Published Online: 2026 February 12 **Research Article**

Combination Antibiotic Therapy with Colistin, Meropenem, and Ampicillin-Sulbactam for Carbapenem-Resistant *Acinetobacter* Infections: A Randomized Controlled Trial

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Received: 2 July, 2025; **Revised:** 3 January, 2026; **Accepted:** 31 January, 2026

Abstract

Background: Multidrug-resistant *Acinetobacter baumannii* infections present significant therapeutic challenges in intensive care unit (ICU) settings. Current evidence on optimal antimicrobial combinations remains limited.

Objectives: This randomized controlled trial aims to compare the efficacy of dual versus triple antibiotic therapy in critically ill patients with carbapenem-resistant *Acinetobacter* infections.

Methods: We conducted a single-center randomized controlled trial at Bohlool Hospital, Gonabad, Iran, between June 2024 and April 2025. Adult ICU patients with culture-confirmed carbapenem-resistant *A. baumannii* (CRAB) infections were randomly assigned (1:1) using block randomization to receive either dual therapy (colistin and ampicillin–sulbactam) or triple therapy (colistin, meropenem, and ampicillin–sulbactam). Outcome assessors were blinded to the treatment assignment. The primary outcome was 14-day clinical success. Secondary outcomes included 14- and 28-day mortality, final outcome, and hospital length of stay.

Results: At day 14, clinical success was achieved in 14/23 (60.9%) dual-therapy versus 19/23 (82.6%) triple-therapy patients (P = 0.102). By day 28, mortality was significantly lower in the triple-therapy group (34.8% vs 65.2%; P = 0.039). There was no significant difference in overall in-hospital mortality (dual: 65.2% vs triple: 73.9%; P = 0.522). Time to discharge among survivors did not differ (P = 0.155).

Conclusions: In this randomized controlled trial, adding meropenem to colistin and ampicillin–sulbactam was associated with reduced 28-day mortality in critically ill carbapenem-resistant *Acinetobacter* infections patients but did not significantly affect final outcome. Larger multicenter trials are warranted to confirm these findings and optimize combination regimens.

Keywords: Acinetobacter baumannii, Drug Resistance, Multiple, Drug Resistance, Bacterial, Colistin, Meropenem, Ampicillin-Sulbactam, Anti-bacterial Agents, Intensive Care Units, Randomized Controlled Trial

1. Background

The widespread and often inappropriate use of antibiotics has led to the global emergence of antimicrobial resistance, now recognized as a major public health threat by the World Health Organization (1-5). Infections caused by multidrug-resistant organisms result in significant morbidity, mortality, and economic burden (6-8). Among hospital-acquired infections, *Acinetobacter baumannii* has emerged as a

How to Cite: Mansouri M, Mardaneh J, Yahaei K, Ahrari Roodi Y, Sahebanmaleki M. Combination Antibiotic Therapy with Colistin, Meropenem, and Ampicillin-Sulbactam for Carbapenem-Resistant Acinetobacter Infections: A Randomized Controlled Trial. Jundishapur J Microbiol. 2026;19(2):e164182. doi: https://doi.org/10.5812/jjm-164182

particularly concerning pathogen, especially in intensive care unit (ICU) settings, due to its ability to persist in the hospital environment and acquire multiple resistance mechanisms (9, 10).

Acinetobacter baumannii is responsible for a wide range of infections including ventilator-associated pneumonia (VAP), bloodstream infections, urinary tract infections, meningitis, and wound infections (11, 12). The increasing prevalence of carbapenem-resistant *A. baumannii* (CRAB) is of particular concern, as carbapenems are often considered one of the last-line antibiotics (13-15). Resistance mechanisms in CRAB include production of β-lactamases (serine and metallo-β-lactamases), efflux pump overexpression, and reduced membrane permeability (9, 10, 16-18). These resistance factors significantly limit treatment options and are associated with poor clinical outcomes.

Recent regional data highlight the extent of the problem. In Southeast Asia, approximately 65% of *Acinetobacter* isolates from ICU-acquired infections were found to be carbapenem-resistant (19). In Iran, a systematic review showed that over half of clinical isolates were resistant to imipenem (20). In the absence of newer agents like cefiderocol — currently unavailable in Iran — treatment often relies on older agents such as colistin, frequently used in combination with meropenem or ampicillin-sulbactam (21-23). While in vitro studies suggest that certain combinations (e.g., colistin plus meropenem) may have synergistic effects, clinical evidence remains scarce and inconclusive. Furthermore, the potential for synergy in triple-drug treatments and the development of resistance during combination therapy are areas of ongoing research. However, there is limited high-quality clinical data to inform practice (24-26).

2. Objectives

To date, few randomized controlled trials (RCTs) have compared combination regimens in patients with CRAB infections. The relative efficacy of triple therapy (colistin+meropenem+ampicillin-sulbactam) compared to dual therapy (colistin+ampicillin-sulbactam) remains unclear. Addressing this gap is essential for optimizing treatment in critically ill patients with limited options. The present study aims to compare the treatment response and clinical outcomes of dual versus triple antibiotic regimens in ICU patients with carbapenem-resistant *Acinetobacter* infection.

