Impact of Appropriate Antimicrobial Therapy on Mortality Associated With Acinetobacter baumannii Bacteremia: Relation to Severity of Infection

Yi-Tzu Lee,1,3,5 Shu-Chen Kuo,1,6 Su-Pen Yang,2,3 Yi-Tsung Lin,1,3 Fan-Chen Tseng,6 Te-Li Chen,1,3,4 and Chang-Phone Fung1,3

1Institute of Clinical Medicine, 2School of Medicine, National Yang-Ming University, and 3Division of Infectious Diseases, and 4Immunology Research Center, Taipei Veterans General Hospital, Taipei; 5Department of Medicine, Chutung Veterans Hospital, Hsinchu County, and 6National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes, Miaoli County, Taiwan

Background. The efficacy of antimicrobial therapy for Acinetobacter baumannii bacteremia has been difficult to establish because of confounding by underlying diseases, severity of infection, and differences in the pathogenicity of Acinetobacter species. This retrospective study was conducted to evaluate the effect of appropriate antimicrobial therapy on 14-day mortality after adjustment for multiple risk factors.

Methods. The population consisted of 252 patients with monomicrobial A. baumannii bacteremia admitted to a large teaching hospital in Taiwan. The isolates were identified to species level using reference molecular methods. Predictors of 14-day mortality were determined by logistic regression analysis. The influence of severity of infection, determined by Acute Physiology and Chronic Health Evaluation (APACHE) II score, on the impact of appropriate use of antimicrobials on 14-day mortality was assessed by including an interaction term.

Results. The overall 14-day mortality rate was 29.8% (75 of 252 patients). The unadjusted mortality rate for appropriate antimicrobial therapy was 13.2% (12 of 91 patients). Appropriate therapy was independently associated with reduced mortality (odds ratio [OR], 0.22; 95% confidence interval [CI], .01–.50; P < .001), and the effect was influenced by APACHE II score (OR for interaction term, 0.90; 95% CI, .82–.98; P = .02). A subgroup analysis revealed that the benefit of appropriate therapy was limited to patients with high APACHE II scores (OR for patients with scores >25 and ≤35, 0.16 [95% CI, .07–.37]; OR for those with scores >35, 0.06; 95% CI, .01–.25).

Conclusions. Appropriate antimicrobial therapy significantly reduced 14-day mortality for A. baumannii bacteremia in severely ill patients.

Acinetobacter baumannii, Acinetobacter nosocomialis (formally Acinetobacter genomic species 13TU), and Acinetobacter pittii (formally Acinetobacter genomic species 3) have emerged as important nosocomial pathogens. Because of their similar phenotypic characteristics, these 3 species cannot be accurately identified to species level by routine diagnostic laboratories [1]. The 3 Acinetobacter species differ in their pathogenicity [2, 3]. A. baumannii tends to be more resistant to antimicrobial agents [2–4]. This increases the likelihood that patients with infections caused by A. baumannii may receive inappropriate antimicrobial therapy and have a greater risk of complications and death [5, 6].

The efficacy of antimicrobial therapy for A. baumannii bacteremia has been difficult to establish in clinical studies because of inclusion of the 3 phenotypically indistinguishable Acinetobacter species that make up the A. baumannii complex and confounding by underlying diseases and severity of infection [7–11]. It is not known whether therapeutic efficacy or lack thereof in previous studies can be attributed to choice
METHODS

Study Population
This study was conducted at Taipei Veterans General Hospital, a 2900-bed, tertiary care teaching hospital in Taipei, Taiwan, during an 8-year period from July 2000 to August 2008. T-VGH is. Charts were reviewed for all patients with ≥1 positive blood culture for A. baumannii who had symptoms and signs of infection. Only the first blood culture was included from patients with ≥2 positive blood cultures. Patients <18 years of age and those with incomplete medical records were excluded. The protocol was approved by the hospital’s institutional review board.

Microbiological Studies
The presumptive identification of the isolates to the level of the A. baumannii complex was determined with the API ID 32 GN system (bioMérieux) or Vitek 2 system (bioMérieux). All A. baumannii complex bloodstream isolates were regrown from storage, identified to species level, and tested for their susceptibility to various antimicrobials. A multiplex polymerase chain reaction method was used to identify A. baumannii to the genomic species level [12]. Antimicrobial susceptibilities were determined by the agar dilution method according to Clinical Laboratory Standards Institute criteria [13]. Multidrug resistance was defined as resistance to ≥3 of the following classes of antimicrobials: antipseudomonal cephalosporins, antipseudomonal carbapenems, ampicillin-sulbactam, fluoroquinolones, and aminoglycosides [1]. Carbapenem resistance was defined as resistance to imipenem or meropenem.

