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Original Article

Risk factors for healthcare-associated infection caused by carbapenem-resistant *Pseudomonas aeruginosa*

Li-Hsin Tsao [a], Chih-Yi Hsin [b], Hsin-Yi Liu [c], Han-Chuan Chuang [c], Li-Yuan Chen [c], Yuarn-Jang Lee [c,d,*]

[a] *Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan*
[b] *Department of Clinical Pharmacy, School of Pharmacy, Taipei Medical University, Taipei, Taiwan*
[c] *Division of Infection Diseases, Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan*
[d] *Department of Infection Control, Taipei Medical University Hospital, Taipei, Taiwan*

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Abstract *Background/purpose:* The incidence of carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) related healthcare-associated infection (HAI) has increased in recent year worldwide. This study is to investigate the risk factors associated with CRPA infections in a university hospital setting in Taiwan to provide more information for clinician and infection control system.
Methods: A retrospective cross-sectional study was conducted from January 1st, 2009 to June 30th, 2014. Patients with *P. aeruginosa* related HAI were included and divided into the CRPA case group and carbapenem-susceptible *Pseudomonas aeruginosa* (CSPA) control group. The medical records were reviewed to identify risk factors for CRPA HAI and mortality. Patients with prior use of any anti-pseudomonal carbapenems were included in subgroup analysis.
Results: 395 cases of *P. aeruginosa* infection were enrolled from total of 3263 HAI events; 63 were CRPA and 332 were CSPA. The prevalence of CRPA was 15.9% (63/395). Significant risk factors related to CRPA infection were longer time at risk, prior use of anti-pseudomonal carbapenems, and prior use of aminoglycoside ($p < 0.05$, 0.01, and 0.05). Furthermore, anti-pseudomonal carbapenem monotherapy did not significantly increase risk for CRPA infection.
Conclusion: The worldwide CRPA prevalence has been on the raise and Taiwan has been also keeping up with the trend. Antimicrobials usage should be monitored carefully, especially with

* Corresponding author. Division of Infection Diseases, Department of Internal Medicine, Taipei Medical University Hospital, No. 252, Wuxing St., Xinyi Dist., Taipei 110, Taiwan. Fax: +886 227203602.
E-mail address: yuarn438@yahoo.com.tw (Y.-J. Lee).

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carbapenems and aminoglycoside. Clinicians should be award of and understand about the risk of CRPA infection, which increases by 1% with each hospitalization day.

Introduction

Antimicrobials resistance has been an ever growing concern globally.[1] Many broad-spectrum antibiotics such as Carbapenems have been widely used and followed by the raise of drug resistance in many microorganisms, one of whom is *Pseudomonas aeruginosa*.[2]

Pseudomonas aeruginosa, as one of the major pathogens of healthcare-associated infections (HAI), is associated with substantial higher mortality and morbidity rates compared to other pathogens.[1,3] Infections caused by *P. aeruginosa* have always been challenging to healthcare providers due to their intrinsic resistance against a wide variety of antimicrobials.[2,4] The 2nd-quarter report of Taiwan Nosocomial Infection Surveillance System (TNIS) from the Center for Disease control (CDC) in Taiwan indicated that 7.5%—9.2% of HAI have been caused by *P. aeruginosa* in 2014.

Carbapenems, a class of broad-spectrum β-lactam antibiotics, are often the last resort against treating nosocomial infections when all else has failed. As a result, resistance to this class of antimicrobials may limit clinical therapeutic choice. According to the annual report of TNIS, carbapenem-resistant *P. aeruginosa* (CRPA) was responsible for approximately 15.5% (medical centers) to 18.8% (regional hospitals) of healthcare-associated *P. aeruginosa* infections during the first half of 2014.

From 2009 to the first half of 2014, in intensive care units (ICU) setting of regional hospitals and medical centers in Taiwan, the overall prevalence of CRPA was between 14% and 20%. Furthermore, if we analyze only the ICUs of Taipei, the prevalence was reported to be even higher, between 15% to 23%. It was no exception for Taipei Medical University hospital (TMUH), a teaching hospital in Taipei. Our rates of CRPA in ICU patients have been on the raise since 2013; the prevalence rate was 10%, and reached 25% for the first half of 2014 and 33.3% during the second half of 2014. As a result, the infection control office of TMUH have been motivated to deal with this healthcare-related epidemic.

This study not only aims to identify the possible risk factors for acquiring healthcare-associated CRPA infection in a university hospital. Moreover, it was conducted with the intention of identifying possible risk factors regarding antibiotics resistance in the effort to guide clinicians in the future to infection control.

Methods

Study population and study design

Taipei Medical university hospital (TMUH) is a private, tertiary care, an 800-bed general teaching hospital in Taiwan. The hospital contains an emergency department with medical and surgical intensive care units.