3. Methods

3.1. Study Design and Setting

This was a single-center, randomized controlled trial conducted at Bohlool Hospital, Gonabad, Iran. Patient enrollment began in June 2024 and was completed in April 2025.

3.2. Eligibility Criteria

Patients were eligible if they were ≥ 18 years old, admitted to the ICU, and had a confirmed or suspected diagnosis of VAP, hospital-acquired pneumonia (HAP), urosepsis, or bloodstream infection. Diagnosis of pneumonia was based on CDC/NHSN criteria (27), requiring clinical signs (e.g., new infiltrate on imaging, fever, leukocytosis/leukopenia, respiratory symptoms) plus microbiological confirmation by isolation of *Acinetobacter* from sputum, tracheal aspirate, or bronchoalveolar lavage (BAL). Ventilator-associated pneumonia was diagnosed in mechanically ventilated patients within 48 hours prior to infection onset. Urosepsis was defined as a positive urine culture ($\geq 10^5$ CFU/mL) with pyuria and systemic inflammatory response syndrome (SIRS), in the absence of other infection sources. The isolation of CRAB from any infection site was also required. In the case of polymicrobial infections, susceptibility of the isolate to fluoroquinolones or any β-lactam antibiotics, prior colistin therapy > 96 hours, pregnancy, known allergy to colistin, meropenem, or ampicillin-sulbactam, and a history of carbapenem-induced seizures, the patient was not included in the study. Patients who died within 48 hours of antibiotic initiation were excluded from the final analysis.

3.3. Randomization and Blinding

Eligible patients were randomized using block randomization (blocks of four, 1:1 allocation) generated via Random Allocation Software. The sequence was managed by an independent researcher not involved in patient care. Participants were assigned to either the dual or triple therapy group using coded identifiers. Outcome assessors were blinded to group allocation.

3.4. Interventions

Patients in the dual therapy group received colistin and ampicillin-sulbactam. The triple therapy group received colistin, meropenem, and ampicillin-

sulbactam. Dosages were as follows: Colistin: Nine million IU loading dose, followed by 4.5 million IU every 12 hours (infused over 1 hour), adjusted for Glomerular Filtration Rate (GFR) (28); meropenem: Two g every 8 hours (3-hour infusion), adjusted for GFR (29); ampicillin-sulbactam: Three g every 6 hours, adjusted for GFR (30). Concomitant antimicrobial therapy for non-*Acinetobacter* pathogens (e.g., gram-positive, fungal, or anaerobic) was permitted as clinically indicated. The dual therapy regimen (colistin+ampicillin-sulbactam) was selected based on common practice and the intrinsic activity of sulbactam against *A. baumannii*. Meropenem was added to form the triple therapy regimen based on in vitro evidence of potential synergy between colistin and carbapenems, even against carbapenem-resistant strains. The rationale was that high-dose, prolonged infusion meropenem might exert a meaningful pharmacodynamic effect and help mitigate the emergence of resistance, despite in vitro resistance testing.

3.5. Outcomes

The primary outcome was clinical success at day 14. "Clinical success" was defined as: Patient alive at day 14, systolic BP > 90 mmHg without vasopressors, ≥ 30% improvement in SOFA score (if initial SOFA ≥ 3) or no worsening (if SOFA < 3), and sterile blood culture (for bacteremic patients). Secondary outcomes included: All-cause mortality at 14 and 28 days, final outcome, and total hospital stay (survivors only).

3.6. Microbiological Analysis

Acinetobacter isolates and carbapenem susceptibility were confirmed at the hospital laboratory using disk diffusion on Mueller-Hinton agar. A 0.5 McFarland suspension was cultured, and resistance was defined as inhibition zones ≤ 19 mm for carbapenems (imipenem or meropenem), per Clinical and Laboratory Standards Institute (CLSI) guidelines.

3.7. Sample Size Calculation

The sample size was calculated based on the primary outcome of clinical success at day 14. Based on prior studies (31, 32), the clinical success rate for colistin-based monotherapy was approximately 40%. We hypothesized that the triple therapy regimen (colistin+meropenem+ampicillin-sulbactam) would achieve a substantially higher success rate of 80%. Using G*Power software (version 3.1), an alpha error of 0.05, and a power of 80%, a sample size of 23 patients per group was calculated to detect this effect size. Accounting for an anticipated dropout or non-evaluability rate of less than 10%, no further inflation of the sample size was deemed necessary. Thus, a total of 46 patients (23 per group) were planned for enrollment. We anticipated a clinical success rate of 40% in the dual therapy group and 80% in the triple therapy group. To detect this difference with 80% power and $\alpha = 0.05$, a sample size of 23 patients per group was calculated.

