DETERMINATION OF FACTORS ASSOCIATED WITH EXTENSIVELY DRUG-RESISTANT *PSEUDOMONAS AERUGINOSA* INFECTION AMONG INTENSIVE CARE UNIT PATIENTS AT ROI ET HOSPITAL, THAILAND

Somkiattiyos Woradet[1], Nuntiput Putthanachot[2], Bhunyabhadh Chaimay[1], Narongchai Sangsa[3] and Phatsaraporn Sirisa[4]

[1]Department of Public Health, Faculty of Health and Sports Science, Thaksin University, Phatthalung Campus, Phatthalung; [2]Department of Clinical Microbiology; [3]Department of Medicine; [4]Department of Infectious Control, Roi Et Hospital, Roi Et, Thailand

Abstract. Drug-resistance is a major problem in Thailand. The aim of this study was to determine the factors associated with extensively drug resistant *Pseudomonas aeruginosa* (XDR-PA) infections among intensive care unit patients at Roi Et Hospital, Thailand in order to guide efforts to reduce the risk for these infections. We retrospectively reviewed the records of intensive care unit (ICU) patients at Roi Et Hospital from 1 January 2014 to 31 December 2015. We compared those with XDR-PA to those without XDR-PA. Inclusion criteria for study subjects were age ≥15 years, being treated in the ICU for ≥48 hours and having laboratory confirmed XDR-PA during the study period at the study hospital. Control patients had the same inclusion criteria as study subjects but did not have XDR-PA. The ratios of cases to controls was 1:2. We used multiple logistic regression analysis to evaluate factors potentially associated with having XDR-PA. A total of 47 cases and 94 controls were included in the study. The mean (range) age of cases were 67 (21-87) years and of controls was 57 (19-87) years. Fifty-five percent of cases and 60% of controls were males. Seventy-nine percent of cases and 61% of controls were married. Factors significantly associated with XDR-PA on multiple logistic regression analysis were age >60 years [Odds Ratio (OR) = 2.60; 95% Confidence Interval (CI): 1.25-5.40], hospitalization for >7 days (OR = 5.86; 95%CI: 2.40-14.34), having an indwelling urinary catheter (OR = 1.97; 95%CI: 1.37-5.41), having had a tracheostomy (OR = 1.83; 95%CI: 1.24-6.30), having an endotracheal tube (OR = 2.56; 95%CI: 1.20-5.45), having mechanical ventilation (OR = 2.81; 95%CI: 1.29-6.11) and having had surgery (OR = 3.72; 95%CI: 1.51-9.12). In our study age >60 years, hospitalization for >7 days, having a urinary catheter, a tracheostomy, an endotracheal tube, mechanical ventilation and surgery were all significantly associated with XDR-PA infection. Urinary catheters and endotracheal tubes should be removed as soon as possible. Patients aged >60 years, who have prolonged hospitalization, or have had surgery, a tracheostomy or mechanical ventilation should be monitored carefully for early signs of infection. Strict infection control measures must be implemented in these patients. Further studies are needed to determine if these measures can reduce the risk for contracting XDR-PA infection in the ICU of the study hospital.

Keywords: medical procedures, extensively drug-resistant, *Pseudomonas aeruginosa*, Intensive care unit

Correspondence: Somkiattiyos Woradet, Department of Public Health, Faculty of Health and Sports Science, Thaksin University, Phatthalung Campus, Paphayom, Phatthalung 93210, Thailand.
Tel: +66 (0) 74 609613; Fax: +66 (0) 74 609613
E-mail: somkiattiyos@tsu.ac.th

INTRODUCTION

Pseudomonas aeruginosa is a gram-negative, non-fermenting bacterial pathogen. *P. aeruginosa* infection is associated with a relatively high mortality rate among those with septicemia (3-38.9%) (Zhang *et al*, 2016; Buehrle *et al*, 2017; Kim *et al*, 2017). One study of *P. aeruginosa* sensitivity reported the following resistance rates: aminoglycosides = 50%, ciprofloxacin = 45.8%, ceftazidime = 70.8%, cefepime = 87.5%, colistin = 62.5% and imipenem = 29.2% (Bagheri-Nesami *et al*, 2017). Drug resistance results in a reduction in medication effectiveness. Multidrug resistance (MDR) is defined as resistance to more than one antimicrobial drug and extensive drug resistance (XDR) is defined as resistance to multiple antimicrobial drugs or resistance to all or nearly all approved antimicrobial drugs. Drug resistant, MDR and XDR *P. aeruginosa* (XDR-PA) have been reported worldwide. (Dou *et al*, 2007; Hashem *et al*, 2016; Kosai *et al*, 2017; Ruiz-Garbajosa and Canton, 2017; Sader *et al*, 2017; Safaei *et al*, 2017; Samad *et al*, 2017).

