JOURNAL OF MEDICAL MICROBIOLOGY

RESEARCH ARTICLE

Mantzarlis *et al.*, *Journal of Medical Microbiology* 2020;69:35–40

DOI 10.1099/jmm.0.001094

MICROBIOLOGY SOCIETY

OPEN MICROBIOLOGY

Risk factors for the first episode of *Acinetobacter baumannii* resistant to colistin infection and outcome in critically ill patients

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Abstract

Introduction. To identify risk factors for the first episode of *Acinetobacter baumannii* resistant to colistin (ABCR) infection in critically ill patients.

Aim. Prospective observational study.

Methodology. ICU patients who required mechanical ventilation for >48 h during a 36 month period. Clinical and microbiological data were studied; characteristics of patients infected with ABCR were compared with those of critically ill patients who presented infection due to *A. baumannii* sensitive to colistin (ABCS).

Results. Twenty patients presented with ABCR infection, and 57 patients ABCS infection. Compared to patients with ABCS infection, patients suffering from ABCR infection had received more frequent and/or for longer duration dosing of several antibiotics active against Gram-negative bacteria ($P<.05$). Moreover, the duration of mechanical ventilation, and the presence of invasive procedures and tracheostomy prior to infection were associated with ABCR infections. The duration of carbapenem administration was an independent risk factor for ABCR infection [odds ratio (OR), 1.21; 95% confidence interval (95%, CI), 1.00 to 1.45; $P=.049$]. Mortality rate for patients with ABCR infection was higher (85 vs 39% for the ABCS group). Sequential organ failure assessment score on admission, Charlson score and ABCR infection were independent risk factors for mortality.

Conclusion. ABCR infection is a life-threatening infection, which might be more common in patients with previous use of antibiotics, especially carbapenems.

INTRODUCTION

The management of multi-drug-resistant (MDR) bacterial infections in intensive care units (ICUs) is a challenging issue for both physicians and infection control teams. Gram-negative bacteria (GNB) account for about 70% of such infections in the ICU setting and are associated with significant morbidity and mortality [1]. For example, in a recent study conducted at our hospital, it was found that infections due to carbapenem-resistant *Klebsiella pneumonia* strains presented higher mortality in comparison to infections due to non-MDR pathogens [2]. *Acinetobacter baumannii* infections are a major problem [3] that may increase mortality [4, 5]. Recently published guidelines for the prevention and management of *A. baumannii* infections reflect increasing concern held by physicians about this life-threatening infection [6]. Moreover, the rate of resistance to colistin in *A. baumannii* strains [7] has increased [8]. Therefore, the recognition of the risk factors associated with ABCR infection is of paramount importance, especially considering that any delay in the administration of potentially active antibiotics is a major determinant of patient outcome [9]. This study aims to identify risk factors and evaluate outcomes associated with infections due to colistin-resistant *A. baumannii*.

PATIENTS AND METHODS

This prospective study took place in the 12-bed ICU of the University Hospital of Larissa, Thessaly, Greece. It was conducted over a 36 month period, between 2013 and 2016. Inclusion criteria were the following: (a) ICU admission for

Received 08 July 2019; Accepted 23 September 2019; Published 24 October 2019

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Keywords: *Acinetobacter baumannii*; colistin resistance; risk factors; mortality.

Abbreviations: ABCR, Acinetobacter baumannii resistant to colistin; ABCS, Acinetobacter baumannii sensitive to colistin; APACHE, Acute physiology and chronic health evaluation score; BSI, Blood stream infection; CI, Confidence interval; GNB, Gram-negative bacteria; ICU, Intensive care unit; MDR, Multi-drug resistant; MIC, Minimum inhibitory concentration; MV, Mechanical ventilation; OR, Odds ratio; SOFA, Sequential organ failure assessment; VAP, Ventilator associated pneumonia.

medical or surgical causes, (b) intubation and mechanical ventilation for >48 h and (c) *A. baumannii* infection. Exclusion criteria were the following: (a) age <18 years old, (b) ICU readmission while still hospitalized, (c) any other co-existing infection. The first episode of *A. baumannii* infection was studied. Infected patients were divided into two different groups: the first consisted of patients who presented infection due to colistin-sensitive *A. baumannii* (ABCS), and the second comprising patients with infection due to colistin-resistant *A. baumannii* (ABCR).