This retrospective cross-sectional study was conducted at TMUH with a time frame set from January 1st, 2009 to June 30th, 2014. Patients were diagnosed as having *P. aeruginosa* related HAI 48 h after admission. The definition of HAI is consistent with the definition and criteria for specific types of infections from CDC.[5]

Patients with *P. aeruginosa* related HAI were included in this study and divided into the CRPA case group and CSPA control group. Patients with incomplete medical record were excluded. The primary outcome was to analyze possible risk factors for CRPA infection and the secondary outcome was to compare the 30-day all-cause mortality rate in two groups analyzed by logistic regression. Patients with prior use of any anti-pseudomonal carbapenems were then selected for subgroup analysis (Fig. 1).

Bacterial isolates and antimicrobial susceptibility testing

Phoenix Automated Microbiology System (Becton Dickinson, Sparks, MD, USA) was used to determine the antimicrobial susceptibility of *P. aeruginosa* isolates. Antimicrobials susceptibility to anti-pseudomonal agents such as imipenem, meropenem, amikacin, ceftazidime, cefepime, ciprofloxacin, gentamycin, levofloxacin, piperacillin, piperacillin/tazobactam, were also determined by the MIC results in the department of laboratory in TMUH according to the criteria of the Clinical and Laboratory Standards Institute (CLSI) guidelines.[6,7]

In our study, CRPA defined as MIC of imipenem and/or meropenem $\geq$8 μg/mL and remained *P. aeruginosa* isolates as CSPA.

Data collection

We reviewed patients' charts for data collection, including patients' age, gender, underlying disease, infection site, ward type, room number, hospitalization days, the time at risk, mortality, the prior exposure of invasive procedure during time at risk, prior use of antimicrobials, and the antimicrobials susceptibility test of the culture. The definition of the time at risk is the number of hospitalization days before positive culture of *P. aeruginosa*.

Invasive procedures such as central catheter (including central venous catheter, permanent catheter, port-A catheter, double lumen catheter, peripherally inserted central catheter and arterial catheter), urinary catheter, chest tube, mechanic ventilation, and extra-corporeal membrane oxygenation (ECMO) were recorded routinely and marked down as prior exposure of invasive procedures as followed during time at risk.

Prior use of antimicrobials was defined as any antimicrobials use within 90 days before the positive *P. aeruginosa*

