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# Risk factors for pneumonia caused by antimicrobial drug-resistant or drug-sensitive *Acinetobacter baumannii* infections

## A retrospective study

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**Abstract**

*Acinetobacter baumannii* (AB) is one of the major types of infection in hospitalized patients. The development of AB resistance is becoming a global clinical challenge. To assist in the clinical management of AB-induced pneumonia, we designed the present retrospective observational study to investigate the risk factors for antimicrobial drug-resistant/-sensitive AB infections.

A total of 214 individuals were reviewed, in which 100 and 55 pneumonia patients were infected with drug-resistant and drug-sensitive AB, respectively. Fifty-nine pneumonia patients without AB infection served as a control group. Age, sex, duration of hospital stay, prior surgery history, the presence of coinfection and companion diseases, routine blood test results, and immunogenicity were recorded. Logistic regression was performed to identify risk factors of AB infections.

Multivariate analysis revealed that long duration of hospital stay (odds ratio = 1.091 [95% CI: 1.010–1.178], $P = .027$) and the absence of coinfection (odds ratio = 0.507 [95% CI: 0.265–0.970], $P = .040$) were independent risk factors for AB infections. Same pattern of risk factors was identified for the drug-sensitive group (long duration of hospital stay: odds ratio = 1.119 [95% CI: 1.016–1.232], $P = .022$; absence of coinfection: odds ratio = 0.328 [95% CI: 0.135–0.797], $P = .014$), while high blood urea nitrogen (odds ratio: 1.382 [95% CI: 1.042–1.833], $P = .025$) was the only significant risk factor for drug-resistant AB infection.

Long duration of hospital stay and the absence of coinfection might predict AB infections in hospitalized patients. Antimicrobial drug-resistant and drug-sensitive AB infections possess different risk factor profiles. A poor kidney function may be predictive of drug-resistant AB infection. Further prospective studies are required to validate our findings.

**Abbreviations:** AB = *Acinetobacter baumannii*, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, COPD = chronic obstructive pulmonary disease, CREA = creatine, DS = drug-sensitive, IDSA = Infectious Diseases Society of America, MDR = multidrug-resistant, RBC = red blood cell, WBC = white blood cell, XDR = extensively drug-resistant.

**Keywords:** *Acinetobacter baumannii*, infection, pneumonia, resistant, risk factor, sensitive

## 1. Introduction

*Acinetobacter baumannii* (AB) is the main type of the *Acinetobacter* species which causes approximately one million cases of infection each year worldwide.[1] AB is commonly transmitted in the hospital through the healthcare providers and contaminated medical equipment because of its ability to survive under starving and desiccation conditions, inducing pulmonary-related diseases such as pneumonia.[2–4] Though controversy, the mortality rate attributed to AB infections was reported to be 26.0% to 61.6%.[5,6] Inappropriate treatment is apparently a contributing factor associated with the increase in mortality rates.

The diagnosis and treatment of AB-induced pneumonia are currently following the guidelines released by the Infectious Diseases Society of America (IDSA) in 2016,[7] but it can be challenging in practice. Pulmonary lesions in imaging can be due to non-infectious diseases such as congestive heart failure, pulmonary atelectasis, and pulmonary infarction; while the colonization of AB in the respiratory tract is not necessarily the cause of imaging abnormalities.[8] Moreover, the emergence of drug-resistance further increases the difficulties in treating AB-induced pneumonia. Starting antimicrobial therapy early is beneficial to the patients, however inappropriate treatment for resistant-type AB infections can increase the healthcare costs and mortality.[9,10] To balance the pros and cons, drug susceptibility tests are useful in guiding the correct treatment decision. Unfortunately, conventional drug susceptibility tests require long processing time and novel molecular tests identifying resistance genes are yet not well-validated.[11] As a result, the initial approach to treat suspected AB-infected patients is usually empirical.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Risk factors predicting drug-resistance in AB can be crucial in the rapid initiation of appropriate antimicrobial therapy. Several general risk factors have been suggested previously, including local outbreak and prior colonization of resistant-type AB, etc.[12] To guide a more precise treatment before receiving the results of drug susceptibility tests, we carried out the present retrospective study to identify more specific risk factors for differentiating AB infections with different resistant-types.

