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ORIGINAL ARTICLE

Risk Factors of Carbapenem-resistant *Acinetobacter baumannii* Infection among Hospitalized Patients

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Objective: A very common pan-resistant pathogen in health care-related infections in Taiwan is carbapenem-resistant *Acinetobacter baumannii* (CRAB), which can increase mortality and health care expenses. Increased resistant bacteria due to increased antimicrobial consumption may be responsible for the soaring percentage (to 70%) of the CRAB infection rate in hospitalized patients. In the present study, we used a case-case-control study in a teaching hospital to investigate factors (especially the prior use of antimicrobials) that affect the development of *A. baumannii* resistance.

Methods: This was a case-case-control design and was composed of two parallel age- and sex-matched control groups, and two experimental groups [i.e., the carbapenem-resistant group ($n = 73$) and the carbapenem-sensitive group ($n = 77$)]. The primary outcome was to identify common risk factors that induce CRAB in hospitalized patients in a teaching hospital in Taiwan.

Results: The common risk factors for infection of patients by CRAB and carbapenem-sensitive *A. baumannii* (CSAB) were previous antimicrobial exposure to piperacillin/tazobactam [odds ratio (OR), 2.5] and amikacin (OR, 2.5), meropenem-treated patients had a 4.99-fold increased risk of CRAB infection, but not CSAB infection, when they were admitted to the hospital within 3 months after the antimicrobial exposure. Diabetic patients were moreover prone to being infected by both CRAB and CSAB with an increased OR of 6.26. Ventilator use increased the OR significantly in CRAB infections and CSAB infections by 13.51-fold and 4.72-fold, respectively.

Conclusion: This study confirms that prior use of antimicrobials such as piperacillin/tazobactam and amikacin can significantly increase CRAB and CSAB infections in hospitalized patients. The prior use of meropenem increased CRAB infections, but not CSAB infections, in patients who were hospitalized 3 months after the drug exposure. Diabetes and ventilator use were also associated with a high rate of CRAB and CSAB infections.

1. Introduction

Carbapenem-resistant *Acinetobacter baumannii* (CRAB) is a very common pan-resistant pathogen in health care-related infections in Taiwan.[1] According to a Taiwan National Health Research Institutes report, the percentage of CRAB has soared from <3% in 2002 to 16% in 2004 to 32% in 2006. The CRAB infection rate in hospitalized patients recently soared to 70%–80%. Once the patients are infected by CRAB, the disease severity, the mortality, days of hospitalization, and the cost are significantly increased. Some researchers suggest that increased antimicrobial consumption may have caused the percentage of CRAB infections to soar. The use of certain antimicrobials may especially induce these resistant bacteria. In a study by the National Taiwan University Hospital (Taipei, Taiwan), the development of CRAB infection has been associated with invasive medical procedures, the length of hospital stay, and a prior history of using cephalosporin, penicillin, and carbapenem.[2] This study unfortunately had limitations such as analyzing antimicrobial agents by a rough category and choosing a control group that cannot represent the real population; these limitations greatly reduced the practicality of the study. Because of concerns of the study's limitations, most physicians and infection control experts in hospitals in Taiwan cannot make a strategic

Conflicts of interest: The authors have no conflicts of interest to declare. All authors contributed equally to this research project.

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decision based on the results of that study. The present study was a case-case-control study, which would minimize these limitations.

2. Methods

The present study design was a retrospective case-case-control study. From January 1, 2009 to June 30, 2011, study cases were collected from hospitalized adult patient data in a teaching hospital. Study cases with impaired patients' data file were excluded. For the control group, patients were excluded when they had been included in either case group. A case-case-control design was actually composed of two parallel case-control studies. Two study groups—the CRAB group (n = 73) and the carbapenem-sensitive *Acinetobacter baumannii* (CSAB) group (n = 77)—were compared with corresponding age- and sex-matched control groups, which both contained an equal number of patients who were not infected. The risk factors were statistically analyzed (Figure 1). By comparing the results of these two case-control studies, the specific risk factors for CRAB infection and the specific risk factors for CSAB infection were analyzed. SPSS version 20 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Category variables were analyzed with the Chi-square test and the continuous variables were analyzed with the Student t test. Our research aimed to find the specific risk factors of CRAB and CSAB infections in hospitalized patients.

