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นิพนธ์ต้นฉบับ
ORIGINAL ARTICLE

ปัจจัยที่มีความสัมพันธ์ต่อการติดเชื้อ *Pseudomonas aeruginosa* สายพันธุ์ดื้อยาต้านจุลชีพในกลุ่ม Carbapenems ในผู้ป่วยที่เข้ารับการรักษาในโรงพยาบาลร้อยเอ็ด ประเทศไทย

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บทคัดย่อ

โรคติดเชื้อฉวยโอกาส *Pseudomonas aeruginosa* ที่ดื้อยาต้านจุลชีพในกลุ่ม carbapenems กำลังเป็นปัญหาสำคัญทั่วโลก ผู้ป่วยที่ติดเชื้อจะทำให้มีความยุ่งยากในการรักษาและมีความเสี่ยงต่อการเสียชีวิตสูงโดยเฉพาะถ้าเกิดการติดเชื้อในกระแสเลือด งานนี้มีวัตถุประสงค์เพื่อศึกษาปัจจัยที่มีความสัมพันธ์ต่อการติดเชื้อ *P.aeruginosa* สายพันธุ์ดื้อยาต้านจุลชีพในกลุ่ม carbapenems ในผู้ป่วยที่เข้ารับการรักษาในโรงพยาบาลร้อยเอ็ด จังหวัดร้อยเอ็ด รูปแบบการศึกษาแบบ hospital based case-control study โดยใช้ฐานข้อมูลจากโรงพยาบาลร้อยเอ็ด เก็บข้อมูลตัวแปรที่สนใจจากเวชระเบียนผู้ป่วยในที่เข้ารับการรักษาระหว่างวันที่ 1 มกราคม พ.ศ. 2557 ถึง วันที่ 31 ธันวาคม พ.ศ. 2558 ขั้นตอนการตรวจวิเคราะห์ทางห้องปฏิบัติการปฏิบัติตามหลักการของ CLSI January, 2010 สถิติที่ใช้ในการวิเคราะห์ข้อมูล ได้แก่ สถิติเชิงพรรณนา การวิเคราะห์ตัวแปรเชิงเดี่ยว และการวิเคราะห์ตัวแปรเชิงพหุ โดยการวิเคราะห์แบบพหุถดถอย ผลการศึกษาพบว่า กลุ่มศึกษา 85 ราย ส่วนมากเป็นเพศหญิงร้อยละ 54.2 อายุเฉลี่ย 62.5 ปี (± SD=16.2) สถานะภาพสมรสคู่ร้อยละ 72.9 ประกอบอาชีพเกษตรกรรมร้อยละ 63.5 กลุ่มควบคุม 85 ราย ส่วนมากเป็นเพศชายร้อยละ 55.3 อายุเฉลี่ย 57.9 ปี (± SD=18.3) สถานะภาพสมรสคู่ร้อยละ 61.2 ประกอบอาชีพเกษตรกรรมร้อยละ 43.5 ปัจจัยที่มีความสัมพันธ์ต่อการติดเชื้อ *P.aeruginosa* สายพันธุ์ดื้อยาต้านจุลชีพในกลุ่ม carbapenems ได้แก่ การมีระยะเวลาครองเตียงมากกว่า 7 วัน ($OR_{Adj.}$ =2.6:95%CI; 1.32-4.87) ผู้ป่วยที่ได้รับการเจาะคอ ($OR_{Adj.}$ =2.0:95%CI; 1.07- 4.79) ใส่ท่อช่วยหายใจ ($OR_{Adj.}$ =2.7:95%CI; 1.31- 5.57) ใส่เครื่องช่วยหายใจ ($OR_{Adj.}$ =3.1:95%CI; 1.42- 6.38) ส่วนความเสี่ยงจากการได้รับยาต้านจุลชีพได้แก่ ยาในกลุ่ม cephalosporins รุ่นที่ 3 ($OR_{Adj.}$ =2.1:95%CI; 1.10- 3.91), carbapenems ($OR_{Adj.}$ =2.9:95%CI; 1.34- 5.68) และ glycopeptides ($OR_{Adj.}$ =3.3:95%CI; 1.95- 11.09) สรุปผลการศึกษาครั้งนี้พบว่าผู้ป่วยที่นอนในโรงพยาบาลนาน และผู้ป่วยที่ได้รับการทำหัตถการด้วย การเจาะคอ ใส่ท่อช่วยหายใจ ใส่เครื่องช่วยหายใจ และการได้รับยา cephalosporins รุ่นที่ 3, carbapenems และ glycopeptides เป็นปัจจัยเสี่ยงที่มีความสัมพันธ์ต่อการติดเชื้อ *P. aeruginosa* สายพันธุ์ดื้อยาต้านจุลชีพในกลุ่ม carbapenems

