Original article:

Carbapenem resistant *Acinetobacter Species* infection in intensive care unit: The outcome and risk factors of mortality

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Abstract:

Objective: *Acinetobacter spp*. infection is a challenging problem in intensive care unit (ICU) because of its multi-drug resistant (MDR) in nature to antibiotic therapy including broad-spectrum carbapenem group. The aims of the study were to determine the risk factors of mortality and the outcome of carbapenem-resistant *Acinetobacter spp.* (CRAs) infection in our ICU. ***Materials and Method:*** This is a retrospective, cross-sectional study, done in 2 years from January 2008 to December 2009. The list of the patients was obtained from hospital nosocomial infection surveillance unit and ICU infection record. The data of the patients were subsequently reviewed from their respective medical records after approval from university ethics committee and hospital medical record unit. ***Results and Discussion:*** A total of 92 patients were reviewed and only 54 were included and analyzed. The prevalence of CRAs over 24 months was 7.3%. Mortality was 50% among the reviewed patients and this contributed 13.6 % of the total ICU mortality. Age was significantly different between survival and non-survival groups; 43.07 (21.09) vs. 57.04 ± 14.33 year old (p = 0.006). Age was also the only significant independent risk factor associated with mortality in CRAs (adjusted OR = 1.045, 95% CI: 1.010, 1.081, p = 0.011). There were no other significant risk factors. The length of ICU stay was 17.00 (13.58) days whereas length of hospital stay was 41.37 (27.66) days in survival group. ***Conclusion:*** CRAs caused 13.6% of total ICU mortality and older age group was the independent risk factor for mortality.

Keywords: Carbapenem; *Acinetobacter spp.*; multi-drug resistant mortality

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Introduction

Acinetobacter spp. emerged as a significant nosocomial pathogen during the late 1970s, probably as a consequence, at least in part, of increasing use of broad-spectrum antibiotics in hospitals. Most clinically significant isolates belong to the species *Acinetobacter baumannii* or its close relatives[1]. *A. baumannii* is an opportunistic gram-negative pathogen with increasing relevance in a variety of nosocomial infections especially among intensive care unit (ICU) patients. The prevalence of *Acinetobacter* blood stream infection (BSI) in Hospital Universiti Sains Malaysia (HUSM) was 6.11% and its attack rate was 2.77 episodes per 1000 hospital admissions. It was located mainly in ICU[2].

Carbapenem has previously been used to treat serious multi-drug resistant (MDR) *Acinetobacter spp.* infections; however, incidences of carbapenem

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resistant *Acinetobacter spp.* (CRAs) are rising in several parts of the world as well as in Malaysia. Carbapenem-resistant *A. baumannii* (CRAB) is a serious ICU problem because of its high mortality rate. The overall 30-day mortality in patients with CRAB infection or colonization was 47.0%. Septic shock and APACHE II score at onset of infection were significantly associated with 30-day mortality[3]. Previous study in our institution showed no independent risk factor for imepenem resistant *A. baumannii* (IRAB) BSI but it was associated with longer bacteraemic days[4] .

The problems of CRAs in our ICU were also as serious as that have been reported from other countries. The aims of the study were to review the outcome and risk factors of mortality between survival and non-survival patients with CRAs in the ICU.

Materials and method

Our study is designed as a retrospective, cross sectional study with adult population of ICU patients who were culture positive for *Acinetobacter spp.* and tested resistant to carbapenem group antibiotic from January 2008 to December 2009. After university ethics committee approval, ICU patients who were infected with Acinetobacter *spp.* were identified from hospital infectious surveillances unit record and ICU surveillances unit record. All identified patients were subsequently reviewed with their medical record for data collection. Those patients who were tested positive with Acinetobacter *spp.* infection less than 48 hours of ICU admission and with a known case of *Acinetobacter spp*. infection prior to ICU admission were excluded from the study. Selected patients were divided into two groups; survival and non-survival groups. Risk factors studied for mortality between the two groups were patients and disease factors. Patients' factors include: age, sex, comorbid disease and APACHE II score. Disease factors are prior to hospital admission, previous ICU admission within 3 months, presence of septic shock, presence of multi-organ failure (MOF), prior antibiotics used and previous surgery. Other factors are invasive procedures and medication used e.g. steroid, immunosuppressive.

