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Research Article

Colistin Combined with Ampicillin–Sulbactam versus Colistin Monotherapy for Carbapenem-Resistant Acinetobacter baumannii Ventilator-Associated Pneumonia: A Retrospective Comparative Non-Randomized Cohort Analysis of Microbiological Eradication and 30-Day Mortality

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ABSTRACT

Background: Carbapenem-resistant *Acinetobacter baumannii* (CRAB) ventilator-associated pneumonia (VAP) is associated with high mortality and limited therapeutic options. In settings where sulbactam–durlobactam is unavailable, colistin-based regimens and ampicillin–sulbactam are frequently used. We performed a limited retrospective comparative cohort analysis of critically ill patients with CRAB-VAP treated with colistin plus ampicillin–sulbactam or colistin monotherapy. The aim of the study is to compare microbiological eradication and 30-day all-cause mortality between colistin combined with ampicillin–sulbactam (combination) and colistin monotherapy in critically ill patients with CRAB-VAP.

Methods: This single-center retrospective, non-randomized comparative analysis included adults with microbiologically confirmed CRAB-VAP treated in a tertiary mixed ICU in Plovdiv, Bulgaria, from January 2025 through March 2026. In the combination group, 15/16 patients received intravenous colistin plus ampicillin–sulbactam 3 g every 8 h (sulbactam 3 g/day) by extended infusion over 3–4 h, while only 1 patient received 4 g of ampicillin–sulbactam every 8 h by extended infusion plus colistin. All patients received a colistimethate sodium (CMS) loading dose of 9 MIU followed by 3 MIU every 8 h in patients with normal renal function, and maintenance adjustment was done according to renal function in patients with renal injury; the monotherapy group received intravenous colistin alone. The primary outcomes were microbiological eradication on follow-up tracheal aspirate culture and 30-day all-cause mortality. Fisher's exact test and Mann–Whitney U test were used for unadjusted comparisons. Given the limited sample size and baseline imbalances, results are interpreted as associations rather than treatment effects.

Results: Eighteen patients were screened for combination treatment; two were excluded: one had bloodstream infection as the primary infectious focus, and one died before antimicrobial treatment initiation, leaving 16 patients in the combination group. Sixteen patients receiving colistin monotherapy in the close time frame were analyzed, for a final cohort of 32 patients. Microbiological eradication occurred in 8/16 (50.0%) patients receiving combination therapy and 4/16 (25.0%) receiving monotherapy (unadjusted odds ratio [OR], 3.00; 95% confidence interval [CI], 0.68–13.3; Fisher's exact p=0.273). Thirty-day all-cause mortality was 5/16 (31.25%) in the combination group and 12/16 (75.0%) in the monotherapy group (unadjusted OR

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for death, 0.15; 95% CI, 0.03–0.76; Fisher's exact p=0.032). Colistin treatment duration was shorter in the combination group than in the monotherapy group: median 9.0 days (IQR, 7.75–10.0) versus 13.5 days (IQR, 9.75–14.0), respectively (Mann–Whitney U=47.0; exact p=0.0017). Patients receiving monotherapy were older and had substantially higher baseline procalcitonin concentrations. These imbalances may have contributed to the observed outcome differences.

Conclusion: In this small, retrospective, non-randomized cohort, colistin plus ampicillin-sulbactam was associated with lower observed 30-day mortality than colistin monotherapy. Microbiological eradication was numerically higher but was not statistically significantly different between groups. Causal inference is not justified because of the small sample, non-randomized treatment allocation, and imbalance in baseline age and inflammatory severity. Prospective multicenter studies with standardized dosing and adequate confounder control are required.

Introduction

Acinetobacter baumannii is a Gram-negative opportunistic coccobacillus and an important cause of healthcare-associated infection in intensive care units worldwide. Carbapenem-resistant *A. baumannii* (CRAB) has been classified by the World Health Organization as a critical-priority pathogen because of the scarcity of effective therapies and the clinical consequences of multidrug-resistant, extensively drug-resistant, and pandrug-resistant isolates [1]. CRAB ventilator-associated pneumonia (VAP) is associated with substantial morbidity and mortality in critically ill patients [2].

