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The prevalence and risk factors of nosocomial *Acinetobacter* blood stream infections in tertiary teaching hospital in north-eastern Malaysia

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Abstract. *Acinetobacter* spp. is a known nosocomial pathogen causing a wide range of clinical diseases mainly pneumonia, wound infections and blood stream infections (BSI). A cross sectional descriptive study was performed to determine the prevalence of *Acinetobacter* infection in Hospital Universiti Sains Malaysia, Kelantan (HUSM). The risk factors of *Acinetobacter* BSI were determined by 1:1 case control analytical study, involving fifty-eight confirmed cases of *Acinetobacter* BSI patients compared to the cases caused by Gram-negative bacteria. The prevalence of *Acinetobacter* BSI in the HUSM was 6.11% (95% CI 4.88-7.53%). The attack rate of *Acinetobacter* BSI was 2.77 episodes per 1000 hospital admissions. *Acinetobacter* BSI patients were mostly located in intensive care unit and had a longer intensive care unit stay. In univariate analysis, the risk factors for *Acinetobacter* BSI include prior exposure to antimicrobial agents such as penicillins, aminoglycosides and cephalosporins, mechanical ventilation, presence of nasogastric tube, arterial catheter and urinary catheter. In multivariate analysis, the independent risk factors for *Acinetobacter* BSI were prior treatment with cephalosporins (OR 3.836 95% CI 1.657-8.881 p=0.002) and mechanical ventilation (OR 3.164 95% CI 1.353-7.397 p=0.008). This study revealed that rational use of antimicrobial agents is of paramount importance to control *Acinetobacter* BSI.

INTRODUCTION

Acinetobacter spp. emerged as very 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 blood stream infection (BSI), pneumonia, meningitis, urinary tract infection, skin and soft tissue infection, wound and burn infection, intravascular devices and implant-related infection (Bergogne-Berezin & Towner, 1996; Wisplinghoff *et al.*, 1999). *Acinetobacter* spp. has been associated with nosocomial transmission, and its resistance to commonly used antimicrobial agents is a rising problem. *Acinetobacter baumannii* also may survive much longer on inanimate environmental surfaces (Wendt *et al.*, 1997). Previous studies had demonstrated that *Acinetobacter* infection associated with high mortality rates i.e. as high as 17–52% in BSI, increase duration of intensive care admission and increase cost of care (Cisneros *et al.*, 1996; Wisplinghoff *et al.*, 2000; Smolyakov *et al.*, 2003).

However, the result of the studies might not represent our local situation since there are very large variations among regions, countries, hospitals or settings. *Acinetobacter* spp. was one of the most common Gram-negative isolated from blood

culture in Hospital Universiti Sains Malaysia (H.U.S.M.). This study was designed to determine the prevalence and find out the risk factors of *Acinetobacter* BSI in HUSM and thus, hopefully results will be obtained from the study to overcome the problem.

MATERIALS AND METHODS

A cross sectional descriptive study was performed to determine the prevalence of *Acinetobacter* infection in HUSM for a one year period. HUSM is an 800-bedded tertiary teaching hospital that is located in Kelantan, a north-eastern 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 attack rate of BSI in hospital was calculated based on the episodes of BSI in one year divided by total number of admission. The attack rate presented per 1000 admissions.

To determine the risk factors, a case control analytical study was conducted. The cases were selected from significant nosocomial *Acinetobacter* BSI; whereas the control group were significant nosocomial other Gram-negative BSI. The definition of nosocomial *Acinetobacter* BSI was based on previous established studies. A case of clinically significant *Acinetobacter* blood stream infection was defined as any patient who had one or more blood cultures positive for *Acinetobacter* spp. collected when evidence of infection is present (Seifert *et al.*, 1995). To comply with definition of nosocomial acquisition, the patient was admitted more than 48 hours, including the 'transfer-in' cases that had been admitted in the respective hospital or HUSM for more than a total of 48 hours. The risk factors and their outcomes were recorded. Polymicrobial infections were excluded from the study.