Lengths of ICU stay and hospital stay were also documented for the survival group. Potential risk factors were analysed by simple and multiple logistic regression test. Chi-square test or Fischer exact test were used for categorical variables and independent t-test for numerical variables. P-value less than 0.05 were statistically significant. Statistical package for social sciences (SPSS) software version 20.0 for Windows was used in all the analyses.

Ethical clearance: After university ethics committee approval, the study was performed.

Results

After a thorough record review from 2008-2009, 92 of ICU patients were identified as CRAs. After preliminary screening, only 54 patients were truly infected with CRAs and were treated accordingly. These patients were reviewed and analyzed. The rest of the patients were categorized as colonizer[19], age below 13 year old [6], missing information and missing data[8] as well as those who had positive culture CRAs < 48 hours of ICU admission[5]. The total of ICU admission during the study period was 1,256 patients and the prevalence of CRAs over 24 months was 7.3%. On descriptive analysis based on Table 1, the majority of patients were males (81.5%), Malay ethnic (88.9%) and had at least 2 or more surgeries done while in the ICU (27%). 61.1% of them had prior usage of carbapenem. The site of the culture was mainly from tracheal aspirate, which comprised 44.4%. 50% of these patients died in ICU. Percentage of mortality due to CRAs in comparison to total ICU mortality during the study period (199 cases) was 13.6% in comparing the survival and non-survival groups, only mean age was significantly different (Table 2). Mean age for survival group was 43.07 (21.09), whereas it was 57.04 (14.33) for non-survival group.

Based on simple logistic regression, age was the only significant risk factor for mortality in the ICU with crude OR of 1.045 and 95% confidence interval of (1.010, 1.081) (Table 3). This was further confirmed with multiple logistic regression analysis that showed adjusted OR of 1.045 and 95% confidence interval of 1.010, 1.081 (Table 4). There were no significant differences in antibiotic treatment of choice between the groups. Length of ICU stay was 17.00 (13.58) days whereas length of hospital stay was 41.37 (27.66) in survival group.

Table 1: Descriptive statistics of Carbapenem Resistant *Acinetobacter spp.* patients (n=54)

Variables	Mean	SD	n	%
Age (years)	50.06	19.20		
Gender				
Female			10	18.5
Male			44	81.5
Race				
Malay			48	88.9
Non-Malay			6	11.11
APACHE II score	16.93	6.99		
Surgery				
0			9	16.7
1			18	33.3
≥2			27	50.0
Corticosteroid			7	13.0
Immunosuppressive therapy			2	3.7
Septic shock			28	51.9
Multi organ failure			33	61.1
Comorbid disease			33	61.1
Previous hospital stay			19	35.2
Previous ICU stay			7	13.0
Invasive procedure			53	98.1
Previous Antibiotic				
Non carbepenam			21	38.9
Carbepenam			33	61.1
Type of Acinetobacter				
Acinetobacter spp.			90	85
Acinetobacter baumanii			16	15
Site of positive culture				
Blood			4	7.4
Tracheal aspiration			24	44.4
BAL			2	3.7
Tissue swab			4	7.4
Combination			20	37.0
Mortality				
Survived			27	50
Not survived			27	50

