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Original Article

A retrospective analysis of carbapenem-resistant *Acinetobacter baumannii* infections in critically ill patients: Experience at a tertiary-care teaching hospital ICU

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ABSTRACT

Background: *Acinetobacter baumannii* is a clinically significant pathogen with a high incidence of multidrug resistance that is associated with life-threatening nosocomial infections. Here, we aimed to provide an insight into the clinical characteristics and outcomes of a unique group of *A. baumannii* infections in which the isolates were resistant to carbapenems and most other antibiotic groups in a tertiary-care intensive care unit (ICU).

Methods: We performed a retrospective observational study in which records of patients hospitalized in the ICU between June 1, 2021 and June 1, 2023 were reviewed. We checked the clinical, laboratory, and microbiological records of all adult patients who had carbapenem-resistant *A. baumannii* (CRAB) infections. Prior antibiotic treatments and definitive antibiotic treatments after culture positivity and susceptibility test results were recorded. C-reactive protein (CRP) and procalcitonin levels and leukocyte counts were noted. Length of ICU stay and 30-day mortality were defined as the outcome parameters.

Results: During the study period, 57 patients were diagnosed with CRAB infections. The respiratory tract was the leading infection site (80.7%). In non-survivors, bloodstream infections (21.9% *vs.* 4.0% P=0.05) and colistin-resistant (col-R) CRAB infections (43.8% *vs.* 24.0%, P=0.12) were more common than in survivors, but these parameters were not statistically significant. The length of ICU stay was not different between survivors and non-survivors. Overall, the rate of col-R among CRAB clinical isolates was 35.1%. The 30-day mortality in all patients with CRAB infection was 56.1%. Mortality in col-R CRAB and colistin-susceptible (col-S) CRAB infections was 70.0% and 48.6%, respectively (P=0.12). Prior carbapenem use was 56.1%. Prior colistin use before col-R and col-S CRAB infections was not significant (35.0% *vs.* 27.0%, P=0.53).

Conclusions: Our study provides real-world data on highly resistant *A. baumannii* infections and shares the characteristics of infections with such resistant strains. Unfortunately, carbapenem resistance in *A. baumannii* is a challenge for intensive care specialists who are faced with few treatment options, and colistin resistance further complicates the problem.

Introduction

Acinetobacter baumannii is a clinically significant pathogen that relates to life-threatening nosocomial infections including pneumonia, bacteremia, and wound and urinary tract infections, especially in the intensive care unit (ICU) setting. The high incidence of multidrug resistant (MDR) *A. baumannii* has markedly reduced the treatment options.[1,2] As a result, MDR *A. baumannii* infections are relevant owing to the increased ICU length of stay and high mortality.[1,3] The rise of MDR *Acinetobacter* infections has necessitated the use of carbapenems both in Turkey and worldwide.[4] The widespread use of carbapenems, especially in ICUs, has resulted in an increase in carbapenem-resistant A. baumannii (CRAB) infections, which is

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a critical (priority 1) microorganism per the World Health Organization (WHO) pathogen list and urgent needs the development of new antibiotics.[5] The prevalence of MDR *Acinetobacter* spp. was reported with increasing frequency by the European Centre for Disease Prevention and Control (ECDC), with rates of carbapenem-resistant strains being >50% in more than half of the European countries.[4,6]

Treatment of CRAB infections often requires colistin methanesulfonate (CMS) because any antibiotic susceptibility other than colistin is hardly detected. However, the widespread use of colistin is now a threat to the emergence of colistin-resistant (col-R) CRAB infections in ICUs.[7–9] More recently, new studies have reported higher mortality rates with col-R CRAB infections,[8–10] and optimal treatment strategies have become more important for these resistant pathogens.

The aim of the study is to provide insight into the clinical characteristics and outcomes of CRAB infections in a tertiary-care ICU.

Methods

This observational retrospective study was conducted in a university hospital medical ICU between June 1, 2021 and June 1, 2023.

The hospital is an 834-bed teaching hospital, and the study was carried out in the 11-bed adult, medical ICU. The latest rates of invasive device-related infections in the unit are as follows: central line-associated bloodstream infections, 0.75%; ventilator-associated pneumonia (VAP), 12.98%; and catheter-associated urinary tract infections, 5.48%.

We reviewed the clinical, laboratory, and microbiological records of all adult patients who had CRAB infections. This study was approved by the local ethics committee on June 1, 2023 (Approval No.: 2023/337).