3. Results

The mean age of the CRAB group patients was 70.8 years (Table 1) and the corresponding mean age of the control group patients was 71.1 years. The mean age of the CSAB group patients and the corresponding mean age of the control group were 71.1 years and 70.8 years, respectively. The pattern of antibiotic use was similar in the age- and sex-matched control groups for the CRAB- and CSAB-infected patient groups ($p > 0.05$).

3.1. Risk factors for CRAB infection

Based on the statistical analysis, three significant trends of high-risk antimicrobial agents that led to antimicrobial-induced resistant CRAB microorganisms at this hospital were (1) piperacillin/tazobactam [OR, 2.5; 95% confidence interval (CI), 1.05–5.98]; (2) amikacin (OR, 2.5; 95% CI, 1.05–5.98); and (3) meropenem (OR, 4.99; 95% CI, 1.04–23.97; Table 2; $p < 0.05$). However, the prior use of cephalosporin of the 1st–4th generations unexpectedly did not contribute to trends of increased CRAB infections in hospitalized patients at the Taipei Medical University Hospital (TMUH; Taipei, Taiwan). A ventilator was installed in 43 (59 %) patients, whereas a ventilator was installed in only 17 (23%) patients in the control group (Table 3).

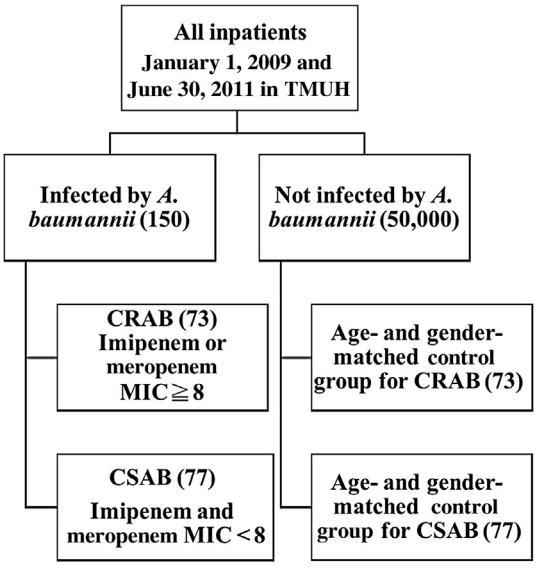

Figure 1 Patient selection flowchart. *A. baumannii* = *Acinetobacter baumannii*; CRAB = carbapenem-resistant *A. baumannii*; CSAB = carbapenem-sensitive *A. baumannii*; MIC = minimal inhibition concentration; TMUH = Taipei Medical University Hospital.

Table 1 Demographics of the patients in the study groups and control groups.

	Study groups			
	CRAB	Control	CSAB	Control
Age (y), mean and range	70.8 27–94	71.1 27–99	71.1 28–99	70.8 28–99
Male (%)	58	55	58	59
Average time at risk (d)	23.9	19.8	18.8	14.5
N	73	73	77	77

Control = age-matched and sex-matched case-case-controls; CRAB = carbapenem-resistant *Acinetobacter baumannii*; CSAB = carbapenem-sensitive *A. baumannii*.

The use of a ventilator resulted in a statistically significant trend with an OR of 4.72 and a 95% CI of 2.31–9.66 ($p < 0.05$). Foley catheterization and central venous pressure (CVP) catheterization did not alter the CRAB infection risk. In the case group, 23 (32%) patients had a diagnosis of diabetes, whereas 5 (7%) patients in the control group had a diagnosis of diabetes (Table 3). The OR was 6.26 and the 95% CI was 2.23–17.59, which indicated a significant trend of increased CRAB infection in patients with diabetes ($p < 0.05$).