The prevalences of drug resistant, MDR-PA and XDR-PA in intensive care units have increased. Gill *et al* (2016) conducted a prospective study in a tertiary care center in India and reported 47.7% of ICU patients had drug resistant *P. aeruginosa*. Trinh *et al* (2017) conducted a case control study in Detroit, Michigan, United States and reported 23.5% of ICU patients had multidrug resistant *P. aeruginosa* (MDR-PA).

Several studies have reported factors associated with drug-resistant *P. aeruginosa*. Sonmezer *et al* (2016) conducted a case control study in Turkey and reported factors associated with meropenem resistance by *P. aeruginosa* included previous use of cefazolin, presence of cerebrovascular disease and use of meropenem; *P. aeruginosa* resistance to ciprofloxacin was also reported to be associated with hospitalization in a neurology intensive care unit and the use of mechanical ventilation. Lamas Ferreiro *et al* (2017) reported patients with a urinary tract infection due to *P. aeruginosa* were more likely to die if they had advanced chronic liver disease, diabetes mellitus or chronic renal failure. Micek *et al* (2015) reported MDR-PA infection was more likely to occur with increasing patient age, having diabetes mellitus, being hospitalized in an intensive care unit; patients with MDR-PA were more likely to die if they had concomitant heart failure, if they were older, if they underwent mechanical ventilation or had bacteremia. Multiple studies have reported if patients become septic with MDR-PA or XDR-PA they are more likely to die (Pena *et al*, 2012; Royer *et al*, 2015; Djordjevic *et al*, 2016; Matos *et al*, 2016; Agarwal *et al*, 2017; Abd-Elmonsef *et al*, 2017).

Roi Et Hospital is a tertiary care hospital serving rural and urban Roi Et Province. The Clinical Microbiology Laboratory and Department of Infectious

Control at Roi Et Hospital have noted an increased incidence of *P. aeruginosa* infection. MDR-PA and XDR-PA have been found at Roi Et Hospital. However, there are few studies of the factors associated with XDR-PA infection among intensive care unit (ICU) patients. The purpose of this study was to determine the factors associated with XDR-PA infection among ICU patients at Roi Et Hospital in order to guide infection prevention and control programs.

MATERIALS AND METHODS

Study site

In this hospital-based case control study we retrospectively reviewed the medical records of ICU patients at Roi Et Hospital, Roi Et Province, Thailand between 1 January 2014 - 31 December 2015 with laboratory diagnosed XDR-PA infection and compared them with ICU patients admitted at the same study institution during the study period who did not have XDR-PA infection at a ratio of cases to controls of 1:2 in order to identify factors associated with XDR-PA.

Criteria for cases and control

Inclusion criteria for cases were having laboratory confirmed XDR-PA infection, having stayed in the ICU of the study institution ≥48 hours and being aged ≥15 years. All cases at the study hospital during the study period were included in the study. Inclusion criteria for controls were not having XDR-PA, having stayed in the ICU at the study institution for ≥48 hours and being aged ≥15 years. Patients with incomplete records were excluded from the study.

Laboratory identification for *P. aeruginosa*

All cases were identified from respiratory secretions cultured on blood agar and MacConkey agar and incubated for 16-18 hours at 33-35˚C. *P. aeruginosa* was identified as beta-hemolytic or gamma-hemolytic (non-hemolytic) colonies on blood agar as non-lactose fermenting. Identification of *P. aeruginosa* was performed using biochemical testing. All laboratory testing was performed by experts in clinical microbiology at the Department of Clinical Microbiology Laboratory, Roi Et Hospital, Roi Et Province, Thailand. Laboratory testing was performed following standard guidelines of the Clinical and Laboratory Standards Institute (CLSI).

Susceptibility testing and detection for extensively drug resistant *P. aeruginosa* infection

Laboratory detection of XDR-PA was performed using the disk diffusion method following the guidelines of the CLSI. The *P. aeruginosa* was grown on Müller-Hinton agar and the selected antibiotics disks were places on the plate which was incubated at 33-35˚C for 16-18 hours. The disks used for the test were those containing gentamicin (GN: 10 μg), ceftazidime (CAZ: 30μg), imipenem (IPM: 10 μg), meropenem (MEM: 10 μg), doripenem (DOR: 10 μg), colistin (CT: 10 μg), piperacilin/tazobactam (TZP: 110 μg), amikacin (AK: 30 μg), trimethoprim/sulfamethoxazole (SXT:1.25/23.5 μg) and ciprofloxacin (CIP: 5 μg). The quality control bacteria used for the study were *S. aureus* ATCC 25923, *E. coli* ATCC 25922, and *P. aeruginosa* ATCC 27853. The definition of XDR-PA was defined as *P. aeruginosa* not susceptible to any of the antipseudomonal categories except colistin (Magiorakos *et al*, 2012).