Specimens were collected according to The Protocol of the Microbiology Laboratory. Blood for blood culture and sensitivity was collected aseptically and inoculated in BACTEC™ (Becton Dickinson, Sparks, Maryland, U.S.A.) bottle. We used 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 then incubated in the BACTEC™ automated blood culture system.

Identification of the species of *Acinetobacter* was done by regular biochemical test and confirmation was done by API 20 NE (bioMérieux, Craponne, France) system.

For every 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 are most probably community acquired and have a longer incubation period.

Results were expressed in terms of the number and percentage or the mean ± standard deviation. For categorical variable, the differences in patient characteristics and risk factors were tested by Chi-square and Fisher's exact test. For continuous variable, the Mann-Whitney test was used. Multiple logistic regression analysis was used to determine independent risk factors and predictors of mortality. The p value of < 0.05 was considered significant. All analyses were done using SPSS software (SPSS, Chicago, Illinois, U.S.A) in Medical Informatics' Laboratory, School of Medical Sciences, Universiti Sains Malaysia.

RESULTS

Prevalence

The prevalence of *Acinetobacter* BSI in the HUSM was 6.11% (95% CI 4.88-7.53%). The prevalence of *Acinetobacter* BSI in intensive care units in HUSM was 8.32% (95% CI 6.06-11.08%) and comprised of 51.2% of total *Acinetobacter* BSI. The attack rate of *Acinetobacter* BSI was 2.77 episodes per 1000 hospital admissions.

Total *Acinetobacter* isolates from blood culture were 111 (82 cases). Among them, six isolates (from six cases) were community acquired (blood culture positive less than 48

hours of admission). Three cases of community acquired were *A. baumannii* and another three were *Acinetobacter lwoffii*.

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

Susceptibility pattern of *Acinetobacter* blood isolates

Figure 1 shows performance of 16 antimicrobial agents tested against blood isolates of *Acinetobacter* spp. in HUSM. Five active antimicrobial agents with susceptibility equal or more than 70% were amikacin, ciproflaxacin, imipenem, netilmycin and cefoperazone/sulbactam. Most of the penicillins and cephalosporins were not active against *Acinetobacter* spp. with susceptibility less than 60%.

The controls

The total number of Gram-negative bacilli isolates other than *Acinetobacter* spp. were 672 (525 cases). The Gram negative blood stream infection cases is summarised in Figure 2. Out of these, 58 cases were randomly selected and included in the study of risk factors and clinical outcomes. The species selected include; *Klebsiella pneumoniae* (15 cases), *Escherichia coli* (12 cases), *Pseudomonas* spp. (10 cases), *Enterobacter* sp. (10 cases), the other *Klebsiella* spp. (3 cases), *Chryseobacterium* spp. (3 cases), *Burkholderia cepacia* (3 cases), *Stenotrophomonas* spp. (1 case) and *Achromobacterium* spp. (1 case).

Patients' characteristic

The patients' characteristic of *Acinetobacter* BSI in comparison with other Gram-negative are shown in the Table 1. In univariate analysis, *Acinetobacter* BSI patients were mostly warded in intensive care settings (p=0.001) and have longer duration of intensive care stay (p=0.010). The common underlying disease in patients with *Acinetobacter* BSI were malignancy (29.30%), trauma (19%), cardiovascular (13.80%) and neonatal related disease (8.60%). The possible primary sources of *Acinetobacter* BSI were found in 43 cases. Pneumonia was the commonest primary source (65.1%), followed by wound Infection (23.2%), catheter related infection (9.3%) and urinary tract infection (2.3%).

Risk factors of *Acinetobacter* BSI

The risk factors that were studied included prior exposure to penicillin, aminogycosides, cephalosporins and carbapenems, underwent planned surgery, unscheduled surgery, mechanical ventilation, ventilator days, having tracheostomy, nasogastric tube, central venous catheter, arterial catheter, urinary catheter, parenteral nutrition, extra ventricular drainage, had underlying diabetes mellitus, renal impairment, solid tumour, haematology malignancy, neutropenia, thrombocytopenia, steroid, chemotherapy and burn.