3.8. Data Collection and Statistical Analysis

Clinical and laboratory data were collected prospectively using standardized forms. Statistical analysis was performed using SPSS version 25. Categorical variables were compared using chi-square or Fisher's exact test. The Shapiro-Wilk test was used to assess the normality of distribution for continuous variables. Based on the results, continuous variables were analyzed using independent samples *t*-test or Mann-Whitney U test. Descriptive statistics were reported as mean ± standard deviation (SD) or median (interquartile range, IQR), as appropriate.

4. Results

4.1. Patient Enrollment and Allocation

A total of 65 ICU patients with *Acinetobacter* infections were assessed for eligibility. Sixteen were excluded due to isolate susceptibility to at least one antibiotic, and two were under 18 years of age (Figure 1). The remaining 47 patients were enrolled and randomized to the dual therapy (n = 23) and triple therapy groups (n = 24). One patient in the triple therapy group died within 48 hours of antibiotic initiation and was excluded. Finally, 46 patients were included in the analysis.

4.2. Baseline Characteristics

Of the included patients, 52.2% were male, with a mean age of 70.89 ± 18.84 years. The most common comorbidity was hypertension (37%), followed by ischemic heart disease (21.7%). There were no statistically significant differences between groups in terms of age, sex, or baseline comorbidities ($P > 0.05$) (Table 1).

4.3. Primary Outcome 14-Day Clinical Success

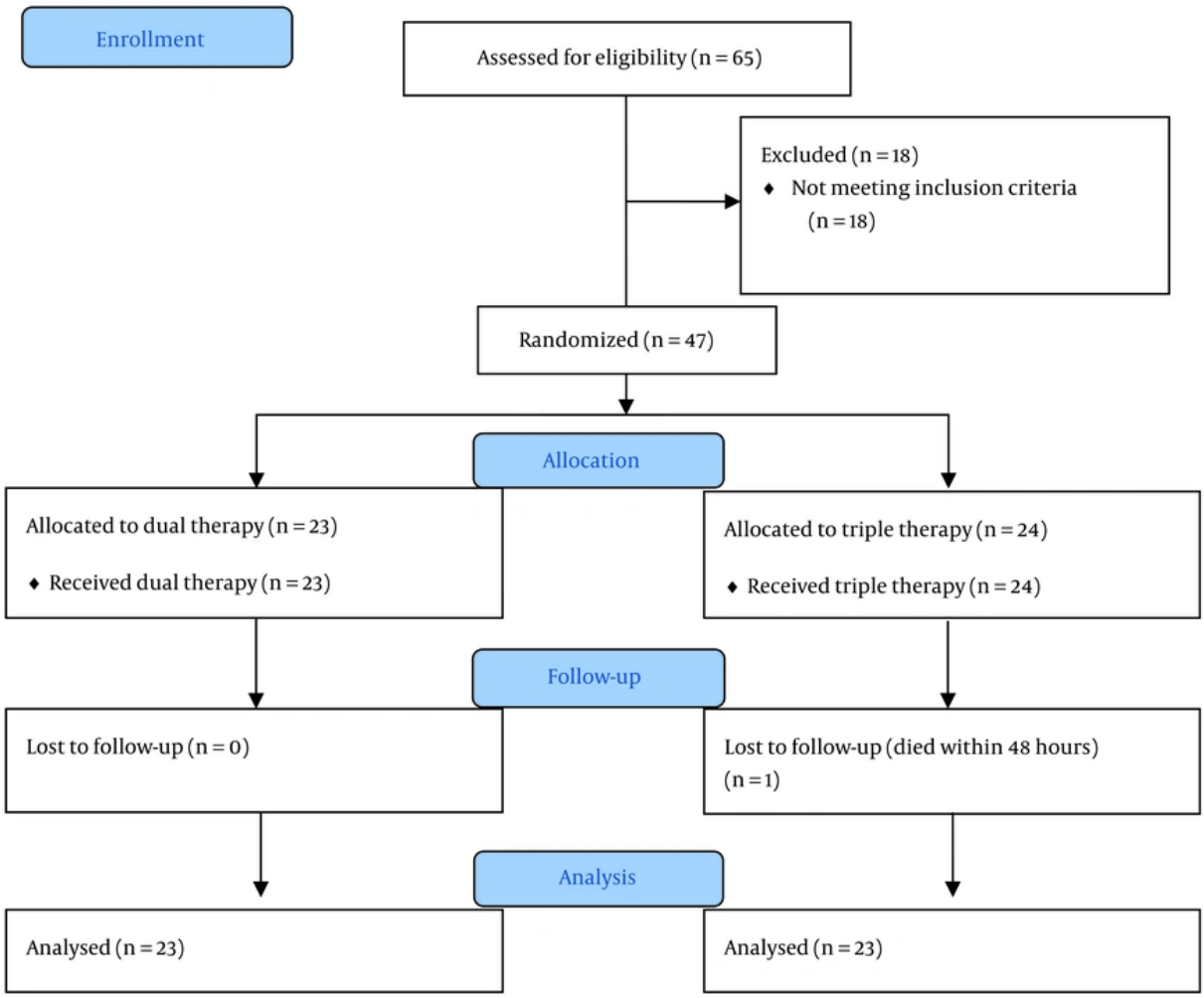

Figure 1. Flow diagram of study

At day 14 after treatment initiation, 13 patients (28.3%) had died. As shown in Table 2, the 14-day mortality rate was higher in the dual therapy group (39.1%) compared to the triple therapy group (17.4%); however, this difference was not statistically significant (P = 0.102). It is noteworthy that clinical success at day 14 corresponded precisely with survival status; all patients who achieved clinical success were alive, while those who did not had died.