Discussion

The prevalence of CRAs isolates in our ICU was 7.3% during the study period of 24 months and only 58% of them were treated as *Acinetobacter* infection. Most of the cultures did not specify the type of *Acinetobacter* species (85%) and only 15% was documented as *A. baumannii.* The previous reported prevalence of CRAs varied from country to country. The annual prevalence of imepenem resistant *A. baumannii* (IRAB) isolates from 1989 to 2004 ranged from 0% to 21% in United States[5]. The prevalence of CRAB in Westmead Hospital, Australia was 4.6%, which was lower than ours. They had 66 positive isolated cultures from 1431 admissions during 24 months and 52% was a true culture[6]. Yearly prevalence surveys in Spain revealed a total of 1168 *A. baumannii* isolates were identified from 246 hospitals/year participated in the survey , yielding an infection prevalence rate of 3/1,000 hospitalized patients. Rate of carbapenem resistance was 34.5% (95% CI, 31.8-37.3), and was even higher among ICU patients (43.8%; 95% CI, 38.9% - 48.7%)[7]. The prospective study of ICU-acquired infection among 683 consecutive patients from 2002 to 2004 in a surgical ICU of a university hospital in Greece showed that the most frequent microorganism found was *A. baumannii* (20.3%)[8]. Another study in Greece showed the incidence of surgical ICU *A. baumannii* acquired infection was 12.6% (52 out of 411)[9]. The National Antimicrobial Resistance Surveillance Thailand (NARST) has reported the dramatic increase of Carbapenem-resistant *A. baumannii* from 2.1% in 2000 to 46.7% in 2005[10].

Our study showed that the main culture site for *Acinetobacter spp.* was from respiratory tract which was 44.4% from tracheal aspirate and 3.7% from broncho alveolar lavage (BAL). Similar findings from Australia review showed that 55.9% (19 out of 34 patients) of CRAB in patients in ICU occurred from pneumonia[6] . The survey from Spain also showed that the most frequent sites of *A. baumannii* infection were the respiratory tract (42.2%). Others were from surgical wound (15.1%), urinary tract (12.9%) and skin (11.7%)[7] .There were few previous studies on the risk factors for CRAs infection. Longer duration of hospital stay until *A. baumannii* is isolated (odds ratio (OR) 1.043; 95% confidence interval (CI) 1.003-1.084), previous antibiotic used (OR: 5.051; 95% CI 1.004-25.396) and ICU stay (OR: 3.100; 95% CI: 1.398-6.873) were independently associated with imipenem resistance[11] .Another multivariate analysis of the risk-factors for colonization/infection

Table 2: Descriptive statistics according to outcome of carbapenem resistance Acinetobacter spp. Patients.

Variables	Survived (n=27)		Not survived (n=27)		P value
Age (years)	43.07	21.09	57.04	14.33	0.006
Gender					
Female	7	25.9	3	11.1	0.293
Male	20	74.1	24	88.9	
Race					
Malay	24	88.9	24	88.9	1.000
Non-Malay	3	11.1	3	11.1	
APACHE II score	15.41	5.83	18.44	7.80	0.111
Surgery					
0	3	11.1	6	22.2	0.513
1	9	33.3	9	33.3	
≥2	15	55.6	12	44.4	
Corticosteroid					
No	23	85.2	24	88.9	1.000
yes	4	14.8	3	11.1	
Immunosuppressive therapy					
No	26	96.3	26	96.3	1.000
Yes	1	3.7	1	3.7	
Septic shock					
No	15	55.6	11	40.7	0.414
Yes	12	44.4	16	59.3	
Multi organ failure					
No	13	48.1	8	29.6	0.264
Yes	14	51.9	19	70.4	
Comorbid					
No	14	51.9	7	25.9	0.093
Yes	13	48.1	20	74.1	
Previous hospital stay:					
No	20	74.1	15	55.6	0.254
Yes	7	25.9	12	44.4	
Previous ICU stay:					
No	25	92.6	22	81.5	0.420
Yes	2	7.4	5	18.5	
Invasive procedures:					
No	1	3.7	0	0.0	1.000
Yes	26	96.3	27	100.0	
Prior use of antibiotic:					
Non-carbepenam	10	37.0	11	40.7	1.000
Carbepenam	17	63.0	16	59.3	

Numerical values are all in mean (SD); Categorical values are in n (%).

Table 3: Simple logistic regression for association between mortality and study factors (n=54).

