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Mortality and clinical outcomes of colistin versus colistin-based combination therapy for infections caused by Multidrug-resistant Acinetobacter baumannii in critically ill patients

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Abstract

Background Multidrug-resistant *Acinetobacter baumannii* emerged as a threatening "superbug" with significant morbidity and mortality and limited antimicrobial therapy options. The results of different antibiotic combination studies are heterogeneous and controversial. Further comparative studies are crucial to overcome such difficult-to-treat infections and to improve patient outcomes. This study investigates the mortality and outcomes of colistin versus colistin-based combination therapy for infections caused by Multidrug-resistant *Acinetobacter baumannii* in critically ill patients.

Methods A retrospective observational study was conducted at an academic tertiary hospital in Khobar City, Eastern Province, Saudi Arabia. Patients who fulfilled the inclusion criteria and were admitted from January 1, 2017, to December 31, 2022, were included. The investigated primary outcome was 30-day mortality, while secondary outcomes were one-year all-cause mortality, clinical cure, microbiologic eradication, and recurrence of *Acinetobacter* infections. Statistical comparisons were employed, and a *P*-value of ≤ .05 was considered significant.

Results Of the 178 patients who fulfilled the inclusion criteria, 47 received colistin only, and 131 received colistin in combinations (55 with carbapenems, 53 with tigecycline, and 23 with both). The estimated 30-day mortality rate of the study population was 22.5%, with statistically insignificant differences in 30-day mortality rates when the colistin group compared to cumulative colistin-based combination (23.4% vs. 22.1%; difference, 1.3 percentage points; 95% confidence interval [CI], 0.487–2.371; $P=0.858$) or subgroups. However, colistin-based combination groups showed better secondary outcomes, with significantly less all-cause mortality and better clinical cure in colistin combination with carbapenems or tigecycline and less *Acinetobacter* infection recurrence in combination with carbapenems.

Conclusions The study findings demonstrate the benefits of investigated colistin combination options that result in less one-year all-cause mortality, better clinical cure, higher microbiologic response, and less infection recurrence. However, no significant differences were observed regarding 30-day mortality. In addition, the study highlights

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the limitations of the available antimicrobial options and the crucial need for new effective antimicrobials and more successful combinations.

Keywords *Acinetobacter baumannii*, Colistin, Carbapenem, Tigecycline, Combination, Outcome

Background

Acinetobacter baumannii (AB) is a coccobacillus aerobic Gram-negative microorganism that has been considered a commensal low-virulence opportunistic pathogen for decades [1]. The significant clinical role of AB as a human pathogen was questionable until the 1990s when new multidrug-resistant *Acinetobacter baumannii* (MDR-AB) strains emerged as an important causative agent of nosocomial infections [2]. It has gradually gained over-extended antibiotic resistance and become one of six "superbugs" in the era of the antimicrobial resistance pandemic [3].

MDR-AB is defined as AB resistant to ≥ 1 agent in ≥ 3 classes of antibiotics [4]. It often targets immune-depleted and critically ill hospitalized patients, especially those on mechanical ventilation or with indwelling central lines. Multiple risk factors of MDR-AB infections have been identified, including contamination of the healthcare environment, MDR-AB strain colonization of hospitalized patients or healthcare providers, breaking of infection control precautions, prolonged hospitalization, malignancy, previous intensive care unit (ICU) admission, especially with respiratory failure, prior exposure to broad-spectrum antibiotics such as fourth-generation cephalosporins or carbapenems [1]. AB became resistant to all beta-lactams, including carbapenems and monobactam, by producing OXA carbapenemases (such as OXA 23, OXA 40, and OXA 58, among others) and serine β-lactamases, or through new mutations targeting penicillin-binding proteins in AB cell wall [2, 5]. In addition, AB gained fluoroquinolone resistance mediated by the emergence of chromosomal mutations targeting resistance regions and became resistant to aminoglycosides by producing 16S rRNA methyltransferases [5]. Consequently, the infections caused by MDR-AB became a healthcare threat due to global spread and lack of optimal antibiotic options to combat difficult-to-treat MDR-AB cases, which led, in turn, to reviving parenteral polymyxins as a last resort therapy option. Colistin (polymyxin E) is a cationic lipopeptide antibiotic produced by *Bacillus polymyxa* var. *Colistinus*. It was introduced in the 1950s but later abandoned in the 1960s in most countries due to its high rate of nephrotoxicity and neurotoxicity. However, with the escalating problem of bacterial multidrug resistance infections and the limitation of antimicrobial therapy options, colistin has been reintroduced to combat Gram-negative infections, including MDR-AB [6].

Nevertheless, the concern about colistin efficacy is raised with further published data reporting a high mortality rate of MDR-AB infections treated with colistin [7]. Moreover, the global impact of the issue is evident as the prevalence of resistance to colistin is increasing in the Eastern Mediterranean and Southeast Asia, with reported prevalence in Lebanon and China at 17% and 12%, respectively [8].

Various approaches, including increasing loading dose, higher maintenance doses, and colistin-based combination therapy (CBCT) with other antibiotics, have been suggested to enhance colistin activity against MDR-AB. There is no conclusive clinical evidence proving that combination therapy leads to better outcomes than monotherapy for MDR-AB. However, in cases of MDR-AB infections, the updated guidelines suggest that combination therapy might improve patients' outcomes [5, 9, 10]. While in vitro studies have shown synergistic effects of CBCT with carbapenems or other antibiotics, clinical studies have yielded inconsistent results regarding the outcomes of CBCT [7]. Multiple studies fail to prove the superiority of double CBCT compared with colistin monotherapy (CMT), and further clinical studies about double and triple CBCT are urgently needed to establish the efficacy of such combinations [11]. Hence, this study aims to compare the clinical outcomes of CMT with double (colistin with meropenem or tigecycline) or triple (colistin, meropenem, and tigecycline) CBCT in critically ill patients with nosocomial infections caused by MDR-AB. The results of this study can provide valuable insights into the optimal therapeutic approach to MDR-AB infections to improve patient outcomes and reduce the emergence of antimicrobial resistance.