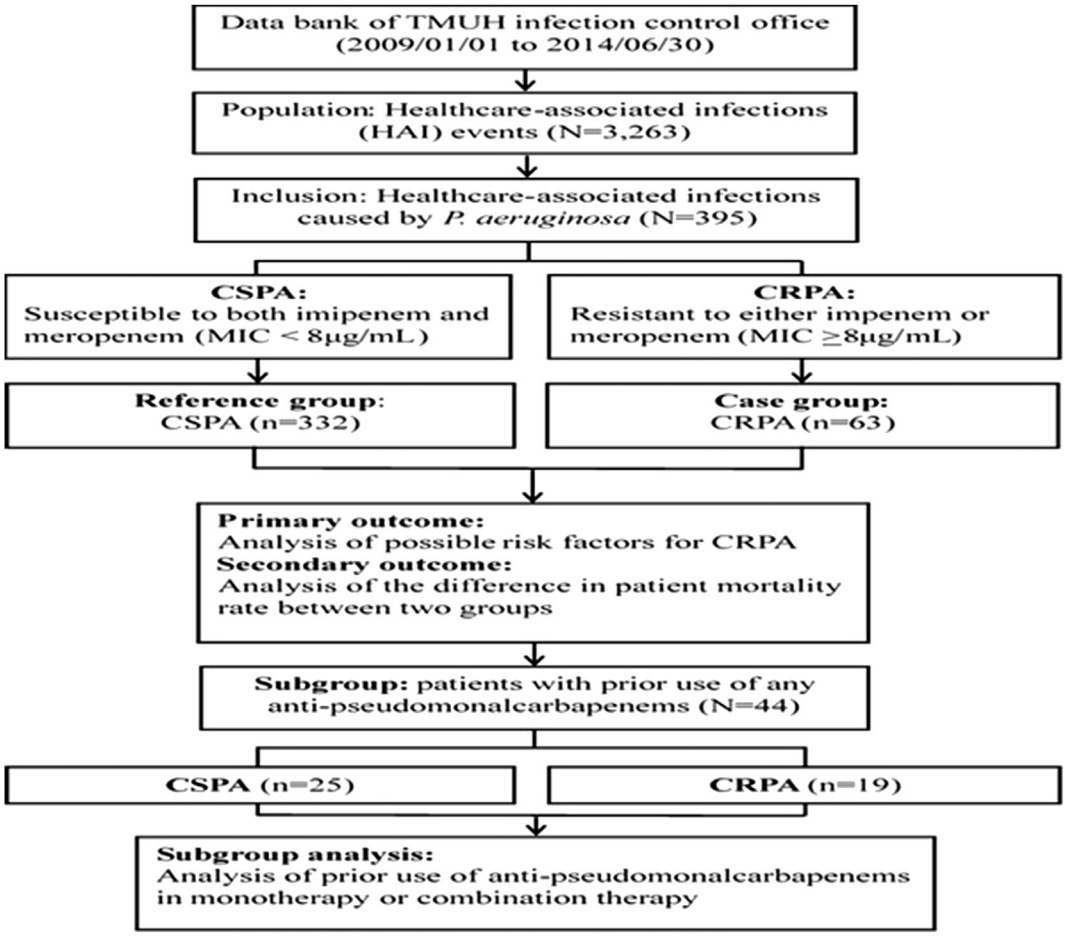

Figure 1. Cross-sectional study design and study flow chart. TMUH: Taipei Medical University Hospital; **MIC:** minimum inhibitory concentration; **CSPA**: carbapenem-susceptible *P. aeruginosa*; **CRPA**: carbapenem-resistance *P. aeruginosa*.

culture. The antimicrobials were classified as followed: penicillin and derivatives, cephalosporins, carbapenems, fluoroquinolone, aminoglycoside, sulfamethoxazole/trimethoprim, vancomycin, teicoplanin, fosfomycin, metronidazole, clarithromycin, erythromycin, clindamycin, tigecycline, doxycycline, colistin and anti-fungal agents.

Statistical analysis

All of data were analyzed by Statistical Package for Social Sciences software for Windows version 20 (SPSS, Inc., Chicago, Illinois, USA). The continuous variables of descriptive statistics were tested by Student's *t*-test while the categorical variables were tested by Chi-square test. A *p*-value less than 0.05 was considered statistically significant. In the inferential statistics, the odds ratios of all variables were analyzed by logistic regression and a *p*-value less than 0.05 was considered to be significant.

Results

Study population

A total of 3263 HAI events were enrolled during the study period. Among them, 395 cases (12.1%) were caused by *P. aeruginosa* and subsequently included to this study. Further analysis showed that 63 (15.9%) were CRPA (case group) and 332 (84.1%) were CSPA (control group).

The average age was 71.2 years old and 62% of them were male. The most common underlying disease was hypertension (52.2%), followed by malignancy (37.0%), diabetes mellitus (29.4%), coronary artery disease (16.7%), stroke (16.7%), and heart failure (10.6%). The statistical breakdown based on infection source was as followed: lower respiratory tract infection (33.4%), urinary tract infection (29.6%), blood stream infection (22.8%) and surgical site infection (7.8%). The average of hospitalization day was 54.2 days while the average time at risk was 27.6 days.

138 (34.9%) events occurred in ICUs, 243 (61.5%) from general wards and most (79.2%) were exposed to some sort of invasive procedure prior to infection confirmation. Furthermore, if we stratify the patients based on departments of admission, internal medicine department had a higher rate of CRPA contraction than in surgical department, both in general ward (37.9% versus 6.4%) and ICU (20.6% versus 11.1%).

Risk factors for CRPA infection

Patients' characteristics and the result of univariate logistic analysis for CRPA and CSPA are illustrated in Table 1.

Table 1 Comparison of demography, clinical characteristics, invasive procedure, and prior antimicrobials use of the Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) group and the Carbapenem-susceptible *Pseudomonas aeruginosa* (CSPA) group.

