Attributable Mortality of Imipenem-Resistant Nosocomial *Acinetobacter baumannii* Bloodstream Infection

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Background: *Uncertainty remains concerning the mortality attributable to infections caused by imipenem-resistant acinetobacter baumannii (IRAB). The authors have sought to examine the impact of this resistance on patient mortality.*
Objective: *To evaluate the effects of imipenem resistance on the mortality of patients with Acinetobacter baumannii bloodstream infection.*
Material and Method: *A cohort study was conducted to compare the survival rates between patients with IRAB and imipenem-susceptible A. baumannii (ISAB) bacteremia.*
Results: *The present study shows 35 patients (52.2%) in an IRAB group died in hospital compared to 26 patients (19.9%) in an ISAB group ($p < 0.001$). Multivariate analysis using Cox's proportional hazard model for controlling the confounding effects due to the severity of underlying diseases, inappropriate antibiotic treatment, and primary source of bacteremia show no statistically significant difference in mortality rates between the two groups.*
Conclusion: *The observed higher mortality rate among patients with an IRAB bloodstream infection may not be attributable to imipenem resistance but may in some part be due to a more severe illness, inappropriate antimicrobial therapy, and primary source of infection.*

Keywords: *Acinetobacter baumannii, Imipenem, Carbapenems, Drug resistance, Cross infection, Bacteremia, Epidemic, Disease outbreaks, Hospital mortality, Virulence factors*

J Med Assoc Thai 2009; 92 (3): 413-9
Full text. e-Journal: *http://www.mat.or.th/journal*

Acinetobacter baumannii is an aerobic, nonfermentative, gram-negative coccobacillus, which may be isolated from soil, water, human skin, and the environment. It is an important opportunistic nosocomial pathogen causing a variety of nosocomial infections, including ventilator-associated pneumonia, bloodstream infection (BSI), urinary tract infection, and meningitis[1]. Infection caused by this organism poses crucial problems for both its treatment and control due to its ability to prolong survival in the environment and rapidly develop resistance to multiple antimicrobial agents.

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Imipenem is a carbapenem antimicrobial agent used to treat a variety of serious infections when an organism is resistant to the primary agent of choice. Imipenem has retained *in vitro* activities that are superior to other antimicrobials, and consequently, in many centers, it is the drug of choice for patients with infection caused by *A. baumannii*.

The presentation of infection caused by imipenem-resistant *A. baumannii* (IRAB) presents clinicians with one of their most difficult therapeutic problems because of the widespread resistance of these bacteria to the other major groups of antibiotics.

Although IRAB is increasingly reported as the cause of outbreaks of nosocomial infections worldwide, including Songklanagarind Hospital[2-9], the virulence of IRAB has not been clearly demonstrated.

The previous studies on clinical outcomes of patients infected with IRAB are limited by the study methodology that includes small sample sizes; inappropriate comparison groups; failure to control for severity of illness before infection; failure to control for site and source of infection and failure to exclude patient colonized with *A. baumannii*.

Uncertainties remain about the mortality attributable to infections caused by IRAB. The authors have, therefore sought to examine the impact of imipenem resistance in *A. baumannii* on the patient mortality. To control for site of infection, the authors limited the present study to BSI, which usually results in a high mortality rate and have a relatively reliable diagnostic criteria.

Material and Method

Setting

A retrospective cohort study was conducted at Songklanagarind Hospital, an 850-bed medical school, training, and referral center in the south of Thailand. The hospital has three intensive care units (ICUs), a 19-bed adult medical-surgical ICU, a seven-bed pediatric ICU, and a 15-unit neonatal ICU.

Study design

To assess the impact of IRAB infection on the mortality outcome of the patients, a retrospective cohort study was conducted comparing the hospital mortality rates between the hospitalized patients who acquired IRAB BSI and the patients who acquired ISAB BSI. The other mortality prognostic factors were used to control for confounding effects.

Sources of data

Data of *A. baumannii* positive blood cultures including the ward and date of isolation, patient identification, and antibiotic sensitivity were retrieved from the microbiology laboratory computer records. A review was made of all the medical records of the patients admitted to the hospital between July 2004 and September 2007 with the recorded data before and after the onset of BSI noted. The present study excluded any patients who were under 15 years old, acquired *A. baumannii* BSI from other hospitals or who had neither the clinical signs nor symptoms indicating BSI at the time the blood culture was taken.

