OUTCOMES AND APPROPRIATENESS OF MANAGEMENT OF NOSOCOMIAL *ACINETOBACTER* BLOODSTREAM INFECTIONS AT A TEACHING HOSPITAL IN NORTHEASTERN MALAYSIA

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Abstract. *Acinetobacter* spp is a known nosocomial pathogen causing a wide range of clinical diseases such as pneumonia, wound infection and bloodstream infections (BSI). The clinical outcomes of acinetobacter BSI were determined by a 1:1 case control study involving 58 confirmed cases of acinetobacter BSI who were compared to other gram-negative infections. The crude mortality of acinetobacter BSI was 47.2%, which was significantly greater than other gram-negative BSI (OR 1.89, 95% CI 1.10-3.24) but there were no significant differences in attributed mortality between the two groups. We found that patients treated in intensive care units (ICU), who had longer ICU stays, who presented with shock or coagulopathy, had prior exposure to carbapenems, had mechanical ventilation, were on a ventilator for longer periods, had a nasogastric tube, had an arterial catheter or had parenteral nutrition at a significantly greater risk of mortality due to acinetobacter BSI. Patients presenting with septic shock (OR 17.95, 95% CI 3.36-95.84) or having a central venous catheter (OR 12.48, 95% CI 1.09-142.68) were independently at higher risk for mortality. Appropriateness of therapy reduced the mortality attributes of acinetobacter BSI (OR 0.197, 95% CI 0.040-0.967) but did not significantly reduce crude mortality in acinetobacter BSI patients. This study shows the importance of preventing acinetobacter BSI and the appropriate use of antimicrobial agents to reduce mortality.

INTRODUCTION

Acinetobacter spp have emerged as important nosocomial pathogens affecting mainly patients with impaired host defences in intensive care settings and are responsible for many hospital outbreaks. *Acinetobacter* spp have been implicated in a variety of nosocomial infections including bloodstream infections (BSI), pneumonia, meningitis, urinary tract infections, skin and soft tissue infections, wound and burn infections, intravascular devices and implant-related infections (Bergogne-Berezin and Towner, 1996; Wisplinghoff *et al*, 1999).

There have been many studies regarding *Acinetobacter* spp, *Acinetobacter baumannii*

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and MDR-Acinetobacter worldwide. *Acinetobacter* spp has repeatedly been reported to be a nosocomial infection. Its resistance to commonly used antimicrobial agents is an increasing problem. *Acinetobacter baumannii* may survive for extended periods on inanimate environmental surfaces (Wendt *et al,* 1997). Previous studies have demonstrated acinetobacter BSI are associated with high mortality rates (17-52%), and increased lengths of stay in intensive care units and greater cost of care (Cisneros *et al,* 1996; Wisplinghoff *et al,* 2000; Smolyakov *et al,* 2003).

These studies might not represent our local situation, since large variations occur among regions, countries, hospitals and other settings. Data from the Infection Control Unit, Hospital Universiti Sains Malaysia (HUSM) for the year 2001 showed that *Acinetobacter* spp were among the most common nosocomial pathogens. *Acinetobacter* spp were the most common gram-negative organism isolated from blood cultures, representing 8.3% of all blood isolates. Unfortunately, to date, there have been no published reports from Malaysia in regard to the various aspects of acinetobacter infection in the hospital. Hence, this study was conducted to determine the clinical outcomes of acinetobacter BSI at the HUSM and thus, hopefully to make a few suggestions to improve outcomes.

MATERIALS AND METHODS

A case-control study was conducted at the HUSM for a period of one year. The HUSM is an 800-bed tertiary level teaching hospital located in Kelantan, a northeastern state of Malaysia. This study was approved by The Scientific and Research Ethical Committee, School of Medical Sciences, USM [USM/PPSP/EthicsCom./2003 (114)].

The cases were selected from significant nosocomial acinetobacter BSI; the control group had other significant nosocomial gram-negative BSI. The risk factors and their outcomes were recorded. Polymicrobial infections were excluded from the study. A significant nosocomial acinetobacter BSI was defined as any case with *Acinetobacter* spp isolated from blood culture, and clinically a BSI or transient BSI, more than 48 hours of admission, including "transferred in" cases admitted at other hospitals or HUSM for a total of at least 48 hours.

Blood for blood culture and sensitivity was collected aseptically and inoculated into a BACTEC™ (Becton Dickinson, US) bottle. We used the automated BACTEC™ blood culture system. After the inoculated BACTEC™ blood culture bottle reached the laboratory, the request form was reviewed and recorded. The specimen was incubated in the BACTEC™ automated blood culture system. Identification of the species of acinetobacter was done by regular biochemical tests and confirmation was done by the API 20 NE (bioMérieux, France) system.