4.4. Secondary Outcomes

14-day mortality: The 14-day mortality rate was 39.1% (9/23) in the dual therapy group and 17.4% (4/23) in the triple therapy group (P = 0.102). 28-day mortality: By day 28, mortality was significantly higher in the dual therapy group (65.2%, 15/23) than in the triple therapy group (34.8%, 8/23) (P = 0.039).

Final outcome: By the end of the study, the overall in-hospital mortality rate was 69.6% (32/46), with no significant difference between the dual (65.2%, 15/23) and triple (73.9%, 17/23) therapy groups (P = 0.522). The rate of discharge was 34.8% (8/23) in the dual therapy group and 26.1% (6/23) in the triple therapy group.

Length of stay: Among patients who were discharged alive, the median time from treatment initiation to discharge was 14 days (IQR 8 - 31) in the dual therapy

Table 1. Baseline Characteristics of the Participants (N = 23) [a]

Characteristics	Dual Therapy	Triple Therapy	P-Value
Demographics			
Gender (male)	13 (56.5)	11 (47.8)	0.555
Age (y)	71.82 ± 22.99	69.95 ± 13.99	0.741
Comorbidities			
Ischemic heart disease	3 (13)	7 (30.4)	0.153
Chronic obstructive pulmonary disease	2 (8.7)	3 (13)	> 0.999
Hypertention	7 (30.4)	10 (43.5)	0.359
Diabetes mellitus	2 (8.7)	3 (13)	> 0.999
Malignancy	3 (13)	1 (4.3)	0.609
Dementia	1 (4.3)	1 (4.3)	> 0.999
Peptic ulcer	2 (8.7)	0 (0)	0.489
Dyslipidemia	0 (0)	2 (8.7)	0.489
End stage renal disease	0 (0)	2 (8.7)	0.489
Femur fracture	1 (4.3)	0 (0)	> 0.999
Transverse myelitis	1 (4.3)	0 (0)	> 0.999
Other	6 (39.1) [b]	6 (39.1) [c]	> 0.05 for all
Source of *Acinetobacter* isolation			
Sputum	17 (73.9)	20 (87)	0.217
Urine	3 (13)	0 (0)	
Wound	2 (8.7)	3 (13)	
Cerebrospinal fluid	1 (4.3)	0 (0)	
Admission to infection onset (d)	16.22 ± 13.54	16.87 ± 8.48	0.846
Status at infection onset			
Decreased level of consciousness	15 (62.2)	18 (78.3)	0.326
Mechanical ventilation	13 (56.5)	19 (82.6)	0.055
Serum creatinine (mg/dL)	1.54 (0.9, 1.91)	1.59 (0.84, 2.57)	0.475
Serum albumin (g/dL)	2.71 ± 0.33	2.62 ± 0.34	0.409
White blood cells ($\times 10^9$/L)	12.0 (8.3, 16.5)	9.7 (7.9, 13.6)	0.368

[a] Values are expressed as No. (%), mean ± SD, or median (IQR).

[b] Including dementia (n = 1), peptic ulcer (n = 2), femur fracture (n = 1), transverse myelitis (n = 1), malignancy (n = 3).

[c] Including dementia (n = 1), dyslipidemia (n = 2), end stage renal disease (n = 2), malignancy (n = 1).

Table 2. Study Outcomes (N = 23) [a]

Outcome	Dual Therapy	Triple Therapy	P-Value
Clinical failure at day 14	9 (39.1)	4 (17.4)	0.102
14-day mortality	9 (39.1)	4 (17.4)	0.102
28-day mortality	15 (65.2)	8 (34.8)	0.039
Final outcome (discharged)	8 (34.8)	6 (26.1)	0.522
Treatment initiation to discharge among patients discharged alive from hospital (d)	14 (8, 31)	35 (20, 49)	0.155

[a] Values are expressed as No. (%) or median (IQR).

group and 35 days (IQR 20 - 49) in the triple therapy group, a difference that was not statistically significant (P = 0.155) (Table 2).

4.5. Adverse Events and Safety

The safety of the treatment regimens was assessed. The incidence of nephrotoxicity, defined as a rise in

serum creatinine by ≥ 0.3 mg/dL or 1.5 times baseline, was 21.7% (5/23) in the dual therapy group and 30.4% (7/23) in the triple therapy group (P = 0.509). No cases of neurotoxicity were reported. No therapy discontinuations due to adverse drug reactions were recorded.