Definitions

NNIS CDC criteria were used for diagnosing nosocomial infection[10], and those patients who did not fulfill the diagnostic criteria for BSI were excluded from the present study. To control for the severity of illness before the onset of *A. baumannii* BSI, the authors measured the American Society Association (ASA) score and Sequential Organ Failure Assessment (SOFA) score of each patient. The ASA score was used to classify the patients into five groups with different degrees of severity of illness at admission[11]. SOFA scores were calculated using the most aberrant physiologic or laboratory variables based on the local laboratory data, vasopressor dosages, and the need for mechanical ventilation[12,13].

A medical patient was defined as one who was cared for primarily by an internist. A patient other than a medical patient was assigned as a surgical patient. Neutropenia was defined as the number of neutrophils less than 500/ml at the time of hospital admission.

The antimicrobial therapy was considered as appropriate if at least one drug to which the isolated *A. baumannii* was *in vitro* susceptible was included in the initial empirical treatment. Such a drug had to be administered for at least 72 hours from the time that the blood specimen cultures were drawn. The administration of an antibiotic to which the isolated *A. baumannii* was *in vitro* resistant or intermediately susceptible was considered as inappropriate empirical treatment.

Outcomes were assessed in terms of in-hospital mortality and the severity grading of BSI. The severity of BSI was evaluated at the time the blood culture was taken and was classified as sepsis, severe sepsis, or septic shock[12].

Statistical analysis

Statistical analysis was executed with STATA 10.0 (Stata Corp. College Station, Tex.). Continuous variables were described as the mean value $\pm$ standard deviation and as the median $\pm$ interquartile range. Survival curves were prepared by means of the Kaplan-Meier method, and univariate survival distributions were compared with the use of a log rank test.

Univariate comparisons between the IRAB and ISAB groups were made using the Chi-square test, Wilcoxon rank sum test, or unpaired t-test, as appropriate. Variables associated with death at a p-value of less than 0.05 were entered in a multivariate survival analysis. The stepwise Cox's proportional hazard model, with time to in-hospital death as the dependent variable was employed for multivariate analysis. A significance level of 0.10 was used to allow a variable to stay in the model. Adjusted associations

were measured in terms of hazard ratios (HR) and the corresponding 95% confidence intervals (CI). In the multivariate model, the continuous and polychotomous variables were transformed into dichotomous variables. In order to minimize the effect of collinearity between the severity index variables (ASA score and SOFA score), the variables that showed weaker associations with the mortality outcome were excluded from the multivariate model.

ASA scores > 3 were used to classify the patients into two groups to make the nearest balance between the patients who survived or died in hospital. In the same way, the length of prior hospital stay was also categorized into two groups using 14 days as a cutoff point. According to the finding of Martin the patient's age $\geq$ 65 years old was associated with an abrupt rising mortality rate among adult patients with sepsis[14], the authors classified patients into two age groups with a cutoff point at 65 years old.

Results

A. baumannii nosocomial BSI were identified in 198 patients and were included in the present study. Of these, 67 of the patients had IRAB and 131 had ISAB. Antibiotic susceptibility of IRAB and ISAB isolated in these patients are illustrated in Table 1. Patient characteristics and outcomes are listed and compared in Table 2. Statistically significant differences were found in gender; presentation of neutropenia; median length of hospital stay before onset of BSI; median SOFA scores; appropriate antibiotic treatment; mortality rate and length of hospital stay after the onset of BSI.

The crude survival rates in the patients with IRAB and ISAB BSI were compared and are displayed in Fig. 1. The survival rates were statistically different between the two groups ($p < 0.0001$). The associations between various prognosis factors and mortality outcome are shown in Table 3. The univariate analysis revealed eight variables that were significantly associated with in-hospital mortality. The ASA score and not the SOFA score was selected to represent the patient severity index and is included in the multivariate model because of its stronger association. During the processes of stepwise multivariate analysis, the variable "pneumonia as the primary source of BSI" was excluded from the analytical model because the p-value was more than 0.1. After adjusting for confounding factors by means of the multivariate analysis, the BSI caused by IRAB was no longer a significant predictor for patient fatality outcome.