Materials and methods

Study design, settings, and participants

The researchers conducted this retrospective observational study at King Fahad Hospital of the University (KFHU), a tertiary care academic hospital with more than 500 beds in Al-Khobar city, Eastern Province, Saudi Arabia. The patient files and electronic records with confirmed MDR-AB nosocomial infections were meticulously reviewed between January 1, 2017, and December 31, 2022, and the patients who fulfilled the following inclusion criteria were included:

1. Critically ill adult patients aged ≥ 18 years.

2. Had a defined bloodstream infection (BSI), hospital-acquired pneumonia (HAP), or ventilator-associated pneumonia (VAP) caused by MDR-AB.
3. The patient was treated with CMT or CBCT with carbapenem, tigecycline, or both for more than 72 h.

The exclusion criteria were:

1. Patients with nosocomial urinary tract infections, skin and soft tissue infections, or other noncritical MDR-AB infections.
2. Patients who were referred to another healthcare facility during the MDR-AB infection episode.
3. Patients with incomplete medical records.

Critically ill patients were those hospitalized with HAP, VAP, or BSI, had a state of ill health and vital organ dysfunction, and were at high risk of imminent death if care was not provided [12].

HAP was defined as "new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin, which includes the new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation" that was developed ≥ 48 h after admission in not mechanically ventilated patients, VAP is defined as pneumonia that was developed at ≥ 48 h after endotracheal intubation in mechanically ventilated patients [13], and BSI was defined as the presence of systemic inflammatory response syndrome and at least one AB-positive blood culture. BSIs were primary or secondary to VAP or HAP (Fig. 2).

The standard applied dosage of tigecycline was 100 mg IV as a loading dose, then 50 mg IV every 12 h, and for meropenem, 1–2 g IV every 8 h. The colistin dosage was applied according to the European Medicine Agency treatment guidelines (2014) up to 2019; thereafter, the applied dosage was according to the International Consensus Guidelines [10, 14]. The dosages of colistin and meropenem were adjusted based on creatinine clearance levels in patients experiencing renal impairment.

The study's primary clinical outcome was 30-day mortality (all-cause mortality occurring within 30 days from the initiation of CMT or CBCT), while the secondary outcomes were one-year all-cause mortality assessed retrospectively by reviewing follow-up records up to one year from the start of antibiotic treatment. The clinical cure is defined as subsiding clinical presentations of HAP, VAP, or BSI within two weeks, such as fever, purulent sputum, leukocytosis, and hypoxemia. Bacteriologic eradication was defined as negative subsequent bacterial cultures within 14 days, and the recurrence of MDR-AB infection was tracked within three months after the first documented episode.

Demographic and clinical data collection

The researchers screened patients' electronic records at KFHU and identified critically ill hospitalized patients with confirmed MDR-AB nosocomial infection during the selected study period. They reviewed hard and electronic files of patients who fulfilled the inclusion criteria to collect needed data, including demographic characteristics, date and site of the MDR-AB infection, comorbidities, baseline laboratory test results, risk factors for developing BSI, HAP, or VAP caused by MDR-AB, empirical antimicrobial therapy, CMT, CBCT, and data related to the primary and secondary defined outcomes.

Microbiological data

The data related to sample collection, microbiological identification, and antibiotic sensitivity testing were collected. Respiratory samples were cultured on MacConkey, chocolate, and blood agar plates (SPML, KSA) and incubated overnight at 35 °C with 5% CO_2. Blood cultures were processed using the Virtuo system (BioMerieux, France) for up to five days, followed by Gram staining and subculture of positively flagging bottles. Suspected AB isolates were identified using VITEK MS (bioMérieux, U.S.), and their antimicrobial susceptibility was tested with VITEK 2. E-tests (AB BIODISK, Sweden) were used to determine MICs for carbapenems and tigecycline, interpreting results according to Clinical & Laboratory Standards Institute guidelines (except for tigecycline, which followed U.S. FDA breakpoints). Control strains (*Klebsiella pneumoniae* [ATCC 700603], *Escherichia coli* [ATCC 25922], and *Pseudomonas aeruginosa* [ATCC 27853]) were included in each AST run. Isolates showing MDR profiles were reported according to standard definition [4].

Statistical analysis

Our study employed a set of comparisons; statistical analysis was performed using the Statistical Product and Service Solutions (SPSS) statistics for Windows, version 28. (IBM Corp., Armonk). Categorical variables were presented as frequency and percentage, while continuous variables were presented as mean ± standard deviation. The chi-square test for categorical variables and the *t*-test for continuous variables were used to compare baseline demographics, clinical data, laboratory findings, and antibiotic therapy profiles. Furthermore, odds ratios (OD) with a 95% confidence interval (IC) were calculated to compare the CMT with different CBCT option outcomes. Kaplan–Meier survival curves for 30-day mortality were drawn. A *P*-value of ≤ 0.05 was considered

the cut-off point for statistically significant differences between variables.