Statistical analysis

Variables of interest in this study were demographic variables (gender, age, marital status, occupational and number of days admitted to hospital) and indepen-

dent variables (medical procedures such as having a urinary catheter, endotracheal tube, mechanical ventilation or surgery). Outcomes of interest in this study were presence or absence of XDR-PA infection. Bivariate analysis was performed using simple logistic regression analysis to investigate associations between examined factors and the presence of XDR-PA infection. Multiple logistic regression analysis was used to investigate associations between medical procedures and XDR-PA infection.

A three phases modeling strategy was used to evaluate potential factors and XDR-PA infection. A model was constructed for each demographic factor and factors from previous studies. The polytomous variables of marital status, education level and occupation were constructed into dummy variables prior to entering them into the model. Continuous variables, such as patient age, were categorized if there was a non-linear relationship. Factors with a p-value ≤0.25 on the Wald's test during crude analysis were entered into the initial model. Using backward elimination, factors with a p-value >0.05 on the Wald's test were eliminated. The p-value of the partial likelihood ratio test was tested by model fitting. The final model included all possible factors. The final model for each medical procedure was performed and adjusted for gender and patient age. Results were presented as odds ratios (OR) with 95 percent confidence intervals (95%CI). No association was defined as an OR that included 1, a negative association was defined as an OR >1 and a positive association as an OR <1.

This study was approved by the director of Roi Et Hospital, and the Ethics Committee of Roi Et Hospital (Ref. No. 003/2559).

RESULTS

A total of 47 cases (55% males) and 94 controls (60% males) were included in the study. The average age (±SD) of cases was 67(±15) years and controls was 57 (±18) years. Among cases and controls, 79% and 61% were married, 77% and 68% had graduated from primary school and 66% and 37% worked in agriculture, respectively (Table 1).

On bivariate analysis, factors significantly associated with XDR-PA were age, length of hospitalization, having a urinary catheter, tracheostomy, endotracheal tube, mechanical ventilation and surgery. On multivariate analysis, factors significantly associated with XDR-PA were: age >60 years (adjusted OR = 2.60; 95%CI: 1.25-5.40), having been in the intensive care unit >7 days (adjusted OR = 5.86; 95% CI: 2.40-14.34), having a urinary catheter (adjusted OR = 1.97; 95%CI:1.37-5.41), having a tracheostomy (adjusted OR = 1.83; 95%CI: 1.24-6.30), having an endotracheal tube (adjusted OR = 2.56; 95%CI: 1.20-5.45), having mechanical ventilation (adjusted OR = 2.81; 95%CI: 1.29-6.11) and having had surgery (adjusted OR = 3.72; 95%CI: 1.51-9.12) (Table 2).

On subgroup analysis for having medical devices for >7 days, factors significantly associated with XDR-PA were having a urinary catheter for >7 days (adjusted OR = 1.95; 95%CI: 1.05-6.59), having an endotracheal tube for >7 days (adjusted OR = 1.86; 95%CI: 1.24-5.44) and having mechanical ventilation for >7 days (adjusted OR = 5.74; 95%CI: 1.35-24.43) (Table 3).

DISCUSSION

In our study, ICU patients with a urinary catheter, tracheostomy, endotracheal

Table 1
Demographic characteristics of cases and controls.

Demographic characteristics	Cases (n = 47)	Controls (n = 94)
	n %	n %
Gender		
Male	26 (55)	56 (60)
Female	21 (45)	38 (40)
Age in years		
≤60	16 (34)	54 (57)
>60	31 (66)	40 (43)
Mean ± SD (Min : Max)	67 ± 15 (21 : 87)	57 ± 18 (19 : 87)
Marital status		
Single	6 (13)	17 (18)
Married	37 (79)	57 (61)
Divorced	4 (8)	20 (21)
Education level		
Primary school	36 (77)	64 (68)
High school	6 (13)	24 (26)
Bachelor's degree	5 (10)	6 (6)
Occupation		
Agricultural worker	31 (66)	35 (37)
Government officer	1 (2)	7 (7)
Business	1 (2)	16 (17)
Worker	2 (4)	13 (14)
Unemployed	12 (26)	23 (25)

SD: standard deviation.

