Pseudomonas aeruginosa Resistance in Southeast Asia

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REVIEW ARTICLE

Pseudomonas aeruginosa Resistance in Southeast Asia

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ABSTRACT

INTRODUCTION: *The increasing number of multidrug-resistant Pseudomonas aeruginosa worldwide need to be continuously monitored to prevent its transmission. This study reviewed multidrug-resistant Pseudomonas aeruginosa in Southeast Asia.*

METHODS: *Pubmed database was searched (January 2013-March 2018) for relevant articles using specific names of all eleven Southeast Asian countries. The articles retrieved were screened and analyzed to meet the inclusion criteria.*

RESULTS: *A total of 17 articles met the inclusion criteria. Vietnam had the most published data included in this study, East Timor, Cambodia, and Laos had none. There are variations among Pseudomonas aeruginosa resistance in Southeast Asia. Thailand had complete data on antibiotic resistance and had the highest resistance rate of almost all antibiotics. Colistin had the lowest resistance rate among all antibiotics.*

CONCLUSIONS: *Colistin had the lowest resistance rate among all antibiotics. Another study with more extensive data should be done to validate this study. Future research should be explicitly providing detail data results for antimicrobial resistance analyses.*

Keywords: *Pseudomonas aeruginosa, antimicrobial resistance, Southeast Asia*

INTRODUCTION

Healthcare-associated infections (HAIs) or previously known as nosocomial infections are an infection that happens within 48 hours after admission in a health care facility. In surgery, the timing can extend up to 30 days (Haque et al., 2018). Surgical site infection (SSI), ventilator-associated pneumonia (VAP), catheter-associated urinary tract infection (CAUTI), and central line-associated bloodstream infection (CLABSI) are examples of HAIs (Al-Tawfiq and Tambyah, 2014). HAIs is major problem due to its high morbidity, mortality, and healthcare cost. The case fatality rate (CFR) for SSI, VAP, CAUTI, and CLABSI are 2.8%, 14.4%, 2.3%, and 12.3%, respectively (Al-Tawfiq and Tambyah, 2014). Most HAIs are caused by multi-drug resistance organisms (MDRO) (Haque et al., 2018). Pseudomonas aeruginosa is one of the most common MDRO that can cause HAIs (Nathwani et al., 2014, Treepong et al., 2018).

Infectious Diseases Society of America (IDSA) even classify P. aeruginosa along with Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinetobacter baumanii, and Enterobacter species as the "ESKAPE" pathogen (Boucher et al., Khuntayaporn et al., 2013). Those bacteria can easily "escape" from antibiotic treatment, and the presence of intrinsic resistance and acquisition of resistance genes results in fewer treatment options for P. aeruginosa infection (Treepong et al., 2018, Boucher et al.). The increasing number of multidrug-resistant P. aeruginosa outbreaks that affected patients' life and numerous healthcare facilities in the last few decades deserves our attention (Wieland et al., 2018). The authors are interested in doing a literature review related to P. aeruginosa because there is no recent review pertaining to P. aeruginosa resistance in Southeast Asia.

METHODS

Search strategy

This research was a systematic review conducted by using the PubMed database as a search engine. The keywords used in the search include "Pseudomonas

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aeruginosa", "Southeast Asia", "Resistance", and specific names of all eleven Southeast Asia countries ("Indonesia", "Singapore", "Thailand", "Vietnam", "Malaysia", "Philippines", "Myanmar" or " Burma", "Brunei" or "Brunei Darussalam", "Timor Leste" or "East Timor"," Cambodia", "Laos" or "Lao PDR" or "Lao People's Democratic Republic"). Filters activated were publications from January 2013 to March 2018, full text available, species found in humans.

Selection criteria and article quality assessment

Inclusion criteria were articles written in English or Indonesian. The articles retrieved were screened by abstract reading by author and co-author independently. Any discrepancy found was being discussed. Scoring systems are used to assess article quality: valid and reliable identification methods, such as using Phoenix® (Becton Dickinson), Vitek® (bioMérieux), internationally standardized biochemical test, molecular (0 = no, 1 = yes); antibiotic susceptibility testing (AST) using an internationally standardized system, e.g., Clinical & Laboratory Standards Institute (CLSI) (0 = no, 1 = yes). Only articles value 2 were analyzed further. Data representing a mix of strains from several countries were excluded.

Data analysis

Data extracted included article information (first author's name, year of publication), study design (location, source of data, source of infection, type of infection, age group, antibacterial resistance), identification and AST method used. Data were analyzed using IBM® SPSS® Statistic 24. (SPSS, Inc, an IBM Company, Chicago, Illinois)

RESULTS

Study selection

Our search identified 91 articles. Of this, 36 were excluded due to duplication and inaccessible full text, 36 more were excluded during abstract screening, and two articles excluded because representing a mix of strains from several countries (Figure 1).