Results

Of the 527 screened patients with identified MDR-AB infection, 178 fulfilled the inclusion criteria. One hundred ten patients (61.8%) were males, and the mean age of the study population was 56.5 ± 20.22 years. Forty-seven patients were treated with CMT, and 131 received CBCT. The colistin combination was with carbapenem in 55, tigecycline in 53, and both in 23 patients (Fig. 1). Twenty-five of the included patients were diagnosed with HAP, 121 had VAP, and 62 had BSI, which was associated in 30 patients with VAP or HAP (Fig. 2). A baseline comparison between CMT and CBCT groups, including age, gender, comorbidities, Charlson comorbidity score, type of infections, risk factors, and laboratory findings, were presented in Table 1 and Table 2. Both groups were similar regarding all compared variables except for a few; for the type of infections, HAP was significantly higher in the CMT group, whereas VAP in the CBCT group ($P=0.031$ and $P=0.030$, respectively). In addition, inserting a

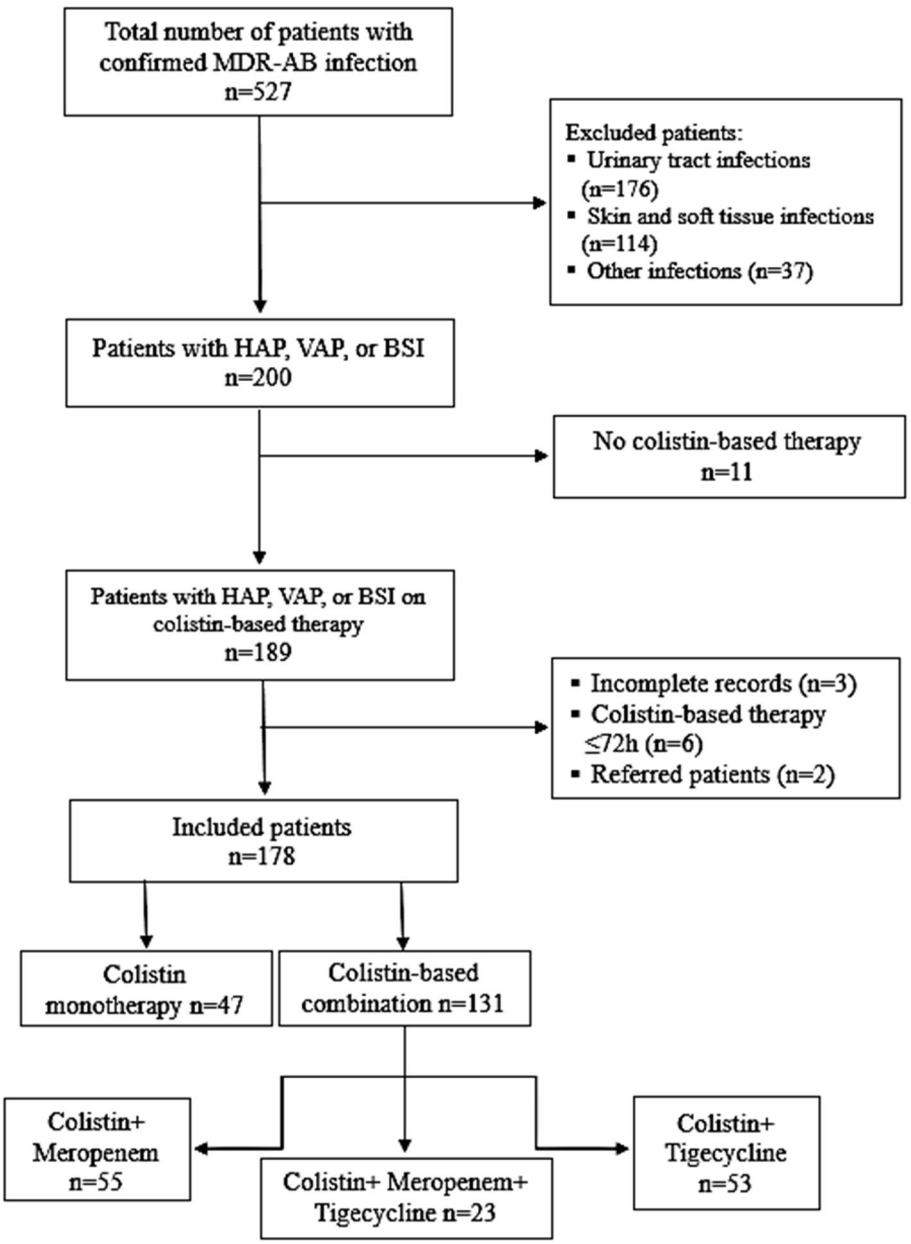
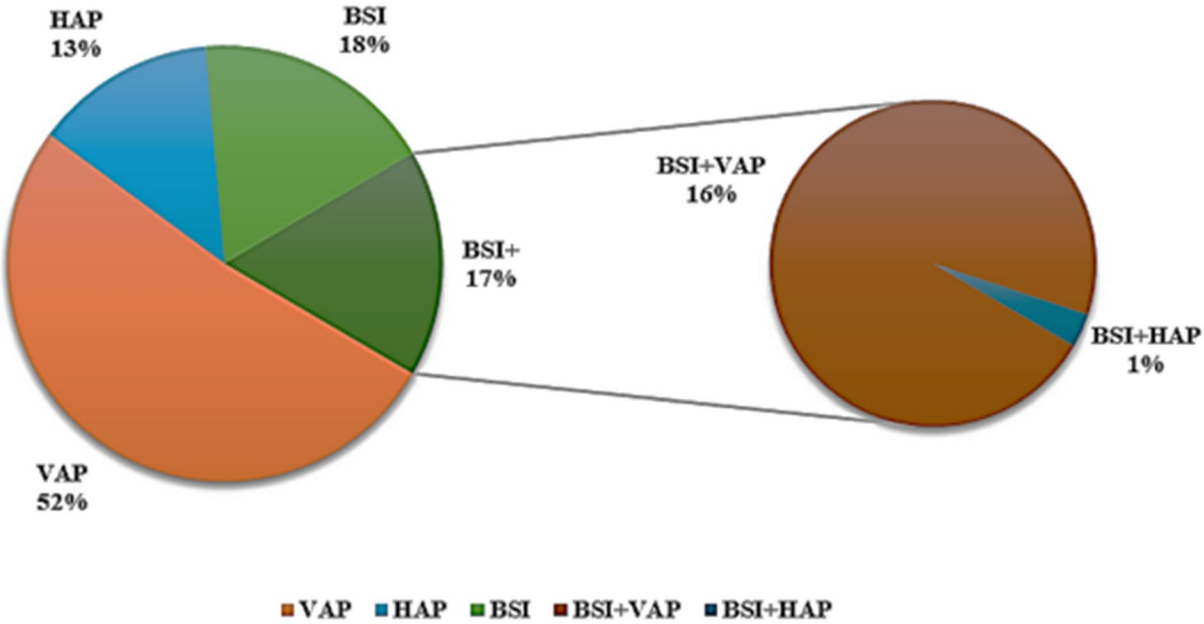