5. Discussion

This randomized clinical trial was conducted to compare the effectiveness of two antibiotic combination regimens in the treatment of patients with carbapenem-resistant *Acinetobacter* infections admitted to the ICU. Baseline characteristics including age, sex, and comorbidities were comparable between the groups. Moreover, the initial infection source was largely similar across groups, with the respiratory tract being the most common. One patient died within 48 hours of initiating antibiotic therapy, and this individual belonged to the triple therapy group. Given the short timeframe, it is unlikely that this death was attributable to the antibiotic regimen. Consequently, this patient was excluded from the final outcome analysis.

The primary outcome assessed was clinical failure or mortality by day 14. Although 14-day mortality was numerically lower in the triple therapy group (17%) compared to the dual therapy group (39%), this difference was not statistically significant. However, by day 28, a significant difference emerged; mortality was lower in the triple therapy group. Despite this, overall in-hospital mortality was high in both groups — 65.2% in the dual therapy group and 73.9% in the triple therapy group — with no statistically significant difference. Despite demonstrating a lower 28-day mortality rate, the addition of meropenem did not translate into a statistically significant improvement in overall survival compared to the dual regimen. The lack of significant difference in final mortality may reflect the high baseline mortality risk inherent to ICU patients with multidrug-resistant gram-negative infections (33-35). Factors such as underlying organ failure, late diagnosis, delays in effective therapy, or non-infectious contributors to death (36, 37) may have diluted the impact of antibiotic regimen.

To our knowledge, no previous clinical trial has directly compared the same regimens used in our study. In a 2022 observational study, Falcone et al. compared colistin-based regimens with cefiderocol-based regimens in patients with severe carbapenem-resistant *Acinetobacter* infections. They reported a 30-day mortality rate of 55.8% in the colistin group versus 34% in the cefiderocol group (21). While cefiderocol was not available in our setting and not used in this study, all patients in our trial received colistin, and the overall 30-day mortality was 50%, consistent with Falcone's findings for colistin-based therapy. A 2019 randomized controlled trial by Dickstein et al. involving 266 patients found that, among those with isolates resistant to both colistin and carbapenems, mortality was higher in the group receiving colistin–meropenem compared to colistin alone (38). In contrast, a 2021 systematic review and meta-analysis by Scudeller et al. examined in vitro studies on the synergistic effects of combination therapy against carbapenem-resistant gram-negative bacilli. The review suggested a high level of synergy between meropenem and colistin (39). This discrepancy highlights the limitation of extrapolating in vitro findings to clinical practice, reinforcing the importance of clinical trials in guiding treatment decisions.

In our study, concurrent use of ampicillin-sulbactam in both groups could have influenced treatment response, so our findings may reflect a three-drug effect rather than meropenem's contribution alone. It is important to note that ampicillin-sulbactam has intrinsic activity against *Acinetobacter* via the sulbactam component (40). According to a 2021 network meta-analysis, combination regimens containing high-dose sulbactam alongside other antibacterial agents — such as colistin — appear to be a promising therapeutic option for treating multidrug-resistant and extensively drug-resistant *A. baumannii* infections (41). Our study adds important real-world evidence to a growing but inconclusive body of data regarding optimal combination therapy for these infections. However, further high-quality clinical trials are needed to confirm their efficacy and safety.

This trial is among the first randomized studies comparing these specific regimens in carbapenem-resistant *Acinetobacter* infections. However, the study has several limitations including small sample size, single-center design, lack of genotypic or minimum inhibitory concentration (MIC)-based resistance profiling, and unmeasured variables such as sequential organ failure assessment (SOFA) score trends. Additionally, colistin resistance testing was not routinely performed, and newer agents like cefiderocol were not available in our setting. Definitive conclusions about the usefulness of combination therapy require

larger, multicenter trials with microbiologic stratification. Future research should also investigate resistance-guided combination strategies to optimize outcomes in this high-risk population.

5.1. Conclusions

In this randomized clinical trial, the addition of meropenem to a dual regimen of colistin and ampicillin–sulbactam was associated with improved 28-day survival in ICU patients with carbapenem-resistant *A. baumannii* infections. Although this benefit did not extend to overall in-hospital mortality, our findings suggest that triple therapy may offer a modest clinical advantage in critically ill patients. Given the high mortality associated with these infections and the limited treatment options, larger multicenter studies are warranted to validate these results and optimize combination therapy strategies in resource-limited settings.

Acknowledgements

We thank the Clinical Research Development Unit at Bohlool Hospital of Gonabad.

Footnotes

AI Use Disclosure: The authors declare that no generative AI tools were used in the creation of this article.

Authors' Contribution: Study concept and design: Y. A. and J. M.; Acquisition of data: K. Y. and M. M.; Drafting of the manuscript: M. M.; Critical revision of the manuscript for important intellectual content: Y. A. and J. M.; Statistical analysis: M. M.; Study supervision: Y. A. and M. S.

Clinical Trial Registration Code: IRCT20240117060720N1 .

Conflict of Interests Statement: The authors declare no conflict of interest.