The burden of carbapenem resistance among *Acinetobacter* spp. remains high in many European settings, including Bulgaria [3-4]. At the Clinic of Anesthesiology and Intensive Care (CAIC), University Hospital "St. George" EAD, Plovdiv, *A. baumannii* remained a frequent ICU isolate during local microbiological surveillance from 2021 to 2025. In this context, optimizing treatment with available antimicrobial agents is clinically important.

Current guidance identifies sulbactam–durlobactam as the preferred option for serious CRAB infection when available [5]. However, access remains limited in many settings. Ampicillin–sulbactam is an alternative option because sulbactam has intrinsic antibacterial activity against *A. baumannii* through binding to penicillin-binding proteins and inhibition of cell-wall synthesis [6]. Colistin disrupts the bacterial outer membrane and may facilitate access of sulbactam to its targets, providing a biologically plausible rationale for combination treatment [6-7]. Clinical data supporting colistin-containing combination regimens remain heterogeneous. Observational studies are vulnerable to confounding by indication, differences in illness severity, dosing variability, and variation in microbiological follow-up. Accordingly, local retrospective analyses should be framed as hypothesis-generating and interpreted cautiously.

This study aimed to compare observed microbiological eradication and 30-day all-cause mortality among patients with CRAB-VAP treated with colistin plus ampicillin–sulbactam versus colistin monotherapy.

Methods

Study design and setting

This was a single-center retrospective, non-randomized comparative cohort study conducted in the 28-bed mixed medical–surgical CAIC, University Hospital "St. George" EAD, Plovdiv, Bulgaria. The observation period was from January 2025 to March 2026.

Treatment allocation was determined by the treating clinical team as part of routine care and was not randomized or protocol-controlled. The study therefore evaluates associations between treatment strategy and outcomes and cannot establish comparative treatment efficacy.

Patient selection

Adults aged 18 years or older were eligible if they met all of the following criteria:

1. Invasive mechanical ventilation for at least 48 h.
2. VAP is defined by a new or worsening radiological infiltrate plus at least two compatible clinical criteria: fever >38.0°C or hypothermia <36.0°C, leukocytosis or leukopenia, or purulent tracheal secretions.
3. Microbiological confirmation of CRAB from tracheal aspirate.
4. Treatment with either colistin plus ampicillin-sulbactam or colistin monotherapy.

Patients were excluded if bloodstream infection rather than VAP was the primary infectious focus, if death occurred before antimicrobial treatment initiation, if therapy was discontinued before meaningful exposure assessment, or if outcome data were insufficient for classification of primary endpoints.

Patient flow

A total of 34 potentially eligible patients were screened: 18 for the combination-treatment strategy and 16 for colistin monotherapy. Two patients from the

combination-treatment screening cohort were excluded. One had bloodstream infection as the primary infectious focus, and one died before antimicrobial treatment initiation. The final analytical cohort included 32 patients: 16 in the colistin plus ampicillin–sulbactam group and 16 in the colistin-monotherapy group.

Treatment regimens

Colistin

All patients with normal renal function in the monotherapy or combination therapy group received colistimethate sodium (CMS) as a 9 million international unit (MIU) intravenous loading dose, followed by 3 MIU intravenously every 8 h, equivalent to 9 MIU/day, when renal function allowed. Maintenance dosing was adjusted according to renal function using the institutional CMS dosing protocol [8]. Group-level CMS dosing characteristics are summarized in Supplementary Table S1.

For internationally interpretable reporting, 1 MIU CMS corresponds approximately to 80 mg CMS and approximately 30 mg colistin base activity (CBA) [8]. Therefore, the 9 MIU loading dose corresponds to approximately 720 mg CMS or 270 mg CBA, and the standard maintenance regimen of 3 MIU every 8 h (9 MIU/day) corresponds to approximately 720 mg CMS/day or 270 mg CBA/day [8].