The association between prior usage of antimicrobial agents and BSI are shown in Table 2. The potential risk factors of *Acinetobacter* BSI that were analysed by univariate analysis are shown in Table 3. The underlying diseases in both groups did not show any significant difference (Table 4). Among all the potentials risk factors, the independent risk factors for *Acinetobacter* BSI were prior treatment with cephalosporines and mechanical ventilation (Table 5).

DISCUSSION

Acinetobacter spp. is one of the most important pathogens in clinical practice. It causes wide variety of nosocomial infection and responsible for many outbreaks especially in intensive care units. However, in this study *Acinetobacter* infections occurred at a relatively constant rate over a one year period and no cluster suggestive of outbreak during the study period. *Acinetobacter* spp. was the second most common nosocomial Gram-negative organism isolated in the whole hospital after

K. pneumoniae. However in the intensive care settings i.e., General Intensive Care Unit (ICU), Neonatal ICU and Neurosurgical ICU, *Acinetobacter* spp. was the most common isolates.

The prevalence of *Acinetobacter* BSI in HUSM was 6.11% and in intensive care settings was 8.32%. These findings were comparable with previous reports 1%-9% (Struelens *et al.*, 1993; Cisneros *et al.*, 1996; Wisplinghoff *et al.*, 2000; Sader *et al.*, 2002). However, there were other previous studies in intensive care units that showed higher prevalence (10.2-18.0%) (Bang *et al.*, 1998; Garcia-Garmendia *et al.*, 2001; Santucci *et al.*, 2003). This present study showed the attack rate of 2.77 episodes per 1000 hospital admissions, which was higher compared to 0.18 - 1.9 episodes per 1000 admissions as reported by previous studies in North America and Spain (Beck-Sague *et al.*, 1990; Tilley & Roberts, 1994; Cisneros *et al.*, 1996; Gómez *et al.*, 1999; Garcia-Garmendia *et al.*, 2001; Valero *et al.*, 2001). This was likely due to high total BSI in HUSM i.e. 45.4 episodes per 1000 admissions (data calculated from our laboratory database using WHONET 5.2). Infection control measures should be improved as well as adherence to antimicrobial protocols so that the attack rate can be reduced.

Our study showed a good distribution between two groups – case and control. In univariate analysis, no significant difference between case and control in terms of ethnic group, gender and sex were noted. There was also no significant difference in the length of hospitalisation and duration of BSI between two groups. The mean interval from admission to acquisition of *Acinetobacter* was 16.60 ± 19.39 days and no statistically significant difference between two groups. This study also agreed with the previous studies that noted *Acinetobacter* as late onset pathogens (mean 14.1 to 32.3 days of admission) (Seifert *et al.*, 1995; Cisneros *et al.*, 1996; Siau *et al.*, 1999; Wisplinghoff *et al.*, 2000; Lee *et al.*, 2004).

More patients with *Acinetobacter* BSI were located in intensive care setting as compared to other Gram-negative BSI (OR 2.39). In this study, probably 63.8% (37 cases) acquired *Acinetobacter* spp. from intensive care settings i.e. 31 cases located in intensive care settings and another six cases were 'transfer-out' from intensive care settings within 48 hours of acquisition of *Acinetobacter* BSI. This finding is expected because the prevalence of *Acinetobacter* BSI is higher in intensive care settings. Conversely, in another study in Hong Kong, only 22% of patients acquired the infection in intensive care settings (Seifert, 1999; Siau *et al.*, 1999). The patients also had significantly longer total intensive care stays (12.72 ± 17.29 days) compared to control (2.97 ± 7.88 days). A longer stay at high risk unit had been identified as risk factors in several studies (Lortholary *et al.*, 1995, Scerpella *et al.*, 1995; Koeleman *et al.*, 1997; Lee *et al.*, 2004).