Data Availability: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

Ethical Approval: This study was approved by the Ethics Committee of Gonabad University of Medical Sciences (IR.GMU.REC.1402.178). The study was conducted in accordance with the Declaration of Helsinki.

Funding/Support: This project was supported by Gonabad University of Medical Sciences.

Informed Consent: Written informed consent was obtained from the participants.

References

1. Chinemerem Nwobodo D, Ugwu MC, Oliseloke Anie C, Al-Ouqaili MTS, Chinedu Ikem J, Victor Chigozie U, et al. Antibiotic resistance: The challenges and some emerging strategies for tackling a global menace. *J Clin Lab Anal*. 2022;**36**(9). e24655. [PubMed ID: 35949048]. [PubMed Central ID: PMC9459344]. https://doi.org/10.1002/jcla.24655.
2. Bocian A, Hus KK. Antibacterial properties of snake venom components. *Chem Pap*. 2020;**74**(2):407-19. https://doi.org/10.1007/s11696-019-00939-y.
3. Akova M. Epidemiology of antimicrobial resistance in bloodstream infections. *Virulence*. 2016;**7**(3):252-66. [PubMed ID: 26984779]. [PubMed Central ID: PMC4871634]. https://doi.org/10.1080/21505594.2016.1159366.
4. Mithuna R, Tharanyalakshmi R, Jain I, Singhal S, Sikarwar D, Das S, et al. Emergence of antibiotic resistance due to the excessive use of antibiotics in medicines and feed additives: A global scenario with emphasis on the Indian perspective. *Emerg Contam*. 2024;**10**(4). https://doi.org/10.1016/j.emcon.2024.100389.
5. Saha M, Sarkar A. Review on multiple facets of drug resistance: A rising challenge in the 21st century. *J Xenobiot*. 2021;**11**(4):197-214. [PubMed ID: 34940513]. [PubMed Central ID: PMC8708150]. https://doi.org/10.3390/jox11040013.
6. Terreni M, Taccani M, Pregnolato M. New antibiotics for multidrug-resistant bacterial strains: Latest research developments and future perspectives. *Molecules*. 2021;**26**(9). [PubMed ID: 34063264]. [PubMed Central ID: PMC8125338]. https://doi.org/10.3390/molecules26092671.
7. Serwecinska L. Antimicrobials and antibiotic-resistant bacteria: A risk to the environment and to public health. *Water*. 2020;**12**(12). https://doi.org/10.3390/w12123313.
8. Uddin TM, Chakraborty AJ, Khusro A, Zidan BRM, Mitra S, Emran TB, et al. Antibiotic resistance in microbes: History, mechanisms, therapeutic strategies and future prospects. *J Infect Public Health*. 2021;**14**(12):1750-66. [PubMed ID: 34756812]. https://doi.org/10.1016/j.jiph.2021.10.020.
9. Valcek A, Nesporova K, Whiteway C, De Pooter T, De Coster W, Strazisar M, et al. Genomic analysis of a strain collection containing multidrug-, extensively drug-, pandrug-, and carbapenem-resistant modern clinical isolates of Acinetobacter baumannii. *Antimicrob Agents Chemother*. 2022;**66**(9). e0089222. [PubMed ID: 35969073]. [PubMed Central ID: PMC9487538]. https://doi.org/10.1128/aac.00892-22.
10. Malta RCR, Ramos G, Nascimento JDS. From food to hospital: We need to talk about Acinetobacter spp. *Germs*. 2020;**10**(4):210-7. [PubMed ID: 33134199]. [PubMed Central ID: PMC7572206]. https://doi.org/10.18683/germs.2020.1207.
11. Gedefie A, Demsis W, Ashagrie M, Kassa Y, Tesfaye M, Tilahun M, et al. Acinetobacter baumannii biofilm formation and its role in disease

pathogenesis: A review. *Infect Drug Resist*. 2021;**14**:3711-9. [PubMed ID: 34531666]. [PubMed Central ID: PMC8439624]. https://doi.org/10.2147/IDR.S332051.