Definitions

VAP is suspected when a patient develops the following symptoms and signs after at least 48 h of mechanical ventilation: at least one of the following; (1) new onset of fever (≥38 °C) or hypothermia (≤35 °C); (2) leukocytosis or leukopenia; and at least two of the following; (3) new onset of purulent sputum or change in character of sputum or increased respiratory secretions, (4) worsening gas exchange (oxygen desaturation, increased oxygen requirement, increased ventilator demand), and (5) new or progressive persistent infiltrate on chest radiography or computed tomography. Deep endotracheal aspirate cultures and microscopic evaluations were assessed if the results were significant for VAP.[11]

Bloodstream infection is defined as a positive blood culture of a recognized pathogen or the combination of clinical symptoms (fever >38 °C, chills, hypotension) and two positive blood cultures of a common skin contaminant from two separate blood samples drawn within 48 h.[12]

Wound infection is described as non-surgical wounds with signs of inflammation, purulent discharge, foul odor, and significant bacterial growth in tissue culture with or without systemic signs.[13]

MDR *Acinetobacter* is defined as acquired nonsusceptibility to at least one agent in three or more antimicrobial categories, whereas CRAB is often resistant to nearly all antibiotic classes including the broad-spectrum carbapenem drugs such as meropenem, imipenem, and doripenem.[14,15]

Data collection

Patients' age, sex, comorbidities, Charlson Comorbidity Index, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and sequential organ failure assessment (SOFA) score at the time of CRAB infection were recorded. Invasive mechanical ventilation requirements, renal replacement therapy, and central venous catheter insertion before the CRAB infection episode were documented. Deep endotracheal aspirate cultures and blood and wound cultures that grew CRAB in patients with the above infection definitions and their resistance patterns were recorded. Prior antibiotic treatments and definitive antibiotic treatments after culture positivity and susceptibility test results were also recorded. C-reactive protein (CRP) and procalcitonin levels and leukocyte counts were noted. For all patients, days from ICU admission to positive infection cultures and days from hospital admission to ICU admission were also recorded. Length of ICU stay and 30-day mortality were defined as the outcome parameters.

Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) (MALDI Biotyper®, Bruker Daltonics GMBH, Bremen, Germany) mass spectrometry was used for bacterial identification and antimicrobial susceptibility tests, per the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards. A broth microdilution test was used for colistin susceptibility in the hospital's central laboratory.

Statistical analysis

SPSS (IBM Corporation, Armonk, NY, USA) version 25.0 was used for all statistical analyses. Quantitative variables were expressed as medians (interquartile range [IQR]) and categorical variables as numbers (percentage). Patient characteristics were described according to study groups (with and without col-R CRAB) and patients (survivors and non-survivors) with formal statistical comparisons. For all comparisons, $P<0.05$ was considered to indicate statistical significance.

Results

According to the hospital and patient records, 582 patients were hospitalized in the ICU during the study period and 57 patients were diagnosed with CRAB infections. The median age was 70 (IQR: 61–83) years, and 33 (57.8%) were male. The median APACHE II score was 25 (IQR: 20–30), the SOFA score was 8 (IQR: 5–10), and the Charlson Comorbidity Index was 7 (IQR: 5–8). Hypertension (64.9%) was the most frequent comorbidity, and the respiratory tract was the leading infection site (80.7%) in CRAB infections, followed by bloodstream (14.0%) and wound infections (5.2%). In two patients, CRAB culture growth was determined in more than one infection site (blood and respiratory tract).

Table 1 represents a descriptive analysis of the baseline characteristics of ICU outcomes of CRAB infections (survivors *vs.* non-survivors). Survivors and non-survivors were similar according to age, comorbidities, severity scores, and some treatment modalities. When compared to survivors, non-survivors had higher malignancy rates (P <0.01) and more invasive mechanical ventilation support (P=0.04). Bloodstream infections (21.9% *vs.* 4.0% P=0.05) and col-R CRAB infections (43.8% *vs.* 24.0%, P=0.12) were more common in non-survivors than survivors, but these differences were not significant. The length of ICU stay was not different between the survivors and non-survivors. The overall rate of col-R among CRAB clinical isolates was 35.1% (20/57) (Table 1). The minimum inhibitory concentration (MIC) range of the col-R isolates was between 4 mg/L and ≥64 mg/L.

