Evaluation of the effect of appropriate antimicrobial therapy on mortality associated with *Acinetobacter nosocomialis* bacteraemia

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Abstract

Appropriate antimicrobial therapy is effective for severe infections caused by *Acinetobacter baumannii*, but efficacy for other *Acinetobacter species* remains to be established. The current study was designed to determine whether appropriate antimicrobial therapy reduces the mortality of patients with *Acinetobacter nosocomialis* bacteraemia. A 9-year retrospective study of 266 patients with monomicrobial *A. nosocomialis* bacteraemia was conducted at a large teaching hospital in Taiwan. Multivariable analysis was performed to evaluate the impact on 14-day mortality according to clinical characteristics, severity of disease and use of appropriate antimicrobial therapy. The influence of APACHE II score on the impact of appropriate antimicrobial therapy was analysed by including an interaction term. The overall 14-day mortality was 9.4%. Multivariable analysis revealed that APACHE II score was the only factor significantly associated with mortality (odds ratio, 1.18; 95% confidence interval, 1.11–1.25; p <0.001). Appropriate antimicrobial therapy was not associated with reduced mortality regardless of disease severity. In the subgroup analyses in patients with different clinical conditions, APACHE II score was consistently an independent factor for 14-day mortality, and appropriate antimicrobial therapy did not affect the mortality in any group. In conclusion, severity of disease, based on the APACHE II score, was the independent risk factor for 14-day mortality for patients with monomicrobial *A. nosocomialis* bacteraemia, even in different clinical conditions. In contrast, appropriate antimicrobial therapy did not reduce the 14-day mortality. The result highlighted a different effect of appropriate antimicrobial therapy on infections caused by two phenotypically undifferentiated *Acinetobacter*.

Keywords: *Acinetobacter nosocomialis*, appropriate antimicrobial therapy, bacteraemia, drug resistance, mortality
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Introduction

The *Acinetobacter baumannii* complex (ABC) has become a leading cause of nosocomial infections [1,2]. ABC is composed of at least three phenotypically undifferentiated *Acinetobacter* species [3]. These include *A. baumannii*, *Acinetobacter nosocomialis* (formally *Acinetobacter* genomic species 13TU) and *Acinetobacter pittii* (formally *Acinetobacter* genomic species 3) [4,5]. These *Acinetobacter* species can only be differentiated by molecular methods [5,6]. They differ in antimicrobial susceptibility, resistance mechanisms and pathogenicity [7–10]. Among them, *A. baumannii* and *A. nosocomialis* account for most nosocomial infections [10].

Appropriate antimicrobial therapy has been shown to be highly effective for many infectious diseases [11,12]. However, the efficacy of appropriate antimicrobial therapy for treatment of *Acinetobacter* infections remains controversial [13–15]. This appears to be confounded by the wide variety of risk factors, co-morbid illnesses, severity of disease, differences in pathogenicity of the three *Acinetobacter* species and clinical endpoints.

Several prior studies have revealed major differences in the clinical characteristics of infections caused by the various *Acinetobacter* species [7–10]. Unfortunately, the efficacy of appropriate antimicrobial therapy for individual species could not be established because the three *Acinetobacter* species were combined in multivariable analyses [7–9]. We recently found that appropriate antimicrobial therapy reduced the 14-day mortality for patients with *A. baumannii* bacteraemia [16]. This was most pronounced for patients with severe disease. The current study, consisting of 266 bacteraemic patients with monomicrobial *A. nosocomialis* bacteraemia, was designed to determine whether appropriate antimicrobial therapy also reduces the mortality of patients with *A. nosocomialis* bacteraemia after stratification by demographic characteristics, predisposing factors, severity of disease and invasive procedures.

Materials and Methods

Study design and data collection

This was a retrospective study conducted at Taipei Veterans General Hospital (T-VGH) during a 9-year period from 2000 to 2008. T-VGH is a 2900-bed tertiary-care teaching hospital located in Taipei, Taiwan. Charts were reviewed for all patients with monomicrobial *A. nosocomialis* bacteraemia. Patients were excluded if they were under 18 years old or if their medical records were not complete.

Medical records were reviewed to extract data, recorded on a standard form, on demographic characteristics, severity of disease, predisposing factors, concurrent invasive procedures, infectious foci and concurrent use of intravenous antimicrobials. Chronic renal diseases were defined as estimated glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2. End-stage renal disease was defined as a GFR less than 10 mL/min/1.73 m^2. Immunosuppressant therapy was defined as treatment for neoplastic diseases and organ transplantation, or use of corticosteroids (equivalent to more than 10 mg of prednisolone daily for 5 days) within 4 weeks of the onset of bacteraemia. Severity of disease was assessed according to the Acute Physiology and Chronic Health Evaluation (APACHE) II score within 24 h of the onset of bacteraemia. This was defined on the day the positive blood culture for *A. nosocomialis* was drawn. The origin of the bacteraemia was defined as previously suggested [17]. Appropriate antimicrobial therapy was defined as the intravenous administration of at least one antimicrobial agent, to which the bacterium was susceptible, at an appropriate dose within 48 h of onset of bacteraemia [18]. The primary outcome measurement was all-cause 14-day mortality. This study was approved by the institutional review board of T-VGH.

Bacterial isolates and identification

Bacterial isolates initially identified as *Acinetobacter* species by the API ID 32 GN system (bioMérieux, Marcy l'Etoile, France) or Vitek 2 system (bioMe′rieux) were collected and stored at −70°C in trypticase soy broth (Difco Laboratories, Detroit, MI) supplemented with 15% glycerol for the following testing. *A. baumannii* was excluded for analysis after identification by a multiplex PCR method described previously [6]. The non-baumannii *Acinetobacter* was identified to the species level by sequencing the intergenic space [19]. Only those confirmed to be *A. nosocomialis* were selected for further testing. The susceptibility of isolates was determined by the agar dilution test according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) [18] and the result was used for determination of the appropriateness of antimicrobial therapy. Imipenem resistance was defined as a minimal inhibitory concentration (MIC) of >4 mg/L. Multidrug resistance was defined as non-susceptible to all agents in at least three classes of antimicrobial agents. These included aminoglycosides, ampicillin/sulbactam, fluoroquinolones, anti-pseudomonas cephalosporins, anti-pseudomonas penicillins and carbapenems. Colistin and tigecycline were not available during the study period.

Statistical analysis

Median values and interquartile ranges (IQRs) were used for continuous variables and the association between non-survivors and survivors was calculated using Student's *t*-test or the Mann–Whitney *U*-test. Categorical variables were presented by percentage and calculated with Fisher's exact test/Pearson chi-square test, as appropriate. Logistic regression models were used to explore independent risk factors for 14 and 28-day mortality. All variables with statistical significance in univariable analyses were entered into multivariable analyses to assess their relationship with mortality. Interactions between APACHE II score and the covariates were also analysed by inclusion of an interaction term. Appropriate antimicrobial therapy and drug resistance were obligatorily added into multivariable analysis regardless of univarible results because they were of interest in the study. Time to 28-day mortality was analysed using Kaplan–Meier survival analysis (log-rank test). All analyses were performed using the Statistical Package for the Social Sciences version 18.0 (SPSS, Chicago, IL, USA). A $p < 0.05$ was considered to be statistically significant.