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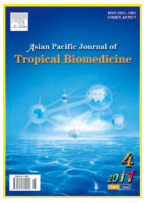

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Risk factors and outcomes of imipenem-resistant *Acinetobacter* bloodstream infection in North-eastern Malaysia

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ABSTRACT

Objective: To determine the risk factors and outcomes of imipenem-resistant *Acinetobacter baumannii* (IRAB) bloodstream infection (BSI) cases, since there is very little publication on *Acinetobacter baumannii* infections from Malaysia. **Methods:** A cross sectional study of 41 cases (73.2%) of imipenem-sensitive *Acinetobacter baumanii* (ISAB) and 15 cases (26.8%) of IRAB was conducted in a teaching hospital which was located at North-Eastern state of Malaysia. **Results:** There was no independent risk factor for IRAB BSI identified but IRAB BSI was significantly associated with longer bacteraemic days [*OR* 1.23 (95% *CI* 1.01, 1.50)]. Although prior use of carbepenems and cephalosporin were higher among IRAB than ISAB group, statistically they were not significant. There was no significant difference in term of outcomes between the two groups. **Conclusions:** Although statistically not significant, this analysis compliments previous publication highlighting the importance of appropriate empiric antibiotic usage in hospital especially carbepenems and need further evaluation with bigger subjects.

1. Introduction

Carbapenems have previously been the main treatment of choice for *Acinetobacter baumannii* (*A. baumannii*) infected patients, but unfortunately the pathogen´s resistance to all conventional antimicrobial agents were increasingly reported worldwide. Multiple risk factors were responsible for the occurrence of carbepenem-resistant *A. baumannii* infections[1-6].

We recently published articles on *Acinetobacter* bloodstream infection (BSI) from Malaysia based on a case-control study in 2003[7,8]. We found that prior exposure to carbapenems has significantly posed a greater risk of mortality due to acinetobacter BSI[8]. Patients on mechanical ventilation and those who had prior exposure to cephalosporins were noted to be at risk of acquisition of acinetobacter BSI[7]. In short, rational use of antimicrobial agents is critically important to prevent acinetobacter BSI as well as to avoid poor outcomes of acinetobacter BSI. As data on acinetobacter infections in Malaysia is scarce, this new analysis aims specifically to determine the risk factors and outcomes of imipenem-resistant *A. baumannii* (IRAB) BSI cases.

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2. Materials and methods

A cross sectional descriptive and case-control study was performed to determine the prevalence, risk factors and outcome of acinetobacter BSI in Hospital Universiti Sains Malaysia (HUSM) that located at North-eastern state in Malaysia and it was published recently[7,8]. We further analysed fifty eight cases of acinetobacter BSI to determine the risk factors and outcomes of IRAB bacteremia. Two cases were excluded from analysis *i.e.* one case of *Acinetobacter iwoffii* and another case lacking imipenem susceptibility data.

Imipenem susceptibility of the strains was determined by disk diffusion method according to Clinical and Laboratory Standards Institute (CLSI) guidelines. The strain was considered as being resistant to imipenem if the zone of inhibition was <13 mm, intermediate when the zone was 14-15 mm, and sensitive when the zone was >16 mm. For analysis, intermediate resistance was grouped as IRAB. Minimal inhibitory concentration was not determined in this study.

The risk factors and outcomes of IRAB bacteremia were determined by comparing the variables in IRAB bacteremia group and those of imipenem-sensitive *A. baumannii*

(ISAB) bacteremia group. Case definitions and criteria in the previous study were applied for the current analysis [7,8]. Briefly, a case of clinically significant *A. baumannii* BSI was defined as any patient who had at least one blood culture positive for *A. baumannii* collected when evidence of infection is present. The risk factors and their outcomes were recorded. Polymicrobial infections were excluded from the study. Appropriate managements were considered if the patient received one *in vitro* active antimicrobial and/or other measures such as surgical drainage, regular dressings and removal of infected devices. The dose of antimicrobial was given according to the standard clinical practice. The patient was considered as cured if all clinical signs and symptoms of infection resolved. Attributable mortality was considered when the death directly related to BSI; *i.e.* death within 72 hours after a blood culture positive or no clinical improvement after a positive blood culture. Crude mortality was all death cases in the study group.