For each case of significant nosocomial acinetobacter BSI, one case of significant gram-negative bacilli (other than *Acinetobacter* spp) BSI was randomly selected as a control. *Salmonella* spp and *Bulkholderia pseudomallei* isolates were excluded as they were most likely community acquired and had a longer incubation period.

Appropriate antibiotic therapy was considered if the patient received one intravenous dose of *in vitro* active antimicrobial (Seifert *et al,* 1995; Cisneros *et al,* 1996). The dose of antimicrobial was given according to the standard clinical practice. The patient was considered cured if all clinical signs and symptoms of infection subsided (Seifert *et al,* 1995). Death was considered related to acinetobacter BSI if the patient died within

72 hours after a blood culture was positive for *Acinetobacter* spp (Seifert *et al*, 1995) or during an acinetobacter BSI. The term attribute death (mortality) was used (Lortholary *et al*, 1995), and is defined as all cases of death directly due to acinetobacter BSI. Whereas, crude mortality was defined as all cases of death without considering the cause (Lortholary *et al*, 1995).

Data were entered and analyzed using SPSS software (SPSS, Chicago). The results are expressed in terms of numbers and percentages or the mean and standard deviation. For categorical variables, the differences in patient characteristics and risk factors were tested using chi-square or Fisher's exact test. For continuous variables, the independent *t*-test or Mann-Whitney test was used. Multiple logistic regression analysis was used to determine independent risk factors and predictors of mortality. A *p*-value of < 0.05 was considered to be statistically significant.

RESULTS

The prevalence of acinetobacter BSI was 6.11% (95% CI 4.88-7.53) and the attack rate was 2.77 episodes per 1,000 hospital admissions. The total number of acinetobacter isolates on blood culture in one-year period were 111 (82 cases). Out of this, six isolates (from six cases) were community acquired (blood culture positive less than 48 hours after admission). Three cases of community acquired infection were *Acinetobacter baumannii* and another three were *Acinetobacter lwoffii*.

Out of 76 cases of nosocomial acinetobacter BSI, 8 cases had mixed growth. Among the nosocomial acinetobacter BSI, all were *Acinetobacter baumannii* except one was *Acinetobacter lwoffii*. Of these cases, 58 were randomly selected in accordance with inclusion criteria for the study on risk factors and clinical outcomes.

The total number of non-*Acinetobacter* spp gram-negative bacilli specimens was 672 (525 cases). Of these, 58 cases of significant BSI were randomly selected and included in the study. The species selected were: *Klebsiella pneumoniae* (15 cases), *E. coli* (12 cases), *Pseudomonas* spp (10 cases), *Enterobacter* sp (10 cases), other *Klebsiella* spp (3 cases), *Chryseobacterium* spp (3 cases), *Burkholderia cepacia* (3 cases), *Stenotrophomonas* spp (1 case) and *Achromobacterium* spp (1 case). Table 1 shows the demographic profiles for both groups.

Clinical outcomes

Clinical outcomes were evaluated for 53 patients with acinetobacter BSI and 56 control patients. Five acinetobacter BSI patients and 2 gram-negative BSI patients left against medical advice. Twenty-five patients in the acinetobacter BSI group died and 14 in the control group died. Table 2 shows the attribute and crude mortality rates for the acinetobacter BSI group compared with the other gram-negative BSI group.

The demographic profiles and underlying diseases did not significantly influence the outcomes of the acinetobacter BSI (Table 3). A comparison of live and the patients with acinetobacter BSI who did and not survive is shown in Table 4. On multivariable analysis, septic shock (p=0.001, adjusted OR 17.950, 95% CI 3.362-95.838) and having a central venous catheter (p=0.042, adjusted OR12.483, 95% CI 1.092-142.68) were independent predictors for mortality among patients with acinetobacter BSI (Hosmer-Lemeshow goodness-of-fit: chi-square = 0.414, df = 2, p-value = 0.813).

Appropriateness of management

Of 52 cases (89.7%) of acinetobacter BSI appropriately managed with antimicrobials

Table 1
Demographic data of acinetobacter blood stream infections compared to other gram-negative blood stream infections.

Variable	*Acinetobacter* (*n*=58)		Other gram-negative (*n*=58)		*p*-value[b]
	Median (Interquartile range)[a]	No. (%)	Median (Interquartile range)[a]	No. (%)	
Age (year)	22.5 (39.0)		25.0 (47.0)		0.672[c]
Ethnic					
Malay		56 (96.6)		53 (91.4)	0.390[d]
Others		2 (3.4)		5 (8.6)	
Gender					
Male		33 (56.9)		32 (55.2)	0.852[d]
Female		25 (43.1)		26 (44.8)	

[a]Nonparametric test, [b]*p*-value significant at <0.05, [c]Mann-Whitney test, [d]Pearson chi-square.