Outcome

The primary outcome was the determination of risk factors for the first episode of ABCR infection in an ICU setting. Secondary outcomes were overall ICU mortality, total ICU stay and total duration of mechanical ventilation.

Definitions

According to the MIC breakpoints provided by the Clinical and Laboratory Standards Institute [10], an *A. baumannii* pathogen with a MIC>2 mg l^{-1} to colistin was considered to be resistant. In the present study, *A. baumannii* infection was defined as the clinical manifestation of infection, which could be microbiologically confirmed by the isolation of the specific pathogen in cultured material. The types of infection were defined according to standardized definitions by the Centers for Disease Control and Prevention/National Healthcare Safety Network [11]. The isolation of *A. baumannii* in biological samples without criteria for clinical infection was considered as colonization. We considered any patient who was transplanted, or received immunosuppressive agents, including corticosteroids as immunocompromised. With the exception of blood cultures, all cultures, including tracheal aspirate were quantitative. Previous hospitalization was defined as admission to hospital or any other health care facility for >48 h during the previous 3 months.

Clinical assessment

For all patients partaking in the study, the following characteristics were recorded: age, sex, illness severity based on acute physiology and chronic health evaluation score II (APACHE II), sequential organ failure assessment (SOFA) score on admission, type of admission (transfer to the ICU from a ward/emergency department), history of hospitalization during the previous 3 months prior to admission, tracheostomy or history of invasive procedures (gastroscopy, colonoscopy or bronchoscopy) or surgery, medical history, history of antibiotic use active against GNB, and duration of antibiotics used. For survivors and non-survivors, several characteristics, which might affect mortality were recorded: age, sex, Charlson score, APACHE II and SOFA scores on admission, need for vasopressors at the onset of infection, invasive procedures, total duration of mechanical ventilation (MV) and sedation and ABCR infection. Exposure to potential risk factors was taken into account only before the isolation of the causative pathogen.

Table 1. Baseline characteristics of participants

	Colistin-sensitive group (*n*=57)	Colistin-resistant group (*n*=20)	*P*
Sex (male)	36 (63)	9 (45)	.192
Age (years)	56 (40, 71)	65 (59, 70)	.088
Medical patients	20 (35)	9 (45)	.437
APACHE II score	17 (13, 22)	19 (16, 26)	.136
SOFA score	7 (5, 10)	8 (6, 10)	.138
Hospitalization in the last 3 months	10 (18)	4 (20)	.750
Admission from ward	25 (44)	14 (70)	.068
Duration of total hospitalization before infection (days)	10 (7, 15)	16 (10, 39)	.003
Charlson score	2 (0, 3)	2 (1, 3)	.525

Data are presented as median (25%, 75% quartiles) or *n* (%); APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; *P*, comparison between the two groups. Results by univariate analysis.

Microbiology

Identification and susceptibility testing of *A. baumannii* blood isolates were performed by the Vitek 2 automated system (bioMerieux, Marcy l' Etoile, France). Determination of MIC to colistin was assessed by the E-test method.

Table 2. Clinical characteristics of participants in the ICU before *A. baumannii* infection

	Colistin-sensitive group (*n*=57)	Colistin-resistant group (*n*=20)	*P*
MV duration (days)	8 (6,11)	12 (8, 33)	.002
Surgical operation	36 (63)	10 (50)	.427
Invasive procedures	4 (7)	5 (25)	.046
Catheterization of urinary bladder prior ICU admission	2 (4)	0 (0)	1.0
Tracheostomy	5 (9)	7 (35)	.010
Sedation	56 (98)	20 (100)	1.0
CVVHDF use	6 (11)	3 (15)	.689
CVVHDF duration (days)	0 (0)	0 (0, 0)	.505

Data are presented as median (25%, 75% quartiles) or *n* (%); MV, mechanical ventilation; ICU, intensive care unit; CVVHDF, continuous veno-venous hemodiafiltration; Invasive procedures, gastroscopy, colonoscopy or bronchoscopy; *P*, comparison between the two groups. Results by univariate analysis.