Weight-normalized exposure was calculated from actual body weight as dose (mg CBA/kg) = administered dose (mg CBA) / actual body weight (kg).

Mean actual body weight was 77 kg in the combination group and 81 kg in the monotherapy group. The 9 MIU loading dose therefore corresponded to approximately 3.5 mg CBA/kg (0.117 MIU/kg) in the combination group and 3.3 mg CBA/kg (0.111 MIU/kg) in the monotherapy group. In patients without renal adjustment, the 9 MIU/day maintenance regimen corresponded to the same values per day (approximately 3.5 and 3.3 mg CBA/kg/day, respectively).

Seven of 16 patients in the colistin plus ampicillin–sulbactam group and 5 of 16 patients in the colistin-monotherapy group required renal adjustment of colistin maintenance therapy. The loading dose was not reduced solely because of renal impairment; maintenance dose and/or interval were adjusted according to estimated creatinine clearance and renal replacement therapy status under the institutional protocol.

Renal-adjusted maintenance doses followed the institutional protocol presented in Supplementary Table S2, based on estimated creatinine clearance (CrCl). Colistin therapeutic drug monitoring was unavailable and unperformed.

Ampicillin–sulbactam

The combination group received ampicillin–sulbactam 3 g intravenously every 8 hours as an extended infusion over 3–4 hours. One patient received 4 g every 8 hours; because this was a single case, no separate analysis of the higher dose was possible. With the 2:1 ampicillin-to-sulbactam formulation used, each 3-g dose contains 1 g of sulbactam; thus, the regimen provided 3 g of sulbactam per day.

This exposure was lower than the high-dose ampicillin–sulbactam regimens evaluated in patients with multidrug-resistant A. baumannii VAP [9] and lower than the 9–12 g/day sulbactam regimens compared in a randomized trial of colistin plus sulbactam [10]; therefore, the regimen used in this cohort should not be characterized as high-dose sulbactam.

Renal dose adjustment

Colistin maintenance dosing was adjusted according to estimated CrCl using the institutional CMS protocol (Supplementary Table S2): CrCl ≥80 mL/min, no adjustment; 50–79 mL/min, 2.5–3.8 mg CBA/kg/day divided every 12 h; 30–49 mL/min, 2.5 mg CBA/kg/day once daily or divided every 12 h; 10–29 mL/min, 1.5 mg CBA/kg every 36 h. The loading dose was not reduced for renal impairment.

Microbiological methods

Tracheal aspirate cultures were obtained at baseline and repeated during treatment according to clinical practice (approximately every 2–3 days, starting from day 5). CRAB identification and antimicrobial susceptibility testing were performed using standard laboratory methods.

Microbiological eradication was defined as conversion from a positive baseline CRAB tracheal aspirate culture to a negative follow-up culture. Patients who died or had no follow-up culture before repeat sampling were classified as not eradicated.

Endpoints

The primary endpoints were microbiological eradication on follow-up tracheal aspirate culture and 30-day all-cause mortality.

Secondary endpoints were changes in leukocyte count and procalcitonin and colistin and ampicillin–sulbactam treatment duration.

Statistical analysis

Categorical variables were compared using two-sided Fisher's exact test. Continuous variables were compared using the two-sided exact Mann–Whitney U test because of the small sample size and possible non-normal distributions. Categorical data are reported as counts and percentages, and continuous data are reported as mean ± standard deviation or median (interquartile range), as appropriate. Crude odds ratios with 95% confidence intervals were used for binary outcomes.

Because the cohort included only 32 patients and 17 deaths, multivariable logistic regression adjusting for

age and procalcitonin was not performed: with fewer than ten outcome events per covariate and near-complete separation of procalcitonin values between groups, such a model would be overfitted and its estimates unreliable. All comparisons are therefore unadjusted and are reported as associations. Thirty-day all-cause mortality was analyzed as a fixed binary endpoint. Complete and reliable individual patient time-to-death or censoring data were unavailable for all participants; therefore, no time-to-event analysis or Kaplan–Meier survival curve was performed.