Table 2
Comparison of attributes and crude mortality rates between acinetobacter blood stream infection and other gram-negative blood stream infection groups.

Outcome	*Acinetobacter* No. (%)	Other gram-negative No. (%)	*p*-value[a]	OR (95%CI)
Attribute mortality	15 (28.3)[b]	12 (21.4)[b]	0.406[c]	1.21 (0.757-1.926)
Crude mortality	25 (47.2)[b]	14 (25.0)[b]	0.016[c]	1.89 (1.104-3.224)

[a]*p*-value significant at <0.05.
[b]Five cases of acinetobacter blood stream infection and two cases of other gram-negative blood stream infections were excluded from the study because they left against medical advice.
[c]Pearson chi-square.

33 (56.9%) were managed with systemic antimicrobials alone and 16 (27.6%) were managed by a combination of antimicrobials and other therapy. Three patients (5.2%) were managed without systemic antimicrobials: surgical drainage, regular dressings and removal of infected devices.

Six cases were treated with inappropriate antibiotics because the sensitivity results were not available until after the patient died (four cases) or the patient had transient bacteremia (one case). In the final case, the management team did not want to change the antibiotics despite reported *in vitro* resistance, since the patient showed clinical improvement.

The appropriate management of acinetobacter BSI is associated with a significantly better outcome BSI [OR 0.197, 95% CI (0.040-0.967), *p*=0.027]. Eleven patients (23.4%) died due to BSI even when appropriate antibiotics were administered. Of the

Table 3
Comparison of demographic profiles between those who died and those who lived in patients with acinetobacter blood stream infection (on univariate analysis).

Demographic profile	Died (*n*=25)		Lived (*n*=28)		*p*-value[b]
	Mean (SD)[a]	No. (%)	Mean (SD)[a]	No. (%)	
Age (year)	35.0 (59.0)		18.5 (28.0)		0.276[c]
Gender					0.958[d]
Males		15 (60.0)		17 (60.7)	
Females		10 (40.0)		11 (39.3)	
Duration of hospitalization (days)	31.0 (20.2)		37.0 (33.4)		0.440[e]
Underlying disease					
Neonatal related illness		5 (20.0)		1 (3.6)	0.060[d]
Malignancy		7 (28.0)		6 (21.4)	0.579[d]
Trauma		2 (8.0)		8 (28.6)	0.056[d]
Diabetes mellitus related disease		5 (20.0)		1 (3.6)	0.060[d]
Renal impairment		5 (20.0)		1 (3.6)	0.060[d]

[a]Median (Interquartile range) for nonparametric test, [b]*p*-value significant at <0.05, [c]Mann-Whitney test
[d]Pearson chi-square, [e]Independent *t*-test.
Five cases exclude from the study because they left against medical advice.

Table 4
Significant predictors of mortality in patients with acinetobacter blood stream infection (on univariate analysis).

Predictor	Died (*n*=25)		Lived (*n*=28)		*p*-value[a]	OR (95%CI)
	Mean (SD)	No. (%)	Mean (SD)	No. (%)		
Located in ICU		21 (84.0)		9 (32.1)	0.000[b]	2.61 (1.486-4.597)
Total ICU stay (days)	18.84 (21.3)		8.39 (12.4)		0.032[c]	
Shock		19 (76.0)		5 (17.9)	0.000[b]	4.26 (1.866-9.706)
Coagulopathy		12 (48.0)		3 (10.7)	0.003[b]	4.48 (1.426-14.070)
Prior exposure to carbapenems		7 (28.0)		0 (0.0)	0.003[b]	
Mechanical ventilation		21 (84.0)		13 (46.4)	0.004[b]	1.81 (1.173-2.790)
Ventilator days	9.80 (10.58)		4.29 (5.64)		0.020[c]	
Nasogastric tube		23 (92.0)		15 (53.6)	0.002[b]	1.72 (1.194-2.471)
Central venous catheter		24 (96.0)		15 (53.6)	0.000[b]	1.79 (1.258-2.553)
Arterial catheter		21 (84.0)		13 (46.4)	0.004[b]	1.81 (1.173-2.790)
Parenteral nutrition		10 (40.0)		2 (7.1)	0.004[b]	5.6 (1.355-23.148)

[a] *p*-value significant at <0.05, [b] Pearson chi-square, [c] Independent *t*-test.
Only statistically significant predictors are shown in the table.
Five cases exclude from the study because they left against medical advice.

Table 5
Comparison of attributed and crude mortality rates in patients with acinetobacter blood stream infection with appropriate management and in appropriate management.