คำสำคัญ: Carbapenems, *Pseudomonas aeruginosa*, ปัจจัยเสี่ยง, โรงพยาบาลร้อยเอ็ด

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ORIGINAL ARTICLE

Factors associated with carbapenem-resistant *Pseudomonas aeruginosa* strain infections among patients at Roi Et Hospital, Thailand

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Abstract

Nosocomial infection caused by carbapenem-resistant *Pseudomonas aeruginosa* strains (CRPA) is a serious problem worldwide. Infected patients are difficult to treat, leading to high mortality rate especially septicemia. The objective of this study was to investigate the factors associated with CRPA infections among patients at Roi Et Hospital, Roi Et Province. Study design was a hospital based case-control study. All processes were conducted at Roi Et Hospital. The variables of interest were retrieved from medical records of patients who admitted during January 1, 2014 to December 31, 2015. The laboratory processes were followed the guidelines of the CLSI January, 2010. Data were analyzed using descriptive statistic, univariable analysis and multivariable analysis by multiple logistic regressions. Of which 85 cases, most of them were female (54.2%) with mean age 62.5±16.2 years, couple status was 72.9 % and agriculture 63.5 %. Of 85 controls, most of them were male (55.3 %) with mean age of 57.9± 18.3 years, couple status was 61.2 % and agriculture 43.5 %. The factors associated with CRPA infections were hospital stay more than 7 days ($OR_{Adj.}$=2.6:95%CI; 1.32-4.87), tracheostomy ($OR_{Adj.}$=2.0:95%CI; 1.07-4.79), endotracheal tube ($OR_{Adj.}$=2.7:95%CI; 1.31-5.57) and mechanical ventilators ($OR_{Adj.}$=3.1:95%CI; 1.42-6.38). Antibiotic exposure included the third-generation cephalosporins ($OR_{Adj.}$=2.1:95%CI; 1.10-3.91), carbapenems ($OR_{Adj.}$=2.9:95%CI; 1.34-5.68) and glycopeptides ($OR_{Adj.}$=3.3:95%CI; 1.95-11.09). In conclusion, the hospitalization, tracheostomy, endotracheal tube, mechanical ventilators, the third-generation cephalosporins, carbapenems and glycopeptides were factors associated with CRPA infections.

Key words: Carbapenems, *Pseudomonas aeruginosa*, Risk factor, Roi Et Hospital

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Background

Pseudomonas aeruginosa (P. aeruginosa) is non- fermentative bacterium that can cause a serious problem worldwide. *P.aeruginosa* is frequently causing agent in the urinary tract, respiratory tract and blood stream infections. [1-3] Infected patients were difficult to treat and had high mortality especially septicemia (8%-18.4%).[2- 4]

The carbapenem-resistant *P.aeruginosa* strains (CRPA) are widely found.[5-7] Previous studies showed that factors associated with CRPA infections were patients who underwent with a mechanical ventilator, long time stay in intensive care unit,[6] hematologic malignancy patients, chronic obstructive pulmonary disease,[3] underwent with urinary tract catheter, surgeries and exposure to some types of antibiotics during admitted.[1] [8-10]

The incidence of *P.aeruginosa* infections at Roi Et Hospital was high (In 2016, 1,504 isolations, multidrug resistant were 532 isolations). And although have many previous studies reported on the incidence and factors associated with CRPA infections but few studies have been conducted in Thailand and non previously study reported from Roi Et Hospital. The aim of this study was to investigate the factors associated with CRPA infections among patients at Roi Et Hospital.