12. Bian X, Liu X, Zhang X, Li X, Zhang J, Zheng H, et al. Epidemiological and genomic characteristics of Acinetobacter baumannii from different infection sites using comparative genomics. *BMC Genomics*. 2021;**22**(1):530. [PubMed ID: 34247587]. [PubMed Central ID: PMC8272988]. https://doi.org/10.1186/s12864-021-07842-5.
13. McCarthy RR, Larrouy-Maumus GJ, Meiqi Tan MGC, Wareham DW. Antibiotic resistance mechanisms and their transmission in Acinetobacter baumannii. *Adv Exp Med Biol*. 2021;**1313**:135-53. [PubMed ID: 34661894]. https://doi.org/10.1007/978-3-030-67452-6_7.
14. Wu HJ, Xiao ZG, Lv XJ, Huang HT, Liao C, Hui CY, et al. Drug-resistant Acinetobacter baumannii: From molecular mechanisms to potential therapeutics (review). *Exp Ther Med*. 2023;**25**(5):209. [PubMed ID: 37090073]. [PubMed Central ID: PMC10119666]. https://doi.org/10.3892/etm.2023.11908.
15. Hillyer T, Benin BM, Sun C, Aguirre N, Willard B, Sham YY, et al. A novel strategy to characterize the pattern of beta-lactam antibiotic-induced drug resistance in Acinetobacter baumannii. *Sci Rep*. 2023;**13**(1):9177. [PubMed ID: 37280269]. [PubMed Central ID: PMC10244389]. https://doi.org/10.1038/s41598-023-36475-9.
16. Kyriakidis I, Vasileiou E, Pana ZD, Tragiannidis A. Acinetobacter baumannii antibiotic resistance mechanisms. *Pathogens*. 2021;**10**(3). [PubMed ID: 33808905]. [PubMed Central ID: PMC8003822]. https://doi.org/10.3390/pathogens10030373.
17. Nguyen M, Joshi SG. Carbapenem resistance in Acinetobacter baumannii, and their importance in hospital-acquired infections: A scientific review. *J Appl Microbiol*. 2021;**131**(6):2715-38. [PubMed ID: 33971055]. https://doi.org/10.1111/jam.15130.
18. Jamal S, Al Atrouni A, Rafei R, Dabboussi F, Hamze M, Osman M. Molecular mechanisms of antimicrobial resistance in Acinetobacter baumannii, with a special focus on its epidemiology in Lebanon. *J Glob Antimicrob Resist*. 2018;**15**:154-63. [PubMed ID: 29859266]. https://doi.org/10.1016/j.jgar.2018.05.022.
19. Teerawattanapong N, Panich P, Kulpokin D, Na Ranong S, Kongpakwattana K, Saksinanon A, et al. A systematic review of the burden of multidrug-resistant healthcare-associated infections among intensive care unit patients in Southeast Asia: The rise of multidrug-resistant Acinetobacter baumannii. *Infect Control Hosp Epidemiol*. 2018;**39**(5):525-33. [PubMed ID: 29580299]. https://doi.org/10.1017/ice.2018.58.
20. Pourhajibagher M, Hashemi FB, Pourakbari B, Aziemzadeh M, Bahador A. Antimicrobial resistance of Acinetobacter baumannii to imipenem in Iran: A systematic review and meta-analysis. *Open Microbiol J*. 2016;**10**:32-42. [PubMed ID: 27099638]. [PubMed Central ID: PMC4814728]. https://doi.org/10.2174/1874285801610010032.
21. 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. [PubMed ID: 35311522]. [PubMed Central ID: PMC9112922]. https://doi.org/10.1128/aac.02142-21.
22. Isler B, Doi Y, Bonomo RA, Paterson DL. New treatment options against carbapenem-resistant Acinetobacter baumannii infections. *Antimicrob Agents Chemother*. 2019;**63**(1). [PubMed ID: 30323035]. [PubMed Central ID: PMC6325237]. https://doi.org/10.1128/AAC.01110-18.
23. Iovleva A, Mustapha MM, Griffith MP, Komarow L, Luterbach C, Evans DR, et al. Carbapenem-resistant Acinetobacter baumannii in U.S. hospitals: Diversification of circulating lineages and antimicrobial resistance. *mBio*. 2022;**13**(2). e0275921. [PubMed ID: 35311529]. [PubMed Central ID: PMC9040734]. https://doi.org/10.1128/mbio.02759-21.
24. Mohd Sazlly Lim S, Sime FB, Roberts JA. Multidrug-resistant Acinetobacter baumannii infections: Current evidence on treatment options and the role of pharmacokinetics/pharmacodynamics in dose optimisation. *Int J Antimicrob Agents*. 2019;**53**(6):726-45. [PubMed ID: 30831234]. https://doi.org/10.1016/j.ijantimicag.2019.02.016.
25. Margalit I, Prendki V, Tishler O, Falcone M, Tiseo G, Leibovici-Weissman Y, et al. Effectiveness and safety of colistin among older adults: A systematic review and meta-analysis. *J Antimicrob Chemother*. 2022;**77**(8):2094-104. [PubMed ID: 35512325]. https://doi.org/10.1093/jac/dkac145.
26. Rafailidis P, Panagopoulos P, Koutserimpas C, Samonis G. Current therapeutic approaches for multidrug-resistant and extensively drug-resistant Acinetobacter baumannii infections. *Antibiotics*. 2024;**13**(3). [PubMed ID: 38534696]. [PubMed Central ID: PMC10967523]. https://doi.org/10.3390/antibiotics13030261.
27. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control*. 2008;**36**(5):309-32. [PubMed ID: 18538699]. https://doi.org/10.1016/j.ajic.2008.03.002.
28. Bennett JE, Dolin R, Blaser MJ. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*. Ninth edition. ed. Philadelphia, USA: Elsevier; 2020.
29. Pai MP, Cojutti P, Pea F. Pharmacokinetics and pharmacodynamics of continuous infusion meropenem in overweight, obese, and morbidly obese patients with stable and unstable kidney function: A step toward dose optimization for the treatment of severe gram-negative bacterial infections. *Clin Pharmacokinet*. 2015;**54**(9):933-41. [PubMed ID: 25850987]. https://doi.org/10.1007/s40262-015-0266-2.
30. Passon SG, Schmidt AR, Wittmann M, Velten M, Baehner T. Evaluation of continuous ampicillin/sulbactam infusion in critically ill patients. *Life Sci*. 2023;**320**:121567. [PubMed ID: 36907327]. https://doi.org/10.1016/j.lfs.2023.121567.
31. Paul M, Daikos GL, Durante-Mangoni E, Yahav D, Carmeli Y, Benattar YD, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: An open-label, randomised controlled trial. *Lancet Infect Dis*. 2018;**18**(4):391-400. [PubMed ID: 29456043]. https://doi.org/10.1016/S1473-3099(18)30099-9.
32. Khalili H, Shojaei L, Mohammadi M, Beigmohammadi MT, Abdollahi A, Doomanlou M. Meropenem/colistin versus meropenem/ampicillin-sulbactam in the treatment of carbapenem-resistant pneumonia. *J Comp Eff Res*. 2018;**7**(9):901-11. [PubMed ID: 30192166]. https://doi.org/10.2217/cer-2018-0037.
33. Kadri SS, Adjemian J, Lai YL, Spaulding AB, Ricotta E, Prevots DR, et al. Difficult-to-treat resistance in Gram-negative bacteremia at 173 US hospitals: Retrospective cohort analysis of prevalence, predictors, and outcome of resistance to all first-line agents. *Clin Infect Dis*. 2018;**67**(12):1803-14. [PubMed ID: 30052813]. [PubMed Central ID: PMC6260171]. https://doi.org/10.1093/cid/ciy378.
34. Kannian P, Mahanathi P, Ashwini V, Vaishnavi M, Priya C. Carbapenem-resistant Gram negative Bacilli are predominantly multidrug or pan-drug resistant. *Microb Drug Resist*. 2021;**27**(8):1057-62. [PubMed ID: 33417816]. https://doi.org/10.1089/mdr.2020.0294.
35. Schwab F, Geffers C, Behnke M, Gastmeier P. ICU mortality following ICU-acquired primary bloodstream infections according to the type