## 2. Methods

### 2.1. Study design

This was a retrospective study conducted at the Wuxi No.2 People's Hospital. Suspected patients for AB infection who underwent microbial diagnostic and drug-susceptibility tests from January 2018 to December 2018 were reviewed. The inclusion criteria included: aged 18 or older; suspected patients for AB infection who underwent microbial diagnostic and drug-susceptibility tests; and complete information obtained. The exclusion criteria included: received antibiotics treatment within 90 days before sample collection; and unconfirmed diagnosis. The study protocol was approved by the Ethics Committee of the Wuxi No.2 People's Hospital (approval no.: 2019Y-817).

Patients' information was collected from the hospital database according to the study protocol. The following data were retrospectively reviewed: age, sex, duration of hospital stay, prior surgery history, the presence of coinfection and companion diseases, pretreatment blood test results, and immunogenicity, where pretreatment blood test results included white blood cell count (WBC), red blood cell count (RBC), aspartate aminotransferase level (AST), alanine aminotransferase (ALT), blood urea nitrogen level (BUN), and creatine level (CREA). Coinfection was defined as other non-AB infections diagnosed, included *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae*, *Monilia albican*, *Proreus penneri*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Stenotrophomonas maltophilia*. Companion diseases were classified into 3 categories: respiratory diseases including bronchiectasis, chronic obstructive pulmonary disease (COPD), interstitial pulmonary disease, lung cancer, pulmonary lesions, and respiratory failure; cardiovascular diseases including acute myocardial infarction, arteriostenosis, atrial fibrillation, and hypertension; and other diseases including acute cholangitis, acute gastroenteritis, acute peritonitis, cerebral infarction, cholelithiasis, diabetes mellitus, esophageal carcinoma, laryngeal carcinoma, Parkinson disease, renal diseases, and urinary tract obstruction.

### 2.2. Diagnostic and drug susceptibility test

Vitek2 (Biomerieux, France) was used according to the manufacturer's instruction to diagnose for infections, confirm the species identification, and determine the type of resistance. Samples used were mainly sputum samples, other samples used included whole blood samples, midstream urine samples, cerebrospinal fluid, etc. The definition of multidrug-resistant (MDR) is the resistance to at least 1 agent in ≥3 different antimicrobial categories. Extensively drug-resistant (XDR) is defined as the resistance to at least one agent in all, but 2 or fewer antibiotic classes.[13] Drug-sensitive (DS) is defined as negative susceptibility test result in at least one antibiotic agent.

### 2.3. Statistical analysis

Unpaired $t$ test (for continuous variables) or chi-square test (for categorical variables) was used to compare the differences between groups when appropriate. Multivariate logistic regression analysis (Forward: likelihood ratio) was used to identify risk factors for AB infection. All analyses were two-tailed. A $P$ value of $<.05$ was considered statistically significant. SPSS 20 (IBM, Armonk, New York, NY) was used for data analysis.

## 3. Results

### 3.1. Study population

A total of 214 individuals were included in the present study. Patients were classified into the Resistant group (n = 100), the Sensitive group (n = 55), and the Control group (n = 59) according to the AB infection status and the type of AB resistance. In the Resistant group, 50 patients were MDR-AB infected and 50 patients were XDR-AB infected. Most of the patients were diagnosed as hospital-acquired pneumonia (96 in the Resistant group and 54 in the Sensitive group), while a few of them had ventilator-associated pneumonia (4 in the Resistant group and 1 in the Sensitive group). Detailed clinical information and the pretreatment blood routine examination and immunogenicity results of the enrolled patients were listed in Tables 1 and 2, respectively. Compared with the Control group, a significantly lower proportion of patients was coinfected by other non-AB pathogens in the Sensitive group ($P = .0398$). All other parameters were comparable between groups.