Materials and methods

Study subjects

For a hospital-based case-control study, all data were retrieved from medical records of patients atRoiEt Hospital, Roi Et Province, Thailand during January 1, 2014 to December 31, 2015. All cases were randomized from patients with CRPA infections, age more than 15 years, admitted more than 48 hours and controls were randomly selected from patients who were non *P. aeruginosa* infections and admitted at the same period with cases.

Laboratory identification of *P. aeruginosa*

All clinical specimens were cultured and identified for *P. aeruginosa* at the Clinical Microbiology Laboratory, Roi Et Hospital. All laboratory processes were followed the standard guideline of Clinical and Laboratory Standards Institute (CLSI January, 2010). All samples were cultured on blood agar and MacConkey agar and incubated at 35±2°C for 16-20 hours. The *P. aeruginosa* identification was performed by using biochemical tests.

Susceptibility testing

The antibiotic susceptibility test was performed by disk diffusion method and laboratory interpreted according to the guidelines of CLSI January, 2010. The carbapenem disks tested included doripenem (DOR:10ug), ertapenem (ETP: 10ug), imipenem (IPM:10ug), meropenem (MEM:10ug). *P. aeruginosa* ATCC 27853 was used as reference strain.

The positive result for CRPAs was *P. aeruginosa* non-susceptible to one or more carbapenems.

Variables of interest

The variables of this study were general characteristics of patients including gender, age,

marital status, occupational and day of admit. The variables of risk factors for CRPA infections included urinary tract catheter, endotracheal tube, nasogastric tube, mechanical ventilators, history of blood transfusion and surgery. The antibiotic exposures were penicillins, cephalosporins, carbapenems, glycopeptides, aminoglycosides, tetracyclines, quinolones and sulfonamides. All variables were categorized into two groups (Yes/No).

Statistical analysis

The descriptive statistics were used to describe to a general characteristics of cases and controls including percent, mean and standard deviation (SD). The univariable analysis was used to explore the risk of CRPA infections and presented crude odds ratio (Crude OR) and their 95% confidence interval. The multivariable analysis by multiple logistic regressions was used to investigate the factors associated with CRPA infections. The significant and medical important factors were included to the model. All model we adjusted by gender and age to control confounder and to present adjusted odds ratio (Adjusted OR) and 95% confident interval. The statistical significance was set at *p*-value <0.05.

Ethics consideration

This research was approved by the Ethics Committee of Roi Et Hospital. The reference number was 003/2559.

Results

The general characteristics of cases and controls

Most of the 85 cases were female (54.2%) with mean age of 62.5±16.2 years, 72.9 % couple and 63.5 % agriculture **(Table 1)**. On the other hand most of the 85 controls were male (55.3 %) with mean age of 57.9±18.3 years, 61.2 % couple and 43.5 % agriculture.

Table1 The general characteristics of the patients and controls

Variables	Cases(85)	Controls(85)	*p*-value
	n(%)	n(%)	
Gender			0.220
Male	39(45.8)	47(55.3)	
Female	46(54.2)	38(44.7)	
Age (years)			0.166
≤ 60	34(40.0)	43(50.6)	
> 60	51(60.0)	42(49.4)	
Mean± SD	62.5±16.2	57.9±18.3	
Min:Max	18:95	19:87	
Marital status			0.338
Single	15(17.6)	15(17.7)	
Couple	62(72.9)	52(61.2)	
Divorce	8(9.5)	18(21.1)	
Occupational			0.412
Agriculture	54(63.5)	37(43.5)	
Business	2(2.4)	6(7.1)	
Employee	13(15.3)	19(22.4)	
Government officer	3(3.5)	8(9.4)	
Unemployed	15(17.7)	21(24.7)	