	CRPA (N = 63) n (%)	CSPA (N = 332) n (%)	OR (95% CI)	*p*
Age[a] (year)	74.9 ± 15.4	70.5 ± 16.4	1.02 (1.00–1.04)*	0.05
Male	40 (63.5)	205 (61.7)	1.01 (0.62–1.88)	0.79
Underlying diseases				
Malignancy (solid)	24 (38.1)	122 (36.7)	1.06 (0.61–1.85)	0.84
Lymphoma or leukemia	1 (1.6)	7 (2.1)	0.75 (0.09–6.19)	0.79
Liver disease	5 (7.9)	23 (6.9)	1.16 (0.42–3.17)	0.78
Diabetes mellitus	17 (27.0)	99 (29.8)	0.87 (0.48–1.59)	0.65
ESRD with dialysis	7 (11.1)	16 (4.8)	2.47 (0.97–6.27)	0.06
Hypertension	41 (65.1)	165 (49.7)	1.89 (1.08–3.31)*	0.03
Heart failure	12 (19.0)	30 (9.0)	2.37 (1.14–4.92)*	0.02
Coronary artery disease	16 (25.4)	50 (15.1)	1.92 (1.01–3.65)*	0.05
Stroke	13 (20.6)	53 (16.0)	1.37 (0.70–2.69)	0.36
Pulmonary disease[b]	3 (4.8)	28 (8.4)	0.54 (0.16–1.84)	0.33
Charlson comorbidity index [a]	4.1 ± 2.8	3.9 ± 2.8		
Infection sites				
RTI	27 (42.9)	105 (31.6)		
UTI	16 (25.4)	101 (30.4)		
BSI	11 (17.5)	79 (23.8)		
SSTI	2 (3.2)	29 (8.7)		
Others	7 (11.2)	18 (5.4)		
Hospitalization[a] (day)	80.0 ± 61.5	49.3 ± 37.1	1.01 (1.01–1.02)***	<0.001
Time at risk[a,c] (day)	47.0 ± 43.3	23.9 ± 23.9	1.02 (1.01–1.03)***	<0.001
Location				
ICU	23 (36.5)	115 (34.6)		
RCC	6 (9.5)	8 (2.4)		
Ward	34 (54.0)	209 (63.0)		
Any invasive procedure	51 (81)	262 (78.9)	1.14 (0.55–2.25)	0.72
Central catheter[d]	34 (54)	161 (48.5)	1.25 (0.73–2.14)	0.43
Urinary catheter	37 (58.7)	167 (50.3)	1.41 (0.82–2.43)	0.22
Chest tube	0 (0)	8 (2.4)		
Mechanical ventilation	23 (36.5)	104 (31.3)	1.26 (0.72–2.21)	0.42
ECMO	0 (0)	7 (2.1)		
Prior antibiotic use				
Anti-pseudomonal penicillin	23 (36.5)	77 (23.2)	1.9 (1.07–3.38)*	0.03
Other penicillins	35 (55.6)	150 (45.2)	1.52 (0.88–2.61)	0.13
Anti-pseudomonal cefalosporins	12 (19)	37 (11.1)	1.88 (0.92–3.84)	0.09
Other cefalosporins	54 (85.7)	266 (80.1)	1.49 (0.70–3.17)	0.30
Anti-pseudomonal carbapenems	19 (30.2)	25 (7.5)	5.3 (2.70–10.42)***	<0.001
Imipenem/cilastin	4 (6.3)	10 (3)	2.18 (0.66–7.19)	0.20
Meropenem	13 (20.6)	17 (5.1)	4.82 (2.21–10.52)***	<0.001
Doripenem	3 (4.8)	0 (0)		
Ertapenem	14 (22.2)	39 (11.7)	2.15 (1.09–4.24)*	0.03
Fluoroquinolones	15 (23.80)	31 (9.3)	3.03 (1.53–6.03)**	0.002
Ciprofloxacin	12 (19)	27 (8.1)	2.66 (1.27–5.58)*	0.01
Levofloxacin	3 (4.8)	4 (1.2)	4.1 (0.90–18.78)	0.07

Table 1 (*continued*)

	CRPA (N = 63) n (%)	CSPA (N = 332) n (%)	OR (95% CI)	*p*
Aminoglycoside	39 (61.9)	125 (37.7)	2.69 (1.55–4.69)***	<0.001
Amikacin	26 (41.3)	60 (18.1)	3.19 (1.79–5.66)***	<0.001
Gentamycin	19 (30.2)	85 (25.6)	1.26 (0.69–2.27)	0.45
Colistin	8 (12.7)	10 (3)	4.68 (1.77–12.39)**	0.002
Anti-fungus agents	6 (9.5)	11 (3.3)	3.07 (1.09–8.64)*	0.03

[a] Mean ± SD.
[b] Pulmonary disease: asthma, chronic obstructive pulmonary disease, bronchiectasis and pneumoconiosis.
[c] Time at risk: hospitalization days before finding positive culture.
[d] Central catheter including Central venous catheter (CVC), permanent catheter, Port-A catheter, double lumen catheter, Peripherally inserted central catheter (PICC) and Arterial Catheter.
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.
BSI: bloodstream infection; **CI:** confidence interval; **CRPA:** carbapenem-resistance *pseudomonas aeruginosa*; **CSPA:** carbapenem-susceptible *pseudomonas aeruginosa*; **ECMO:** extra-corporeal membrane oxygenation; **ESRD:** end stage renal disease; **ICU:** intense care unit; **OR:** odds ratio; **RCC:** respiratory care center; **RTI:** lower respiratory tract infection; **SSTI:** skin and soft tissue infection; **UTI:** urinary tract infection.