Fig. 1 MDR-AB colistin-based therapy study flow chart



VAP	HAP	BSI	BSI+VAP	BSI+HAP
92	24	32	29	1

Fig. 2 Patient stratification according to type of infection. HAP, hospital-acquired pneumonia; BSI, bloodstream infection; VAP, ventilator-associated pneumonia

central venous catheter was significantly higher in the CBCT group, while receiving empirical antibiotic therapy was significantly higher in the CMT group (Table 1). Regarding the baseline laboratory findings, hemoglobin was slightly higher in the CBCT group, while neutrophil percentage was higher in the CMT group (Table 2). The univariate analysis of 30-day mortality showed that the frequency of BSI, previous immunosuppressive therapy, and receiving empirical therapy before AB-targeted therapy were significantly higher in non-survivors (Table 3).

The estimated 30-day mortality rate as a primary outcome was 22.5%. The 30-day mortality of CMT vs. cumulative CBCT (Fig. 3) showed no significant difference (23.4% vs. 22.1%; difference, 1.3 percentage points; 95% confidence interval [CI], 0.487–2.371; $P=0.858$). Statistical insignificance of 30-day mortality was also observed when the CMT group was compared to other CBCT with tigecycline (23.4% vs. 20.8%; difference, 2.6 percentage points; 95% CI, 0.452–3.007; $P=0.503$), meropenem (23.4% vs. 25.5%; difference, −2.1 percentage points; 95% CI, 0.361–2.218; $P=0.810$), or both (23.4% vs. 17.4%; difference, 6 percentage points; 95% CI, 0.407–5.179; $P=0.566$) (Fig. 4).

In contrast, the CBCT options demonstrate better secondary outcomes compared to CMT. The cumulative CBCT showed less one-year all-cause mortality ($P=0.001$), better clinical cure ($P=0.007$), and less recurrence ($P=0.012$). Also, the combination with tigecycline or carbapenem was significantly superior to CMT regarding all-cause mortality ($P=0.002$ and $P=0.001$, respectively) and clinical cure ($P=0.015$ and $P=0.003$, respectively). In addition, significantly less recurrence was observed in combination with carbapenem ($P=0.004$) (Table 4).

Discussion

AB has gradually become a difficult-to-treat "superbug" with limited available antimicrobial options and high therapy failure rates. Our comparative study findings provide insights into commonly available antimicrobial options for combating MDR-AB infections; five important outcomes for CMT and CBCT (with meropenem, tigecycline, or both) were compared.

The reviewed literature indicates that colistin is not the optimal antimicrobial for treating severe MDR-AB infections such as HAP, VAP, or BSI. The colistin limitations include suboptimal plasma and bronchoalveolar lavage concentrations, increased nephrotoxicity, and an observed high mortality rate of MDR-AB infections (> 40%) treated with colistin [7, 15, 16]. In addition,

Table 1 Baseline demographic, clinical characteristics, and risk factors of the study population

	Colistin monotherapy (*n* = 47)	Colistin-based combination therapy (*n* = 131)	*P*-value
Age (in years) **(mean ± SD)**	58.872 ± 23.058	55.649 ± 19.206	0.351
Gender (male)	27 (57.4%)	83 (63.4%)	0.474
Comorbidities			
Diabetes mellitus	20 (42.6%)	54 (41.2%)	0.873
Hypertension	25 (53.2%)	57 (43.5%)	0.253
Myocardial infarction	2 (4.3%)	14 (10.7%)	0.244
Heart failure	7 (14.9%)	12 (9.2%)	0.275
Peripheral vascular disease	3 (6.4%)	3 (2.3%)	0.189
Cerebrovascular disease	11 (23.4%)	31 (23.7%)	0.971
Hemiplegia or paraplegia	7 (14.9%)	23 (17.6%)	0.676
Dementia or chronic cognitive deficit	2 (4.3%)	6 (4.6%)	0.926
Chronic pulmonary disease	2 (4.3%)	17 (13%)	0.097
Connective tissue disease	0	3 (2.3%)	0.567
Liver disease	0	3 (2.3%)	0.567
Renal disease	11 (23.4%)	17 (13%)	0.092
Malignancy	5 (10.6%)	6 (4.6%)	0.131
Charlson Comorbidity score (mean ± SD)	4.13 ± 3.117	3.48 ± 2.869	0.582
Type of infection			
Bloodstream infection	16 (34%)	46 (35.1%)	0.895
Hospital-acquired pneumonia	11 (23.4%)	14 (10.7%)	0.031*
Ventilator-associated pneumonia	26 (55.3%)	95 (72.5%)	0.030*
Risk factors			
Previous steroid use	18 (38.3%)	55 (42%)	0.659
Previous hospitalization[1]	1 (2.1%)	3 (2.3%)	0.947
Previous antibiotics[2]	42 (89.4%)	116 (88.5%)	0.880
Prior AB infection[2]	5 (10.6%)	5 (3.8%)	0.082
AB colonization	20 (42.6%)	61 (46.6%)	0.636
Length of stay before infection	30.979 ± 34.76	20.137 ± 22.308	0.147
Central venous catheter	36 (76.6%)	117 (89.3%)	0.031*
Mechanical ventilation	44 (93.6%)	126 (96.2%)	0.466
Inotropic support	29 (61.7%)	92 (70.2%)	0.282
Continuous renal replacement therapy	8 (17%)	25 (19.1%)	0.755
Concomitant infection	22 (46.8%)	55 (42%)	0.567
Prior empirical antibiotic therapy	36 (76.6%)	79 (60.3%)	0.045*
Length of Intensive care unit stays	37.680 ± 26.697	32.939 ± 28.598	0.323
Length of hospital stays	75.702 ± 68.335	65.573 ± 53.061	0.301

[1] Within the last 6 months, [2]Within the last 3 months, * *P*-value is significant

the prevalence of AB colistin resistance is increasing globally, with high documented resistance rates in the Eastern Mediterranean and Southeast Asia [8]. Multiple antibiotic combinations have been suggested to manage difficult-to-treat MDR-AB infections, such as colistin combinations with carbapenems, tigecycline, rifampicin, sulbactam, ampicillin/sulbactam, and ceftolozan/tazobactam [17–20]. However, the outcomes of such combinations are still controversial.