p-value from *Chi-Square* Test

Factors associated with carbapenem-resistant *P. aeruginosa* infections

The multivariable analysis on the factors associated with CRPA infections revealed patients stayed in the hospital more than 7 days ($OR_{Adj.}$ =2.6:95%CI; 1.32-4.87), tracheostomy ($OR_{Adj.}$ =2.0:95%CI; 1.07-4.79), endotracheal tube ($OR_{Adj.}$ =2.7:95%CI; 1.31-5.57) and mechanical ventilators ($OR_{Adj.}$=3.1: 95%CI; 1.42-6.38) were risks of CRPA infection **(Table2)**. Meanwhile, patients underwent with urinary tract catheter, nasogastric tube, surgery and blood transfusion were statistically non-significant.

Table2 The factors associated with carbapenem-resistant *P. aeruginosa* infections

Variables	Cases n=85(%)	Controls n=85(%)	OR_C(95%CI)	OR_A(95%CI)	*p*-value
Day of admitted					0.009**
≤7 days	39(45.9)	55(64.7)	1	1	
>7 days	46(54.1)	30(35.3)	2.2(4.01-1.17)	2.6(4.87-1.32)	
Blood transfusion					0.146
No	55(64.7)	64(75.0)	1	1	
Yes	30(35.3)	21(25.0)	1.5(2.90-0.80)	1.6(3.09-0.84)	
Surgery					0.170
No	62(72.9)	68(80.0)	1	1	
Yes	23(27.1)	17(20.0)	1.4(3.30-0.72)	1.6(3.86-0.78)	
Urinary tract catheter					0.464
No	59(69.4)	56(65.9)	1	1	
Yes	26(30.6)	29(34.1)	0.8(1.30-0.53)	0.9(1.37-0.49)	
Nasogastric tube					0.974
No	69(81.2)	67(78.8)	1	1	
Yes	16(18.8)	18(21.2)	0.9(1.28-0.75)	1.0(1.37-0.77)	
Tracheostomy					0.004*
No	69(81.2)	76(89.4)	1	1	
Yes	16(18.8)	9(10.6)	1.9(4.71-1.02)	2.0(4.79-1.07)	
Endotracheal tube					0.007*
No	53(62.4)	69(81.2)	1	1	
Yes	32(37.6)	16(18.8)	2.6(5.23-1.29)	2.7(5.57-1.31)	
Mechanical ventilators					0.004*
No	54(63.5)	71(83.5)	1	1	
Yes	31(36.5)	14(16.5)	2.9(6.00-1.41)	3.1(6.38-1.42)	

OR_C= Crude Odds ratio, OR_A= Adjusted Odds ratio, 95%CI= 95 % confidence interval, *p*-value frommultiple logistic regression

The analysis of antibiotic exposure associated with carbapenem-resistant P. aeruginosa infections

The multivariable analysison antibiotic exposure associatedwith the CRPA infections revealed statistical significance with the third-generation cephalosporins ($OR_{Adj.}$ = 2.1: 95%CI; 1.10-3.91), carbapenems ($OR_{Adj.}$ = 2.9: 95%CI; 1.34-5.68) and glycopeptides ($OR_{Adj.}$ = 3.3: 95%CI; 1.95-11.09) **(Table 3)**.