This study identified 74.1% possible portal site of BSI based on clinical and/or microbiological features. Another 25.9% (15 cases) were probably primary BSI. Nosocomial pneumonia, as expected, was the main source of BSI (48.3%) due to high prevalence rate of the *Acinetobacter* ventilator-associated pneumonia. All but four (85.7%) were mechanically ventilated. Wound infection (including secondary meningitis) and intravascular catheter were only responsible for 17.2% and 6.9% respectively. Urinary tract had low prevalence of *Acinetobacter* infection, and was expected to be less common cause of secondary BSI (1.7%). The previous study failed to determine the portal of entry in up to 49% (54 cases) and they found intravenous catheter being the most frequent source (22%) (Wisplinghoff *et al.*, 2000).

Prior treatment with broad spectrum antimicrobial agents was a frequent finding among patients with *Acinetobacter* BSI (91.4%). Prior exposure to penicillins, aminoglycosides and cephalosporins were seen significantly more in *Acinetobacter* BSI group compared to control group ($p<0.05$). The use of broad spectrum antimicrobial agents have been identified as risk factors for acquisition of *Acinetobacter* infections in several other studies (Peacock *et al.*, 1988; Struelens *et al.*, 1993; Lortholary *et al.*, 1995; Koeleman *et al.*, 1997; Garcia-Garmendia *et*

al., 2001; Smolyakov *et al.*, 2003; Lee *et al.*, 2004). Garcia-Garmendia *et al.* (2001) had discouraged the overzealous use of broad-spectrum antibiotics in critically ill patients whenever possible. Prior exposure to carbapenems in *Acinetobacter* BSI group (12.1%) was noted more than control group (8.6%) but the difference was not statistically significant. This was probably due to limited usage of carbapenems in HUSM. Only twelve of total patients (10.3%) had history of exposure to carbapenems. However, we had reported that the exposure to carbapenems was a significant predictor of mortality (*p* value 0.003), in which all seven patients treated with carbapenems died (Deris *et al.*, 2009).

Several invasive procedures which were significant risk factors by univariate analysis in previous studies were also found to be significant in this present study (Buxton *et al.*, 1978; Castle *et al.*, 1978, , Beck-Sague *et al.*, 1990; Struelens *et al.*, 1993; Wisplinghoff *et al.*, 1999; Garcia-Garmendia *et al.*, 2001). The factors include mechanical ventilation, nasogastric tube, arterial catheter and urinary catheter. The ventilator days prior to acquisition was significantly longer in *Acinetobacter* BSI (9±15.5 days) compared to other Gram-negative BSI (5±8.6 days). This finding was parallel with a previous report (Peacock *et al.*, 1988). These invasive procedures might reflect the severity of the illness and part of the intensive care management. A few other risk procedures were seen more in *Acinetobacter* BSI than in control group but the difference was not statistically significant. Those procedures include previous surgery (both schedule and unscheduled), tracheostomy, central venous catheter and extra-ventricular drainage. Parenteral nutrition was administered more in control group without statistical significant, contradictory to the previous finding (Beck-Sague *et al.*, 1990).

In contrast to previous study that found *Acinetobacter* BSI are related to immunosuppresion and acute renal failure (Garcia-Garmendia *et al.*, 2001), this study did not find any significant difference between *Acinetobacter* BSI group and control group in terms of immune and host defence status. Haematology malignancy, neutropenia, thrombocytopenia and history of chemotherapy were seen more in control group. One of the major factors contributing to these findings were because of 37.9% (22 cases) of control group have underlying maliganancy compare to 29.3% (17 cases) in *Acinetobacter* BSI group. This led to increase immunosupression factors in control group. It was noted that *Acinetobacter* spp. is not a common pathogen in oncology/haematology units. It only accounted for about 5.7-14.3% of total Gram-negative organism (Alangaden *et al.*, 2002, Jugo *et al.*, 2002). Presence of diabetes mellitus was more common in the control group. This is parallel with the previous study that found presence of diabetes mellitus decreased the incidence of *A. baumannii* bacteremia (Garcia-Garmendia *et al.*, 2001).

