The Clinical Characteristics, Carbapenem Resistance, and Outcome of Acinetobacter Bacteremia According to Genospecies

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Abstract

Background: Few clinical data are available on the relationship between genospecies and outcome of Acinetobacter bacteremia, and the results are inconsistent. We performed this study to evaluate the relationship between genospecies and the outcome of Acinetobacter bacteremia.

Methods: Clinical data from 180 patients who had Acinetobacter bacteremia from 2003 to 2010 were reviewed retrospectively. The genospecies were identified by rpoB gene sequence analysis. The clinical features and outcomes of 90 patients with A. baumannii bacteremia were compared to those of 90 patients with non-baumannii Acinetobacter bacteremia (60 with A. nosocomialis, 17 with Acinetobacter species “close to 13 TU”, 11 with A. pittii, and two with A. calcoaceticus).

Results: A. baumannii bacteremia was associated with intensive care unit-onset, mechanical ventilation, pneumonia, carbapenem resistance, and higher APACHE II scores, compared to non-baumannii Acinetobacter bacteremia (P<0.05). In univariate analyses, age, pneumonia, multidrug resistance, carbapenem resistance, inappropriate empirical antibiotics, higher APACHE II scores, and A. baumannii genospecies were risk factors for mortality (P<0.05). Multivariate analysis revealed A. baumannii genospecies (OR, 3.60; 95% CI, 1.56–8.33), age, pneumonia, and higher APACHE II scores to be independent risk factors for mortality (P<0.05).

Conclusion: A. baumannii genospecies was an independent risk factor for mortality in patients with Acinetobacter bacteremia. Our results emphasize the importance of correct species identification of Acinetobacter blood isolates.

Introduction

The spread of multidrug-resistant (MDR) Acinetobacter strains among critically ill, hospitalized patients, and subsequent epidemics, have become an increasing cause for concern [1,2]. These organisms are one of the most common causes of infection in patients in the intensive care unit (ICU) and are associated with a greater risk of hospital death by causing catheter-related infection, pneumonia, urinary tract infection, wound infection, and primary bacteremia in patients with critical illness [3–6]. The organisms’ ability to accumulate diverse mechanisms of resistance limits therapeutic agents and makes the infection difficult to treat [7].

To date, more than 30 Acinetobacter species have been described [8]. Among these, Acinetobacter baumannii (genotype 2) is the most commonly found in clinical specimens. However, recently, infection caused by other Acinetobacter species belonging to the A. calcoaceticus-A. baumannii (ACB) complex, including A. nosocomialis (known also as 13 TU), A. calcoaceticus (genotype 1), A. pittii (genotype 3), and Acinetobacter genomic species “close to 13 TU”, has caused concern [9,10]. Although these are increasingly reported as human pathogens with the introduction of genotyping, it is impossible to distinguish these from A. baumannii by automation systems or phenotypic tests [9,11].

For these reasons, it is important to know whether or not the clinical features, risk factors, and outcomes differ according to species. To date, few studies have been published that evaluate this matter using genotypic assays in patients with Acinetobacter bacteremia [12–14]; however, among these reports, the influence of genospecies on outcome is inconsistent. Thus, we compared the clinical features, antimicrobial resistance, and outcome of bacteremia caused by A. baumannii versus non-baumannii ACB complex strains.
### Patients and Methods

**Ethics**

This study was approved by the Institutional Review Board of Chonnam National University Hospital. A waiver of consent was granted given the retrospective nature of the project.

**Patients**

All adult patients (age, ≥16 years) with bacteremia caused by ACB complex who were admitted to Chonnam National University Hospital (1000 beds; Gwang-ju, Republic of Korea) from January 2003 to December 2010 were included. Only patients with their first episode of *Acinetobacter* bacteremia were included.

### Data Collection

Demographic and clinical data were collected by reviewing the electronic medical records of the patients and included comorbid conditions, duration of ICU and hospital stay, use of a ventilator, and use of central venous catheters at the time of bacteremia onset. The severity of patient infection was evaluated using Acute Physiology and Chronic Health Evaluation (APACHE) II scores within 24 h of bacteremia onset.

