Impact of imipenem resistance on mortality in patients with Acinetobacter bacteraemia

Ki Tae Kwon1, Won Sup Oh1, Jae-Hoon Song1,2*, Hyun-Ha Chang3, Sook-In Jung4, Shin-Woo Kim3, Seong Yeol Ryu5, Sang Taek Heo6, Dong Sik Jung1, Ji-Young Rhee1, Sang Yop Shin1, Kwan Soo Ko2, Kyong Ran Peck1 and Nam Yong Lee7

1Division of Infectious Diseases, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Kangnam-ku, Seoul 135-710, Korea; 2Asian-Pacific Research Foundation for Infectious Diseases (ARFID), 50 Irwon-dong, Kangnam-ku, Seoul, Korea; 3Division of Infectious Diseases, Kyungpook National University Hospital, 50 Samduk-2ga, Jung-gu, Daegu, Korea; 4Division of Infectious Diseases, Chonnam National University Hospital, 8 Hak-dong, Dong-gu, Gwangju, Korea; 5Department of Infectious Diseases, Keimyung University Dongsan Medical Center, 194 Dongsan-dong, Jung-gu, Daegu, Korea; 6Division of Infectious Diseases, Cheju National University Hospital, Cheju National University, 154 Samdo-2 dong, Jeju City, Cheju, Korea; 7Department of Laboratory Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Kangnam-ku, Seoul, Korea

Received 26 June 2006; returned 2 August, 2006; revised 1 November 2006; accepted 9 November 2006

Objectives: To investigate the impact of imipenem resistance on the mortality rate among patients with Acinetobacter bacteraemia.

Methods: A retrospective, pairwise-matched (1:1), risk-adjusted (age, Pitt bacteraemia score) cohort study was performed at three tertiary care hospitals in Korea from January 2000 to June 2005.

Results: Forty patients with imipenem non-susceptible Acinetobacter bacteraemia (INAB group) and 40 matched subjects (1:1 ratio) with imipenem-susceptible Acinetobacter bacteraemia (ISAB group) were included. Both groups had similar clinical features related to the severity of illness. The 30 day mortality rate was higher in the INAB group (57.5%) than the ISAB group (27.5%) (P = 0.007). The rate of discordant antimicrobial therapy was higher in the INAB group (65.0%) than the ISAB group (20.0%) (P < 0.001). The 30 day mortality rate was higher in the patients with discordant antimicrobial therapy (67.6%) than concordant antimicrobial therapy (23.9%) (P < 0.001). Multivariate analysis showed that age, the Pitt bacteraemia score, immunosuppressive status, and discordant antimicrobial therapy were independent risk factors for 30 day mortality among patients with Acinetobacter bacteraemia (P < 0.05). When discordant antimicrobial therapy was excluded in the multivariate analysis, the imipenem resistance was associated with 30 day mortality (P = 0.005).

Conclusions: Imipenem resistance has a significant impact on the mortality rate among patients with Acinetobacter bacteraemia, and this is mainly attributable to the higher rate of discordant antimicrobial therapy.

Keywords: matched cohort study, attributable mortality, discordant antimicrobial therapy

Introduction

Increasing reports of fatal Acinetobacter infections that cause pneumonia, meningitis, endocarditis, and bacteraemia underline the clinical importance of this pathogen. The overall mortality rate associated with Acinetobacter bacteraemia is approximately 25% and ranges from 5% in general wards to 54% in intensive care units.1–4

Acinetobacter species have a propensity for the rapid development of antimicrobial resistance to many classes of...
antibiotics. By reason of best activity, carbapenems have been preferred for use in serious Acinetobacter infections. However, the prevalence of carbapenem-resistant strains has recently been increasing in hospital settings, especially among critically ill patients. Moreover, the majority of carbapenem-resistant strains were also multidrug or pandrug resistant, which could affect the clinical outcome of serious Acinetobacter infections. However, the impact of carbapenem resistance on the outcome of such infections has not yet been clearly evaluated.

To assess the clinical impact of imipenem resistance on the mortality rate among patients with Acinetobacter bacteraemia, we performed risk factor analysis for in-hospital 30 day mortality due to all causes.