The possible risk factors for acquisition of *Acinetobacter* BSI were not only the history of antimicrobial treatment, invasive procedures and host defence status, but also variables related to patient characteristics and hospitalisation. Controlling these variables can be accomplished either by including them in multivariate analysis or by matching them during the selection of the control group. In this study, the control group were selected randomly. Therefore, multivariate analysis was performed to find the genuine risk factors for *Acinetobacter* BSI. It was noted that prior treatment with cephalosporins (OR 3.836) and mechanical ventilation (OR 3.164) had been two independent risk factors for *Acinetobacter* BSI.

With the increased number of elderly and immunocompromised status; and advancement of medical and surgical interventions, nosocomial infection becomes a major problem in clinical practice. Use of devices, implanted foreign materials and organ transplantation for example, were among the important risk factors for nosocomial infection. Rational and appropriate use of antimicrobial agents is of paramount important to minimize the risk of resistant organism.

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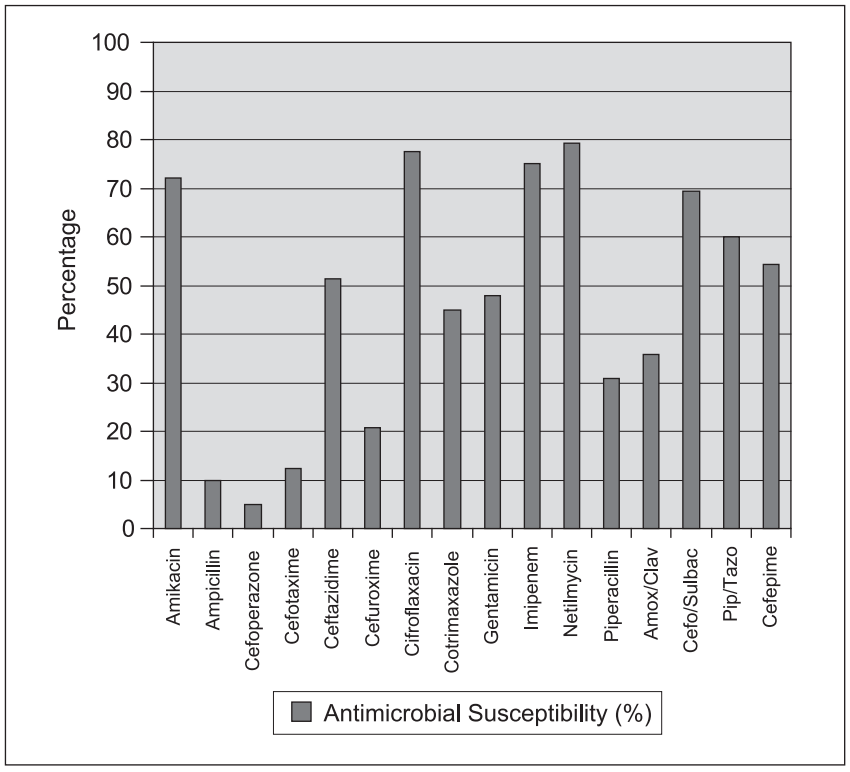

Figure 1. Percentage of susceptibility of *Acinetobacter* spp. from blood specimen to various antimicrobial agents.