### Microbiological Tests

*Acinetobacter* was identified using the automated system Vitek 2 (bioMérieux, Marcy l’Etoile, France). *Acinetobacter* species were determined on the basis of partial *rpoB* gene sequences (468 bp) detected using the primers Ac1055F (GTGATAAR-ATGGCBBGTCGT) and Ac1598R (GCGCRTCAGATYTTCCTCRT), as described by us previously [15,16]. In vitro susceptibility testing was conducted using Vitek 2 (bioMérieux).

### Table 1. Comparison of the clinical features of bacteremia caused by *A. baumannii* (*n* = 90) or non-*baumannii* ACB complex (*n* = 90).

| Variables                        | No. (%) of patients with bacteremia caused by | *P* value |
|----------------------------------|---------------------------------------------|-----------|
|                                  | *Acinetobacter baumannii* (*n* = 90) | Non- *baumannii* ACB complex (*n* = 90) |           |
| **Demographic data**             |                                              |           |
| Age                              | 60 ± 17                                     | 58 ± 18   | 0.45     |
| Male gender                      | 62 (69)                                     | 53 (59)   | 0.16     |
| **Underlying illness**           |                                              |           |
| Ischemic heart disease           | 25 (28)                                     | 16 (18)   | 0.11     |
| Trauma                           | 13 (14)                                     | 16 (18)   | 0.54     |
| Diabetes mellitus                | 11 (12)                                     | 14 (16)   | 0.52     |
| Cancer                           | 8 (9)                                       | 12 (13)   | 0.34     |
| Cerebrovascular accident         | 7 (8)                                       | 8 (9)     | 0.79     |
| Chronic liver disease            | 14 (16)                                     | 3 (3)     | 0.01     |
| End-stage renal disease          | 4 (4)                                       | 4 (4)     | >0.99    |
| Benign biliary disease           | 7 (8)                                       | 7 (8)     | >0.99    |
| **Primary site of infection**    |                                              |           |
| Vascular catheter                | 27 (30)                                     | 27 (30)   | >0.99    |
| Pneumonia                        | 29 (32)                                     | 16 (18)   | 0.03     |
| Primary bacteremia               | 8 (9)                                       | 18 (20)   | 0.03     |
| Intra-abdominal                  | 12 (13)                                     | 9 (10)    | 0.49     |
| Urinary tract                    | 3 (3)                                       | 7 (8)     | 0.33     |
| Soft tissue or wound             | 7 (8)                                       | 7 (8)     | >0.99    |
| **Other characteristics**        |                                              |           |
| Length of hospitalization (day)  | 12 (7, 21)                                  | 11 (7, 22) 0.90 |
| ICU stay at culture              | 77 (86)                                     | 57 (63)   0.001 |
| Mechanical ventilation           | 64 (71)                                     | 44 (49)   0.002 |
| MDR                              | 69 (77)                                     | 29 (32)   <0.001 |
| Carbapenem-resistance            | 51 (57)                                     | 12 (16)   <0.001 |
| APACHE II score                  | 18 ± 7                                      | 17 ± 8    0.30   |
| **Outcomes**                     |                                              |           |
| 30-day mortality                 | 35 (39)                                     | 14 (16)   <0.001 |
| Acinetobacter-related mortality  | 33 (37)                                     | 11 (12)   <0.001 |

ACB, *A. calcoaceticus-A. baumannii*; ICU, intensive care unit; MDR, multidrug resistance; APACHE, acute physiology and chronic health evaluation.

Continuous variables were expressed as means ± SDs or medians (IQRs) and were compared by the Student’s *t* test or Mann-Whitney *U* test.

<sup>1</sup>Until the onset of *Acinetobacter* bacteremia.

doi:10.1371/journal.pone.0065026.t001
Definitions

Multidrug resistance (MDR) was defined if an isolate showed resistance to more than one of the following five antimicrobial agents: imipenem, ciprofloxacin, amikacin, ceftazidime, and piperacillin/tazobactam, in accordance with Paterson’s suggestion [17]. Appropriate empirical antibiotics was defined as the use of at least one antibiotic to which the Acinetobacter strain was susceptible within 48 days from the onset of bacteremia. Mortality was defined as Acinetobacter-related in the absence of another definite cause of death [18].

