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

Konstantinos Mantzarlis*, Demosthenes Makris and Epaminondas Zakynthinos

**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
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 |

**Microbiology**

Identification and susceptibility testing of A. baumannii blood isolates were performed by the Vitek 2 automated system (bioMérieux, 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 (%); APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; P, comparison between the two groups. 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 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 tigecycline             | 0 (0)                             | 8 (40)                            | <.001|
| Duration of tigecycline 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.
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.

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

|                         | Colistin-sensitive 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.

### 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 ABR, especially for the critically ill patients.

According to our results, the previous use of colistin was not a predetermining factor of ABR infection. In fact, there was an indication towards an increased number of patients who received colistin to present ABR infection. (21 vs 40% in the colistin-sensitive and resistant group, respectively, $P=.138$). The fact that almost 50% more patients had received carabapenems 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 ABR 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 ABR 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 ABR 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, ABR in our case.

Regarding mortality, our study revealed that ABR 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 ABR infection, and also the need for judicious use of antibiotics and several other treatment options like mechanical ventilation. Moreover, patients infected with ABR 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 ABR 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.

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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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