In the CRPA group, the average of hospitalization days was 80 days and time at risk was 47 days, which were 1.6-fold and 2-fold significant longer than the CSPA group (49.3 days and 23.9 days), respectively. There were 36.5% CRPA events and 34.6% CSPA events observed in ICUs. In the univariate logistic analysis of risk factor for CRPA HAI acquisition, the current results showed that older patients were more likely to be infected by CRPA ($p = 0.05$). Patients in the CRPA group with underlying diseases such as hypertension, heart failure, coronary artery disease ($p < 0.05$) were significantly higher than in CSPA group. Moreover, the longer time at risk significantly increased the risk to get CRPA infection ($p < 0.001$).

The results of multivariate analysis (Table 2) showed time at risk ($p < 0.05$), prior use of either anti-pseudomonal carbapenems ($p < 0.01$) or aminoglycoside ($p < 0.05$) significantly increased CRPA risk, which might have contributed the development of drug-induced antibiotic resistance in *P. aeruginosa*.

In subgroup analysis, prior use of anti-pseudomonal carbapenems in monotherapy did not significantly increase the risk to get CRPA infections (OR: 4.50, 95% CI: 0.48–42.25) compared to combination therapy by the univariate logistic regression.

Mortality and outcomes

The 30-day all-cause mortality rate in the CRPA group was 30.2% (19 events), while 31.9% (106 events) in the CSPA group. The analysis of the multivariate logistic regression showed that patients with underlying disease of malignancy (adjusted OR: 2.05, 95% CI: 1.15–3.68) and invasive procedure of central line during time at risk (adjusted OR: 1.82, 95% CI: 1.07–3.09) were significantly associated with a higher mortality rate. However, patients infected by CRPA did not have higher mortality rate compared with those patients with CSPA infections (adjusted OR: 0.70, 95% CI: 0.97–1.33) (Table 3).

Discussion

P. aeruginosa, as one of major cause of HAI due to it's minimal nutrition requirements, can be found almost everywhere in the hospital including inanimate objects.[8,9] This study was a retrospective cross-sectional study. And the study design may decline confounding factors of environmental risks by collecting data from same hospital. In addition, only patients who were confirmed to have HAI caused by *P. aeruginosa* were included in this study to avoid the bias that might be caused by patients with colonization.

Table 2 Multivariate analysis of risk factor for acquisition of Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) related hospital-associated infections (HAI).

Risk factor	AOR[a] (95% CI)	*p*
Time at risk[b,c] (day)	1.02 (1.00–1.02)*	0.05
Prior antibiotic use		
Anti-pseudomonal carbapenems	3.91 (1.49–10.28)**	0.006
Aminoglycoside	2.09 (1.09–4.01)*	0.031
Amikacin	3.19 (1.79–5.66)***	<0.001
Gentamycin	1.26 (0.69–2.27)	0.45

[a] Adjusted OR were obtained from multivariate logistic regression after adjusting age, hypertension, heart failure, coronary artery disease, prior use CVC, prior use piperacillin/tazobactam, cepirome, ceftriaxone, anti-pseudomonal carbapenems, ertapenem, ciprofloxacin, aminoglycoside, vancomycin, clarithromycin, colistin and anti-fungal agents(items of $p < 0.05$ while univariate analysis).
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.
[b] Mean ± SD.
[c] Time at risk: hospitalization days before finding positive culture.

Table 3 The risk factors for 30 days all cause mortality in patients with *Pseudomonas aeruginosa* infections.