Statistical Analysis

Categorical variables were compared using Fisher’s exact test or the Pearson χ² test, and continuous variables were compared using Student’s t-test or Mann-Whitney rank sum test, as appropriate. Variables with P values ≤0.10 in the univariate analysis were included in the multivariate analysis. Multivariate analyses were performed using a logistic regression model in the backward stepwise conditional manner. All tests of significance were two-tailed, and P values ≤0.05 were deemed to indicate statistical significance. Statistical analyses of the data were performed using SPSS 16.0 software.

Table 2. Risk factors for 30-day mortality in 180 patients with Acinetobacter bacteremia.

| Variables                  | Univariate analysis | Multivariate analysis |
|----------------------------|---------------------|-----------------------|
|                            | No.(%) of patients  | P value   | Odds ratio (95% CI) | P value |
| Survivor (n = 131)         | Non-survivor (n = 49)|          |                      |        |
| Age                       | 55±18               | 69±12     | <0.001               | 1.07 (1.03–1.10) | <0.001 |
| Vascular catheter infection | 44 (34)            | 10 (20)   | 0.086                |         |
| Pneumonia                 | 23 (18)            | 22 (45)   | <0.001               | 2.72 (1.16–6.37) | 0.021 |
| APACHE II score           | 16±7               | 22±7      | <0.001               | 1.12 (1.06–1.19) | <0.001 |
| MDR                       | 62 (47)            | 36 (74)   | 0.002                |         |
| Carbapenem resistance     | 38 (29)            | 27 (55)   | 0.001                |         |
| Inappropriate empirical antibiotics | 65 (50) | 37 (76) | 0.002                |         |
| A. baumannii genospecies  | 55 (42)            | 35 (71)   | <0.001               | 3.60 (1.56–8.33) | 0.003 |

APACHE, acute physiology and chronic health evaluation; MDR, multidrug resistance.

aContinuous variables were expressed as means ± SDs and were compared by the Student’s t test.

doi:10.1371/journal.pone.0065026.t002

Figure 1. Kaplan-Meier curves of survival in 90 patients with A. baumannii bacteremia and 90 patients with non-baumannii ACB complex bacteremia.

doi:10.1371/journal.pone.0065026.g001
performed using SPSS software (version 19.0; SPSS Inc., Chicago, IL, USA).

**Results**

**Study Population and Genospecies Distribution**

During the study period, we identified 180 isolates of the ACB complex, including 90 (50%) A. baumannii, 60 (33%) A. nosocomialis, 17 (9%) Acinetobacter genomic species “close to 13 TU”, 11 (6%) A. pittii, and two (1%) A. calcoaceticus.

**Comparison of the Clinical Features of Bacteremia Caused by A. baumannii versus Non-baumannii ACB Complex**

The clinical features of bacteremia caused by A. baumannii (n = 90) and non-baumannii ACB complex (n = 90) bacteria are shown in Table 1. Demographic data were not different between the two groups. ICU onset, mechanical ventilation, and underlying chronic liver disease were risk factors for A. baumannii bacteremia, compared to non-baumannii Acinetobacter bacteremia (P<0.05). Pneumonia, MDR, and carbapenem resistance were more commonly found in A. baumannii bacteremia, while primary bacteremia was more commonly caused by non-baumannii Acinetobacter (P<0.05). No significant difference in clinical features was observed between bacteremia caused by A. nosocomialis, Acinetobacter species “close to 13 TU”, and A. pittii (data not shown).

**Risk Factors for 30-day Mortality in Patients with Acinetobacter Bacteremia**

Risk factors for 30-day mortality in the 180 patients with Acinetobacter bacteremia are shown in Table 2. In the univariate analysis, A. baumannii genospecies, age, pneumonia, MDR, carbapenem resistance, inappropriate empirical antibiotics, and APACHE II score were each associated with 30-day mortality (P<0.05). Multivariate analysis included the following variables: A. baumannii genospecies, APACHE II score, age, pneumonia, vascular catheter infection, inappropriate empirical antibiotics, MDR and carbapenem resistance. The independent risk factors for 30-day mortality identified in the multivariate logistic regression analysis included A. baumannii genospecies (OR, 3.60; 95% CI, 1.56–8.33), pneumonia, age, and APACHE II score (Table 2).