The results were expressed in terms of the number and percentage or the mean (standard deviation). For categorical variable, the differences in patient characteristics, risk factors and outcomes were tested using simple logistic regression. For continuous variable, independent-t test or Mann-Whitney test was used. Multiple logistic regression analysis was used to determine independent risk factors. The *P* value of <0.05 was considered as significant. All analyses were done using SPSS software (SPSS, Chicago, Illinois, U.S.A -licensed to Universiti Sains Malaysia).

3. Results

There was no cluster of acinetobacter BSI to suggest any outbreak identified. A total of 56 cases analysed of which 41 cases (73.2%) were ISAB and 15 (26.8%) were IRAB. The demographic profiles of acinetobacter BSI and the potential risk factors of IRAB were shown in Table 1. IRAB group has significantly longer bacteraemia days and had arterial catheter *in-situ* comparing to ISAB group (Table 1). In multivariable analysis of the demographic data and risk factors, IRAB BSI were significantly associated with longer bacteraemia duration [adjusted *OR* (95% *CI* 1.23 (1.01, 1.50)] with the final model was checked for fitness (Hosmer-Lemeshow goodness-of-fit: *Chi* square=7.96, *df*=6, *P* value = 0.241).

Out of fifteen cases of IRAB, only two cases of *A. baumannii* were resistant to all tested antimicrobial agents. One of the patients was treated surgically to remove possible primary source. The patient was recovered from bacteraemia episode but eventually died of underlying

Table 1

Demographic data of *A. baumannii* bacteraemia and potential risk factors of imipenem-resistant *A. baumannii* bacteraemia in Hospital Universiti Sains Malaysia analysed by univariate analysis.

Variable		*A. baumannii* Freq (%)/ Mean (sd)		*P* value#	*OR* (95% *CI*)
		Imipenem sensistive *n*=41	Imipenem resistant *n*=15		
Gender					
	Male	23 (56.10)	9 (60.00)	0.794[a]	0.85 (0.26-2.84)
	Female	18 (43.90)	6 (40.00)		
Age (y)		26.2 (22.88)	40.1 (26.85)	0.060[b]	1.02 (1.00-1.05)
Length of hospital stay (days)		32.8 (25.04)	32.3 (16.35)	0.939[b]	1.00 (0.97-1.02)
Duration of hospitalization before bacteraemia (days)		14.8 (13.16)	14.7 (14.01)	0.968[b]	1.00 (0.96-1.04)
Duration of bacteraemia (days)		4.1 (2.88)	6.1 (3.26)	0.031[b]	1.23 (1.01-1.50)
Location					
	ICU Setting	20 (48.8)	11 (73.3)	0.102[a]	0.35 (0.10-1.27)
	Non ICU Setting	21 (51.2)	4 (26.7)		
Total ICU stay (days)*		6.0 (17.0)	15.0 (14.0)	0.129[c]	1.01 (0.97-1.04)
Prior exposure to antimicrobial agents					
	Penicillins	25 (61.0)	8 (53.3)	0.607[a]	0.73 (0.22-2.41)
	Aminogycosides	15 (36.6)	2 (13.3)	0.109[a]	0.27 (0.05-1.35)
	Cephalosporins	26 (63.4)	13 (96.7)	0.109[a]	3.75 (0.74-18.92)
	Carbepenems	3 (7.3)	4 (26.7)	0.068[a]	4.61 (0.89-23.76)
Procedures					
	Mechanical ventilation	24 (58.5)	12 (80.0)	0.148[a]	2.83 (0.69-1.60)
	Nasogastric tube	27 (65.9)	14 (93.3)	0.068[a]	7.26 (0.86-61.02)
	Planned surgery	9 (22.0)	3 (20.0)	0.875[a]	0.89 (0.20-3.85)
	Emergency surgery	12 (29.3)	6 (40.0)	0.448[a]	1.61 (0.47-5.53)
	Tracheostomy	7 (17.1)	2 (13.3)	0.736[a]	0.75 (0.14-4.08)
	Central catheter	27 (65.9)	14 (93.3)	0.068[a]	7.26 (0.86-61.02)
	Arterial catheter	23 (56.1)	13 (86.7)	0.048[a]	5.09 (1.02-25.48)
	Urinary catheter	24 (58.5)	14 (93.3)	0.064[a]	4.60 (0.92-23.11)
	Parenteral nutrition	7 (17.1)	4 (26.7)	0.427a	1.77 (0.43-7.19)
Underlying diseases					
	Diabetes mellitus	5 (12.2)	1 (6.7)	0.560[a]	0.51 (0.06-4.80)
	Renal impairment	5 (12.2)	3 (20.0)	0.464[a]	1.80 0.37-8.68)
	Solid tumour	7 (17.1)	2 (13.3)	0.736[a]	0.75 (0.14-4.08)
	Hematological malignancy	4 (9.8)	2 (13.3)	0.703[a]	1.42 (0.23-8.71)