Table3 The antibiotic exposure and their association with carbapenem-resistant *P. aeruginosa* infections

Variables	Cases n=85(%)	Control n=85(%)	OR_C(95%CI)	OR_A(95%CI)	*p*-value
1st Cephalosporins					0.395
No	75(88.2)	72(84.7)	1	1	
Yes	10(11.8)	13(15.3)	0.7(1.79-0.30)	0.6(1.76-0.24)	
2nd Cephalosporins					0.070
No	68(80.0)	76(89.4)	1	1	
Yes	17(20.0)	9(10.6)	2.1(5.05-0.88)	2.5(6.40-0.96)	
3rd Cephalosporins					0.023*
No	33(38.8)	47(55.3)	1	1	
Yes	52(61.2)	38(44.7)	1.9(5.59-1.06)	2.1(3.91-1.10)	
Penicillins					0.934
No	69(81.2)	72(84.7)	1	1	
Yes	16(18.8)	13(15.3)	1.3(2.87-0.59)	0.9(2.23-0.45)	
Carbapenems					0.006*
No	46(54.1)	66(77.7)	1	1	
Yes	39(45.2)	19(22.3)	2.6(5.23-1.29)	2.9(5.68-1.34)	
Glycopeptides					0.020*
No	74(54.1)	84(87.0)	1	1	
Yes	11(45.2)	4(13.0)	3.0(9.86-1.92)	3.3(11.09-1.95)	
Aminoglycosides					0.641
No	72(84.7)	70(82.4)	1	1	
Yes	13(15.3)	15(17.6)	0.8(1.89-0.37)	0.9(1.88-0.36)	
Sulfonamides					0.263
No	75(88.2)	69(81.2)	1	1	
Yes	10(11.8)	16(18.2)	0.6(1.35-0.24)	0.7(1.45-0.26)	
Fluoroquinolone					0.526
No	77(90.1)	79(92.9)	1	1	
Yes	8(9.9)	6(7.1)	1.4(4.13-0.45)	1.3(4.49-0.46)	

OR_C= Crude Odds ratio, OR_A= Adjusted Odds ratio, 95%CI= 95 % confidence interval, *p*-value frommultiple logistic regression

Discussion

This study investigated the factors associated CRPA infections among Thai patients and the analyzed revealed that patients admitted more than 7 days, underwent the tracheostomy, endotracheal tube and mechanical ventilators were risks of CRPA infections consistent with previous studies. The report from Spain and Lithuania revealed risk of CRPA infections and risks of death were patients underwent with urinary catheter (2.1 times), mechanical ventilation (13.67 times), patients hospitalized in the ICU (8.51 times) and central vein catheter (4.44 times). [11] [12] Meanwhile this study inconsistent with previous studies In Korea, Turkey and Taiwan, they found patients with diabetes mellitus (2.82 times), radiologic score ≥5 (4.56 times), surgical procedure (76.8 times) and patients having antifungal therapy were risks of CRPA infections. [13-15]

Our study also investigated the association between antibiotic used as a risk of CRPA infections. The data analysis revealed that patients exposed to the third-generation cephalosporins, carbapenems and glycopeptides were the factors associated with CRPA infections consistent with many studies. The study from China found that the risk factors for these pathogen infections were imipenem, the third cephalosporins, piperacillin/tazobactam (PIP/TAZ), quinolones, and aminoglycoside exposed[16] One study from Turkey showed that risk factors of CRPA infections were patients exposed to vancomycin, PIP/TAZ, and imipenem.[17] A study at Maryland (USA) reported that risk factors of CRPA infections were imipenem, PIP/TAZ, vancomycin and aminoglycoside therapy.[18] A study from Korea found out that patients with unitial fluoroquinolone andcarbapenem treatment were independent risk factors for CRPA infections.[13] The report from Turkey showed that carbapenem exposure was increased risk of CRPA infections with 15.7 times.[14] Meanwhile our study revealed statistical non-significance with PIP/TAZ, quinolones, vancomycin fluoroquinolones, and aminoglycoside. However, this study inconsistent with previous studies reported from Spain, Korea and Taiwan they found a fluoroquinolone clinical used was important factors associated with CRPA infections. [11] [13] [15]

Conclusion

Patients who stayed in the hospital more than 7 days, underwent with tracheostomy, endotracheal tube, mechanical ventilators and exposure to the third-generation cephalosporins, carbapenems and glycopeptides were risks of CRPA infections.

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