The Kaplan-Meier survival curves for Acinetobacter bacteremia caused by A. baumannii and non-baumannii ACB complex strains are shown in Figure 1. The 30-day survival rate was 84% (72/90) in patients with non-baumannii ACB complex bacteremia compared to 61% (55/90) in those with A. baumannii bacteremia (log-rank test; P<0.001). No significant difference in survival was identified between patients with A. nosocomialis bacteremia (83%; 50/60), Acinetobacter species “close to 13 TU” bacteremia (88%; 15/17), and A. pittii bacteremia (91%; 10/11).

**Discussion**

In this study, we found that genospecies A. baumannii was independently associated with poor outcome in patients with ACB complex bacteremia.

Non-baumannii ACB complex are increasingly reported as a cause of bacteremia because of the introduction of genospecies identification. Recent studies showed that A. nosocomialis and A. pittii comprised 27% and 9% of ACB complex bacteremia in Taiwan [13] and 21% and 8% in the USA [14], respectively, which is less prevalent than A. baumannii. However, A. nosocomialis and A. pittii were sevenfold more prevalent causes of bacteremia than A. baumannii in Norway [19]. In our study, the proportion of non-baumannii species was 30%, and Acinetobacter genomic species “close to 13 TU”, newly defined as a member of the ACB complex [9], comprised a higher proportion, in contrast to previous reports. This finding suggests that the distribution of prevalent genospecies differs geographically.

Previous studies reported the differences in clinical features between A. baumannii bacteremia and non-baumannii ACB complex bacteremia [12–14]. ICU onset, mechanical ventilation, higher Pitt bacteremia scores, and chronic obstructive pulmonary disease were factors associated with A. baumannii bacteremia, compared to non-baumannii ACB complex bacteremia in those studies. MDR, carbapenem resistance, and pneumonia were more commonly found in A. baumannii bacteremia, while primary bacteremia itself was more commonly caused by non-baumannii ACB complex bacteria. Similar results were found in our study. MDR was more commonly found in A. baumannii than non-baumannii ACB complex blood isolates, in agreement with our previous studies [13]. Additionally, we found chronic liver disease, which is prevalent in Korea, as another risk factor for A. baumannii bacteremia.

The relationship between genospecies and outcome of Acinetobacter bacteremia was evaluated in some studies; however, the results are inconsistent. In previous studies, which did not identify ACB complex bacteria to the species level with genotyping assays and did not include genotype as a confounding factor in analysis, carbapenem resistance was revealed as an independent risk factor for mortality in ACB complex bacteremia [20]. However, Chung et al. reported that A. baumannii species, and not carbapenem resistance, was an independent predictor of mortality in ICU patients with Acinetobacter bacteremia in Taiwan [12]. However, another study performed at the same hospital during a similar period reported that bacteremia due to MDR strains, but not A. baumannii per se, appeared to be associated with a poor outcome [13].

In the current study, we also found that A. baumannii species, rather than antibiotic resistance, mainly affected mortality, in accordance with a previous [12] and a more recent study performed in the USA [14]. Recently, Peleg et al. suggested that in vitro and in vivo virulence characteristics differed among individual strains of the ACB complex [21], which provides further evidence of the impact of genospecies on the outcome of Acinetobacter bacteremia. Our data also suggest that genotype might be a more significant predictive factor for mortality than carbapenem resistance and that genospecies should be included as a confounding factor in any analysis of risk factors for mortality in patients with Acinetobacter infections, because genospecies is significantly associated with MDR and carbapenem resistance [22,23] and can affect the outcome. Moreover, our data provide more evidence of the importance of correct genospecies identification, which can predict the outcome of Acinetobacter bacteremia.

Our study had several limitations. First, since it was retrospective in design, the factors influencing the physicians’ choice of antibiotics were not determined, and they may have influenced our results as unmeasured confounding factors in the analysis. Second, the current study was performed in a single center; for this reason, factors such as the rate of referrals or surgery for complex disorders could have impacted the results.

In conclusion, our data showed that A. baumannii genospecies is an independent predictor of mortality in patients with ACB complex bacteremia, emphasizing the importance of genotyping for correct species identification and prognosis prediction.
Author Contributions
Conceived and designed the experiments: HCJ KHP. Performed the experiments: KHP SYL KSK. Analyzed the data: KHP HCJ. Contributed reagents/materials/analysis tools: JHS SHK MOJ SJK SIJ EKC. Wrote the paper: KHP HCJ.

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