Table 3. Antibiotics administered to participants before *A. baumannii* infection

	Colistin-sensitive group (*n*=57)	Colistin-resistant group (*n*=20)	*P*
Antibiotics last 3 months	4 (7)	3 (15)	.367
Antibiotics during hospitalization prior to infection	57 (100)	20 (100)	–
Use of carbapenems	17 (30)	12 (60)	.003
Duration of carbapenem use (days)	0 (0, 2)	4 (0, 8)	.012
Use of antipseudomonal penicillins	17 (30)	12 (60)	.030
Duration of antipseudomonal penicillin use (days)	0 (0, 2)	3 (0, 7)	.023
Use of quinolones	12 (21)	11 (55)	.009
Duration of quinolone use (days)	0 (0, 0)	3 (0, 12)	.002
Use of cephalosporin 3d generation	24 (42)	5 (25)	.194
Duration of cephalosporin 3d generation use (days)	0 (0, 4)	0 (0, 1)	.114
Use of cephalosporin fourth generation	4 (7)	7 (35)	.005
Duration of cephalosporin fourth generation use (days)	0 (0, 0)	0 (0, 4)	.003
Use of colistin	12 (21)	8 (40)	.138
Duration of colistin use (days)	0 (0)	0 (0, 4)	.087
Use of tygecycline	0 (0)	8 (40)	<.001
Duration of tygecycline use (days)	0 (0, 0)	0 (0, 7)	<.001
Use of aminoglycosides	1 (2)	4 (20)	.015
Duration of aminoglycoside use (days)	0 (0, 0)	0 (0, 0)	.005

Data are presented as median (25%, 75% quartiles) or *n* (%); *P*, comparison between the two groups. Appropriate antibiotic therapy referred to the administration at least one of the *in vitro* active antimicrobials against the study isolates for at least 48 h. Results by univariate analysis.

Statistical analysis

Results are presented as frequency (%) for qualitative variables or median (25th, 75th quartiles) for quantitative variables. Normality of data distribution was assessed by the Kolmogorov/Smirnov test. Qualitative variables were compared using the chi square test or Fisher's exact test where appropriate; quantitative variables were compared by the Mann–Whitney test. Multivariate analyses were performed to determine variables associated with ABCR infection or mortality. Only variables with a *P*-value <.05 were used in the binary logistic regression model. SPSS software (SPSS 17.0, Chicago, IL) was used for data analysis.

RESULTS

A total of 798 patients were studied. There were 77 (9.6%) patients infected with *A. baumannii*. Of these, 57 patients were infected with ABCS and 20 patients with ABCR. The first group of patients included 19 (33%) blood-stream infections (BSIs), 36 (63%) cases of ventilator-associated pneumonia (VAP), 1 (2%) case of central nervous system infection and 1 (2%) case of urinary tract infection. BSIs for the second group were 14 (70%) and VAP cases 6 (30%). ABCS was isolated at median 8 (6, 11) and ABCR at 12 (8, 28) ICU day (*P*=.006). Participant characteristics are presented in Tables 1–3. A secondary analysis between patients that presented BSI was conducted.

Risk factors for ABCR infection

Baseline characteristics between groups are presented in Table 1. There were no differences between the two groups. Patients who had had long periods of mechanical ventilation or had undergone tracheostomy or invasive procedures prior to infection exhibited higher incidence of ABCR infection (*P*<.05, Table 2). Regarding antibiotic use prior to the infection, carbapenems, antipseudomonal penicillins, quinolones, fourth generation cephalosporins, tigecycline and aminoglycosides were administered more frequently and for longer periods to patients with ABCR infection (*P*<.05, Table 3). Multivariate analysis revealed that the duration of carbapenem use was an independent risk factor for ABCR infection [OR, 1.21; (95% CI), 1.00 to 1.45; *P*=.049]. Surprisingly, colistin use before infection was not statistically different between the two groups. The only risk factors for patients that presented BSI due to ABCR were the duration of administration of tigecycline (*P*=.002) and aminoglycosides (*P*=.037).