The primary outcome investigated in our study was 30-day mortality. As presented in Figs. 3. and 4, Kaplan–Meier curves did not demonstrate significant differences in the 30-day mortality regardless of antimicrobial therapy options. These findings were consistent with previously reported outcomes regarding the combination with carbapenem, which showed comparable 30-day mortality [21–24]. In contrast, the efficacy of tigecycline in treating MDR-AB infections was quite controversial despite the

Table 2 Baseline laboratory test results of the study population

	Colistin monotherapy (*n* = 47)	Colistin-based combination therapy (*n* = 131)	*P*-value
White blood cells (WBC)	12.336 ± 8.732	14.095 ± 13.942	0.420
Hemoglobin (Hb)	8.770 ± 2.164	9.666 ± 2.472	0.029*
Platelets	186.091 ± 141.368	214.705 ± 153.981	0.266
Neutrophils (%)	76.481 ± 15.661	68.363 ± 23.056	0.027*
Prothrombin time (PT)	22.143 ± 17.684	20.014 ± 13.712	0.401
partial thromboplastin time (PTT)	49.153 ± 25.046	47.791 ± 20.592	0.714
C-reactive protein (CRP)	10.208 ± 8.228	8.650 ± 7.598	0.240
Procalcitonin	7.256 ± 13.525	7.683 ± 27.504	0.919
Total Protein	5.672 ± 1.0634	5.6696 ± 1.36642	0.991
Albumin	2.715 ± 0.639	2.757 ± 0.715	0.723
Aspartate transferase (AST)	44.810 ± 38.404	87.810 ± 159.898	0.070
Alanine transaminase (ALT)	46.890 ± 55.194	56.260 ± 80.844	0.463
Blood urea nitrogen (BUN)	50.940 ± 35.724	44.570 ± 40.463	0.342
Creatinine	1.697 ± 1.18654	1.757 ± 1.4151	0.795
Creatinine Clearance (CrCl)	67.896 ± 46.802	75.364 ± 49.434	0.369

* *P*-value is significant

synergistic effect observed in combination with colistin in vitro [25]. Earlier comparative studies reported a significantly higher mortality rate in ICU patients treated with tigecycline if its minimum inhibitory concentration (MIC) was more than 2 μg/mL [26]. In addition, comparing tigecycline monotherapy or (in combinations) with CMT or other CBCT reveals higher ICU mortality rates in patients treated with tigecycline options [18, 27]. However, the updated guideline of the Infectious Diseases Society of America (IDSA) for the management of infections caused by Gram-negative pathogens, international consensus guidelines for the optimal use of polymyxins, and European Society of Clinical Microbiology and Infectious Diseases guidelines considered the combination of tigecycline in high doses as a suitable option to treat moderate to severe MDR-AB infections [5, 9, 10].

A few previously conducted studies investigated the effectiveness of triple combinations. A study conducted by Abdul-Mutakabbir et al. demonstrates in vitro restored synergy of the triple CBCT (colistin, tigecycline, and meropenem) to previously AB-resistant isolates [28]. However, there is a lack of published comparative clinical studies proving such synergy in daily practice. In our study, the 30-day mortality rate of the triple CBCT was 17.4%, lower than the 30-day mortality of CMT or investigated double CBCT combinations, but this improvement was statistically insignificant.

Regarding the secondary outcomes, our study's one-year all-cause mortality rates were significantly lower in the CBCT groups compared to CMT, except for the colistin combination with tigecycline, which demonstrated less one-year all-cause mortality but was insignificant (Table 4).

In contrast, a review comparing MDR-AB therapy options, including CMT and colistin/ tigecycline combination, did not show any significant differences in all-cause mortality between investigated therapy options [29]. Also, Kwon et al. reported comparable all-cause mortality rates of CMT and tigecycline monotherapy [30]. This discrepancy in mortality rates may be explained by the heterogenicity of patient groups treated for MDR-AB infections and the differences in AB resistance mechanisms. Furthermore, the cause of death in MDR-AB-infected patients is frequently multifactorial, which may limit using of mortality as a reliable comparison variable.

In terms of the clinical cure, the cure rate was lower in the CMT group (27.7%) compared to all CBCT options, with the higher significant cure rate observed in combination with carbapenem (54.5%), which is consistent with previous studies showed better clinical outcomes of colistin /carbapenem combination compared to CMT [31, 32]. However, other earlier studies, including an international, randomized, double-blinded, controlled trial (OVERCOME study) by Kaye et al., an open-label, randomized controlled trial by Paul et al., as well as a meta-analysis conducted by Huang et al., did not reveal significant differences regarding the clinical response of both options [21, 23, 24, 33]. The discrepancy in our findings regarding the clinical cure with Kay et al. and Paul et al. randomized trials may be due to differences in the groups studied; 22% of patients included in Kaye et al.