Ethics

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by the Commission on Scientific Ethics of Medical University–Plovdiv (Opinion/Registration No. PKHE-117/29.07.2026; Protocol No. 10, dated 8 July 2026). In its opinion, the Commission confirmed that the research met the applicable standards and criteria for scientific and ethical conduct and complied with the Declaration of Helsinki, the principles of Good Clinical Practice, and applicable Bulgarian laws and regulations governing clinical and scientific research involving human participants. No intervention beyond standard clinical care was performed.

Results

The final analytical cohort consisted of 32 patients, 16 in each treatment group. Baseline differences were present. Patients receiving colistin monotherapy were older than patients receiving colistin plus ampicillin–sulbactam (60.4 ± 19.3 versus 46.2 ± 20.5 years; p=0.048). Baseline procalcitonin was also higher in the monotherapy group (median 124.0 [IQR 69.0–130.5] versus 1.3 [0.7–2.1] ng/mL; p=0.009). The typical local CRAB antimicrobial susceptibility profile is presented in Table 1. Baseline characteristics and clinical outcomes are summarized in Table 2. These findings suggest differences in baseline risk and inflammatory severity. They are clinically important potential confounders of both mortality and microbiological outcomes.

Primary outcomes

Microbiological eradication was documented in 8/16 (50.0%) patients in the combination group and 4/16 (25.0%) patients in the monotherapy group. The crude OR for eradication was 3.00 (95% CI, 0.68–13.3; two-sided Fisher's exact p=0.273). Thirty-day all-cause mortality occurred in 5/16 (31.25%) patients in the combination group and 12/16 (75.0%) patients in the monotherapy group. The crude OR for death was 0.15 (95% CI, 0.03–0.76; two-sided Fisher's exact p=0.032).

Secondary outcomes

The day of ICU-acquired VAP onset was comparable between groups: median 10.0 days (IQR 8–15) in the combination group and 11.0 days (IQR 6–14) in the monotherapy group (p=0.730).

Baseline leukocyte count was 15.2 ± 6.3 × 10⁹/L in the combination group and 10.7 ± 14.2 × 10⁹/L in the monotherapy group (p=0.068). Colistin treatment duration was significantly shorter in the combination group than in the monotherapy group: median 9.0 days (IQR 7.75–10.0; range 6–12) versus 13.5 days (IQR 9.75–14.0; range 6–16), respectively (Mann–Whitney U=47.0; two-sided exact p=0.0017). Ampicillin–sulbactam was co-administered for the entire colistin course in the combination group (median 9.0 days; IQR 7.75–10.0).

Discussion

In this retrospective, non-randomized comparative cohort, colistin plus ampicillin–sulbactam was associated with lower observed 30-day all-cause mortality than colistin monotherapy. Microbiological eradication was numerically more frequent in the combination group, but the between-group difference was not statistically significant.

Table 1- Typical local CRAB antibiogram

Antibiotic	Result	Comment
Imipenem	Resistant	Carbapenem resistance
Meropenem	Resistant	Carbapenem resistance
Cefepime	Resistant	—
Ceftazidime	Resistant	—
Piperacillin–tazobactam	Resistant	—
Ciprofloxacin	Resistant	—
Levofloxacin	Resistant	—
Gentamicin	Resistant	—
Amikacin	Resistant	—
Trimethoprim–sulfamethoxazole	Resistant	—
Ampicillin–sulbactam	Variable	Interpretation should be based on current susceptibility criteria and dose exposure
Colistin	Susceptible	Interpret with the current accepted testing methodology