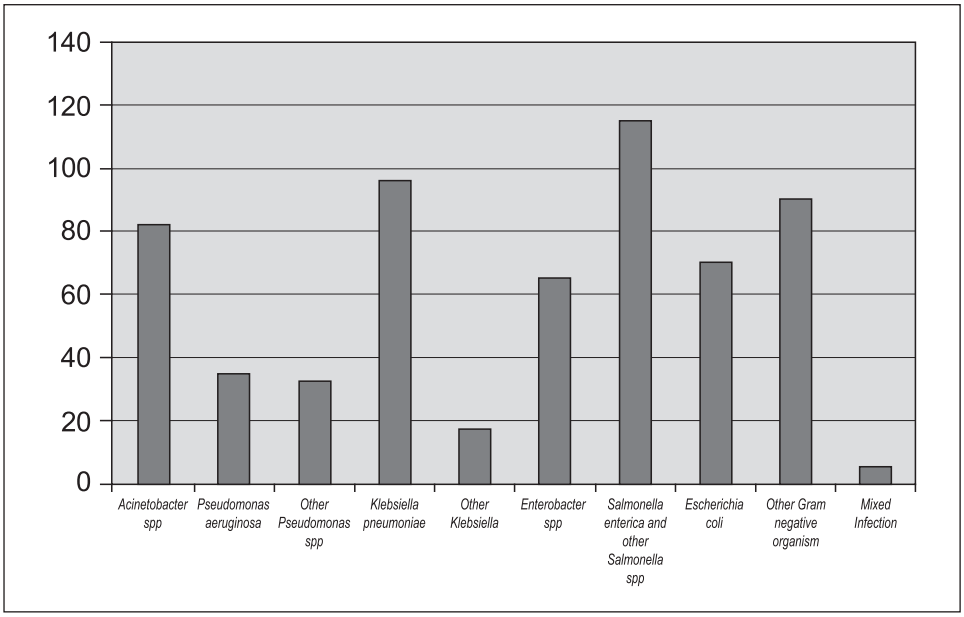

Figure 2. Summary of Gram-negative blood stream infection cases during study period.

Note: Figures above are for the article on pages: 123-129.

Table 1. Demographic data of *Acinetobacter* blood stream infection compared to Other Gram-negative blood stream infection

Variable	*Acinetobacter* *n=58* Mean (sd)*/ Freq (%)	Other Gram negative *n=58* Mean (sd)*/ Freq (%)	*p* value#	OR (95% CI)
Ethnic				
Malay	56 (96.6)	53 (91.4)	0.242[a]	2.642
Others	2 (3.4)	5 (8.6)		(0.491, 14.206)
Gender				
Male	33 (56.9)	32 (55.2)	0.852[a]	1.072
Female	25 (43.1)	26 (44.8)		(0.515, 2.33)
Age (y)*	22.50 (38.75)	25.00 (47.00)	0.672[b]	
Length of hospital stay (days)	34.52 (27.06)	26.36 (18.01)	0.059[c]	
Duration of hospitalization before BSI (days)	16.60 (19.39)	13.52 (13.73)	0.325[c]	
Duration of BSI (days)	4.69 (3.12)	3.91 (2.33)	0.132[c]	
Location				
ICU Setting	31 (53.4)	13 (22.4)	0.001[a]	3.974
Non ICU Setting	27 (46.6)	45 (77.6)		(1.778, 8.884)
Total ICU stay (days)	12.72 (17.29)	2.97 (7.88)	0.010[c]	

* Median (Interquartile Range) for nonparametric test
** BSI – Blood stream infection
# *p* value significant at <0.05
[a] Pearson Chi square
[b] Nonparametric Test (Mann-Whitney Test)
[c] Independent t Test

Table 2. Prior exposure to antimicrobial therapy as risk factors in *Acinetobacter* blood stream infection compared to other Gram-negative blood stream infection

Antimicrobial	*Acinetobacter* No (%)	Other Gram Negative No (%)	*p* value#	OR (95% CI)
Penicillins	34 (58.6)	22 (37.9)	0.026[a]	2.318 (1.101, 4.881)
Aminogycosides	18 (31.0)	9 (15.5)	0.048[a]	2.450 (0.994, 6.042)
Cephalosporins	40 (69.0)	17 (29.3)	<0.001[a]	5.359 (2.425, 11.847)
Carbapenems	7 (12.1)	5 (8.6)	0.542[a]	1.455 (0.434 - 4.881)

p value significant at <0.05
[a] Pearson Chi square

Note: Tables above are for the article on pages: 123-129.