P value significant at <0.05, * Median (Interquartile range), [a] Simple logistic regression, [b] Independent t test, [c] Mann-Whitney test

Table 2
Outcomes of imipenem-resistant *A. baumannii* bacteraemia in Hospital Universiti Sains Malaysia analysed by univariate analysis.

Variable	*A. Baumannii* Freq (%)/ Mean (sd)		*P* value#	*OR* (95% *CI*)
	Imipenem sensistive *n*=41	Imipenem resistant *n*=15		
Appropriate management	38 (92.7)	12 (80.0)	0.191	3.17 (0.56-17.81)
Outcome *				
– Crude mortality	15 (40.5)	9 (64.3)	0.136	0.38 (0.11-1.36)
– Attributable mortality	9 (24.3)	6 (42.9)	0.201	2.33 (0.64-8.54)

P value significant at <0.05, *Five cases of acinetobacter bacteraemia were excluded from the outcome study because they left against medical advice.

illness. The second case died directly due to acinetobacter infection. At the study time, polymyxin B and colistin were not the standard treatment for acinetobacter BSI. There was no significant difference in the appropriateness of treatment and outcomes between IRAB and ISAB. The summary of treatment appropriateness and outcome were shown in Table 2.

4. Discussion

With this limited number of patients, we found 26.8% of acinetobacter was resistant to imipenem. Outbreak of IRAB infections was previously associated with selective pressure of antibiotic particularly imipenem[3-5]. In this study, prior exposure to carbapenems was noted in IRAB than in ISAB group but the difference was not statistically significant (*P*=0.068). This was probably due to limited usage of carbapenems in HUSM at that time. Only twelve patients (10.3%) in previous study had history of exposure to carbapenems[7]. As predicted, the IRAB cases were noted to have longer duration of bacteraemia compared to ISAB group probably due to delay in commencement of appropriate antibiotics. Only two cases of pan-drug resistant *A. baumannii* were identified and no significant difference in overall appropriateness of treatment among IRAB and ISAB groups.

We found the arterial catheterizations were significantly associated with IRAB in univariate analysis but this variable was not significant after multivariable analysis. The previous study had shown that arterial catheterization was an independent risk factor for infection/colonization of carbepenem-resistant *A. baumannii*[5]. Other studies had shown that the independent risk-factors for the acquisition of carbepenem/imipenem-resistant *A. baumannii* include admission into hospitals with more than 500 beds[1], previous admission to intensive care unit[2-4], longer duration of hospitalization[2] (ICU[6]) stay before infection, previous admission to respiratory care unit[3], a urinary catheter [1], history of surgery[1], previous antimicrobial treatment [1,2], previous use of multiple classes of antibiotics[3], and previous use of imipenem[3,4] (as monotherapy[5]), aminoglycosides[6] or third-generation cephalosporins[4].