**Patients and methods**

**Study design and population**

A retrospective, pairwise matched cohort study was conducted in three tertiary care hospitals: Samsung Medical Center [1250 beds, including 65 intensive care unit (ICU) beds], Seoul; Chonnam National University Hospital (1061 beds, including 88 ICU beds), Gwangju; and Kyungpook National University Hospital (925 beds, including 41 ICU beds), Daegu, Korea.

All consecutive cases of nosocomial Acinetobacter bacteraemia in hospitalized patients diagnosed between January 2000 and June 2005 were electronically sorted from the database of the clinical microbiology laboratory in each hospital. Exposed subjects were defined as patients with imipenem non-susceptible (intermediate or resistant) Acinetobacter bacteraemia (INAB). An equal number of matched unexposed subjects (1:1 ratio) were selected among patients with imipenem-susceptible Acinetobacter bacteraemia (ISAB), on the basis of age (±5 years) and the Pitt bacteraemia score (+1 point) as the index of disease severity. When several unexposed subjects matched, the subject who had a Pitt bacteraemia score and an admission date closest to those of the exposed subjects was chosen.

Acinetobacter bacteraemia was diagnosed if the isolation of Acinetobacter species from one or more blood cultures was accompanied by two or more of the following conditions: fever (temperature >38°C), hypothermia (temperature <36°C), tachypnoea (respiratory rate >24 breaths/min), tachycardia (pulse rate >90 beats/min), leucocytosis (white cell count >12 000 cells/mm³), or leucopenia (white cell count <4000 cells/mm³). When a patient had more than one bacteraemic episode, only the first episode was included.

**Data collection**

Blood cultures were processed in each clinical microbiology laboratory using the Bactec 9240 blood culture system (Becton Dickinson, Cockeysville, MD, USA). Identification and antimicrobial susceptibility tests for Acinetobacter species were performed with Neg Combo 32 panels of the MicroScan system (Dade Behring, West Sacramento, CA, USA) or GIN and GNS 434 cards of the Vitek system (BioMérieux, Hazelwood, MO, USA). The MIC and interpretation results from the automated systems were comparable to CLSI guidelines. Multidrug resistance (MDR) was defined as the microorganism being not susceptible to more than three of the following eight antimicrobial agents: ampicillin/sulbactam, aztreonam, ceftazidime, ciprofloxacin, gentamicin, imipenem, piperacillin and trimethoprim/sulfamethoxazole. Pandrug resistance (PDR) was defined as the microorganism being not susceptible to any available antimicrobial agents except colistin.

Data on clinical or laboratory parameters were collected, including demographic characteristics, underlying conditions, clinical manifestations, laboratory results, radiographic findings, antimicrobial therapy, clinical course, and death. The primary focus of bacteraemia was determined by the investigators on the basis of a patient’s medical records. The severity of illness was assessed by using the Pitt bacteraemia score and Charlson’s weighted index of co-morbidity.

To analyse the impact of antimicrobial resistance on a clinical outcome, the concordance of antimicrobial therapy was assessed. Concordant antimicrobial therapy was defined as the microorganism being susceptible to at least one of the antimicrobials administered after the onset of bacteraemia, while discordant therapy was defined as the microorganism being not susceptible to any of the prescribed antimicrobials. To compare the clinical outcomes between the groups, 5 day, 10 day and 30 day in-hospital mortalities due to all causes were assessed. Attributable mortality rate was determined by subtracting the crude mortality rate of unexposed subjects from that of the exposed subjects.

**Statistical analysis**

The matched-pairs design was disregarded in this study because the outcome variable was not imipenem resistance but 30 day mortality. Data collected in a matched-pairs design are sometimes analysed as if the data were not matched. Comparisons between two groups were carried out using the χ² or Fisher’s exact T-test for categorical variables and the Mann–Whitney U-test for continuous variables. To assess the relationship between the 30 day mortality and a set of variables, a multiple logistic regression model was used. The results of these logistic regression analyses were reported as adjusted odds ratio (OR) with 95% confidence interval (CI). The 30 day cumulative survivals of the two groups were compared using the method of Kaplan–Meier with the log-rank test. All P values were 2-tailed, and P<0.05 was considered to be statistically significant. SPSS for Windows (version 11.5 software package; SPSS Inc., Chicago, IL, USA) was used for this analysis.

**Ethic**

This study was approved by the Institutional Review Board at Samsung Medical Center (# 2006-05-043) with an exemption from receiving the informed consent. All data collected from this study were kept confidential.