Data Collection
Medical records were reviewed to extract clinical information, including demographic characteristics; comorbid conditions; duration of intensive care unit (ICU) and hospital stays; time of receipt, dose and route of therapy with individual antimicrobial drugs; and the presence of a ventilator, central venous catheters, a nasogastric tube, or a Foley catheter at the time of bacteremia onset. The onset of bacteremia was defined as the day when the blood culture that eventually yielded A. baumannii was obtained. Episodes of bloodstream infection were considered acquired in the ICU if they appeared within 48 hours after ICU admission. Immunosuppressive therapy was defined as receipt of cytotoxic agents within 6 weeks, corticosteroids at a dosage equivalent to or higher than 15 mg of prednisolone daily for 1 week within 4 weeks, or other immunosuppressive agents within 2 weeks before bacteremia onset. Neutropenia was defined as an absolute neutrophil count <0.5 × 10^9 neutrophils/L. Recent surgery was defined as operations performed within 4 weeks before the onset of bacteremia. Renal impairment was defined as an estimated glomerular filtration rate ≤60 mL/min/1.73 m^2. The primary infection source of bacteremia was determined according to the definitions of the Centers for Disease Control and Prevention [14]. Polymicrobial bacteremia was defined as isolation of ≥1 microorganisms other than A. baumannii from blood during the same bacteremic episode. The severity of patient infection was evaluated using the Acute Physiology and Chronic Health Evaluation (APACHE) II score [15] within 24 hours before bacteremia onset.

Appropriate antimicrobial therapy was defined as administration of ≥1 antimicrobial agent, to which the causative pathogen was susceptible in vitro, within 48 hours after the onset of bacteremia, with an approved route and dosage appropriate for end organ function. Antimicrobial therapy that did not meet this definition was considered inappropriate. Monotherapy with an aminoglycoside was not considered an appropriate therapy. The primary outcome measure was all-cause 14-day mortality after the onset of A. baumannii bacteremia.

Statistical Analysis
The χ^2 with Yate’s correction or Fisher’s exact test was used to compare discrete variables; the Student’s t test or Mann-Whitney rank sum test was used to analyze continuous variables as appropriate. Logistic regression models were used to explore independent risk factors for 14-day mortality. Univariable analyses were performed separately for each of the risk factors to ascertain the odds ratio (OR) and 95% confidence interval (CI). All biologically plausible variables with a P value <.20 in the univariable analysis were considered for inclusion in the logistic regression model in the multivariable analysis. A backward selection process was utilized. Interactions between the APACHE II score and the covariates were also examined in the logistic regression model. Calculations of stratum-specific ORs and 95% CI in the presence of interaction terms all followed previous statistic methods, using coefficients and covariance from the model [16]. The time to mortality, defined as the interval between bacteremia onset and death, was analyzed using Kaplan-Meier survival analysis. Differences were considered statistically significant at P < .05. All the analyses were processed with Statistical Package for the Social Sciences (SPSS) software version 18.0.
RESULTS

During the 8-year study period, 252 patients were found to meet the criteria of monomicrobial *A. baumannii* bacteremia. They were derived from a population of 735 patients who had ≥1 blood culture positive for the *A. baumannii* complex. Of these, 335 patients (45.6%) were found to have bloodstream isolates that were genomically identified as *A. baumannii*. We
excluded from the study 83 patients (24.8%) with polymicrobial bacteremia.

A total of 121 patients (48.0%) acquired *A. baumannii* bacteremia in the ICU. The overall 14-day mortality rate of *A. baumannii* bacteremia was 29.8% (75 of 252). The unadjusted mortality for appropriate antimicrobial therapy was 13.2% (12 of 91). The demographic and clinical characteristics of the survivors and nonsurvivors at 14 days after the *A. baumannii* bacteremia are shown in Table 1. There were no significant differences between survivors and nonsurvivors in demographic characteristics and comorbid conditions other than those shown in the table. Nonsurvivors were more likely to have had malignancy and immunosuppressive therapy but less likely to have had recent surgical procedures. Nonsurvivors had significantly higher APACHE II scores, and higher rates of central venous catheters, Foley catheters, nasogastric tubes, and ventilator use.

