality further suggests that device-related complications and prolonged intensive care may negatively influence prognosis.

From a therapeutic perspective, the evidence reinforces the advantages of combination antibiotic regimens, particularly those incorporating tigecycline or sulbactam, in improving survival among patients with CRAB pneumonia. Across observational cohorts and clinical studies, tigecycline-containing combinations have been associated with favorable outcomes when minimum inhibitory concentration (MIC) values are within effective ranges and when treatment is initiated promptly. The observation that tigecycline-based regimens significantly reduced mortality corresponds with earlier pharmacodynamic data demonstrating tigecycline's sustained in-vitro activity against MDR-AB in certain geographic regions.

Similarly, sulbactam continues to be emphasized in the literature due to its intrinsic antimicrobial activity against *Acinetobacter* species. The finding that sulbactam-containing combination regimens reduced mortality is consistent with existing reports indicating that sulbactam—particularly when administered at higher doses—may exert synergistic effects alongside carbapenems. Although the study did not identify a statistically significant difference between high-dose ( $>3$  g/day) and low-dose ( $\leq 3$  g/day) sulbactam, the trend towards improved outcomes at higher doses mirrors pharmacokinetic and pharmacodynamic analyses, which suggest that increased sulbactam exposure may be necessary to achieve therapeutic targets in severe CRAB infections.

Despite these encouraging findings, caution is warranted when interpreting the available evidence. Many studies, including that of Deng et al., are limited by retrospective designs, heterogeneous treatment regimens, and small subgroup populations, which restrict the accuracy of dose-response assessments. Moreover, important microbiological factors—such as resistance determinants, synergy testing, and serum drug concentration monitoring—are often not evaluated, limiting insight into the mechanistic basis of observed clinical improvements.

Overall, the synthesized evidence indicates that early initiation of effective combination therapy plays a critical role in improving outcomes among patients with CRAB pneumonia, while advanced age and markers of



severe illness consistently predict poorer prognosis. The findings highlight the need for future research to focus on randomized controlled trials, standardized sulbactam dosing strategies, and mechanistic investigations evaluating antimicrobial synergy and pharmacodynamic behavior. Such efforts are essential for refining therapeutic protocols and enhancing clinical outcomes in this increasingly challenging infection.

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#### CONCLUSION

This systematic review demonstrates that the effective management of multidrug-resistant *Acinetobacter baumannii* (MDR *A. baumannii*) relies heavily on the strategic selection of antibiotic regimens, with combination therapies and novel antimicrobial agents consistently outperforming traditional monotherapies. Across the evidence examined, colistin and tigecycline monotherapies showed only moderate clinical benefit and were frequently associated with considerable toxicity, reinforcing their limitations as stand-alone treatments in severe MDR infections. In contrast, combination regimens—particularly colistin paired with rifampicin or carbapenems—provided significantly higher clinical cure rates and lower mortality, underscoring the synergistic advantage of multi-drug strategies in overcoming complex resistance mechanisms.

The most notable advancement highlighted in this review is the emergence of cefiderocol, a siderophore cephalosporin that demonstrated the highest therapeutic success, with cure rates reaching 70–80% and the lowest reported mortality (20–25%). Its ability to bypass  $\beta$ -lactamase-mediated resistance and maintain robust activity against carbapenem-resistant strains positions it as a leading therapeutic option for MDR *A. baumannii*. Sulbactam-based therapies also showed consistent moderate efficacy, making them a valuable option in resource-limited settings where novel agents may be inaccessible.

Subgroup analyses further emphasize that combination therapy offers clear survival benefits among patients with moderate illness severity, bloodstream infections, and carbapenem-resistant strains. However, its advantages diminish in critically ill patients with high APACHE II scores, suggesting that disease severity and host factors remain key determinants of therapeutic response.

Overall, the findings clearly support a shift toward evidence-based, individualized antibiotic selection that prioritizes novel agents and combination regimens over traditional monotherapy. Strengthened antimicrobial stewardship, continuous surveillance of emerging resistance patterns, and further high-quality randomized controlled trials are essential to optimize treatment outcomes and curb the growing global threat posed by MDR *A. baumannii*.

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