Table 3. Potential risk procedures in *Acinetobacter* blood stream infection compared to other Gram-negative blood stream infection using univariate analysis

Procedure	*Acinetobacter* Mean (sd)	*Acinetobacter* No (%)	*Other Gram Negative* Mean (sd)	*Other Gram Negative* No (%)	*p* value[#]	OR (95% CI)
Planned Surgery		13 (22.4)		10 (17.2)	0.485[a]	1.387 (0.553, 3.477)
Unscheduled Surgery		18 (31.0)		11 (19.0)	0.133[a]	1.923 (0.813, 4.546)
Mechanical Ventilation		36 (62.1)		15 (25.9)	<0.001[a]	4.691 (2.125, 10.353)
Ventilator Days	6.62 (8.49)		2.97 (7.88)		0.018[b]	
Tracheostomy		9 (15.5)		5 (8.6)	0.254[a]	1.947 (0.610 - 6.212)
Nasogastric Tube		41 (70.7)		24 (41.4)	0.001[a]	3.417 (1.582, 7.378)
Central Venous Catheter		43 (74.1)		36 (62.1)	0.163[a]	1.194 (0.928 - 1.537)
Arterial Catheter		36 (62.1)		19 (38.8)	0.002[a]	3.359 (1.566, 7.203)
Urinary Catheter		39 (67.2)		23 (39.7)	0.003[a]	3.124 (1.461, 6.678)
Parenteral Nutrition		12 (20.7)		17 (29.3)	0.284[a]	0.629 (0.269,1.473)
Extra Ventricular Drainage		11 (19.0)		5 (8.6)	0.106[a]	2.481 (0.803 - 7.662)

[#] p value significant at <0.05
[a] Pearson Chi square
[b] Independent t Test

Note: Table above is for the article on pages: 123-129.

Table 4. The underlying diseases of *Acinetobacter* blood stream infection compared to other Gram-negative blood stream infection using univariate analysis

Underlying Diseases	*Acinetobacter* *n=58* No (%)	Other Gram Negative *n=58* No (%)	*p* value[#]	OR (95% CI)
Diabetes Mellitus	6 (10.3)	8 (13.8)	0.569[a]	0.721 (0.234 - 2.227)
Renal Impairment	8 (13.8)	8 (13.8)	1.000[a]	1.000 (0.348 - 2.873)
Solid Tumour	11 (19.0)	11 (19.0)	1.000[a]	1.000 (0.395 - 2.530)
Hematology Malignancy	6 (10.3)	11 (19.0)	0.189[a]	0.493 (0.169 - 1.437)
Neonatal related disease	6 (10.3)	8 (13.8)	0.569[a]	0.721 (0.234 - 2.227)
Burn	1 (1.7)	1 (1.7)	1.000[a]	1.000 (0.061 - 16.379)

[#] *p* value significant at <0.05
[a] Pearson Chi square

Table 5. The risk factors for *Acinetobacter* blood stream infection compared to the other Gram-negative blood stream infection using multiple regression models

Risk Factors	Crude OR (95% CI)	*p* value[#]	Adjusted OR (95% CI)	*p* value[#]
Prior Treatment with Cephalosporins	5.359 (2.425, 11.847)	<0.001	3.836 (1.657, 8.881)	0.005
Usage of Mechanical Ventilation	4.691 (2.125, 10.353)	<0.001	3.164 (1.353, 7.397)	0.008

[#] *p* value significant at <0.05
* Only statistically significant risk factors are shown in the table
** The multiple logistic regression is fit (Hosmer-Lemeshow goodness-of-fit: Chi square = 0.205, df = 2, p value = 0.903)

Note: Tables above are for the article on pages: 123-129.