The bloodstream isolates from nonsurvivors had a significantly greater rate of resistance to carbapenems than those from survivors. There were no significant differences in resistance to ciprofloxacin, amikacin, gentamicin, ceftazidime, cefepime, piperacillin-tazobactam, and ampicillin-sulbactam between isolates from survivors and nonsurvivors (data not shown). Survivors were significantly more likely than nonsurvivors to have received appropriate antimicrobial therapy. The only significant difference in the source of bacteremia between survivors and nonsurvivors was that it was more likely to have originated from the respiratory tract in nonsurvivors. Factors that significantly predicted 14-day mortality in logistic regression analysis are shown in Table 2. Multivariable analysis revealed that receipt of appropriate antimicrobial therapy was independently associated with reduced mortality (*P* < .001). Malignancy and APACHE II score were independent predictors of mortality (*P* = .002 and *P* < .001, respectively).

To clarify how the severity of infection modified the impact of appropriate antimicrobial therapy on 14-day mortality, interactions between APACHE II score and appropriate antimicrobial therapy were added to the logistic regression model. The interaction term was statistically significant (OR, 0.90; 95% CI, 0.82–0.98; *P* = .02) using the APACHE II score as a continuous variable. To demonstrate the impact of appropriate antimicrobial therapy on 14-day mortality in patients with different severity of infection, APACHE II scores were categorized into 4 groups (Table 3) and added to the model along with its interaction term. Adjusted ORs for appropriate antimicrobial therapy administered to subgroups encompassing 4 ranges of APACHE II scores are shown in Table 3. Among patients with scores ≤15 or scores >15 and ≤25, appropriate antimicrobial therapy was not associated with a significantly better outcome. However, among patients with scores >25 and ≤35 or scores >35, appropriate antimicrobial therapy significantly reduced the 14-day mortality (OR, 0.16 [95% CI, 0.07–0.37] vs 0.06 [95% CI, 0.01–0.25], respectively). The APACHE II scores were also categorized into 4 groups based on their quartile distribution, and similar magnitude of associations and trend were also obtained (data not shown). The effect of appropriate antimicrobial therapy on 28-day survival was analyzed in the same fashion as the above analyses.

### Table 2. Logistic Regression Analysis of Predictors for 14-Day Mortality Among Patients With *Acinetobacter baumannii* Bacteremia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariable Analysis</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td><em>P</em></td>
</tr>
<tr>
<td>Cerebral vascular accident</td>
<td>0.42 (.19–95)</td>
<td>.04</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.79 (1.02–3.13)</td>
<td>.04</td>
</tr>
<tr>
<td>Acquired in ICU</td>
<td>1.46 (.85–2.52)</td>
<td>.17</td>
</tr>
<tr>
<td>Recent surgery</td>
<td>0.44 (.24–.81)</td>
<td>.009</td>
</tr>
<tr>
<td>Immunosuppressive therapy</td>
<td>1.95 (1.13–3.38)</td>
<td>.02</td>
</tr>
<tr>
<td>Presence of central venous catheter</td>
<td>1.90 (1.09–3.31)</td>
<td>.02</td>
</tr>
<tr>
<td>Foley catheter use</td>
<td>2.22 (1.22–4.04)</td>
<td>.009</td>
</tr>
<tr>
<td>Nasogastric tube use</td>
<td>3.06 (1.50–6.23)</td>
<td>.002</td>
</tr>
<tr>
<td>Ventilator use</td>
<td>3.19 (1.76–6.75)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>1.17 (1.12–1.21)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Carbapenem resistance</td>
<td>2.03 (1.14–3.62)</td>
<td>.02</td>
</tr>
<tr>
<td>Appropriate antimicrobial therapy</td>
<td>0.24 (.12–.47)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Respiratory tract as source of infection</td>
<td>2.60 (1.45–4.66)</td>
<td>.001</td>
</tr>
</tbody>
</table>

All biologically plausible variables with a *P* value < .20 in the univariable analysis were considered for inclusion in the logistic regression model in the multivariable analysis. A backward selection process was utilized. We found that only malignancy, APACHE II, and appropriate therapy were independent (statistically significant) factors for 14-day mortality.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; ICU, intensive care unit.
results were similar to those using all-cause 14-day mortality as the primary outcome measure (data not shown).