Table 2- Baseline characteristics and outcomes

Parameter	Colistin + ampicillin–sulbactam (n=16)	Colistin monotherapy (n=16)	Statistical note
Age, mean ± SD, years	46.2 ± 20.5	60.4 ± 19.3	p=0.048
PCT at treatment start, median (IQR), ng/mL	1.3 (0.7–2.1)	124.0 (69.0–130.5)	p=0.009
VAP onset day from ICU admission, median (IQR)	10.0 (8–15)	11.0 (6–14)	p=0.730
Leukocyte count at treatment start, mean ± SD, ×10⁹/L	15.2 ± 6.3	10.7 ± 14.2	=0.068
Renal-adjusted CMS maintenance dosing, n/N (%)	7/16 (43.75)	5/16 (31.25)	Institutional renal protocol
Colistin TDM performed	0/16 (0)	0/16 (0)	Not available
Microbiological eradication, n/N (%)	8/16 (50.0)	4/16 (25.0)	Crude OR 3.00; 95% CI 0.68–13.3; Fisher's exact p=0.273
30-day all-cause mortality, n/N (%)	5/16 (31.25)	12/16 (75.0)	Crude OR 0.15; 95% CI 0.03–0.76; Fisher's exact p=0.032
Colistin treatment duration, median (IQR), days	9.0 (7.75–10.0)	13.5 (9.75–14.0)	Mann–Whitney U=47.0; exact p=0.0017
Colistin treatment duration, range, days	6–12	6–16	—
Ampicillin–sulbactam duration, median (IQR), days	9.0 (7.75–10.0), if coterminous with colistin	Not applicable	—

These results should be interpreted cautiously because treatment assignment was not randomized, and important baseline imbalances were present: patients treated with monotherapy were older and had markedly higher baseline procalcitonin concentrations. Both variables may be associated independently with disease severity and mortality. The local CRAB antimicrobial susceptibility profile is summarized in Table 1. The observed microbiological eradication rate was 50.0% in the combination group and 25.0% in the monotherapy group. The crude odds ratio favored combination therapy, but the confidence interval was wide and included the null value (OR 3.00; 95% CI 0.68–13.3; p=0.273).

The study therefore did not demonstrate a statistically significant difference in microbiological eradication. The endpoint may also have been affected by missing follow-up cultures, death before repeat sampling, extubation, and variation in microbiological sampling.

Thirty-day mortality was 31.25% in the combination group and 75.0% in the monotherapy group. The unadjusted mortality association was statistically significant (OR 0.15; 95% CI 0.03–0.76; p=0.032), but it may have been influenced by confounding by indication, age, baseline inflammatory severity, comorbidity, renal dysfunction, source control, timing of antimicrobial therapy, adjunctive treatment, and other differences in supportive care. The study was not designed or powered to determine whether the mortality difference was independent of these factors. Colistin treatment duration was shorter in the combination group than in the monotherapy group. This difference may reflect clinical response, differential survival, clinician-directed treatment decisions, or baseline case-mix differences. It should not be interpreted as evidence that shorter therapy caused better outcomes.

Ampicillin–sulbactam was co-administered throughout the colistin course (median 9.0 days). The pharmacologic rationale for combining colistin with ampicillin–sulbactam is biologically plausible. Colistin disrupts the bacterial outer membrane, and sulbactam has intrinsic activity against A. baumannii through penicillin-binding protein targets. However, the current study cannot determine whether the observed association reflects pharmacologic synergy, differences in baseline risk, differences in drug exposure, or unmeasured confounding. Moreover, the sulbactam exposure in this cohort (3 g/day) was lower than in high-dose regimens, so the findings cannot be extrapolated to 9–12 g/day sulbactam strategies.

All patients received a 9 MIU CMS loading dose and, when renal function permitted, a 3 MIU every-8-hour maintenance regimen. Renal dose adjustment was required in 7 patients in the combination group and 5 patients in the monotherapy group. Because colistin therapeutic drug monitoring was not available, individual drug exposure could not be confirmed. This pharmacokinetic uncertainty is a further limitation, particularly in critically ill patients with changing renal function, augmented renal clearance, obesity, or renal replacement therapy. Multivariable adjustment for age

and procalcitonin was considered but not performed because the small cohort and the limited number of events would produce an overfitted, unstable model. Larger studies are needed to determine whether the mortality association persists after adjustment for these confounders.