of pathogen: A prospective cohort study in 937 Germany ICUs (2006-2015). *PLoS One*. 2018;**13**(3). e0194210. [PubMed ID: 29518133]. [PubMed Central ID: PMC5843291]. https://doi.org/10.1371/journal.pone.0194210.

36. Velez JW, Aragon DC, Donadi EA, Carlotti A. Risk factors for mortality from sepsis in an intensive care unit in Ecuador: A prospective study. *Medicine*. 2022;**101**(11). [PubMed ID: 35356943]. [PubMed Central ID: PMC10684228]. https://doi.org/10.1097/MD.0000000000029096.
37. Vallet H, Schwarz GL, Flaatten H, de Lange DW, Guidet B, Dechartres A. Mortality of older patients admitted to an ICU: A systematic review. *Crit Care Med*. 2021;**49**(2):324-34. [PubMed ID: 33332816]. https://doi.org/10.1097/CCM.0000000000004772.
38. Dickstein Y, Lellouche J, Ben Dalak Amar M, Schwartz D, Nutman A, Daitch V, et al. Treatment outcomes of colistin- and carbapenem-resistant Acinetobacter baumannii infections: An exploratory subgroup analysis of a randomized clinical trial. *Clin Infect Dis*. 2019;**69**(5):769-76. [PubMed ID: 30462182]. https://doi.org/10.1093/cid/ciy988.
39. Scudeller L, Righi E, Chiamenti M, Bragantini D, Menchinelli G, Cattaneo P, et al. Systematic review and meta-analysis of in vitro efficacy of antibiotic combination therapy against carbapenem-resistant Gram-negative bacilli. *Int J Antimicrob Agents*. 2021;**57**(5):106344. [PubMed ID: 33857539]. https://doi.org/10.1016/j.ijantimicag.2021.106344.
40. Chu H, Zhao L, Wang M, Liu Y, Gui T, Zhang J. Sulbactam-based therapy for Acinetobacter baumannii infection: A systematic review and meta-analysis. *Braz J Infect Dis*. 2013;**17**(4):389-94. [PubMed ID: 23602463]. [PubMed Central ID: PMC9428054]. https://doi.org/10.1016/j.bjid.2012.10.029.
41. Liu J, Shu Y, Zhu F, Feng B, Zhang Z, Liu L, et al. Comparative efficacy and safety of combination therapy with high-dose sulbactam or colistin with additional antibacterial agents for multiple drug-resistant and extensively drug-resistant Acinetobacter baumannii infections: A systematic review and network meta-analysis. *J Glob Antimicrob Resist*. 2021;**24**:136-47. [PubMed ID: 32889142]. https://doi.org/10.1016/j.jgar.2020.08.021.