To compare the varying effect of appropriate and inappropriate antimicrobial therapy on the outcome in patients with different severity of infection, Kaplan-Meier survival curves were developed for each of the 4 groups categorized by APACHE II scores. Although no significant differences in survival were noted between patients receiving appropriate versus inappropriate antimicrobial therapy in groups 1 \((P = .96\) by log-rank test) and 2 \((P = .22\) by log-rank test) (figures not shown), there was a significant advantage in survival for appropriate compared to inappropriate use of antimicrobial therapy in groups 3 \((P = .01\) by log-rank test) and 4 \((P < .001\) by log-rank test) (Figures 1A and 1B, respectively). The differences were more pronounced in the more severely ill patients in group 4 than in group 3. A comparison of the demographic and clinical characteristics between patients who received appropriate (91 patients) or inappropriate antimicrobial therapy (161 patients) revealed no difference in age, sex, comorbid conditions, APACHE II score, source of infection, multidrug resistance, acquisition of bacteremia in ICU, or days of hospitalization before bacteremia (data not shown). The only risk factor for inappropriate antimicrobial therapy was the carbapenem resistance of the \(A.\ baumannii\) isolates. The antimicrobials used for the patients are shown in Table 4. For patients who received appropriate antimicrobial therapy, no individual antimicrobial class was associated with a better or worse outcome after a multivariable analysis (data not shown).

**DISCUSSION**

The association between appropriate antimicrobial therapy and mortality for \(A.\ baumannii\) bacteremia has been difficult to establish because of confounding by underlying diseases, severity of infection, and infection with a mixture of \(Acinetobacter\) species. This retrospective study was conducted to evaluate the effect of appropriate antimicrobial therapy on the 14-day mortality of patients with genomically identified monomicrobial \(A.\ baumannii\) bacteremia after adjustment for multiple risk factors. We found that appropriate antimicrobial therapy decreased mortality among the most severely ill patients.

Although \(A.\ baumannii\) has similar phenotypic reactions as that of \(A.\ nosocomialis\) and \(A.\ pittii\) [1], \(A.\ baumannii\) is clearly distinct from the latter 2 \(Acinetobacter\) species because of its resistance to more classes of antimicrobial agents and its association with a worse clinical outcome [2–3]. The inclusion of different \(Acinetobacter\) species in a study would complicate the interpretation of the results. Therefore, it is reasonable to separate \(A.\ baumannii\) from other \(Acinetobacter\) species in the studies, including for outcome analysis.

The effects of inappropriate antimicrobial therapy have been found to be less detrimental in patients who are not severely ill and the most severely infected patients with short life expectancies [17]. Our observation that appropriate antimicrobial therapy did not significantly benefit patients with APACHE II

### Table 3. Adjusted Odds Ratios of Appropriate Antimicrobial Therapy for 14-Day Mortality Among Patients With \(Acinetobacter\) \(baumannii\) Bacteremia, Stratified by Severity of Infection

<table>
<thead>
<tr>
<th>Group</th>
<th>APACHE II Score</th>
<th>Patients, No.</th>
<th>14-Day Mortality, %</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\leq 15)</td>
<td>50</td>
<td>4.0</td>
<td>1.04 (.19–5.74)</td>
</tr>
<tr>
<td>2</td>
<td>&gt;15 and (\leq 25)</td>
<td>98</td>
<td>14.3</td>
<td>0.40 (.15–1.10)</td>
</tr>
<tr>
<td>3</td>
<td>&gt;25 and (\leq 35)</td>
<td>62</td>
<td>41.9</td>
<td>0.16 (.07–.37)</td>
</tr>
<tr>
<td>4</td>
<td>&gt;35</td>
<td>42</td>
<td>78.6</td>
<td>0.06 (.01–.25)</td>
</tr>
</tbody>
</table>

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; OR, odds ratio.

**Figure 1.** Kaplan-Meier survival curves at 28 days after \(Acinetobacter\) \(baumannii\) bacteremia onset for patients receiving appropriate or inappropriate antimicrobial therapy, stratified by severity of infection. **A,** Group 3, with APACHE II scores \(>25\) and \(\leq 35\). **B,** Group 4, with APACHE II scores \(>35\). Abbreviation: APACHE II, Acute Physiology and Chronic Health Evaluation II.
scores ≤ 25 is in accord with the previous assumption. It is reasonable to assume that less severely ill patients infected with pathogens that are mildly virulent should have a better prognosis and might recover without specific therapeutic interventions. However, in contradiction to the previous assumption, we showed that appropriate antimicrobial therapy was the potential life-saving measure for the patient group with the most severe illness. Based on these observations, we recommend that severity of infection needs to be included in clinical trials that evaluate the impact of appropriate antimicrobial therapy on the mortality caused by A. baumannii infections.