3.2. Risk factors for CSAB infection

In the CSAB infection group, a significant trend of increased infection was observed after the prior use of piperacillin/tazobactam and

Table 2 Prior use of antimicrobial agents and the risk of infection of inpatients by carbapenem-resistant *Acinetobacter baumannii*.*

CRAB	Case		Control		Chi-square analysis	
	N	%	*N*	%	OR	95% CI
Amoxicillin and clavulanate	12	16	11	15	1.11	0.45–2.70
Oxacillin	6	8	4	5	1.54	0.42–5.72
Piperacillin and tazobactam	19	26	9	12	2.50†	1.05–5.98
Cefazolin	10	14	46	63	0.09	0.04–0.21
Cefmetazole	5	7	8	11	0.6	0.19–1.92
Cefpirome	4	5	2	3	2.06	0.37–11.60
Ceftriazone	3	4	1	1	3.09	0.31–30.38
Cefepime	4	5	1	1	4.17	0.46–38.28
Clarithromycin	4	5	2	3	2.06	0.37–11.6
Flumarin	12	16	6	8	2.20	0.78–6.21
Fosfomycin	5	7	2	3	2.61	0.49–13.91
Vancomycin	8	11	3	4	2.87	0.73–11.29
Gentamicin	5	7	23	32	0.16	0.06–0.45
Levofloxacin	1	1	2	3	0.49	0.04–5.56
Tigecycline	2	3	3	4	0.66	0.11–4.05
Ertapenem	4	5	2	3	2.06	0.37–11.60
Ciprofloxacin	11	15	5	7	2.41	0.79–7.33
Amikacin	19	26	9	12	2.50†	1.05–5.98
Meropenem	9	12	2	3	4.99†	1.04–23.97

* The CRAB case group consists of patients with a positive culture for carbapenem-resistant *Acinetobacter baumannii* that was collected from the Taipei Medical University Hospital (TMUH; Taipei, Taiwan) infection control data bank from January 1, 2009 to June 30, 2011. The CRAB control group consists of age- and sex-matched patients who were hospitalized at TMUH from January 1, 2009 to June 30, 2011. The number "0" indicates zero prescriptions of ampicillin and sulbactam.
† Indicates the odds ratio for $p < 0.05$.
CI = confidence interval; CRAB = carbapenem-resistant *Acinetobacter baumannii*; OR = odds ratio.

Table 3 Prior invasive procedures and underlying diseases in hospitalized patients and the risk of infection by carbapenem-resistant *Acinetobacter baumannii*.

CRAB	Case		Control		Chi-square analysis	
	N	%	*N*	%	OR	95% CI
Foley	42	58	50	68	0.62	0.32–1.23
CVP	30	41	27	37	1.19	0.61–2.31
Ventilator	43	59	17	23	4.72*	2.31–9.66
Stroke	1	1	4	5	0.24	0.03–2.20
Renal disease	5	7	6	8	0.82	0.24–2.82
Cancer	22	30	18	25	1.32	0.64–2.74
Diabetes	23	32	5	7	6.26*	2.23–17.59

* Indicates the odds ratio for $p < 0.05$.
CI = confidence interval; CRAB = carbapenem-resistant *Acinetobacter baumannii*; CVP = central venous pressure monitor; Foley = urinary tract catheter; OR = odds ratio.

amikacin with an OR of 4.15 (95% CI, 1.56–11.03) and 5.48 (95% CI, 1.51–19.94), respectively (Table 4; $p < 0.05$). Cephalosporin in the 1^{st}–4^{th} generations; aminoglycosides; and flouroquinolones did not show a trend of increasing CSAB infection in this hospital.

A ventilator was installed in 36 (47%) patients, whereas 4 (5%) patients in the control group were connected to a ventilator (Table 5). The use of ventilator resulted in a statistically significant trend with an OR of 16.0 and a 95% CI of 5.33–48.22 ($p < 0.05$). However, Foley catheterization and CVP catheterization did not increase the CRAB infection risk in patients hospitalized at the TMUH. A history of diabetes was a risk factor that was highly associated with CSAB infection in the present study (OR, 8.7; 95% CI, 3.15–24.05; Table 5). However, other diseases such as stroke, cancer, renal disease, and liver disease were not risk factors.

4. Discussion

At the TMUH, the likelihood of inpatients being infected by CRAB is growing yearly to as much as 80%.[3] Revealing the risk factors associated with the development of CRAB is necessary to improve the health care service at the TMUH. At this hospital, the present study reveals that the common risk factors for infection by CRAB and CSAB were a patient's prior exposure to antimicrobials such as piperacillin/tazobactam and amikacin. The present major findings are consistent with many previous reports showing that substantial antimicrobial

Table 4 Prior use of antimicrobial agents and the risk of infection of inpatients by carbapenem-sensitive *Acinetobacter baumannii*.