### 3.2. Univariate analyses of risk factors for AB infection

First, we analyzed the AB infection group as a whole (the combination of the Resistant and Sensitive groups). Long duration of hospital stay was identified as a significant risk factor of AB infection ($P < .05$; Table 3). Also, higher age and the absence of coinfection seemed to associate with AB infection, though not statistically significant ($P < .10$). Next, we divided the AB infection group into the Resistant group and the Sensitive group to further discover additional parameters associating with the type of AB resistance (Table 3). For the Resistant group, higher BUN was identified as a significant risk factor of resistant-type AB infection ($P < .05$), while longer duration of hospital stay and lower AST seemed to associate with resistant-type AB infection ($P < .10$). For the Sensitive group, long duration of hospital stay and the absence of coinfection were identified as significant risk factors of sensitive-type AB infection ($P < .05$), while a higher age seemed to associate with sensitive-type AB infection ($P < .10$).

### 3.3. Multivariate analyses of risk factors for AB infection

In multivariate analyses, long duration of hospital stay (odds ratio: 1.091 [95% CI: 1.010–1.178], $P = .027$) and the absence of coinfection (odds ratio: 0.507 [95% CI: 0.265–0.970], $P = .040$) were identified as independent risk factors for AB infections (Fig. 1A). Again, we divided the AB infection group according to the type of AB resistance for further analysis. For the Resistant group, high BUN (odds ratio: 1.382 [95% CI: 1.042–1.833], $P = .025$) was the only independent risk factor for resistant-type AB infections (Fig. 1B). For the Sensitive group, long duration of hospital stay (odds ratio: 1.119 [95% CI: 1.016–1.232], $P = .022$) and the absence of coinfection (odds ratio: 0.328 [95% CI: 0.135–0.797], $P = .014$) were identified as independent risk factors for sensitive-type AB infections (Fig. 1C).

**Table 1**

**Patients' demography.**

| Parameter | Resistant group (n = 100) | Sensitive group (n = 55) | Control group (n = 59) | *P value | #P value |
|---|---|---|---|---|---|
| Age, y | 73.1 ± 13.5 | 74.2 ± 10.0 | 69.6 ± 17.4 | .2814 | .2493 |
| Gender, n (%) | | | | .5640 | .6841 |
| Male | 78 (78.0) | 38 (69.1) | 43 (72.9) | | |
| Female | 22 (22.0) | 17 (30.9) | 16 (27.1) | | |
| Hospital stay, d | 9.4 ± 5.8 | 9.9 ± 6.4 | 7.8 ± 3.5 | .1719 | .1408 |
| Prior surgery history, n (%) | | | | .2601 | .3513 |
| Yes | 6 (6.0) | 3 (5.5) | 1 (1.7) | | |
| No | 94 (94.0) | 52 (94.5) | 58 (98.3) | | |
| Coinfection, n (%) | | | | .2225 | .0398 |
| Presence | 29 (29.0) | 11 (20.0) | 23 (39.0) | | |
| Absence | 71 (71.0) | 44 (80.0) | 36 (61.0) | | |
| Companion disease, n (%) | | | | | |
| Respiratory diseases | 17 (4.0) | 5 (20.0) | 12 (20.8) | .6721 | .1172 |
| Cardiovascular diseases | 12 (2.0) | 8 (1.8) | 8 (5.7) | .8074 | 1 |
| Other diseases | 4 (9.0) | 5 (10.9) | 5 (30.2) | .2935 | 1 |

For the pretreatment blood routine examination and immunogenicity results (Table 2), the Resistant group had a significantly higher BUN than the Control group ($P = .0038$). No statistically significant difference was observed for other parameters.

* $P$ value comparing the Resistant and Control groups.

# $P$ value comparing the Sensitive and Control groups. Age and hospital stay were expressed as mean ± standard deviation.