Table 4. Duration of ICU stay, death, mechanical ventilation and sedation in patients infected with sensitive or resistant to colistin *A. baumannii*

	Colistin-senesitive group (*n*=57)	Colistin-resistant group (*n*=20)	*P*
ICU duration (days)	26 (15, 37)	16 (11, 45)	.272
BSI	19 (33)	14 (70)	.008
Death	22 (39)	17 (85)	.001
Need for vasopressors at infection's onset	42 (74)	16 (80)	.765
Appropriate antibiotic therapy	50 (87)	0 (0)	.016
Days alive after the onset of infection until death for non-survivors	12 (2, 30)	3 (2, 8)	.053
MV duration (days)	20 (13, 30)	15 (12, 42)	.803
Duration of sedation (days)	8 (4, 16)	11 (6, 18)	.181

Data are presented as median (25%, 75% quartiles) or *n* (%); ICU, intensive care unit; MV, mechanical ventilation; BSI, blood-stream infection; *P*, comparison between the two groups. Results by univariate analysis.

Mortality and morbidity indices in patients with ABCR infection

Patients that presented ABCR infection in comparison to the patients who presented ABCS infection had increased mortality [17 (85%) vs 22 (39%), *P*=.001] (Table 4). Other indices such as total ICU stay, total mechanical ventilation duration and sedation duration were not statistically different after univariate analysis. Mortality for patients that presented BSI due to ABCR was 85%. It was 57% for those with ABCS. Mortality was not different between the two groups (*P*=.131). Compared to non-survivors, survivors had a younger age, lower SOFA and APACHE II scores on admission. They also had a lower Charlson score, longer total ICU stay and a higher incidence of ABCR infection and BSI (*P*<.05) (Table 5). Multivariate analysis showed that the SOFA score (1.26; 1.02 to 1.57; *P*=.035), Charlson score (1.63; 1.09 to 2.44; *P*=.018) and ABCR infection (8.56; 1.98 to 39.03; *P*=.004) were independent risk factors for ICU mortality.

DISCUSSION

In the present study, we aimed to identify clinical risk factors for the first episode of ABCR infection in an ICU, since it is an emerging problem worldwide [12]. This is the first study that takes into account patients infected by *A. baumannii* who did not present co-infections with other bacteria. Our findings suggest that ABCR infection was associated with the prior use of antibiotics, and especially carbapenems. ABCR infection was also related to longer duration of mechanical ventilation, the presence of tracheostomy and invasive procedures prior to the infection. Moreover, ABCR infection was an independent risk factor for mortality in the ICU.

Data regarding ABCR infections are limited. Most studies include patients hospitalized in several wards and not especially in an ICU [8]. To our knowledge, this is the first study that aimed to identify the risk factors for ABCR infection for critically ill patients as a specific population.

Previous use of several antibiotics was a predetermining factor for the acquisition of ABCR infection. Furthermore, the duration of prior carbapenem use was the only independent risk factor. The fact that the use of antibiotics promotes infections caused by carbapenem-resistant *A. baumannii* strains is well documented [13–16], but data for colistin-resistant pathogens are lacking. Only rare references can be found in the literature regarding this kind of infection [8, 17, 18] and all of them include mixed populations of critically and non-critically ill patients. Therefore, our study underlines the importance

Table 5. Characteristics of survivors and non-survivors in the ICU

	Survivors (*n*=38)	Non-survivors (*n*=39)	*P*
Sex (male)	22 (58)	23 (59)	.814
Age (years)	56 (35, 69)	63 (54, 73)	.029
Medical patients	14 (37)	15 (38)	1.0
APACHE II score	16 (12, 21)	19 (16, 24)	.008
SOFA score	6 (4, 8)	8 (6, 11)	.004
Charlson score	1 (0, 2)	2 (1, 4)	.003
Total ICU duration (days)	29 (18, 38)	16 (11, 32)	.023
MV total duration (days)	22 (14, 30)	16 (11, 38)	.318
Sedation total duration (days)	8 (4, 17)	10 (5, 16)	.547
Colistin-resistant *A. baumannii* infection	3 (8)	17 (44)	.001
Patients with BSI	10	23	.006
Patients with VAP	26 (68)	16 (41)	.022

Data are presented as median (25%, 75% quartiles) or *n* (%); ICU, intensive care unit; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; MV, mechanical ventilation; *P*, comparison between the two groups. Results by univariate analysis.

of the previous use of antibiotics as a risk factor for ABCR, especially for the critically ill patients.