**Results**

**Patient characteristics**

Data from a total of 512 cases of nosocomial Acinetobacter bacteraemia from three hospitals were collected between January 2000 and June 2005. Of these, 40 cases (7.8%) met all of the criteria for INAB. These comprised 18 cases from Samsung Medical Center, 12 from Chonnam National University...
Hospital, and 10 from Kyungpook National University Hospital. Of the 298 evaluable cases with ISAB, 40 matched unexposed subjects (1:1 ratio) were selected.

The characteristics of the INAB and ISAB groups are shown in Table 1. The clinical features related to the severity of infection (age, hospital stay before the onset of bacteraemia, bacteraemic episodes in ICU, presence of polymicrobial bacteraemia, primary focus of bacteraemia, acute renal failure, immunosuppression, mechanical ventilation, underlying malignancy, Pitt bacteraemia score, and Charlson’s weighted index of co-morbidity) were similar between the two groups. In both groups, catheter-related infection was the most common primary focus of the Acinetobacter bacteraemia, followed by pneumonia and intra-abdominal infection. Among 40 imipenem non-susceptible strains, 22 (55.0%) belonged to the imipenem-resistant Acinetobacter baumannii complex (ABC), 17 (42.5%) were imipenem-intermediate ABC, and one (2.5%) was imipenem-resistant Acinetobacter lwoffii. Among 40 imipenem-susceptible strains, 39 (97.5%) belonged to ABC, and one (2.5%) was A. lwoffii.

### Impact of antimicrobial resistance on mortality

The INAB group isolates were more often resistant to all eight antimicrobial agents (ampicillin/sulbactam, aztreonam, ceftazidime, ciprofloxacin, gentamicin, imipenem, piperacillin and trimethoprim/sulfamethoxazole) than the ISAB group isolates ($P < 0.05$). Also, the MDR rate was higher in the INAB group (95.0%) than the ISAB (40.0%) group ($P < 0.001$).

The 5, 10 and 30 day cumulative mortality rates were higher in the INAB group (37.5%, 50.0%, 57.5%) than the ISAB group (12.5%, 17.5%, 27.5%) ($P < 0.05$) (Figure 1). Compared with the ISAB group, the relative risk for the 30 day mortality and attributable 30 day mortality rate of the INAB group were 2.019 (95% CI, 1.18–3.69) and 30.0%, respectively. In a total of 13 (2.5%) pandrug-resistant Acinetobacter bacteraemia, the 30 day mortality rate was 53.8% and the median survival was 12 days.

### Impact of discordant antimicrobial therapy on mortality

The prevalence of antimicrobial concordance and the interrelation between imipenem resistance and antimicrobial concordance for the 30 day mortality rate are shown in Table 2. The rate of discordant antimicrobial therapy was higher in the INAB group (65.0%) than the ISAB group (20.0%) ($P < 0.001$). Compared with the ISAB group, the relative and attributable risks of the INAB group for discordant antimicrobial therapy were 3.25 (95% CI, 1.67–6.28) and 35%.

### Table 1. Clinical characteristics of 80 patients with Acinetobacter bacteraemia, according to imipenem susceptibility

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>INAB group $a$ ($n = 40$)</th>
<th>ISAB group $b$ ($n = 40$)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>$47 \pm 24.1$</td>
<td>$47 \pm 24.5$</td>
<td>0.862</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>28/12</td>
<td>29/11</td>
<td>0.805</td>
</tr>
<tr>
<td>Hospital stay prior to bacteraemia (days)</td>
<td>$29 \pm 25.4$</td>
<td>$24 \pm 22.4$</td>
<td>0.303</td>
</tr>
<tr>
<td>Bacteraemic episodes in ICU</td>
<td>27 (67.5)</td>
<td>28 (70.0)</td>
<td>0.813</td>
</tr>
<tr>
<td>Episodes of polymicrobial bacteraemia</td>
<td>11 (27.5)</td>
<td>15 (37.5)</td>
<td>0.340</td>
</tr>
<tr>
<td>Primary focus of bacteraemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>catheter-related infections</td>
<td>14 (35.0)</td>
<td>15 (37.5)</td>
<td>0.816</td>
</tr>
<tr>
<td>pneumonia</td>
<td>10 (25.0)</td>
<td>8 (20.0)</td>
<td>0.592</td>
</tr>
<tr>
<td>intra-abdominal infections</td>
<td>7 (17.5)</td>
<td>8 (20.0)</td>
<td>0.775</td>
</tr>
<tr>
<td>others</td>
<td>9 (22.5)</td>
<td>9 (22.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>13 (32.5)</td>
<td>6 (15.0)</td>
<td>0.066</td>
</tr>
<tr>
<td>Immunosuppressive status prior to bacteraemia</td>
<td>14 (35.0)</td>
<td>13 (32.5)</td>
<td>0.813</td>
</tr>
<tr>
<td>Mechanical ventilation during bacteraemia</td>
<td>18 (45.0)</td>
<td>20 (50.0)</td>
<td>0.654</td>
</tr>
<tr>
<td>Underlying malignancy</td>
<td>19 (47.5)</td>
<td>20 (50.0)</td>
<td>0.823</td>
</tr>
<tr>
<td>Pitt bacteraemia score</td>
<td>$3.8 \pm 2.0$</td>
<td>$3.8 \pm 2.2$</td>
<td>0.831</td>
</tr>
<tr>
<td>Charlson’s weighted index of co-morbidity</td>
<td>$2.8 \pm 2.7$</td>
<td>$2.9 \pm 2.2$</td>
<td>0.517</td>
</tr>
</tbody>
</table>