Baseline characteristics of the groups according to colistin susceptibility are presented in Table 2. Patients with col-R CRAB infections had significantly more renal replacement therapy (P<0.01). The 30-day mortality in all patients with CRAB infection was 56.1%. Mortality in col-R CRAB and colistin-susceptible (col-S) CRAB infections was 70.0% and 48.6%, respectively (P=0.12).

Prior carbapenem use before CRAB infection was 56.1%. Prior colistin use before col-R and col-S CRAB infections were not statistically significant (35.0% and 27.0%, respectively, P=0.53).

Overall antibiotic susceptibilities of the 57 CRAB strains were as follows: 35.1% pan-drug resistant (including colistin), 47.4% were only colistin susceptible, 15.8% were colistin and trimethoprim-sulfamethoxazole (TMP-SMX) susceptible, and 1.7% were only TMP-SMX susceptible.

CMS was the preferred agent for the treatment of CRAB infections. Treatment of col-R CRAB infections included a combination of intravenous fosfomycin (7/20), tigecycline (9/20), and ampicillin-sulbactam (4/20) with carbapenems and/or CMS in our ICU.

Discussion

This study reported the clinical characteristics and outcomes of a unique group of *A. baumannii* infections in which the isolates were resistant to carbapenems and most other antibiotic groups. CRAB infections were mostly associated with VAP in our patient population (80.7%), and malignancy and invasive mechanical ventilation were the risk factors for mortality. These results are in accordance with some previous studies.[16,17]

According to a systematic analysis, the frequency of CRAB isolates has reached ≥80% in Turkey. It has been reported that carbapenem and colistin resistance of *A. baumannii* strains in our countrywide hospitals in 2021 was 91.1% and 10.9%, respectively.[18]

CMS is usually a last-resort antibiotic in the treatment of CRAB infections, either alone or in combination with other agents such as tigecycline, ampicillin-sulbactam, or carbapenems. Nevertheless, expanded use of colistin has increased resistance and limited the treatment choices against this pathogen. Qureshi et al.[10] noted that prior colistin use was the most com-

Table 1
Comparison of clinical characteristics, colistin resistance, and ICU outcomes of CRAB infections between survivor and non-survivor patients.

Parameters	Total (n=57)	Survivors (n=25)	Non-Survivors (n=32)	P-value
Age (years)	70.0 (61.0–83.0)	71.0 (64.0–82.5)	67.0 (58.0–87.0)	0.95
Male	33 (57.8)	15 (60.0)	18 (56.2)	0.77
APACHE II score	25 (20–30)	25 (20–29)	28 (19–30)	0.34
SOFA score	8 (5–10)	6 (4.5–8.5)	8 (6–11)	0.17
Charlson Comorbidity Index	7 (5–8)	6 (5–8)	7 (5–8)	0.63
Comorbidities				
HT	37 (64.9)	15 (60.0)	22 (68.7)	0.49
DM	33 (57.8)	11 (44.0)	12 (37.5)	0.62
CAD	28 (49.1)	12 (48.0)	16 (50.0)	0.88
CHF	23 (40.3)	10 (40.0)	13 (40.6)	0.96
Malignancy	20 (35.1)	4 (16.0)	16 (50.0)	<0.01
COPD	16 (28.1)	8 (32.0)	8 (25.0)	0.55
CRF	6 (10.5)	4 (16.0)	2 (6.2)	0.23
Invasive mechanical ventilation	54 (94.7)	22 (88.0)	32 (100.0)	0.04
Indwelling central venous catheter	43 (75.4)	18 (72.0)	25 (78.1)	0.59
Renal replacement therapy	14 (24.5)	5 (20.0)	9 (28.1)	0.47
Infection site				
Pulmonary	46 (80.7)	23 (92.0)	23 (71.9)	0.06
Blood	8 (14.0)	1 (4.0)	7 (21.9)	0.05
Wound	3 (5.2)	1 (4.0)	2 (6.2)	0.70
Colistin resistance	20 (35.1)	6 (24.0)	14 (43.8)	0.12
CRP (mg/L)	85 (53–125)	71 (51–120)	94 (53–138)	0.34
Procalcitonin (ng/mL)	0.78 (0.19–1.84)	0.34 (0.12–2.33)	1.22 (0.39–1.70)	0.13
Leucocyte ($\times 10^9$/L)	10.1 (5.5–14.2)	10.4 (6.3–14.2)	9.8 (4.2–14.3)	0.90
Preadmission hospital LOS (days)	4 (1–17)	4 (1–11)	5 (1–23)	0.43
Length of ICU stay (days)	30 (14–46)	38 (16–47)	27 (13–40)	0.23
Preinfection ICU LOS (days)	11 (5–16)	12 (6.5–22)	9 (3–16)	0.55