Variables	Crude OR (95% CI)	P-value
Age (years)	1.045 (1.010, 1.081)	0.011
Gender		
Female	1	0.172
Male	2.800 (0.639, 12.263)	
Race		
Malay	1	>0.950
Non-Malay	1.000 (0.183, 5.460)	
APACHE II score	1.069 (0.984, 1.162)	0.115
Surgery		
0	1	
1	0.500 (0.095, 2.645)	0.415,0.256
≥2	0.400 (0.0824, 1.942)	
Corticosteroid		
No	1	0.686
Yes	0.719 (0.145, 3.569)	
Immunosuppressive therapy		
No	1	>0.950
Yes	1.000 (0.059, 16.854)	
Septic shock		
No	1	0.278
Yes	1.818 (0.618, 5.352)	
Multi organ failure		
No	1	0.166
Yes	2.205 (0.720, 6.753)	
Co-morbidities		
No	1	0.054
Yes	3.077 (0.979, 9.668)	
Previous hospital stay		0.158
No	1	
Yes	2.286 (0.725, 7.202)	
ICU stay		
No	1	0.239
Yes	2.841 (0.500, 16.138)	
Invasive procedure		
No	1	>0.950
Yes	0.000 (0.000, 0.000)	
Antibiotic before		
Non carbepenam	1	0.780
Carbepenam	0.856 (0.286, 2.558)	

Interpretation: At univariable analysis, variable age, gender, APACHE II score, multi-organ failure, co-morbidities, previous hospital stay and ICU stay have p-value of less than 0.25. These variables were selected for multivariable analysis.

Table 4: Multiple logistic regression to determine the association between mortality and study factors (n=54)

Variables	Adj. b	Adjusted OR	95% CI	Wald	df	P-value
Age	0.044	1.045	1.010, 1.081	6.414	1	0.011

Forward and Backward LR method applied, Constant = -2.220, Hosmer and Lemeshow Test, p value = 0.800, Classification table overall percentage correct = 64.81%, Area under ROC cure = 68.86%. No multicollinearity detected. Final regression equation; Log(Y) =-2.220 + 0.044*age. Interpretation: In the final logistic regression model, age is significantly associated with increased risk of dying in our study subjects. One year increase in age will increase in the risk of dying by 1.045 times (adjusted OR=1.045, 95% CI: 1.010, 1.081, p=0.011).

with MDR *A. baumannii* revealed an independent association with the presence of an arterial catheter (OR, 1.13; 95% CI, 1.03-1.25) and administration of imipenem as monotherapy (OR, 11.12; 95% CI, 2.33-53.09)[12]. A study in Brazil during two periods of time revealed prior infection, mechanical ventilation and central venous catheter showed significant risk factors. Carbapenem and third-generation cephalosporin used displayed a tendency to be risk factors[13] .A study in US showed that prior carbapenem use was independently associated with IRAB infection or colonization (adjusted odds ratio, 3.04 [95% confidence interval, 1.07-8.65])[5].

The percentage of mortality due to CRAs in comparison to total ICU mortality during the study period (199 cases) in our study was 13.6%. It is 50% of the mortality if we compare it the total cases of CRAs. In comparing survival and non-survival group, only mean age was significantly different. Mean age for survival group was 43.07 (21.09), whereas non-survival group was 57.04 (14.33) year old. Age also was the only independent risk factor for mortality in our study. The study in Turkey on patients with MDR *Acinetobacter calcoaceticus to Acinetobacter baumannii* complex (Acb complex) bacteraemia revealed 63% of the overall mortality in 14 days. Multivariate analysis showed that diabetes mellitus (RR, 1.68; 95% CI, 1.22-1.76), carbapenem resistance (RR, 1.63; 95% CI, 1.19-1.89) and septic shock (RR, 1.65; 95% CI, 1.23-1.85) were independent risk factors for 14-day mortality[14]. Another study showed that the prognostic features of MDR *A. baumannii* leading to mortality revealed a significant association with hypotension or shock (OR, 24.63; 95% CI, 1.56-387.56) at the time of

bacterial isolation[12] . CRAs survival group in our study had 17.00 (13.58) days of ICU stay and 41.37 (27.66) of hospital stay. Other study also showed that if compared with patients with imipenem-susceptible *A. baumannii* infection or colonization, patients with IRAB infection or colonization had a longer hospital stay after culture (median, 21 vs. 16 days) and greater hospital charges after culture (mean, $334,516 vs. $276,059)[5].