Data are number (%) of patients or mean value ± standard deviation.

$a$Includes patients with imipenem-intermediate or -resistant Acinetobacter bacteraemia.

$b$Includes patients with imipenem-susceptible Acinetobacter bacteraemia.
Among a total of 80 enrolled cases, the 30 day mortality rate was higher in patients treated with discordant antimicrobial therapy (67.6%) than concordant antimicrobial therapy (23.9%) (\(P < 0.001\)). In the INAB group, discordant antimicrobial therapy (73.1%) resulted in a higher 30 day mortality rate than concordant antimicrobial therapy (28.6%) (\(P = 0.007\)). While the 30 day mortality rate was higher in the patients treated with discordant antimicrobial therapy (50.0%) than concordant antimicrobial therapy (21.9%) in the ISAB group, the difference between the two groups was not statistically significant due to the small number of cases with discordant antimicrobial therapy (\(P = 0.182\)). The 30 day mortality rates for the INAB and the ISAB groups were not significantly different in the patients treated with concordant (28.6% versus 21.9%, \(P = 0.713\)) and discordant antimicrobial therapy (73.1% versus 50.0%, \(P = 0.388\)). These findings showed that discordant antimicrobial therapy was a more significant risk factor than imipenem resistance for the 30 day mortality.

### Risk factors for mortality associated with Acinetobacter bacteraemia

Univariate analysis of risk factors showed that age (OR, 1.02; 95% CI, 1.00–1.04; \(P = 0.049\)), the Pitt bacteraemia score (OR, 1.58; 95% CI, 1.23–2.02; \(P < 0.001\)), acute renal failure (OR, 4.13; 95% CI, 1.27–12.4; \(P = 0.012\)), pneumonia as a primary focus of bacteraemia (OR, 3.63; 95% CI, 1.20–11.03; \(P = 0.023\)), mechanical ventilation during bacteraemia (OR, 3.44; 95% CI, 1.3–8.70; \(P = 0.009\)), Charlson’s weighted index of co-morbidity ≥3 points (OR, 3.69; 95% CI, 1.45–9.40; \(P = 0.006\)), imipenem resistance (OR, 3.57; 95% CI, 1.4–9.08; \(P = 0.008\)), multidrug resistance (OR, 10.33; 95% CI, 2.77–38.62; \(P = 0.001\)), and discordant antimicrobial therapy (OR, 6.65; 95% CI, 2.48–17.86; \(P < 0.001\)) were significantly associated with 30 day mortality in patients with *Acinetobacter* bacteraemia. The 30 day mortality rate was significantly lower in patients with catheter-related infections (\(P = 0.015\)).