Data are presented as n (%) or median (interquartile range).
APACHE: Acute physiology and chronic health evaluation score; CAD: Chronic artery disease; CHF: Chronic heart failure; COPD: Chronic obstructive pulmonary disease; CRAB: Carbapenem-resistant *A. baumannii*; CRF: Chronic renal failure; CRP: C-reactive protein; DM: Diabetes mellitus; HT: Hypertension; ICU: Intensive care unit; LOS: Length of stay; SOFA: Sequential organ failure assessment score.

Table 2
Comparison of demographics, baseline characteristics, ICU outcomes, prior antibiotic use, and mortality of col-R and col-S CRAB infections.

Parameters	Total (*n*=57)	Col-R (*n*=20)	Col-S (*n*=37)	*P*-value
Age (years)	70 (61–83)	68 (60–81)	72 (62–85)	0.36
Male gender	33 (57.9)	10 (50.0)	23 (62.1)	0.37
APACHE II score	25 (20–30)	29 (19–36)	25 (20–29)	0.13
SOFA score	8 (5–10)	8 (5–10)	8 (5–10)	0.83
Charlson Comorbidity Index	7 (5–8)	6 (5–8)	7 (5–8)	0.49
Comorbidities				
HT	37 (64.9)	14 (70.0)	23 (62.2)	0.55
DM	33 (57.9)	8 (40.0)	15 (40.5)	0.96
CAD	28 (49.1)	7 (35.0)	21 (56.8)	0.11
CHF	23 (40.3)	3 (15.0)	20 (54.1)	<0.01
Malignancy	20 (35.1)	9 (45.0)	11 (29.7)	0.24
COPD	16 (28.1)	3 (15.0)	13 (35.1)	0.11
CRF	6 (10.5)	3 (15.0)	3 (8.1)	0.41
Invasive mechanical ventilation	54 (94.7)	19 (95.0)	35 (94.6)	0.94
Indwelling central catheter	43 (75.4)	16 (80.0)	27 (72.9)	0.55
Renal replacement therapy	14 (24.6)	9 (45.0)	5 (13.5)	<0.01
Infection site				
Pulmonary	46 (80.7)	14 (70.0)	32 (86.5)	0.13
Blood	8 (14.0)	5 (25.0)	3 (8.1)	0.08
Wound	3 (5.3)	1 (5.0)	2 (5.4)	0.94
CRP (mg/L)	85 (53–125)	70 (44–95)	97 (56–130)	0.46
Procalcitonin (ng/mL)	0.78 (0.19–1.84)	1.11 (0.27–4.57)	0.74 (0.18–1.35)	0.35
Leucocyte ($\times 10^9$/L)	10.1 (5.5–14.2)	10.3 (4.2– 18.2)	9.7 (6.8–14.1)	0.85
Preadmission hospital LOS (days)	4 (1–17)	3 (1–15)	5 (1–20)	0.47
Length of ICU stay (days)	30 (14–46)	29 (13–48)	32 (16–42)	0.85
Preinfection ICU LOS (days)	11 (5–16)	9 (5–23)	12 (4–16)	0.72
Prior carbapenem use	32 (56.1)	12 (60.0)	20 (54.1)	0.66
Prior colistin use	17 (30.0)	7 (35.0)	10 (27.0)	0.53
30-day mortality	32 (56.1)	14 (70.0)	18 (48.6)	0.12

Data are presented as *n* (%) or median (interquartile range).
APACHE: Acute physiology and chronic health evaluation score; CAD: Chronic artery disease; CHF: Chronic heart failure; Col-R: Colistin resistant; Col-S: Colistin sensitive; COPD: Chronic obstructive pulmonary disease; CRAB: Carbapenem-resistant *A. baumannii*; CRF: Chronic renal failure; CRP: C-reactive protein; DM: Diabetes mellitus; HT: Hypertension; ICU: Intensive care unit; LOS: Length of stay; SOFA: Sequential organ failure assessment score.

mon risk factor for colistin resistance. Another study about risk factors for col-R CRAB infections in ICU patients reported that prior colistin use was 40%.[19] In our patient population, a similar rate of prior colistin use was detected among col-R CRAB infections (35.0%), but it was not statistically different from that of col-S CRAB infections (27.0%). It is possible that one or two clones arising from prior colistin use in patients had the chance to spread in the unit during the study period.