Limitations

As with any retrospective, single-center study, these results should be interpreted in the context of its design. Treatment was allocated by the treating physicians rather than randomized, and the monotherapy group was older (60.4 vs. 46.2 years) and had higher baseline procalcitonin (124.0 vs. 1.3 ng/mL). Given the modest cohort (16 patients per group; 17 deaths), multivariable adjustment was not feasible; the findings therefore represent unadjusted associations, and the eradication comparison had limited statistical power. Colistin was administered as a fixed MIU regimen with protocol-based renal adjustment, and individual exposure could not be confirmed because therapeutic drug monitoring was unavailable; weight-normalized doses are estimates based on group mean body weight. Sulbactam exposure (predominantly 3 g/day) was below that of high-dose regimens, so extrapolation to 9–12 g/day strategies is not possible.

Colistin duration differed between groups (9.0 vs. 13.5 days), which may partly reflect differential survival; follow-up cultures were clinically directed, and patients who died before repeat sampling were classified as not eradicated. Mortality was analyzed as a fixed 30-day endpoint, as complete time-to-event data for Kaplan–Meier analysis were unavailable. Finally, the results reflect local epidemiology and practice, and two of 18 screened combination-group patients were excluded (one primary bloodstream infection, one death before treatment initiation). Larger prospective studies are warranted to confirm these observations.

Conclusion

Among 32 critically ill patients with CRAB-VAP in this retrospective, non-randomized single-center cohort, colistin plus ampicillin-sulbactam was associated with lower observed 30-day mortality than colistin monotherapy. Microbiological eradication was numerically higher with combination therapy but was not statistically significantly different between groups. These findings are hypothesis-generating and do not prove comparative efficacy because treatment groups differed in age and baseline procalcitonin, the sample was small, and residual confounding is likely. Prospective multicenter studies with standardized dosing, verified sulbactam exposure, pharmacokinetic monitoring, predefined microbiological follow-up, and adequate confounder control are needed.

Ethics approval and consent to participate

This study was approved by the Commission on Scientific Ethics of Medical University–Plovdiv (Opinion/Registration No. PKHE-117/29.07.2026; Protocol No. 10, dated 8 July 2026). In its opinion, the Commission confirmed that the research met the applicable standards and criteria for scientific and ethical conduct and complied with the Declaration of Helsinki, the principles of Good Clinical Practice, and applicable Bulgarian laws and regulations governing clinical and scientific research involving human participants.

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Supplementary

Supplementary Table S1- Colistimethate sodium dosing and renal adjustment

Variable	Combination group	Monotherapy group
Patients, n	16	16
CMS loading dose	9 MIU IV	9 MIU IV
Standard maintenance regimen when renal function allowed	3 MIU IV every 8 h	3 MIU IV every 8 h
Standard total daily dose when renal function allowed	9 MIU/day	9 MIU/day
Approximate standard total daily CBA exposure	≈270 mg CBA/day (720 mg CMS/day)	≈270 mg CBA/day (720 mg CMS/day)
Patients requiring renal adjustment, n/N (%)	7/16 (43.75)	5/16 (31.25)
Patients not requiring renal adjustment, n/N (%)	9/16 (56.25)	11/16 (68.75)
Colistin TDM	Not available	Not available
Exact renal categories and dose/interval modifications	See Supplementary Table S2.	See Supplementary Table S2.

Supplementary Table S2- Institutional protocol for colistin dosing, CAIC "St. George", Plovdiv, Bulgaria (MIU equivalents calculated as 1 MIU ≈ 30 mg CBA)

Renal function	Maintenance dose, CBA	Approximate MIU equivalent	Suggested frequency
CrCl ≥80 mL/min	2.5–5 mg CBA/kg/day	0.083–0.167 MIU/kg/day	No adjustment: 3 MIU every 8 h
CrCl 50–79 mL/min	2.5–3.8 mg CBA/kg/day	0.083–0.127 MIU/kg/day	Divided every 12 h
CrCl 30–49 mL/min	2.5 mg CBA/kg/day	0.083 MIU/kg/day	Once daily or divided every 12 h
CrCl 10–29 mL/min	1.5 mg CBA/kg	0.050 MIU/kg	Every 36 h