When multivariate analysis was performed to compare the relative contribution of risk factors associated with 30 day mortality, the following factors were found to be significant:

### Table 3. Multivariate analysis of risk factors for 30 day mortality among patients with *Acinetobacter* bacteraemia

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Model I OR (95% CI)</th>
<th>P value</th>
<th>Model II OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(^b)</td>
<td>1.05 (1.00–1.09)</td>
<td>0.034</td>
<td>1.05 (1.00–1.09)</td>
<td>0.005</td>
</tr>
<tr>
<td>Pitt bacteraemia score(^b)</td>
<td>1.99 (1.38–2.97)</td>
<td>0.001</td>
<td>1.89 (1.32–2.72)</td>
<td>0.001</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>2.83 (0.50–16.02)</td>
<td>0.238</td>
<td>1.76 (0.41–7.60)</td>
<td>0.448</td>
</tr>
<tr>
<td>Imunosuppressive status</td>
<td>6.53 (1.15–36.96)</td>
<td>0.034</td>
<td>5.61 (1.20–26.26)</td>
<td>0.029</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1.22 (0.23–6.52)</td>
<td>0.819</td>
<td>1.99 (0.45–8.71)</td>
<td>0.362</td>
</tr>
<tr>
<td>Charlson’s WIC ≥3 points</td>
<td>2.85 (0.23–6.52)</td>
<td>0.157</td>
<td>2.69 (0.71–10.14)</td>
<td>0.144</td>
</tr>
<tr>
<td>Imipenem resistance</td>
<td>3.90 (0.90–16.98)</td>
<td>0.070</td>
<td>6.91 (1.79–26.65)</td>
<td>0.005</td>
</tr>
<tr>
<td>Discordant therapy</td>
<td>6.05 (1.34–27.29)</td>
<td>0.019</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; Charlson’s WIC, Charlson’s weighted index of co-morbidity.

\(^a\)Discordant antimicrobial therapy was excluded in multivariate analysis.

\(^b\)Per 1 point increase in score.
mortality, age, the Pitt bacteraemia score, immunosuppressive status, and discordant antimicrobial therapy were independent risk factors for 30 day mortality among patients with Acinetobacter bacteraemia ($P < 0.05$) (model I in Table 3). When discordant antimicrobial therapy was excluded in the multivariate analysis, the imipenem resistance was associated with 30 day mortality ($P = 0.005$) (model II in Table 3). The Nagelkerke R Squares of model I and II were 0.619 and 0.555.

### Discussion

Since the emergence of carbapenem-resistant Acinetobacter infection was first reported in New York in 1991, nosocomial outbreaks have been reported from centres throughout the world. Incidences of carbapenem-resistant Acinetobacter species are increasing worldwide. In 2001, the International Network for the Study and Prevention of Emerging Antimicrobial Resistance (INSPEAR) defined the emergence of carbapenem resistance in Acinetobacter species as a sentinel global event, warranting prompt epidemiological and microbiological interventions. However, the effect of carbapenem or MDR on the outcome of patients with Acinetobacter bacteraemia has not been clearly defined. A recent study demonstrated that patients with MDR Acinetobacter bacteraemia had a higher mortality rate, a longer hospital stay, and greater medical costs compared with non-MDR Acinetobacter bacteraemia.

Our matched, severity-adjusted cohort study showed that the rate of MDR, the rate of discordant antimicrobial therapy, and the 30 day mortality rate were all significantly higher in the INAB group than the ISAB group. The 30 day mortality rate was significantly higher in the group treated with discordant antimicrobial therapy than concordant therapy. Multivariate analysis showed that discordant antimicrobial therapy had a more significant impact on the 30 day mortality than imipenem resistance. These findings demonstrate that imipenem resistance is frequently associated with MDR, and subsequently leads to discordant antimicrobial therapy, which affects an unfavourable outcome in patients with Acinetobacter bacteraemia.

There are some limitations in our study, which was a retrospective analysis with a small number of strains with full resistance to imipenem interpreted by automated systems. We did not consider other treatment factors that may have contributed to adverse outcomes such as improper dosing, a delay in treatment, surgery, and other procedures. Other outcome parameters such as time to the resolution of bacteraemia or length of hospital stay (LOS) were not evaluated because our retrospective data were incomplete and unable to define the exact duration of bacteraemia, and most patients had severe co-morbidities, which made LOS very variable.

In conclusion, imipenem resistance had a significant impact on the mortality rate among patients with Acinetobacter bacteraemia, and this was mainly due to a higher rate of discordant antimicrobial therapy. To treat the severe infections caused by Acinetobacter strains with imipenem resistance, antimicrobial agents with a high susceptibility rate such as colistin or tigecycline should be considered. Prospective studies are warranted to investigate the clinical impact of resistance and treatment options for MDR and PDR Acinetobacter infections.

### References