**Table 2**

**Pretreatment blood routine examination and immunogenicity results.**

| Parameter | Resistant group (n = 100) | Sensitive group (n = 55) | Control group (n = 59) | *P value | #P value |
|---|---|---|---|---|---|
| WBC, $10^9$/L | 10.96 ± 3.51 | 10.61 ± 3.22 | 10.94 ± 3.12 | .7686 | .6297 |
| RBC, $10^{12}$/L | 3.97 ± 0.83 | 3.84 ± 0.85 | 3.98 ± 0.94 | .7562 | .5683 |
| ALT, U/L | 33.2 ± 13.7 | 35.0 ± 16.0 | 36.0 ± 16.2 | .2502 | .6408 |
| AST, U/L | 30.2 ± 15.6 | 34.3 ± 20.4 | 35.1 ± 19.2 | .1553 | .5784 |
| BUN, mmol/L | 5.96 ± 1.29 | 5.15 ± 1.44 | 5.42 ± 1.56 | .0038 | .1534 |
| CREA, μmol/L | 76.33 ± 28.19 | 68.62 ± 24.42 | 72.45 ± 26.07 | .4670 | .3673 |
| Immunogenicity, n (%) | | | | .7111 | .6712 |
| Immunocomprimised | 6 (6.0) | 3 (5.5) | 2 (3.4) | | |
| Immunocompetent | 94 (94.0) | 52 (94.5) | 57 (96.6) | | |

* $P$ value comparing the Resistant and Control groups.

# $P$ value comparing the Sensitive and Control groups. WBC, RBC, ALT, AST, BUN, and CREA levels were expressed as mean ± standard deviation.

**Table 3**

**Risk factors for drug-resistant or drug-sensitive AB infections.**

| | AB infection group | | Resistant group | | Sensitive group | |
|---|---|---|---|---|---|---|
| Parameters | Odds ratio (95% CI) | P | Odds ratio (95% CI) | P | Odds ratio (95% CI) | P |
| Age | 1.019 (0.998–1.041) | .074 | 1.319 (0.627–2.776) | .465 | 1.023 (0.996–1.052) | .094 |
| Gender | 1.107 (0.561–2.182) | .770 | 1.015 (0.994–1.037) | .166 | 0.832 (0.370–1.870) | .656 |
| Hospital stay | 1.081 (1.004–1.164) | .038 | 1.078 (0.996–1.168) | .063 | 1.095 (1.002–1.197) | .045 |
| Prior surgery history | 3.575 (0.443–28.86) | .232 | 3.702 (0.435–31.53) | .231 | 3.346 (0.338–33.17) | .302 |
| Coinfection | 0.544 (0.289–1.027) | .061 | 0.639 (0.324–1.260) | .196 | 0.391 (0.168–0.909) | .029 |
| Companion diseases | | | | | | |
| Respiratory diseases | 0.648 (0.298–1.411) | .274 | 0.802 (0.353–1.823) | .599 | 0.392 (0.128–1.196) | .100 |
| Cardiovascular diseases | 0.944 (0.391–2.279) | .899 | 0.869 (0.333–2.268) | .775 | 1.085 (0.377–3.123) | .880 |
| Other diseases | 0.666 (0.214–2.075) | .483 | 0.450 (0.116–1.747) | .249 | 1.080 (0.295–3.955) | .907 |
| Blood routine examination | | | | | | |
| WBC | 0.991 (0.905–1.085) | .844 | 1.002 (0.911–1.104) | .960 | 0.967 (0.860–1.087) | .576 |
| RBC | 0.933 (0.660–1.320) | .697 | 0.992 (0.685–1.437) | .967 | 0.844 (0.557–1.279) | .423 |
| ALT | 0.990 (0.971–1.010) | .347 | 0.987 (0.966–1.009) | .246 | 0.996 (0.973–1.019) | .741 |
| AST | 0.989 (0.973–1.006) | .210 | 0.983 (0.965–1.002) | .083 | 0.998 (0.979–1.017) | .822 |
| BUN | 1.140 (0.908–1.430) | .259 | 1.382 (1.042–1.833) | .025 | 0.883 (0.683–1.140) | .339 |
| CREA | 1.002 (0.990–1.013) | .780 | 1.005 (0.993–1.017) | .388 | 0.994 (0.979–1.009) | .417 |
| Immunogenicity | 1.757 (0.368–8.381) | .480 | 1.819 (0.355–9.320) | .473 | 1.644 (0.264–10.23) | .594 |

ALT = alanine aminotransferase, AST = aspartate aminotransferase level, BUN = blood urea nitrogen level, CI = confidence interval, CREA = creatine level, DS = drug-sensitive, MDR = multidrug-resistant, RBC = red blood cell count, WBC = white blood cell count, XDR = extensively drug-resistant.