tube, mechanical ventilation or surgery were at greater risk for developing a XDR-PA infection. A study from Ecuador (Salgado *et al*, 2017) also found patients who had a urinary catheter, central line or mechanical ventilation were at increased risk for bacterial infection. Willmann *et al* (2014) found patients in Germany with a urinary catheter or a central venous catheter were at increased risk for bacterial infection. A multicenter study from USA, France, Germany, Italy and Spain (Micek *et al*, 2015) found diabetic patients admitted to the ICU who had mechanical ventilation were at increased risk of infection. Matos *et al* (2016) found patients of a study in Brazil who had a urinary catheter or mechanical ventilation were at increased risk of infection. A study from Spain found an association between fluoroquinolones exposure and XDR-PA bacteremia (Pena *et al*, 2012). A study from Turkey found previous meropenem or cefazolin exposure was related to meropenem resistant *P. aeruginosa* (Sonmezer *et al*, 2016). Previous exposure to ciprofloxacin was associated with XDR-PA infection in study from Germany (Willmann *et al*, 2014). A study from Greece found among patients with hematological malignancy perior exposure to a fluoroquinolones was associated with XDR-PA infection

Table 2
Bivariate analysis and multivariate analysis of factors associated with extensively drug-resistant *P. aeruginosa* infection.

Variables	Cases (n = 47)	Controls (n = 94)	Crude OR (95%CI)	Adjusted OR (95%CI)	p-value
	n %	*n* %			
Gender					0.693
Male	26 (55)	56 (60)	1	1	
Female	21 (45)	38 (40)	1.19 (0.58 - 2.41)	1.15 (0.56 - 2.39)	
Age in years					0.010
≤60	16 (34)	54 (57)	1	1	
>60	31 (66)	40 (43)	2.62 (1.26 - 5.42)	2.60 (1.25 - 5.40)	
Ward					0.335
Surgical ICU	22 (47)	49 (52)	1	1	
Medicine ICU	25 (53)	45 (48)	1.24 (0.61 – 2.46)	1.44 (0.68 – 3.46)	
Hospital stay in days					<0.001
≤7	8 (17)	49 (52)	1	1	
>7	39 (83)	45 (48)	5.30 (2.24 - 12.56)	5.86 (2.40 - 14.34)	
Urinary catheter					0.003
No	28 (60)	70 (74)	1	1	
Yes	19 (40)	24 (26)	1.98 (1.08 - 4.16)	1.97 (1.37 - 5.41)	
Tracheostomy					0.002
No	39 (83)	85 (90)	1	1	
Yes	8 (17)	9 (10)	1.94 (1.13 - 5.39)	1.83 (1.24 - 6.30)	
Endotracheal tube					0.015
No	21 (45)	60 (64)	1	1	
Yes	26 (55)	34 (36)	2.18 (1.07 - 4.55)	2.56 (1.20 - 5.45)	
Mechanical ventilation					0.009
No	23 (49)	68 (72)	1	1	
Yes	24 (51)	26 (28)	2.73 (1.31 - 5.66)	2.81 (1.29 - 6.11)	
Surgery					0.004
No	29 (62)	73 (78)	1	1	
Yes	18 (38)	21 (22)	2.26 (1.26 - 5.42)	3.72 (1.51 - 9.12)	

OR: Odds Ratio; ICU: intensive care unit.

(Samonis *et al*, 2014).

Our study had limitations, we did not take into consideration types of antibiotics uses or other non-procedure treatment factors. Another limited factor of the study was small sample size which may not give enough power to detect some factors.

In summary, factors associated with XDR-PA in our study were having a urinary catheter, tracheostomy, endotracheal tube, mechanical ventilation or surgery. Emphasis should be placed on early removal of using catheters, early extubation, maintaining proper technique when

Table 3
Association between medical procedures and extensively drug-resistant *P. aeruginosa* infection.

Variables and length of present	Cases (n = 47)	Controls (n = 94)	Crude OR (95%CI)	Adjusted OR (95%CI)	p-value
	n %	n %			
Urinary catheterization					0.001
≤7	7 (37)	13 (54)	1	1	
>7	12 (63)	11 (46)	2.02 (1.59 - 6.93)	1.95 (1.05 - 6.59)	
Tracheostomy presence					0.718
≤7	3 (38)	4 (44)	1	1	
>7	5 (62)	5 (56)	1.41 (0.19 - 9.31)	1.49 (0.17 - 12.86)	
Endotracheal intubation					0.002
≤7	11 (42)	19 (56)	1	1	
>7	15 (58)	15 (44)	1.72 (1.16 - 4.84)	1.86 (1.24 - 5.44)	
Mechanical ventilation					0.018
≤7	6 (25)	14 (54)	1	1	
>7	18 (75)	12 (46)	3.50 (1.05 - 11.65)	5.74 (1.35 - 24.43)	

OR: Odds Ratio.

caring for tracheostomy and avoidance of unnecessary mechanical ventilation. Further studies are needed to determine if modifying these factors can reduce the risk of XDR-PA among ICU patients in the study institution.

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