Table 3 Univariate analysis of 30-day mortality variables among included patients

	Survivors ($n=138$)	Non-survivors ($n=40$)	*P*-value
Age (mean ± SD)	56.362 ± 20.401	56.975 ± 20.084	0.867
Gender (male)	88 (63.8%)	22 (55%)	0.315
Comorbidities			
Diabetes mellitus	57 (41.3%)	17 (42.5%)	0.892
Hypertension	62 (44.9%)	20 (50.0%)	0.571
Myocardial infarction	13 (9.4%)	3 (7.5%)	0.709
Heart failure	15 (10.9%)	4 (10.0%)	0.875
Peripheral vascular disease	6 (4.3%)	0	0..334
Cerebrovascular disease	35 (25.4%)	7 (17.5%)	0.303
Hemiplegia or paraplegia	26 (18.8%)	4 (10%)	0.189
Dementia or chronic cognitive deficit	7 (5.1%)	1 (2.5%)	0.686
Chronic pulmonary disease	15 (10.9%)	4 (10.0%)	0.875
Connective tissue disease	3 (2.2%)	0	0.347
Liver disease	2 (1.4%)	1 (2.5%)	0.536
Renal disease	20 (14.5%)	8 (20.0%)	0.340
Malignancy	6 (4.3%)	5 (12.5%)	0.072
Charlson Comorbidity score	3.565 ± 2.932	3.900 ± 2.968	0.527
Type of infection			
Bloodstream infection	42 (30.4%)	20 (50.0%)	0.022*
Hospital-acquired pneumonia	19 (13.8%)	6 (15.0%)	0.844
Ventilator-associated pneumonia	98 (71.0%)	23 (57.5%)	0.107
Risk factors			
Previous immunosuppressive therapy	49 (35.5%)	24 (60.0%)	0.005*
Previous hospitalization[1]	3 (2.2%)	1 (2.5%)	0.903
Previous antibiotics[2]	124 (89.9%)	34 (85.5%)	0.392
Prior AB infection[2]	8 (5.8%)	2 (5.0%)	0.847
AB colonization	64 (46.4%)	17 (42.5%)	0.665
Central venous catheter	119 (86.2%)	34 (85.0%)	0.844
Mechanical ventilation	132 (95.7%)	38 (95.0%)	0.861
Inotropic support	91 (65.9%)	30 (75.0%)	0.280
Continuous renal replacement therapy	24 (17.4%)	9 (22.5%)	0.464
Concomitant infection	55 (39.9%)	22 (55.0%)	0.089
Empirical antibiotic therapy	81 (58.7%)	34 (85%)	0.002*
Therapy Option			
Colistin monotherapy	36 (26.1%)	11 (27.5%)	0.859
Colistin-based combination	102 (73.9%)	29 (72.5%)	0.858
With tigecycline	42 (30.4%)	11 (27.5%)	0.721
With carbapenem	41 (29.7%)	14 (35.0%)	0.524
With tigecycline and carbapenem	19 (13.8%)	4 (10.0%)	0.532

[1] Within the last 6 months, [2] Within the last 3 months, * *P*-value is significant

trial were infected with carbapenem-resistant Enterobacteriaceae, while Paul et al. included patients with urosepsis in addition to those with VAP, HAP, or BSI.

Regarding the CBCT with tigecycline, our study demonstrated a significantly better cure rate than CMT (Table 4). An earlier study compared the clinical response of four treatment options for MDR-AB infections: tigecycline monotherapy, tigecycline-based combinations, CMT, and CBCT without tigecycline, revealed higher clinical failure in tigecycline groups [18]. Also, in their systematic review and meta-analysis, Kengkla et al. found that triple coverage (colistin, sulbactam, and tigecycline) demonstrated the highest clinical success. However, the tigecycline-based options were less effective [29]. In contrast, Kim et al. found comparable clinical success of CBCT and tigecycline-based therapy and concluded that

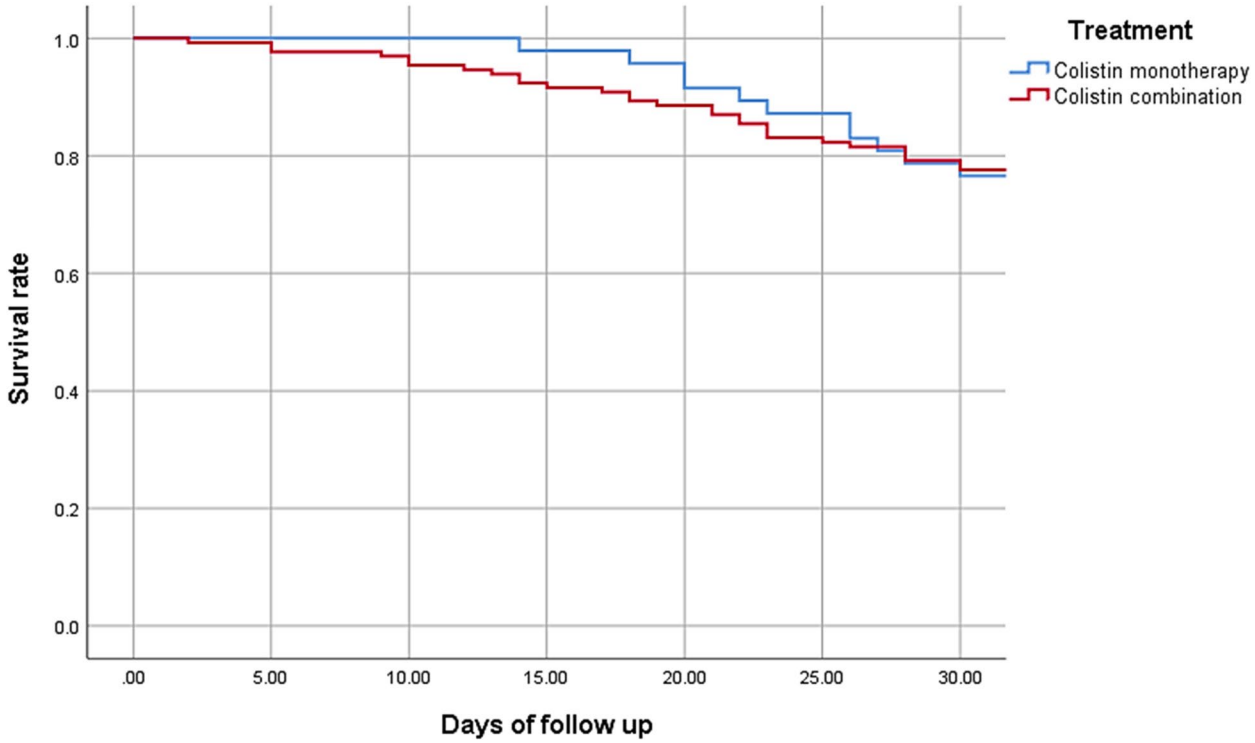


Fig. 3 Kaplan–Meier curves of 30-day mortality of colistin monotherapy vs. colistin-based combination therapy