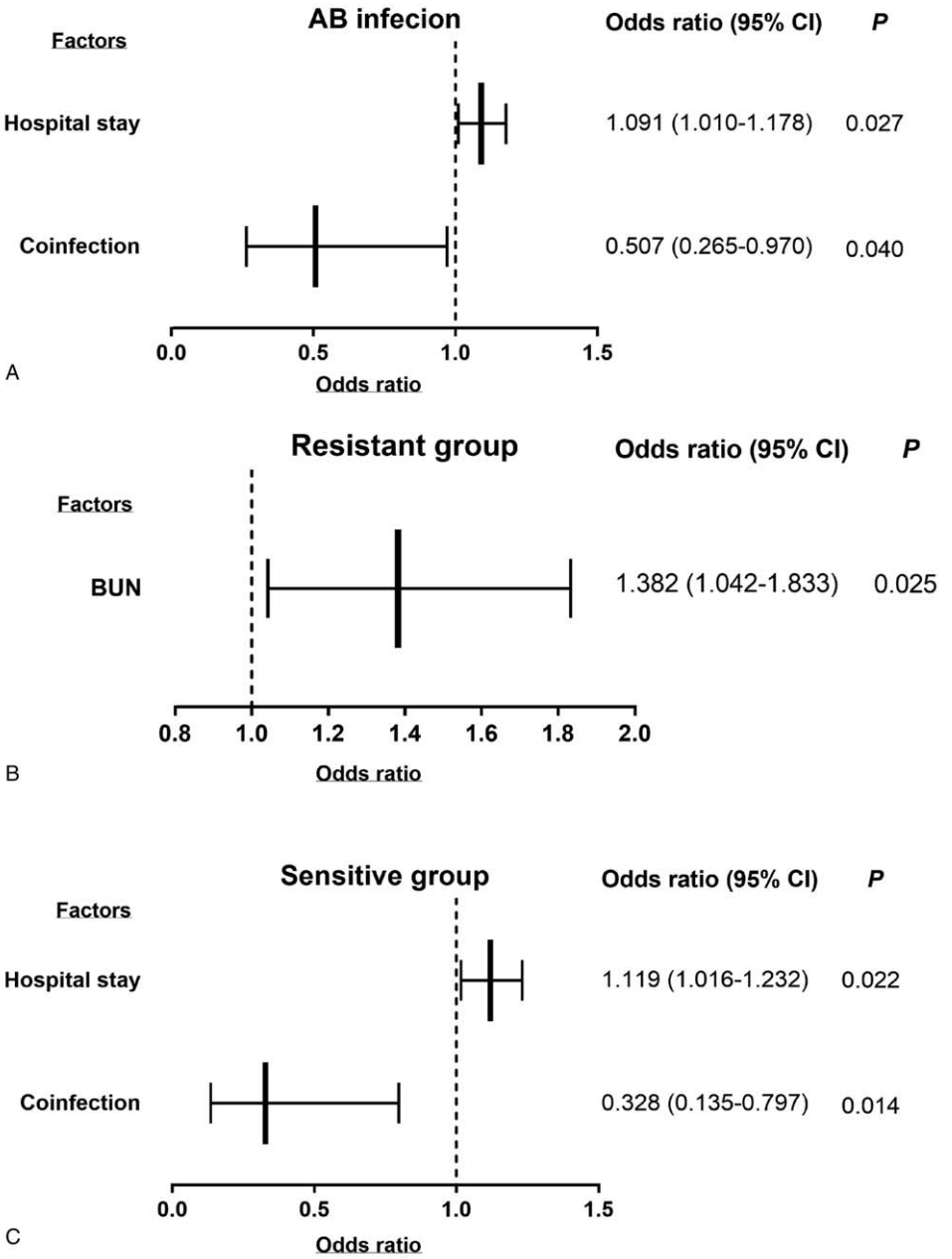


**Figure 1.** The forest plots of risk factors for AB infection. The forest plots of risk factors for (A) the AB infection group, (B) the Resistant group, and (C) the Sensitive group. The middle bold line indicates the odds ratio and the left and right lines indicate the 95% confidence interval.