	Mortality (N = 125)	Survival (N = 270)	Mortality versus survival Adjusted	*p*
	n (%)	n (%)	OR (95% CI)	
Age[a] (year)	72.8 ± 15.0	70.4 ± 16.9	1.01 (1.00–1.03)	0.27
CRPA	19 (15.2)	44 (16.3)	0.70 (0.97–1.33)	0.27
Underlying disease				
Malignancy (solid)	57 (45.6)	89 (33.0)	2.05 (1.15–3.68)*	0.02
Lymphoma or leukemia	2 (1.6)	6 (2.2)	0.61 (0.11–3.24)	0.56
Liver disease	11 (8.8)	17 (6.3)	1.44 (0.61–3.43)	0.41
Diabetes Mellitus	34 (27.2)	82 (30.4)	0.75 (0.43–1.33)	0.33
ESRD with dialysis	9 (7.2)	14 (5.2)	1.15 (0.42–3.18)	0.79
Hypertension	64 (51.2)	142 (52.6)	0.88 (0.51–1.53)	0.65
Heart failure	17 (13.6)	25 (9.3)	1.55 (0.71–3.39)	0.27
Coronary artery disease	28 (22.4)	38 (14.1)	1.57 (0.80–3.07)	0.19
Stroke	18 (14.4)	48 (17.8)	0.88 (0.44–1.75)	0.71
Pulmonary disease[b]	9 (7.2)	22 (8.1)	0.78 (0.32–1.89)	0.59
Charlson comorbidity index[a]	4.6 ± 2.67	3.47 ± 2.8	1.09 (0.95–1.24)	0.21
Location				
ICU	57 (45.6)	80 (30.0)	1.45 (0.74–2.73)	0.299
RCC	1 (0.8)	13 (4.8)	0.09 (0.01–0.91)	0.041
Ward	67 (53.6)	176 (65.2)	1	
Infection site				
RTI	49 (39.2)	83 (30.7)	1.50 (0.55–4.07)	0.43
UTI	24 (19.2)	93 (34.4)	0.67 (0.24–1.91)	0.45
SSTI	4 (3.2)	27 (10.0)	0.41 (0.10–1.69)	0.22
BSI	40 (32.0)	50 (18.5)	1.70 (0.61–4.75)	0.31
Invasive procedure				
Central line[c]	82 (65.6)	113 (41.9)	1.82 (1.07–3.09)*	0.03
Urinary catheter	68 (54.4)	136 (50.4)	1.44 (0.81–2.56)	0.21
Chest tube	5 (4.0)	3 (1.1)	2.85 (0.42–19.41)	0.29
Mechanical ventilation	51 (40.8)	76 (28.1)	1.12 (0.60–2.10)	0.73
ECMO	4 (3.2)	3 (1.1)	1.58 (0.22–11.38)	0.65

[a] Mean ± SD.
[b] Pulmonary disease: asthma, chronic obstructive pulmonary disease, bronchiectasis and pneumoconiosis.
[c] Central catheter including Central venous catheter (CVC), permanent catheter, Port-A catheter, double lumen catheter, Peripherally inserted central catheter (PICC) and Arterial Catheter.
*$p < 0.05$.
BSI: bloodstream infection; **CI:** confidence interval; **CRPA:** carbapenem-resistance *pseudomonas aeruginosa*; **ECMO:** extra-corporeal membrane oxygenation; **ESRD:** end stage renal disease; **ICU:** intense care unit; **OR:** odds ratio; **RCC:** respiratory care center; **RTI:** lower respiratory tract infection; **SSTI:** skin and soft tissue infection; **UTI:** urinary tract infection.

Several studies have reported that risk factors associated with CRPA acquisition are the presence of multiple comorbidities, length of hospitalization, receiving invasive procedures and prior use of antibiotics.[10–17] Consistent with many other studies,[11–13,18] there was a positive correlation between the length of hospitalization stays prior to CRPA confirmation and the rate of CRPA contraction. Our study indicated the risk of CRPA infection increasing 1% with each hospitalization day.

In a six-month prospective study in 1997, there were 22.1% of resistant *P. aeruginosa* isolates found in the medical ICU but only 13.7% in the surgical ICU.[19] The higher rate of CRPA HAI in internal medicine department than in surgical department is observed in our study. The possible explanation might be related to the increased rate of antimicrobials prescription in the internal medicine wards.

Prior antimicrobials use was reported to be associated with the development of drug resistance in the CRPA infection.[20,21] Either individual susceptibility or the indirect effect of cross-transmission influence to drug-resistance strains were theories acquisition of CRPA.[22] Another subgroup analysis was conducted regarding the prior use of antimicrobials during 90 days before the discovery of positive *P. aeruginosa* cultures. Compared to other studies that defined prior antibiotic exposure as 14–40 days before confirmed infection, we delineated prior use as 90 days prior.[10–12,14] After adjusting for covariates, prior use of anti-pseudomonal carbapenems ($p < 0.001$) and aminoglycoside ($p < 0.05$) showed a was associated with a significant rise in CRPA infections.

In many previous case–control studies, prior use of anti-pseudomonal carbapenems such as imipenem and

meropenem had been commonly reported as one of the risk factors[10–12,15,16,23] and this concept of drug-induced resistance have been well-established.[24–26] Although previous studies show that aminoglycoside use is associated with CRPA both in a population-based ecological study[14] and an individual-level case–control study,[16] there is a lack of evidence for aminoglycoside-induced CRPA. Furthermore, although there was a reported emergence of carbapenem resistance associated with the previous use of fluoroquinolone in a 2014 Taiwan study,[17] our study could not confirm such clams.