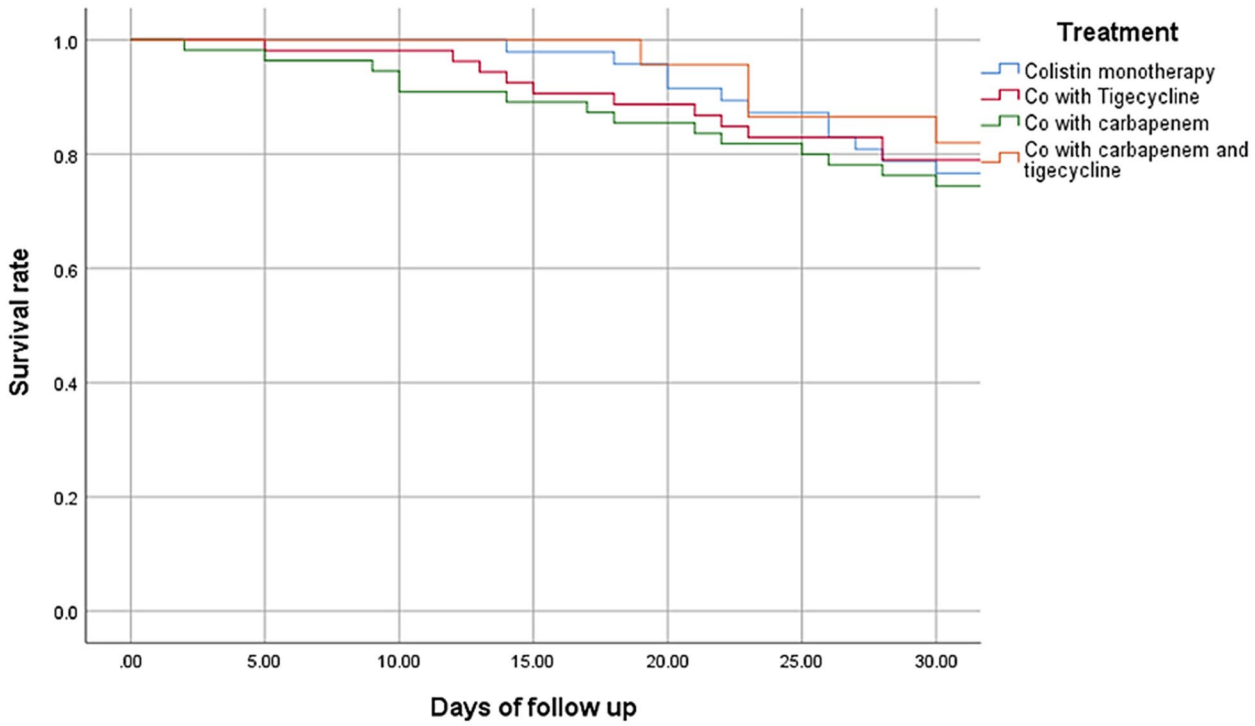


Fig. 4 Kaplan–Meier curves show 30-day mortality of all investigated antimicrobial combination therapy options

Table 4 Secondary outcomes of MDR-AB infections treated with CMT versus CBCT options

One-year All-cause mortality	**Survivors n (%)**	**Non-survivors n (%)**	**OR (95% CI)**	*P*-value
CMT	12 (25.5%)	35 (74.5%)		
All CBCT	69 (52.7%)	62 (47.3%)	3.25 (1.55–6.80)	0.001*
Combination with tigecycline	29 (54.7%)	24 (45.3%)	3.52 (1.51–8.25)	0.002*
Combination with carbapenem	32 (58.2%)	23 (41.8%)	4.06 (1.74–9.46)	0.001*
Combination with tigecycline and carbapenem	8 (34.8%)	15 (65.2%)	1.56 (0.53–4.58)	0.211
Clinical cure	**Yes n (%)**	**No n (%)**	**OR (95% CI)**	***P*-value**
CMT	13 (27.7%)	34 (72.3%)		
All CBCT	64 (48.9%)	67 (51.1%)	2.50 (1.21–5.16)	0.007*
Combination with tigecycline	26 (49.1%)	27 (50.9%)	2.52 (1.09–2.81)	0.015*
Combination with carbapenem	30 (54.5%)	25 (45.5%)	3.14 (1.37–7.2)	0.003*
Combination with tigecycline and carbapenem	8 (34.8%)	15 (65.2%)	1.39 (0.48–4.07)	0.271
Bacteriologic eradication	**Yes n (%)**	**No n (%)**	**OR (95% CI)**	***P*-value**
CMT	26 (55.3%)	21 (44.7%)		
All CBCT	81 (65.9%)	42 (34.1%)	1.55 (0.78–3.09)	0.205
Combination with tigecycline	30 (60.0%)	20 (40.0%)	1.21 (0.54–2.71)	0.641
Combination with carbapenem	37 (74.0%)	13 (26.0%)	2.29 (0.98–5.40)	0.056
Combination with tigecycline and carbapenem	14 (60.9%)	9 (39.1%)	1.26 (0.45–3.47)	0.440
Recurrence	**No recurrence n (%)**	**Recurrence n (%)**	**OR (95% CI)**	***P*-value**
CMT	9 (42.9%)	12 (57.1%)		
All CBCT	58 (72.5%)	22 (27.5%)	3.51 (1.30–9.48)	0.012*
Combination with tigecycline	21 (63.6%)	12 (36.4%)	2.33 (0.76–7.14)	0.137
Combination with carbapenem	28 (82.4%)	6 (17.6%)	6.22 (1.81–21.39)	0.004*
Combination with tigecycline and carbapenem	9 (69.2%)	4 (30.8%)	3.00 (0.69–12.93)	0.141

CMT Colistin monotherapy, *CBCT* Colistin-based combination therapy, *OR* odds ratio, *CI* confidence interval; * *P*-value is significant

combination therapy, in general, is better than monotherapy [34].