With regard to the issues of in vitro testing of β-lactams or β-lactamase inhibitor combinations against A. baumannii [1], it has been suggested that the definition of appropriate antimicrobial therapy should be restricted to fluoroquinolones and antipseudomonal carbapenems in cases of carbapenem-susceptible A. baumannii. Using this definition, we obtained similar results (data not shown). This finding, together with the consistent results obtained using different outcome measures (14- and 28-day mortality), supports the robustness of the main conclusions.

The emergence of carbapenem-resistant A. baumannii worldwide has severely restricted the selection of appropriate therapy. Other studies [18, 19] have found a link between carbapenem resistance and mortality. We found that carbapenem resistance was associated with 14-day mortality at bivariate analysis, but resistance is not an independent risk factor for mortality. The higher mortality rates in patients who acquired carbapenem-resistant A. baumannii might be attributed to more frequent inappropriate antimicrobial therapy. Earlier detection of patients with infections caused by carbapenem-resistant A. baumannii based on the exposure risks [20, 21], use of molecular methods that can rapidly identify A. baumannii [12, 22, 23], and its carbapenem-resistant determinants [24, 25] should help select the most appropriate antimicrobial agents.

The weakness of this study is the retrospective design required to enroll sufficient patients for detailed analysis at a single tertiary care medical center. However, the study was strengthened by the inclusion of a large number of patients with various severity of infection, with genomically defined A. baumannii bacteremia, and a well defined end point of 14-day mortality.

In conclusion, we found that appropriate antimicrobial therapy reduces the 14-day mortality associated with A. baumannii bacteremia in severely ill patients. Earlier detection of A. baumannii bacteremia and carbapenem resistance should help reduce the use of inappropriate antimicrobial therapy.

### Table 4. Antimicrobials Used in 252 Patients With Acinetobacter baumannii Bacteremia

<table>
<thead>
<tr>
<th>Main Agents Used</th>
<th>Patients, No.</th>
<th>APACHE II Score, Median (IQR)</th>
<th>Appropriate Antimicrobial Therapy</th>
<th>Combination Antimicrobial Therapy</th>
<th>14-Day Nonsurvivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipseudomonal penicillins&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25</td>
<td>30 (22.5–36)</td>
<td>10 (40.0)</td>
<td>2 (8.0)</td>
<td>13 (62.0)</td>
</tr>
<tr>
<td>Antipseudomonal cephalosporins&lt;sup&gt;b&lt;/sup&gt;</td>
<td>50</td>
<td>24.5 (17–32)</td>
<td>22 (44.0)</td>
<td>8 (16.0)</td>
<td>21 (42.0)</td>
</tr>
<tr>
<td>Antipseudomonal fluoroquinolones&lt;sup&gt;c&lt;/sup&gt;</td>
<td>15</td>
<td>25 (20–32)</td>
<td>3 (20.0)</td>
<td>1 (6.7)</td>
<td>5 (33.3)</td>
</tr>
<tr>
<td>Antipseudomonal carbapenems&lt;sup&gt;d&lt;/sup&gt;</td>
<td>72</td>
<td>25 (21–32.75)</td>
<td>35 (48.6)</td>
<td>1 (1.4)</td>
<td>18 (25.0)</td>
</tr>
<tr>
<td>Ampicillin-sulbactam or sulbactam</td>
<td>37</td>
<td>20 (15–27)</td>
<td>22 (69.5)</td>
<td>5 (13.5)</td>
<td>6 (16.2)</td>
</tr>
<tr>
<td>Nonantipseudomonal β-lactams&lt;sup&gt;e&lt;/sup&gt;</td>
<td>45</td>
<td>18 (13–25.5)</td>
<td>2 (4.4)</td>
<td>6 (13.3)</td>
<td>7 (15.6)</td>
</tr>
</tbody>
</table>

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; IQR, interquartile range.

<sup>a</sup> Including piperacillin, piperacillin-tazobactam, and ticarcillin-clavulanate.

<sup>b</sup> Including cefoperazone, ceftazidime, cefepime, and ceft(ziprem.

<sup>c</sup> Including ciprofloxacin and levofloxacin.

<sup>d</sup> Including imipenem and meropenem.

<sup>e</sup> Including penicillin, amoxicillin-clavulanate, cefazolin, cefotaxime, cefotaxime, and fomoxef.

### Notes

**Acknowledgments.** The authors wish to express their appreciation to Calvin M. Kunin for his critical review of the manuscript.

**Financial support.** This work was supported by the Taipei Veterans General Hospital (grants V100C-025 and V10E4-005), the National Science Council (grant NSC98-2314-B-010-010-MY3), and the Yen Tjing Ling Medical Foundation (grant CI-99-18).

**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

### References