CSAB	Case		Control		Chi-square analysis	
	N	%	*N*	%	OR	95% CI
Oxacillin	6	8	4	5	1.54	0.42–5.70
Amoxicillin and clavulanate	10	13	6	8	1.77	0.61–5.13
Piperacillin and tazobactam	20	26	6	8	4.15*	1.56–11.03
Cefazolin	19	25	55	71	0.13	0.06–0.27
Ceftriaxone	2	3	2	3	1	1
Cefmetazole	11	14	8	10	1.44	0.54–3.80
Cefepime	3	4	1	1	3.08	0.31–30.30
Cefpirome	6	8	0	0	na	na
Clarithromycin	1	1	4	5	0.24	0.03–2.20
Vancomycin	7	9	2	3	3.75	0.75–18.67
Gentamicin	17	22	25	32	0.59	0.29–1.21
Ertapenem	4	5	3	4	1.35	0.29–6.25
Flumarin	6	8	4	5	1.54	0.42–5.70
Tigecycline	2	3	1	1	2.03	0.18–22.83
Meropenem	3	4	1	1	3.08	0.31–30.30
Ciprofloxacin	4	5	1	1	4.16	0.45–38.14
Amikacin	14	18	3	4	5.48*	1.51–19.94
Fosfomycin	4	5	0	0	na	na

* Indicates the odds ratio for $p < 0.05$.
CI = confidence interval; CSAB = carbapenem-sensitive *Acinetobacter baumannii*; na = not available; OR = odds ratio.

Table 5 Prior invasive procedures and underlying diseases in hospitalized patients and risk of infection by carbapenem-sensitive *Acinetobacter baumannii*.

CSAB	Case		Control		Chi-square analysis	
	N	%	*N*	%	OR	95% CI
Foley	38	49	49	64	0.56	0.29–1.06
CVP	24	31	29	38	0.75	0.38–1.46
Ventilator	36	47	4	5	16.0*	5.33–48.22
Renal disease	2	3	8	10	0.23	0.05–1.12
Stroke	2	3	4	5	0.49	0.09–2.74
Cancer	36	47	30	39	1.38	0.73–2.61
Diabetes	29	38	5	6	8.7*	3.15–24.05

* Indicates the odds ratio for $p < 0.05$.
CI = confidence interval; CSAB = carbapenem-sensitive *Acinetobacter baumannii*; CVP = central venous pressure monitor; Foley = urinary tract catheter; OR = odds ratio.

consumption at a hospital would lead to a high frequency of bacteria resistant to certain antimicrobials.[4] The prior exposure of patients to aminoglycosides such as amikacin has consistently been identified as a high-risk factor for CRAB infection.[5–8]

In addition to the prior use of amikacin, the frequent use of the combined piperacillin/tazobactam, and the use of amikacin indeed led to the risk of nosocomial infection by CRAB bacteria in patients hospitalized at the TMUH. Previous exposure of patients with derivatives of cephalosporin interestingly was not a risk factor for CRAB infection at this hospital. These findings are in contrast to an early report indicating that the prior use of ceftazidine and/or cephalosporin may be associated with infection by CRAB and/or imipenem-resistant *A. baumannii*.[9,10] The reason the present results differ from these early reports may be because the hospital infection control committee at the TMUH (but not outside hospitals) tightly control the prescription of the third and fourth generations of cephalosporins. The prescription frequency of the third and fourth generations of cephalosporins is relatively low at this teaching hospital, compared to other health care providers.

Piperacillin/tazobactam has broad spectrum antimicrobial activity against Gram-positive and -negative pathogens and anaerobes such as *Pseudomonas, Staphylococcus, Escherichia,* and *Klebsiella*.[7,11–13] Similar to our present finding that piperacillin/tazobactam was a risk factor at the TMUH, many other health care providers have also found that they become a correlated risk factor for patients developing CRAB nosocomial infections because the drug is widely prescribed by many health care providers for empirical antimicrobial treatment when patients have a history of diabetes and/or autoimmune disease.[12] With this information in mind, the infection control committee of this hospital has requested attending physicians to reduce the frequency of using piperacillin/tazobactam as the empirical treatment for nosocomial infections. In the near future, this limited controlled use of piperacillin/tazobactam may help reduce the nosocomial infection of inpatients by CRAB and CSAB bacteria at the TMUH.