Antibiotic options for CRAs treatment are limited. Our study showed various antibiotic combinations have been used for the treatment of CRAs; nevertheless, there were no differences between survival and non-survival groups. A study on prolonged outbreak of carbapenem-resistant *A. baumannii* in German revealed that the outbreak strain was resistant to penicillins, cephalosporins, ciprofloxacin, gentamicin, tobramycin, imipenem and meropenem and carried the bla (OXA-23)-like gene[15]. Most of our CRAs cases were only sensitive to colistin and polymyxins. Both antibiotics have been found to have similar efficacy and toxicity[16] .Other studies recommended the use of old drugs (e.g. colistin), unusual drugs (e.g. sulbactam) or drugs with which there is presently little clinical experience (e.g. tigecycline) for the treatment of carbapenem-resistant strains. A review on the use of tigercycline for MDR *Acinetobacter* infections showed that tigecycline had considerable, though not consistent, antimicrobial activity against MDR (including carbapenem-resistant) *Acinetobacter* spp. However, data to support its clinical use, particularly for ventilator-associated pneumonia or bacteraemia, caused by these pathogens are still limited[17-20].

There were few limitations in our study. This was a retrospective data over only two years and some of the data were missing. This review was also mainly from the medical records of the patient and documented results from the microbiology laboratory. Some of the documented results did not specify the exact species of *Acinobacter* and just stated resistant to carbapenam group in general without specifying the type of carbapenam. However, we hope the findings from this small retrospective study would initiate bigger prospective studies on this issue.

Conclusion

CRAs is becoming a more serious infection in ICU all over the world. Our study showed that out of 54 patients treated for CRAs infection, 50% could not survive and died in ICU. This contributed 13.6% of total ICU mortality. The independent risk factor for mortality in this group was the older age factor.

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Conflict of interest

The authors declare no conflict of interests in this study

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References:

1. Towner KJ. Acinetobacter: an old friend, but a new enemy. J Hosp Infect 2009; 73:355-63. https://doi.org/10.1016/j.jhin.2009.03.032
2. Deris Z, Harun A, Omar M, Johari M. The prevelence and risk factors of nosocomial Acinetobacter blood stream infections in tertiary teaching hospital in north-eastern Malaysia. Tropical Biomedicine 2009; 26:123-29.
3. Prates CG, Martins AF, Superti SV et al. Risk factors for 30-day mortality in patients with carbapenem-resistant Acinetobacter baumannii during an outbreak in an intensive care unit. Epidemiol Infect.1-8.
4. Deris ZZ, Shafie MZ, Harun A. Risk factors and outcomes of imepenem-resistant Acinotobacter bloodstream infection in North-eastern Malaysia. Asian Pacific Journal of Tropical Biomedicine 2011; 1:313-15. https://doi.org/10.1016/S2221-1691(11)60050-6
5. Lautenbach E, Synnestvedt M, Weiner MG et al. Epidemiology and impact of imipenem resistance in Acinetobacter baumannii. Infect Control Hosp Epidemiol 2009; 30:1186-92. https://doi.org/10.1086/648450
6. Playford EG, Craig JC, Iredell JR. Carbapenem-resistant Acinetobacter baumannii in intensive care unit patients: risk factors for acquisition, infection and their consequences. J Hosp Infect. 2007; 65:204-11. https://doi.org/10.1016/j.jhin.2006.11.010
7. Asensio A, Canton R, Vaque J et al. [Prevalence of infection by carbapenem-resistant Acinetobacter baumannii in Spain (1999-2005)]. Enferm Infecc Microbiol Clin 2008; 26:199-204. https://doi.org/10.1016/S0213-005X(08)72691-0
8. Markogiannakis H, Pachylaki N, Samara E et al. Infections in a surgical intensive care unit of a university hospital in Greece. Int J Infect Dis 2009; 13:145-53. https://doi.org/10.1016/j.ijid.2008.05.1227
9. Katsaragakis S, Markogiannakis H, Toutouzas KG et al. Acinetobacter baumannii infections in a surgical intensive care unit: predictors of multi-drug resistance. World J Surg 2008; 32:1194-202. https://doi.org/10.1007/s00268-008-9571-3
10. Apisarnthanarak A, Buppunharun W, Tiengrim S, Sawanpanyalert P, Aswapokee N. An overview of antimicrobial susceptibility patterns for gram-negative bacteria from the National Antimicrobial Resistance Surveillance Thailand (NARST) program from 2000 to 2005. J Med Assoc Thai 2009; 92 Suppl 4:S91-4.
11. Baran G, Erbay A, Bodur H et al. Risk factors for nosocomial imipenem-resistant Acinetobacter baumannii infections. Int J Infect Dis 2008; 12:16-21. https://doi.org/10.1016/j.ijid.2007.03.005
12. Del Mar Tomas M, Cartelle M, Pertega S 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; 11:540-6. https://doi.org/10.1111/j.1469-0691.2005.01184.x
13. Romanelli RM, Jesus LA, Clemente WT et al. Outbreak of resistant Acinetobacter baumannii-measures and proposal for prevention and control. Braz J Infect Dis 2009; 13:341-7. https://doi.org/10.1590/S1413-86702009000500005
14. Metan G, Sariguzel F, Sumerkan B. Factors influencing survival in patients with multi-drug-resistant Acinetobacter bacteraemia. Eur J Intern Med 2009; 20:540-4. https://doi.org/10.1016/j.ejim.2009.05.005
15. Kohlenberg A, Brummer S, Higgins PG et al. Outbreak of carbapenem-resistant Acinetobacter baumannii carrying the carbapenemase OXA-23 in a German university medical centre. J Med Microbiol 2009; 58:1499-507. https://doi.org/10.1099/jmm.0.012302-0
16. Oliveira MS, Prado GV, Costa SF, Grinbaum RS, Levin AS. Polymyxin B and colistimethate are comparable as to efficacy and renal toxicity. Diagn Microbiol Infect Dis 2009; 65:431-4. https://doi.org/10.1016/j.diagmicrobio.2009.07.018
17. Gilad J, Carmeli Y. Treatment options for multidrug-resistant Acinetobacter species. Drugs 2008; 68:165-89. https://doi.org/10.2165/00003495-200868020-00003
18. Haque, M. (2019). Antibiotic Use, Antibiotic Resistance, and Antibiotic Stewardship - A Global Public Consequences. Bangladesh Journal of Medical Science, 18(2), 169-170. https://doi.org/10.3329/bjms.v18i2.40680 https://doi.org/10.3329/bjms.v18i2.40680
19. Onifade, E., Ogbonna, I., Ikwebe, J., & Aremu, S. (2019). Profiling of the bacterial pathogens associated with hospital acquired infections in hospitals within makurdi metropolis, middle belt, nigeria. Bangladesh Journal of Medical Science, 18(2), 368-378. https://doi.org/10.3329/bjms.v18i2.40710 https://doi.org/10.3329/bjms.v18i2.40710
20. Karageorgopoulos DE, Kelesidis T, Kelesidis I, Falagas ME. Tigecycline for the treatment of multidrug-resistant (including carbapenem-resistant) Acinetobacter infections: a review of the scientific evidence. J Antimicrob Chemother 2008; 62:45-55. https://doi.org/10.1093/jac/dkn165