Outcome	Appropriate therapy No. (%)	No appropriate therapy No. (%)	*p*-value[a]	OR (95% CI)
Attributed mortality	11(23.4)[b]	4(66.7)[b]	0.027[c]	0.197 (0.040-0.967)
Crude mortality	21(44.7)[b]	4(66.7)[b]	0.310[c]	0.670 (0.350-1.283)

[a]*p*-value significant at <0.05.
[b]Five cases excluded from the study because they left against medical advice.
[c]Pearson chi-square.

six patients who were not managed with appropriate antibiotics, 4 (66.7%) died. The appropriateness of management did not seem to influence the crude mortality rate of the patients (p=0.310). Of 53 patients, 21 (44.7%) died in spite of appropriate management (Table 5).

DISCUSSION

In this study, the crude death rate in patients with acinetobacter BSI was significantly higher than in the control group (OR 1.89). The crude mortality rate of 47.2% is comparable with other studies (31.0-51.9%) (Beck-Sagué *et al*, 1990; Tilley and Roberts, 1994; Seifert *et al*, 1995; Cisneros *et al*, 1996; Gómez *et al*, 1999; Wisplinghoff *et al*, 1999; Smolyakov *et al*, 2003). The wide range of crude mortality rates reflects differences in severity of underlying diseases. The death rate directly due to acinetobacter BSI was 28.3% (15 cases), which is comparable to other studies (16.9-34.2%) (Lortholary *et al*, 1995; Seifert *et al*, 1995; Cisneros *et al*, 1996; Valero *et al*, 2001).

Some researchers have reported an attributable death rate of only 5.6-6.9% because of low case numbers and differences in study populations (Siau *et al*, 1999; Wisplinghoff *et al*, 1999). Our findings were similar to Lortholary *et al* (1995) who noted acinetobacter BSI was associated with higher mortality rates than the underlying diseases themselves (Lortholary *et al*, 1995). We found 60% of our subjects died directly due to acinetobacter BSI compared to only 40% due to other causes. Lortholary *et al* (1995) also found that colonization/infection with acinetobacter was independently associated with death. Screening for *Acinetobacter* spp was beyond the scope of this study.

As reported in previous studies, we noted that appropriateness of management did not significantly reduce the crude mortality rate in acinetobacter BSI patients (Tilley and Roberts, 1994; Lortholary *et al*, 1995; Seifert *et al*, 1995; Loh *et al*, 2006). Some investigators had different findings because their strains were more resistant to antimicrobial agents and this led to more occurrences of inappropriate treatment (Gómez *et al*, 1999; Smolyakov *et al*, 2003). Our study found appropriateness of therapy can reduce mortality attributed to acinetobacter BSI (OR 0.197 95% CI 0.040-0.967, p=0.027). Our study noted a 76.6% cure rate with appropriate therapy, and this is comparable to another study (Levin *et al*, 2003). It has also been reported that inappropriateness of antimicro-

bial therapy results in a poor prognosis (Cisneros *et al*, 1996).

A greater risk of mortality was noted in patients in intensive care units (OR 2.6), presenting with shock (OR 4.3) or coagulopathy (OR 4.5), who were mechanically ventilated (OR 1.8), had a central venous catheter (OR 1.7), an arterial catheter (OR 1.8), a nasogastric tube (OR 1.7) or who were given parenteral nutrition (OR 5.6). These patients were also had longer intensive care stays and more ventilator days. Patients who presented with septic shock and had a central venous catheter were independently at higher risk of mortality. Previous researchers have also found that septic shock is an independent predictor of mortality (Seifert *et al*, 1995). Prior exposure to carbapenems was a significant predictor of mortality (p=0.003); all 7 patients treated with carbapenems died.

Since this was a retrospective study, a major limitation was the difficulty in assessing the severity of the underlying illness during hospitalization. Neither the McCabe classification nor the APACHE II score was applied in our setting during the study period. Underlying illness has been reported as a significant risk factor for acinetobacter BSI (Lortholary *et al*, 1995; Wong *et al*, 2002) and is a predictor for mortality in patients with acinetobacter BSI (Lortholary *et al*, 1995; Seifert *et al*, 1995; Wong *et al*, 2002; Levin *et al*, 2003).

In conclusion, acinetobacter BSI is associated with a high mortality rate. Avoidable predictors of mortality should be modified to reduce mortality among acinetobacter BSI patients. These include shortening ICU stay, rational used of carbapenem antibiotics and minimal use of invasive procedures, including mechanical ventilation, nasogastric tubes, central venous catheters and parenteral nutrition. Whenever a patient has a positive blood culture for *Acinetobacter* spp, appropriate management should be instituted to prevent the mortality.

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