Table 1. Antibiotic susceptibility of IRAB* and ISAB[a] isolated from hemocultures of the patients with BSI[b]

Antibiotic class	ISAB	IRAB
Gentamicin	77.8%	12.3%
Amikacin	87.7%	21.9%
Ampicillin	2.5%	0.0%
Cefotaxime	10.8%	1.4%
Cefoxitin	3.8%	0.0%
Ceftazidime	70.4%	8.2%
Ceftriaxone	7.7%	0.0%
Cefuroxime	10.8%	0.0%
Ciprofloxacin	87.3%	68.0%
Cotrimoxazole	94.4%	12.3%
Sulperazone	100.0%	71.4%
Meropenem	100.0%	0.0%

* Imipenem-resistant *A. baumannii*
[a] Imipenem-susceptible *A. baumannii*
[b] Bloodstream infection

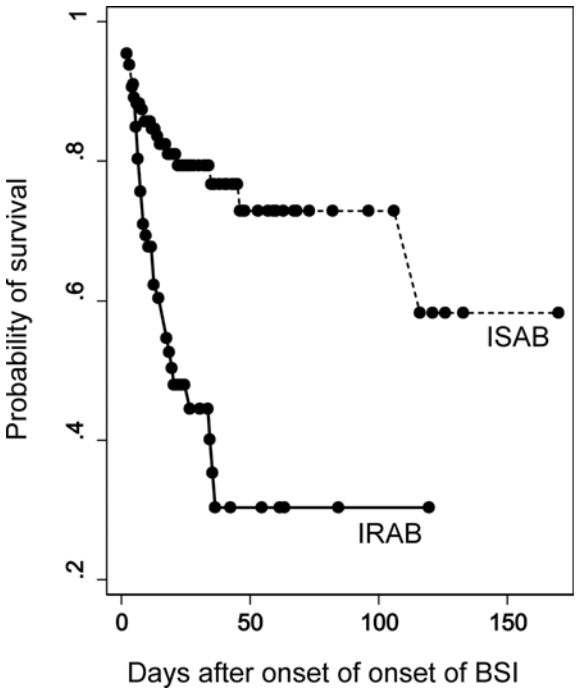

Fig. 1 The Kaplan-Meier cumulative survival curves for patients with imipenem-resistant *A. baumannii* (IRAB) bloodstream infection (BSI) represents as solid line and imipenem-susceptible *A. baumannii* (ISAB) BSI (broken line)

Table 2. Comparison of the patient's characteristics before the onset of bacteremia and the outcomes between the patients with imipenem-resistant *A. baumannii* (IRAB) bloodstream infection and the patients with imipenem-susceptible *A. baumannii* (ISAB) bloodstream infection

Patient characteristics and outcomes	ISAB* (n = 131)	IRAB[a] (n = 67)	p-value
Characteristics			
Male gender[b]	59.5%	44.8%	0.048
Age (mean ± SD)[c]	50.8 ± 19.7	56.1 ± 19.4	0.070
Medical patient[b]	52.2%	47.8%	0.060
Present of neutropenia[b]	6.9%	22.4%	0.002
ASA score[d]	3.1 ± 0.7	3.2 ± 0.8	0.300
ASA score >3[b]	26.0%	31.3%	0.400
Prior hospital stay[e]	7 ± 11	16 ± 29	<0.001
SOFA score[f]	4 ± 6	5 ± 4	0.010
Acquired bacteremia in ICU[b]	24.4%	37.3%	0.060
Primary source of BSI			
Pneumonia[b]	15.3%	20.9%	0.300
Catheter related[b]	43.5%	49.3%	0.400
Others[b]	16.8%	7.5%	0.070
Unidentified[b]	24.4%	22.4%	0.700
Appropriate antibiotic treatment[b]	87.8%	61.2%	<0.001
Outcomes			
In-hospital mortality rate[b]	19.9%	52.2%	<0.001
Length of hospital stay			
Total LOS[g]	27 ± 37	37 ± 32	0.070
LOS after bacteremia[h]	16 ± 23	9 ± 15	0.010
Severity grading of BSI[b]			
Sepsis	67.2%	52.2%	
Severe sepsis	16.0%	20.9%	
Septic shock	16.8%	26.9%	0.100