Additionally, we subdivided the Resistant group into the MDR group and the XDR group to see if the risk factor pattern was different for infection with different extent of AB resistance. For the MDR group, long duration of hospital stay (odds ratio: 1.113 [95% CI: 1.006–1.232], $P = .037$) and low AST (odds ratio: 0.967 [95% CI: 0.944–0.991], $P = .008$) were identified as independent risk factors for AB infections. However, no risk factor was identified for the XDR group.

## 4. Discussion

The overuse of antibiotics has resulted in a selection force leading to the development of multidrug-resistant microbial clone. A large surveillance program reported that a significant trend of reducing drug-susceptibility rates was observed in *Acinetobacter calcoaceticus*-AB complex during 1997 to 2016.[14] In fact, the acquired resistance of AB is currently capable of conferring resistant to virtually all kinds of available antimicrobial agents including aminoglycosides, cephalosporins, and fluoroquinolones.[1,15] Even for carbapenems which are generally used to treat resistant-type AB infection, various mechanisms of resistance have been recently uncovered.[16,17] The emergency of AB resistance has established into a global health problem. The Infectious Diseases Society of America (IDSA) has announced the ESKAPE pathogens (including AB) which require specific concerns.[18,19] Since then, the majority of infected patients were still receiving empirical treatment, possibly causing poor treatment outcomes.[20,21] Development of novel antibiotics

and strictly control the use of antibiotics are the most effective means to suppress the spread of resistant-type AB, however, these require time and significant efforts. Whole genome sequencing of the isolated resistant strains may lead to the discovery of resistance biomarkers, but this requires large, systematic study to confirm.[22] Therefore, we carried out this retrospective study to identify risk factors for AB infections with different types of resistance, aiming to guide the empirical treatment decision and reduce the chance of inappropriate therapy in resistant-type AB infections.

Our results indicated that a long duration of hospital stay and the absence of coinfection were independent risk factors for AB infections. Several recent studies also supported that a longer hospital stay increases the risk of AB infection.[23,24] We found that the absence of coinfection to be an additional risk factor. Consistent with our results, the coinfection of other bacteria was rare in AB-infected patients.[25] When analyzing a particular type of AB resistance, the risk factors were slightly different among the subgroups of patients. The Sensitive group shared the same risk factors as the entire AB infection group. In contrast, only high BUN was identified to be an independent risk factor in the Resistant group. This is different from the previous studies where COPD was identified as a common risk factor for both the MDR- and XDR-AB infections.[26–28] We suggested that this disagreement was due to the small number of COPD patients (n = 21, where 11 patients in the Resistant group, 3 patients in the Sensitive group, and 7 patients in the Control group) recruited in our study cohort.

There are several potential limitations in the present study. First, this was a single-centered retrospective study with a relatively small sample size for each subgroup. Second, several clinical factors such as mortality were not recorded and thus related analysis cannot be carried out. Nevertheless, the preliminary results of this study provided evidence for designing further investigational studies to confirm the clinical value of these identified risk factors in guiding empiric therapy. Indeed, a recent study from Grochowalska et al[29] has suggested that the risk factor algorithm might be useful in guiding initial empiric therapy.

In summary, our study revealed that different AB-resistant type had different risk factor profiles, which can be useful in guiding the initial empirical treatment of AB-induced pneumonia. A prospective study with a larger sample size is warranted to validate our findings.

## Author contributions

Feng Wu: Protocol development, Data collection, Data analysis, Manuscript writing.
Renjing Hu: Protocol development, Data analysis, Manuscript proofreading.

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