The overall colistin susceptibility of CRAB isolates in our ICU was 63.2%. There was no other antibiotic class susceptibility except for TMP-SMX (15.8%) among col-S CRAB isolates. It is obvious that the most preferred agent for the treatment of these infections was CMS. However, this carried the risk of more colistin side effects and probably more col-R CRAB infections, for which we do not have much treatment options. Nearly half of the col-R CRAB strains in this study had higher colistin MICs (≥64 mg/L).

Colistin heteroresistance may be a factor that favors the selection of col-R strains during treatment, but the impact of this phenomenon on the treatment outcomes requires further studies.[18,19]

An increasing mortality rate was reported in previous studies on CRAB infections, especially in critically ill patients.[20,21] A report from Brazil stated that increased CRAB incidence in ICU patients resulted in higher mortality rates (79.6%), although none of them were col-R. The authors also reported that several unfavorable clinical conditions of the patients played a role in the poor outcomes.[22] Lee et al.[21] reported 69.9% mortality in imipenem-resistant *A. baumannii* bacteremia of which VAP was the primary infection focus; furthermore, the authors linked this high mortality rate with delayed appropriate antibiotic initiation. In our study, the mortality rate in col-S CRAB infections was 48.6%, a relatively low rate compared with the reported extensively drug-resistant (XDR) phenotype CRAB infections. This may be explained by two factors. The first one may be the early initiation of effective antibiotic therapy in our unit. The second explanation may be that the most prevalent infection focus in our study was VAP (80.7%), which is relatively better controlled than bloodstream infection with an appropriate initial therapy. Besides, early effective treatment may have probably prevented secondary bacteremia owing to VAP in our patient population. The mortality rate of our patients with col-R CRAB infection was high (70.0%) although it did not reach statistical significance. Karakonstantis and Saridakis[18] reported 55.1% mortality in ICU patients with col-R CRAB bacteremia and Mantzarlis et al.[19] reported that the mortality rates among 20 patients with col-R and 57 patients with col-S CRAB infections were 85% and 39%, respectively.

There are limited therapeutic options for the treatment of CRAB infections. The Infectious Diseases Society of America (IDSA) guidelines have suggested the use of ampicillin-sulbactam (6–9 g sulbactam) in combination with at least one agent for the treatment of CRAB infections. The other suggested treatments were polymyxin B, high-dose minocycline or high-dose tigecycline, or cefiderocol. Combination

therapy with two active agents was recommended at least until clinical improvement.[23] In our patient population, ampicillin-sulbactam, tigecycline, and intravenous fosfomycin with carbapenems and/or CMS were used for the treatment of CRAB infections. Intravenous fosfomycin deserves attention in combination therapies with its favorable pharmacokinetic/pharmacodynamic (PK/PD) properties and relatively fewer side effects especially in pan-drug resistant *A. baumannii* infections when there is no other antibiotic choice left. There are case reports and case series using fosfomycin as a companion drug with better results. Larger studies are needed to reveal the impact of fosfomycin on clinical outcomes when used in combination with the treatment of such highly resistant Gram-negative infections.[24,25]

This study has some limitations. First, because of the retrospective single-center nature of this study, the results cannot be easily generalized. Second, the sample size was quite small is probably why most of the data are not statistically significant. We were unable to compare CRAB infections with carbapenem-susceptible *A. baumannii* infections since most ICU isolates were CRAB. Additionally, we did not check the clonality of the strains and did not study the genetic patterns of resistance.

Despite these limitations, the study provides clinical and laboratory data on highly resistant *A. baumannii* infections in critically ill patients. Further well-powered studies with sufficient sample size will be beneficial. Carbapenem resistance in *A. baumannii* is a significant clinical challenge to intensivists who are already faced with very limited treatment options, and colistin resistance further complicates the problem.

Author Contributions

Leyla Ferlicolak: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Neriman Defne Altintas:** Conceptualization, Methodology, Supervision. **Fugen Yoruk:** Conceptualization, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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Ethics Statement

This study was approved by the local ethics committee on June 1, 2023 (Approval No.: 2023/337).

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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