* Patients with imipenem-resistant *A. baumannii* bloodstream infection

[a] Patients with imipenem-susceptible *A. baumannii* bloodstream infection

[b] Chi-square test statistics

[c] Mean ± SD, years; unpaired t-test statistics

[d] American Society of Anesthesia score, mean ± S.D; unpaired t-test statistics

[e] Length of hospital stay (LOS) before onset of *A. baumannii* bloodstream infection, days; median ± interquartile range (IQR); Wilcoxon ranksum test statistics

[f] Sequential Organ Failure Assessment score on one day before onset of bloodstream infection, median ± IQR; Wilcoxon ranksum test statistics

[g] Total length of hospital stay, days, median ± IQR; Wilcoxon ranksum test statistics

[h] Length of hospital stay (LOS) after onset of *A. baumannii* bloodstream infection, days; median ± interquartile range (IQR); Wilcoxon ranksum test statistics

Discussion

The observed higher mortality rate in the IRAB group (Fig. 1, Table 2) was possibly not attributable directly to the virulence of IRAB but may be due to confounding effects of the severity of the underlying disease, inappropriate antibiotic therapy and the primary source of infection. The authors postulated the mechanism of the higher mortality outcome in the patient with IRAB BSI and have demonstrated this in Fig. 2.

It can be seen in Table 2 that those patients with characteristics that indicated a more severe illness (neutropenia, high SOFA score, admitted to ICU) trend to be infected with IRAB rather than ISAB. On the other hand, infection with IRAB was associated with inappropriate antibiotic treatment

Table 3. Crude and adjusted hazard ratios (HR) of in-hospital mortality in patients with *A. baumannii* bloodstream infection

Prognosis factors	Unadjusted			Adjusted		
	HR	95% CI	p-value	HR	95% CI	p-value
Age ≥ 65 years	1.2	0.7-2.1	0.4	-	-	-
Male gender	0.9	0.6-1.6	0.9	-	-	-
Medical patient	3.3	2.0-5.7	<0.001	2.4	1.4-4.3	0.003
Prior hospital stay > 14 days*	1.4	0.8-2.3	0.2	-	-	-
Present of neutropenia	4.1	2.3-7.4	<0.001	3.6	1.8-7.3	<0.001
ASA score > 3[a]	3.1	1.9-5.2	<0.001	2.7	1.6-4.6	<0.001
SOFA score ≥ 15[b]	2.2	1.3-3.7	0.002	-	-	-
IRAB bacteremia[c]	3.2	1.9-5.4	<0.001	1.7	0.9-2.9	0.06
Acquired bacteremia in ICU	2.5	1.5-4.2	<0.001	2.4	1.4-4.1	0.002
Pneumonia as the primary source of BSI	2.0	1.2-3.6	0.01	-	-	-
Appropriate antibiotic treatment	0.3	0.2-0.5	<0.001	0.3	0.2-0.6	<0.001

* Length of hospital stay (LOS) before onset of *A. baumannii* bloodstream infection

[a] American Society of Anesthesia score

[b] Sequential Organ Failure Assessment score

[c] Imipenem-resistant *A. baumannii* bacteremia compare to imipenem-susceptible *A. baumannii* bacteremia

for that infection. An initial inappropriate empirical antimicrobial therapy was a significant independent prognosis factor for in-hospital mortality (Table 3) and this finding is consistent with other reports[15-18].

Apostolopoulou and Rodriguez have found that hospital acquired pneumonia trends to develop in patients with a more severe underlying disease[19,20]. Ibrahim has demonstrated that the severity of a patient's illness was associated with both the development of ventilator-associated pneumonia (VAP) and bacteremia[21]. Agbaht et al compared bacteremic and nonbacteremic VAP and found that bacteremia in patients with VAP was more often caused by a multiresistant microorganism and was associated with a higher risk of death even when the severity of illness was accounted for[22]. The present study revealed that 15.3% of ISAB BSI and 20.9% of IRAB BSI had nosocomial pneumonia as the primary sources (Table 2) and that this group had a significantly higher mortality rate (HR = 2.0, p = 0.01) compared to other primary sources.