Antimicrobial susceptible test in this study has showed that the susceptible rate of *P. aeruginosa* isolated from CRPA group were still with over toward certain drugs such as amikacin, piperacillin/tazobactam, gentamycin, ciprofloxacin, levofloxacin and piperacillin. The cross-resistance pattern in *P. aeruginosa* between carbapenems and other antimicrobials were similar to other previous study.[14,15]

A prior study indicated monotherapy may play a part in the development of drug resistance in *P. aeruginosa*,[24,27] but currently, it still remains inconclusive. Many other researches focused on outcome and safety comparing Carbapenem monotherapy and combination therapy. According to past pharmacokinetic and pharmacodynamic studies, continuous infusion of carbapenem as a monotherapy was performed rigorously in our hospital for years to enhance the therapeutic effects while reducing adverse reactions. Thus, our subgroup analysis aimed to investigate the association between drug resistance and the use of Carbapenems in either monotherapy or combination therapy. The outcome did not reveal any statistical significance due to the lack of power with regards to the insufficient patient count in the combination therapy group.

There was no difference in the mortality rate of patients between the CRPA group and CSPA group, consistent with preceding review articles in Taiwan.[17] There were two studies that revealed several factors related to mortality such as severe sepsis, high-risk source, severity of illness, and capacity of CRPA to form biofilm.[28,29] In this study, the presence of underlying diseases such as malignancy and prior use of central line were statistical significant risk factors for increasing mortality rate, which indicated that the deaths might be related to malignancy and the use of central lines reflected critical illness. We believe the severity of comorbidity and critical illness are contributory factors to increasing mortality.

We recognize that there are several limitations to our study. Primarily, this was a retrospective observational study, thus there were several variables that weren't able to be controlled at beginning of the study design. The multivariate logistic regression model was therefore used to adjust the baseline of patients. Secondly, the limited number of study patients restricted the matching of the case and control group which might lead to some unforeseen confounding factors of bacteria transmission in the environment. In addition, inadequate sampling might also result in the lack of power for some critical factors. Furthermore, we had no control over patients' prior exposure to antimicrobials as well at the adherence and compliance to such medications. Besides, the time at risk could possibly be underestimated if patients were transferred from other hospital. Lastly, this study did not register the genotype or mechanism of CRPA isolates, which was important information for back-tracing the source of infection, and this might lead to another study.

In conclusion, the current results have revealed that three specific risk factors for CRPA infections among HAI patients in TMUH as followed: the days of hospitalization before positive culture, a prior use of anti-pseudomonal carbapenems, and a prior use of aminoglycoside. Anti-pseudomonal carbapenem monotherapy did not significantly increase the risk to get CRPA infection. Contrary to most earlier studies, mortality was not linked with carbapenem resistance in our study. Further study on larger populations with carbapenem use would be needed to confirm the association between monotherapy and increasing risk of CRPA infection, and even to possibly conduct a bacterial genomic study for epidemiology to further improve our healthcare system.

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References

1. Thabit AK, Crandon JL, Nicolau DP. Antimicrobial resistance: impact on clinical and economic outcomes and the need for new antimicrobials. *Expet Opin Pharmacother* 2015;**16**:159–77.
2. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis* 2009;**48**:1–12.
3. Driscoll JA, Brody SL, Kollef MH. The epidemiology, pathogenesis and treatment of *Pseudomonas aeruginosa* infections. *Drugs* 2007;**67**:351–68.
4. Livermore DM. Of pseudomonas, porins, pumps and carbapenems. *J Antimicrob Chemother* 2001;**47**:247–50.
5. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;**36**(5):309–32.
6. Clinical and Laboratory Standards Institute. *Performance standards for antimicrobial susceptibility testing. 21st informational supplement. CLSI document M100eS20*. Wayne, PA: CLSI; 2011.
7. Approved Standard 9th Edition. *CLSI document M07eA9 methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically*. Wayne, PA: Clinical and Laboratory Standards Institute; 2012.
8. Moore NM, Flaws ML. Epidemiology and pathogenesis of *Pseudomonas aeruginosa* infections. *Clin Lab Sci* 2011;**24**:43–6.
9. Falkinham 3rd JO, Hilborn ED, Arduino MJ, Pruden A, Edwards MA. Epidemiology and ecology of opportunistic premise plumbing pathogens: *Legionella pneumophila*, *Mycobacterium avium*, and *Pseudomonas aeruginosa*. *Environ Health Perspect* 2015;**123**:749–58.
10. Zavascki AP, Cruz RP, Goldani LZ. Risk factors for imipenem-resistant *Pseudomonas aeruginosa*: a comparative analysis of two case-control studies in hospitalized patients. *J Hosp Infect* 2005;**59**:96–101.
11. Ozkurt Z, Ertek M, Erol S, Altoparlak U, Akcay MN. The risk factors for acquisition of imipenem-resistant *Pseudomonas aeruginosa* in the burn unit. *Burns* 2005;**31**:870–3.