According to our results, the previous use of colistin was not a predetermining factor of ABCR infection. In fact, there was an indication towards an increased number of patients who received colistin to present ABCR infection. (21 vs 40% in the colistin-sensitive and resistant group, respectively, *P*=.138). The fact that almost 50% more patients had received carbapenems than colistin may have affected our results. A prospective trial could lend further insight regarding this point, but our study was a 'real-world' clinical study. Therefore, we cannot ascertain whether this hypothesis has any validity. It should also be noted that results of similar studies are conflicting: in one study all the patients with an infection caused by ABCR had received colistin [8], whereas in another, colistin was not a risk factor for such an infection [18]. Another hypothesis is that heteroresistance may play a role: subpopulations of colistin-resistant strains may be present, and the subsequent use of antibiotics may facilitate the pathogens to grow and to thereafter be the causative agent of the infection. The fact that heteroresistance was observed in patients who never received colistin is supportive of this hypothesis [12, 19]. Moreover, the fact that the *mcr*-1 gene responsible for colistin resistance was detected in several types of pathogens that were carbapenem resistant may also explain the results [20, 21]. However, further research is needed.

Mechanical ventilation was also a predetermining factor for ABCR infection, along with invasive procedures and the presence of tracheostomy before the infection in the ICU. Although typical indices of severity such as APACHE II and SOFA scores are not different between the two groups, mechanical ventilation or the presence of tracheostomy and the need for more invasive treatment modalities may indicate patients with more severe disease. Patients infected with ABCR were also in the hospital for a longer period before the onset of infection. Our speculation is that patients with severe disease, with physiological defense barriers interrupted by several treatment modalities, who were hospitalized for a period long enough in order to be colonized, and the use of antibiotics may kill pathogens that are sensitive to these antibiotics but drug-resistant pathogens will survive and therefore patients may suffer from infections caused by MDR pathogens, ABCR in our case.

Regarding mortality, our study revealed that ABCR infection affects survival, since it was an independent risk factor for death, along with SOFA and Charlson scores. The result underlines the importance of the ABCR infection, and also the need for judicious use of antibiotics and several other treatment options like mechanical ventilation. Moreover, patients infected with ABCR died sooner after the onset of the infection in comparison to patients infected with ABCS. Although it is very difficult to attribute death to the infection, the fact that ABCR patients died sooner in comparison to patients infected with ABCS may be explained by the lack of appropriate therapy and perhaps the virulence of the colistin-resistant strains. Our results are contradictory to another study where colistin resistance was associated with significantly lower mortality among patients infected by carbapenem-resistant *A. baumannii* strains [22]. Although resistance to antibiotics is not associated with virulence [23], facts that may explain the different result include the different method for susceptibility testing and the different patient populations.

Our study presents a few limitations. Nonetheless, being performed at a single centre and having a small overall number of patients may limit generalizability. Pathogen transmission mechanisms between the patients were not studied. Moreover, we did not examine resistance mechanisms, the heteroresistance phenomenon, and therefore we cannot exclude the possibility that colistin resistance might emerge in individual patients under the selective pressure of antibiotics, as was demonstrated in a previous study [8]. In our case, the fact that colistin was not a risk factor for infection weakens the aforementioned assumption.

In conclusion, an *A. baumannii* infection in critically ill patients is deleterious, especially if the pathogen presents resistance to colistin. Previous administration of antibiotics and the use of several treatment modalities are predetermining factors for this specific infection. The high rates of mortality revealed in our study should alert physicians and more studies should be conducted in order to investigate the mechanisms of infection and various treatment options. At the time, the selective use of invasive procedures and antibiotics, and appropriate de-escalation might be an option for infection restriction.

Funding information
The authors received no specific grant from any funding agency.

Acknowledgements
We thank Elena Chatzinikou and Ross J. Robertson for their assistance in editing the paper.

Conflicts of interest
The authors declare that there are no conflicts of interest.

Ethical statement
The study was approved by the Institutional Review Board/Ethics Committee of the University Hospital of Larissa, and informed consent was obtained from the participants.

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