Meropenem is a frequently used carbapenem antimicrobial agent at the TMUH. It was not associated with CSAB infection in the present study; this finding of increased risk of CRAB infection confirmed many early reports that had a similar result.[7,11,12,14] These early reports also consider imipenem as a risk factor. However, this finding was not observed in the present study.

At the current practice at the TMUH most physicians are aware of the risk of imipenem-induced seizures. Therefore, imipenem is not frequently used as the first-line antimicrobial agent. Thus, meropenem rather than imipenem was identified as a risk factor for nosocomial infections of patients by CSAB and CRAB bacteria in the present study.

The present finding of prior ventilator use as a major risk factor that contributed to CRAB and CSAB nosocomial infections at the

TMUH. This finding confirmed previous reports from intensive care units (ICUs) worldwide.[6,15–17] The outbreaks of CRAB infections in Korean ICUs are spread primarily by health care workers and by environmental contamination when opening the T-tube for trachea suction and/or ventilator systems.[18] The use of a closed trachea suction system has significantly reduced the outbreaks of CRAB infections in the ICU. This reduction is augmented by cleaning the ICU environment and hand washing by health care providers because CRAB microbes can survive for a long time in contaminated dry and wet areas. Drug-resistant germs may be carried by physicians who work at two separate clinical units revealed by a single source of bacteria gene transfer pattern.

The present study reveals another problem related to prior use of a possibly contaminated ventilator system, which in fact increased the risk of infection by CRAB (13-fold) or by CSAB (4-fold) at the TMUH health care system. Several contributing factors may lead to this finding such as: (1) an impaired coughing ability in ventilated patients; (2) the intraluminal biofilm of the trachea acting as a hideout site; (3) the leaking of oropharyngeal secretion; (4) the transfer of contaminated fluid into the lower respiratory track; and (5) improper hand and instrument cleaning by health care providers. The CRAB-infected patients under ventilation assistance often develop pneumonia with a high mortality rate.

The present study unexpectedly determined that patients with a history of diabetes mellitus were associated with a significant trend of increased nosocomial infections (OR, 6.26) by CRAB and CSAB. These diabetic patients may have a weaker immune system because of impaired mast cell function and neutrophil adhesion, increased leukocyte apoptosis, and reduced lymph node retention capacity.[19] A significant decrease in the first-line defence of diabetic patients and a high serum sugar level may increase by several folds their risk of nosocomial CRAB and CSAB infections in hospital wards. Whether the proper control of hyperglycemia would reduce the risk of CRAB nosocomial infections in hospitalized diabetic patients remains to be studied.

There were limitations in this study. One, the number of cases was limited. Two, we performed a retrospective case-case-control study with all the inherent problems related to this study design. Three, this study did not have information about antimicrobial agents the patients used outside the TMUH. Fourth, the minimum duration of antibiotic exposure leading to the development of a multiple–drug-resistant phenotype was unknown. Despite these limitations, the present results confirm the early findings that the overuse of antimicrobial agents will increase *A. baumannii* infection because of the creation of multiple–drug-resistant bacteria. In fact, the prior use of meropenem 3 months prior to admission to the hospital was identified as a significant risk factor for the increased trend in subsequent nosocomial infection by CRAB.

In conclusion, the infection control measurements (e.g., proper hand washing, suction/ventilator decontamination, and environmental cleaning)[20,21] and pharmacist intervention in the management of proper antimicrobial use (e.g., the antimicrobial stewardship program)[22] need to be employed in the TMUH system to curtail increased nosocomial infections by CRAB bacteria. The aforementioned actions require the consensus and cooperation of all health care providers in the TMUH patient care system. Hospital pharmacists should also actively participate in preventing nosocomial infections by drug-resistant bacteria using pharmacist interventions in the proper antimicrobial management and under the auspice of the antimicrobial stewardship program of the health care system.[23] In addition to the enthusiasm and support of hospital clinical pharmacists, additional support is essential from the hospital administrator on policy or on resource. If the hospital administration would pay attention and give full support on the antimicrobial stewardship and the infection control program, then the clinical problem of antimicrobial-resistant and CRAB infection outbreaks can be controlled in the near future at this health care system.

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