12. Onguru P, Erbay A, Bodur H, Baran G, Akinci E, Balaban N, et al. Imipenem-resistant *Pseudomonas aeruginosa*: risk factors for nosocomial infections. *J Kor Med Sci* 2008;**23**:982—7.
13. Eagye KJ, Kuti JL, Nicolau DP. Risk factors and outcomes associated with isolation of meropenem high-level-resistant *Pseudomonas aeruginosa*. *Infect Control Hosp Epidemiol* 2009;**30**:746—52.
14. Lautenbach E, Weiner MG, Nachamkin I, Bilker WB, Sheridan A, Fishman NO. Imipenem resistance among *Pseudomonas aeruginosa* isolates: risk factors for infection and impact of resistance on clinical and economic outcomes. *Infect Control Hosp Epidemiol* 2006;**27**:893—900.
15. Troillet N, Samore MH, Carmeli Y. Imipenem-resistant *Pseudomonas aeruginosa*: risk factors and antibiotic susceptibility patterns. *Clin Infect Dis* 1997;**25**:1094—8.
16. Fortaleza CM, Freire MP, Filho Dde C, de Carvalho Ramos M. Risk factors for recovery of imipenem- or ceftazidime-resistant *Pseudomonas aeruginosa* among patients admitted to a teaching hospital in Brazil. *Infect Control Hosp Epidemiol* 2006;**27**:901—6.
17. Lin KY, Lauderdale TL, Wang JT, Chang SC. Carbapenem-resistant *Pseudomonas aeruginosa* in Taiwan: prevalence, risk factors, and impact on outcome of infections. *J Microbiol Immunol Infect* 2016;**49**:52—9.
18. Zhang JF, Chen BL, Xin XY, Zhao HB, Wang HY, Song H, et al. Carbapenem resistance mechanism and risk factors of *Pseudomonas aeruginosa* clinical isolates from a University Hospital in Xi'an, China. *Microb Drug Resist* 2009;**15**:41—5.
19. Cailleaux V, Mulin B, Capellier G, Julliot MC, Thouverez M, Talon D. Epidemiological study of variations in beta-lactam antibiotic susceptibility of *Pseudomonas aeruginosa* in two intensive care units. *J Hosp Infect* 1997;**37**:217—24.
20. Peterson LR. Squeezing the antibiotic balloon: the impact of antimicrobial classes on emerging resistance. *Clin Microbiol Infect* 2005;**11**(Suppl 5):4—16.
21. Pakyz AL, Oinonen M, Polk RE. Relationship of carbapenem restriction in 22 university teaching hospitals to carbapenem use and carbapenem-resistant *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2009;**53**:1983—6.
22. Lipsitch M, Samore MH. Antimicrobial use and antimicrobial resistance: a population perspective. *Emerg Infect Dis* 2002; **8**(4):347—54.
23. Voor In 't Holt AF, Severin JA, Lesaffre EM, Vos MC. A systematic review and meta-analyses show that carbapenem use and medical devices are the leading risk factors for carbapenem-resistant *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2014;**58**:2626—37.
24. Slama TG. Clinical review: balancing the therapeutic, safety, and economic issues underlying effective anti pseudomonal carbapenem use. *Crit Care* 2008;**12**:233.
25. Vurma-Rapp U, Kayser FH, Hadorn K, Wiederkehr F. Mechanism of imipenem resistance acquired by three *Pseudomonas aeruginosa* strains during imipenem therapy. *Eur J Clin Microbiol Infect Dis* 1990;**9**:580—7.
26. Tsai MH, Wu TL, Su LH, Lo WL, Chen CL, Liang YH, et al. Carbapenem-resistant-only *Pseudomonas aeruginosa* infection in patients formerly infected by carbapenem-susceptible strains. *Int J Antimicrob Agents* 2014;**44**:541—5.
27. Zanetti G, Bally F, Greub G, Garbino J, Kinge T, Lew D, et al. Cefepime versus imipenem-cilastatin for treatment of nosocomial pneumonia in intensive care unit patients: a multicenter, evaluator-blind, prospective, randomized study. *Antimicrob Agents Chemother* 2003;**47**:3442—7.
28. Suárez C, Peña C, Gavaldà L, Tubau F, Manzur A, Dominguez MA, et al. Influence of carbapenem resistance on mortality and the dynamics of mortality in *Pseudomonas aeruginosa* bloodstream infection. *Int J Infect Dis* 2010;**14**(Suppl 3):e73—8.
29. Jeong SJ, Yoon SS, Bae IK, Jeong SH, Kim JM, Lee K. Risk factors for mortality in patients with bloodstream infections caused by carbapenem-resistant *Pseudomonas aeruginosa*: clinical impact of bacterial virulence and strains on outcome. *Diagn Microbiol Infect Dis* 2014;**80**:130—5.