The recent study did not show a significantly better clinical cure rate for triple CBCT compared to CMT. However, in daily practice, such a combination is usually given to critically ill patients with more complicated infections and suspected poor outcomes. The triple combinationstill needs to be investigated. We found only one case report of using this combination in a renal transplant patient with MDR-AB bacteremia treated successfully with a favorable outcome [35].

Concerning bacteriologic response, the CBCT options demonstrated better bacteriologic eradication compared to CMT; however, the differences were statistically insignificant (Table 4).

Previous studies have also reported comparable bacteriologic eradication rates, whether AB-infected patients received CMT, ampicillin /sulbactam, or colistin /carbapenems [21, 23, 24, 36]. In addition, other published data showed better bacteriologic outcomes of colistin /carbapenem combination than CMT, whereas the tigecycline-based combination had less bacteriologic response [19, 26, 28, 29].

Regarding the recurrence of MDR-AB infections, CBCT groups showed less recurrence; the lowest rate was observed in the colistin /carbapenem combination group (17.6%), which was statistically significant compared to the CMT group (57.1%). The recurrence of AB infections is rarely investigated; in a previous study, the reported recurrence rate was 5.6% among patients with AB bacteremia, defined as relapse or reinfection [37]. The high rates of AB infection recurrence may reflect insufficient infection control interventions and suboptimal antimicrobial therapy with unfavorable outcomes.

Indeed, most published data demonstrate suboptimal clinical cures and limited microbiological response for the available antimicrobial therapy options, with relatively high failure rates even with dual combinations. This underscores the need for new effective antimicrobial agents or an alternative triple suitable combination to improve MDR-AB infection management. The updated IDSA guideline recommended the

combination of sulbactam-durlobactam /carbapenems as the preferred regimen to treat MDR-AB moderate to severe infections [5]. However, further comparative studies are needed to establish the superiority of such a combination.

Concerning mortality risk factors in patients with AB infection, previous studies reported the central lines, intubation, mechanical ventilation, ICU stay, AB pneumonia, longer hospital stays before developing AB bloodstream infection, malignancy, and high Acute Physiology and Chronic Health Evaluation (APACHE)-II score as mortality risk factors [38, 39]. The recent study identified the presence of AB bloodstream infection, previous immunosuppressive therapy, and receiving empirical antibiotic therapy as risk factors associated significantly with higher mortality.

Finally, our study has notable limitations. It is a retrospective observational study, which might be influenced by unmeasured confounders that could significantly affect the link between the administered antimicrobials and the observed outcomes. Furthermore, intrinsic limitations of retrospective study design, including the possibility of selection bias, information bias, and low quality of evidence, also impact the generalizability of the study results. Moreover, using colistin as a last resort antimicrobial to fight MDR-AB was not supported by molecular testing for the colistin resistance mechanism, which may affect the demonstrated outcomes of CMT and other investigated combinations.

Conclusions

This comparative study highlights the limitations of CMT and other investigated CBCT options for treating MDR-AB infections. It demonstrates the benefits of combination options, such as reduced one-year all-cause mortality, better clinical cure, higher microbiologic response, and less AB infection recurrence. However, the high mortality rates underscore the urgent need for developing new potent antimicrobials. Furthermore, the study results emphasize the need for additional comparative research, including prospective randomized controlled trials, large-scale studies using systematic molecular diagnostics, and investigating available triple combination therapy options.

Abbreviations

AB	*Acinetobacterbaumannii*
MDR-AB	Multidrug-resistant Acinetobacter baumannii
ICU	Intensive care unit
BSI	Bloodstream infection
HAP	Hospital-acquired pneumonia
VAP	Ventilator-associated pneumonia
CMT	Colistin monotherapy
CBCT	Colistin-based combination therapy
IDSA	Infectious Diseases Society of America

Supplementary Information

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Supplementary Material 1.

Authors' contributions

Dr. Marwan Jabr Alwazzeh (M.J.A.), Dr. Jumanah Algazaq (J.A.), Dr. Fatimah Ali Al-Salem (F.A.A.), Dr. Fatimah Alabkari (F.A.), Dr. Sara M. Alwarthan (S.A.), Dr Mashael Alhajri (M.A.H), Dr. Bashayer M. AlShehail (B.A.S.), Dr. Amani Alnimr (A.A.), Dr. Ahmad Wajeeh Alrefaai (A.W.A.), Dr. Faten Hussain Alsaihati (F.H.A.), Fahd Abdulaziz Almuhanna (Fa. A.A) Conceptualization, M.J.A., and J.A.; Methodology, M.J.A, S.A. and M.A.H.; Formal Analysis, J.A., B.A.S., A.A.; Data Curation, F.A.A., F.A, A.W.A, and F.H.A.; Writing – Original Draft Preparation, M.J.A., J.A., A.W.A., and S.A.; Writing – Review & Editing, M.J.A., Fa.A.A, and B.A.S., and M.A.H. All authors reviewed the final manuscript.
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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

The study was conducted according to the Declaration of Helsinki of the World Medical Association on ethical principles of medical research. The research project has been approved by the Institutional Review Board (IRB) at Imam Abdulrahman bin Faisal University (IRB-2024–01–263). The IRB waived the need for informed consent from the patients involved as the data were analyzed retrospectively and anonymously.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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