We noted that 64.3% of patients with IRAB BSI died, in which 42.9% was directly due to the IRAB infection. However there was no statistically significant difference between IRAB and ISAB BSI group. In the previous study, IRAB BSI group showed significantly higher mortality rate but after controlling the confounding factors, the attributable mortality were not significant[9]. Similar observation has been reported by Tomas *et al*[5]. The observed higher mortality rate among patients with an IRAB BSI were not directly due to the infection[9]. In a prognostic study among carbepenem-resistant *A. baumannii*, Tomas *et al* found that hypotension or shock at the time of bacterial isolation were significantly lead to mortality[5].

We have shown that the appropriate therapy significantly reduce the mortality attribute to acinetobacter BSI[8]. Erbay *et al* recently reported that 25.5% reduction in the overall crude mortality rate was associated with adequate early empirical antimicrobial therapy[10]. In case of IRAB BSI, effective antimicrobial agents are very limited and are usually reserved for severe infections. This causes great challenge in the near future when acinetobacter predominantly resistant to most of the commonly used as first line antimicrobial agents for severe infections.

Although statistically not significant, this analysis compliments previous publication highlighting the importance of appropriate empiric antibiotic usage in hospital especially carbepenems. Based on this analysis, we planned a proper case-control study on the risk factors, outcomes, minimum inhibitory concentration pattern and molecular epidemiology/clonality of acinetobater BSI strain.

Conflict of interest statement

We declare that we have no conflict of interest.

References

[1] Cisneros JM, Rodríguez-Baño J, Fernández-Cuenca F, Ribera A, Vila J, Pascual A, et al. Risk-factors for the acquisition of imipenem-resistant *Acinetobacter baumannii* in Spain: a nationwide study. *Clin Microbiol Infect* 2005; **11**: 874-879.
[2] Baran G, Erbay A, Bodur H, Öngürü P, AkIncI E, Balaban N, et al. Risk factors for nosocomial imipenem-resistant *Acinetobacter baumannii infections. Int J Infect Dis* 2008; **12**: 16-21.
[3] Jamulitrat S, Thongpiyapoom S, Suwalak N. An outbreak of imipenem-resistant *Acinetobacter baumannii* at Songklanagarind hospital: the risk factors and patient prognosis. *J Med Assoc Thai* 2007; **90**: 2181-2191.
[4] Lee SO, Kim NJ, Choi SH, Hyong Kim T, Chung JW, Woo JH, et al. Risk factors for acquisition of imipenem-resistant *Acinetobacter baumannii*: a case-control study. *Antimicrob Agents Chemother* 2004; **48**: 224-228.
[5] Tomas MDM, Cartelle M, Pertega S, Beceiro A, Llinares P, Canle D, et al. Hospital outbreak caused by a carbapenem-resistant strain of *Acinetobacter baumannii*: patient prognosis and risk-factors for colonisation and infection. *Clin Microbiol Infect* 2005; **11**: 540-546.
[6] Katragkou A, Kotsiou M, Antachopoulos C, Benos A, Sofianou D, Tamiolaki M, et al. Acquisition of imipenem-resistant *Acinetobacter baumannii* in a pediatric intensive care unit: a case-control study. *Intensive Care Med* 2006; **32**: 1384-1391.
[7] Deris ZZ, Harun A, Omar M, Johari MR. The prevalence and risk factors of nosocomial *Acinetobacter* blood stream infections in tertiary teaching hospital in north-eastern Malaysia. *Trop Biomed* 2009; **26**: 123-129.
[8] Deris ZZ, Harun A, Shafei MN, Rahman RA, Johari MR. Outcomes and appropriateness of management of nosocomial *Acinetobacter* bloodstream infections at a teaching hospital in northeastern Malaysia. *Southeast Asian J Trop Med Public Health* 2009; **40**: 140-147.
[9] Jamulitrat S, Arunpan P, Phainuphong P. Attributable mortality of imipenem-resistant nosocomial *Acinetobacter baumannii* bloodstream infection. *J Med Assoc Thai* 2009; **92**: 413-419.
[10] Erbay A, Idil A, Gözel MG, Mumcuoglu I, Balaban N. Impact of early appropriate antimicrobial therapy on survival in *Acinetobacter baumannii* bloodstream infections. *Int J Antimicrob Agents* 2009; **34**: 575-579.