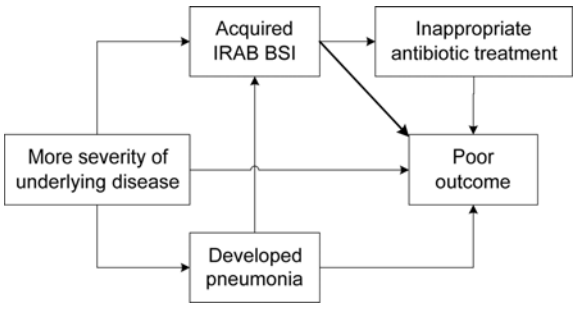

Fig. 2 The postulated mechanism of attributable mortality outcome in patients with imipenem-resistant *A. baumannii* bloodstream infection (IRAB BSI)

Gender has been found as an independent determinant factor for severe sepsis fatality in two studies[23,24]. However, in the present study the authors could not demonstrate a relationship between patient gender and mortality associated with BSI. Similarly, a patient's age has been identified as an independent risk factor for sepsis and sepsis mortality in other studies but not in the present study[14,25].

The number of neutrophils played an important role in the host's defense mechanism against *A. baumannii*[26]. The authors found that neutropenia was a significant prognosis factor for patient mortality after the onset of BSI.

The similar report regarding virulence of multidrug-resistant *A. baumannii* was done by Sunenshine[27]. The study conducted in all sites of infection and found the mortality rates were not significantly different between patients who acquired IRAB and ISAB.

Acknowledgment

The study was supported by a Department Research Grant from the Faculty of Medicine at Prince of Songkla University.

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การเสียชีวิตเนื่องจากการติดเชื้อในกระแสโลหิตในโรงพยาบาลจากเชื้อ Acinetobacter baumannii ที่ดื้อยา imipenem

สีลม แจ่มอุลิตรัตน์, ปราณี อรุณพันธ์, ปาริชาต ไพนุพงศ์

***ภูมิหลัง**: ปรากฏว่ายังมีความไม่มั่นใจว่าการดื้อยา imipenem ของเชื้อ Acinetobacter baumannii จะเป็นเหตุที่ทำให้ผู้ป่วยติดเชื้อเสียชีวิตมากขึ้นหรือไม่*

***วัตถุประสงค์**: การศึกษานี้มุ่งเน้นที่จะตรวจสอบผลกระทบของการดื้อยานี้ต่อการเสียชีวิตของผู้ป่วย*

***วัสดุและวิธีการ**: การศึกษาทำโดยเปรียบเทียบอัตราตายของผู้ป่วยติดเชื้อ A. baumannii ในกระแสโลหิตระหว่างกลุ่มที่เชื้อดื้อยา และกลุ่มที่เชื้อไม่ดื้อยา*

***ผลการศึกษา**: อัตราการเสียชีวิตในโรงพยาบาลของผู้ป่วยในกลุ่มเชื้อดื้อยา (35 ราย คิดเป็นร้อยละ 52.2) สูงกว่าเมื่อเทียบกับกลุ่มเชื้อไม่ดื้อยา (26 ราย คิดเป็นร้อยละ 19.9) อย่างมีนัยสำคัญทางสถิติ ($p < 0.001$) แต่เมื่อใช้การวิเคราะห์ทางสถิติแบบพหุคูณ โดยใช้แบบจำลอง Cox proportional hazard ควบคุมอิทธิพลของตัวแปรความรุนแรงของโรค การเหมาะสมในการให้ยาปฏิชีวนะรักษา และแหล่งที่มาปฐมภูมิของเชื้อแล้ว พบว่าความแตกต่างข้างต้นไม่มีนัยสำคัญอีกต่อไป*

***สรุป**: อัตราตายที่สูงขึ้นในผู้ป่วยที่ติดเชื้อ A. baumannii ที่ดื้อยา imipenem น่าจะเกิดจากความรุนแรงของโรคเดิมที่ผู้ป่วยเป็นอยู่การให้ยาปฏิชีวนะรักษาไม่เหมาะสม และแหล่งที่มาปฐมภูมิของเชื้อ*