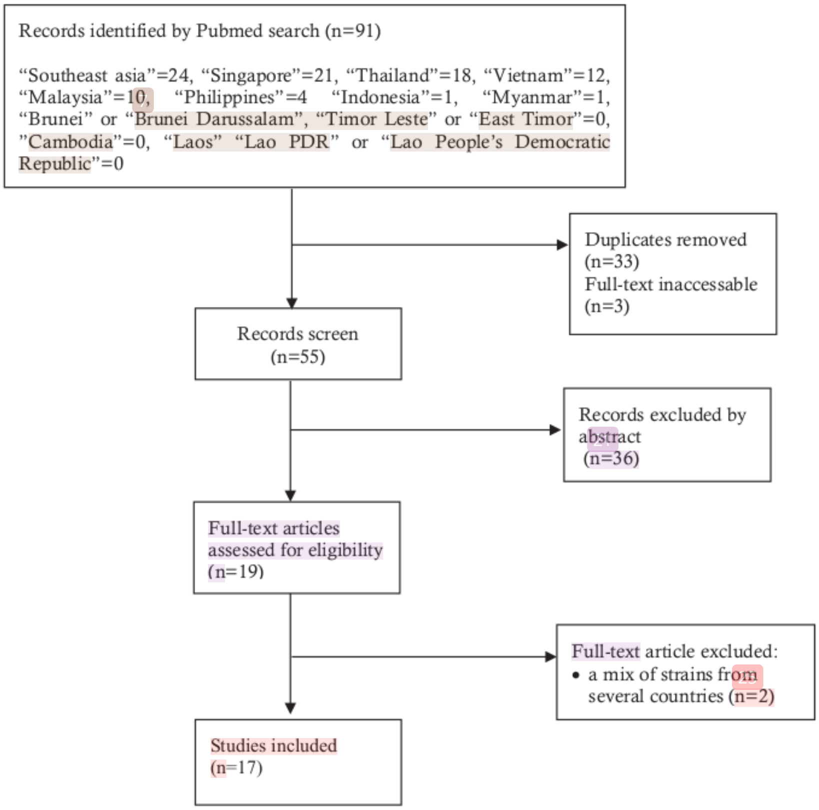

Figure 1. PRISMA Diagram of the article selection procedure

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Table 1. Characteristic of the articles included

Characteristic	Frequency N (%)	References
Publication Year		
2013	7 (41.2)	(Apisarnthanarak *et al.*, 2013, Karuniawati *et al.*, 2013, Khuntayaporn *et al.*, 2013, Kiddee *et al.*, 2013, Kor *et al.*, 2013, Lim *et al.*, 2013a, Tada *et al.*, 2013)
2014	2 (11.8)	(Biedenbach *et al.*, 2014, Cheng *et al.*, 2014)
2015	2 (11.8)	(Teo *et al.*, 2015, Wong *et al.*, 2015)
2016	5 (29.4)	(Biedenbach *et al.*, 2016, Kazmierczak *et al.*, 2016, Le *et al.*, 2016, Phu *et al.*, 2016, Tada *et al.*, 2016)
2017	1 (5.9)	(Tran *et al.*, 2017)
Country		
Indonesia	1 (5.9)	(Karuniawati *et al.*, 2013)
Malaysia	2 (11.8)	(Kor *et al.*, 2013, Wong *et al.*, 2015)
Singapore	3 (17.6)	(Lim *et al.*, 2013a, Cheng *et al.*, 2014, Teo *et al.*, 2015)
Thailand	3 (17.6)	(Khuntayaporn *et al.*, 2013, Kiddee *et al.*, 2013, Apisarnthanarak *et al.*, 2013)
Vietnam	7 (41.2)	(Tada *et al.*, 2013, Biedenbach *et al.*, 2014, Biedenbach *et al.*, 2016, Le *et al.*, 2016, Phu *et al.*, 2016, Tada *et al.*, 2016, Tran *et al.*, 2017)
Multinational	1 (5.9)	(Kazmierczak *et al.*, 2016)
Study Design		
Cross sectional/ Case Series	10 (58.8)	(Karuniawati *et al.*, 2013, Kor *et al.*, 2013, Wong *et al.*, 2015, Teo *et al.*, 2015, Khuntayaporn *et al.*, 2013, Kiddee *et al.*, 2013, Biedenbach *et al.*, 2014, Biedenbach *et al.*, 2016, Tada *et al.*, 2016, Tran *et al.*, 2017)
Retrospective	3 (17.6)	(Lim *et al.*, 2013a, Cheng *et al.*, 2014, Tada *et al.*, 2013)
Surveillance	3 (17.6)	(Phu *et al.*, 2016, Le *et al.*, 2016, Kazmierczak *et al.*, 2016)
Review	1 (5.9)	(Apisarnthanarak *et al.*, 2013)
Age		
0-18	1 (5.9)	(Le *et al.*, 2016)
>18	4 (23.5)	(Teo *et al.*, 2015, Tran *et al.*, 2017, Lim *et al.*, 2013a, Phu *et al.*, 2016)
All ages	12 (70.6)	(Karuniawati *et al.*, 2013, Kor *et al.*, 2013, Wong *et al.*, 2015, Khuntayaporn *et al.*, 2013,

Characteristic	Frequency N (%)	References
		Kiddee *et al*., 2013, Biedenbach *et al*., 2014, Biedenbach *et al*., 2016, Tada *et al*., 2016, Cheng *et al*., 2014, Tada *et al*., 2013, Kazmierczak *et al*., 2016, Apisarnthanarak *et al*., 2013)
Type of Infection		
Hospital-acquired	14 (82.3)	(Karuniawati *et al*., 2013, Kor *et al*., 2013, Teo *et al*., 2015, Khuntayaporn *et al*., 2013, Kiddee *et al*., 2013, Biedenbach *et al*., 2014, Biedenbach *et al*., 2016, Tada *et al*., 2016, Tran *et al*., 2017, Lim *et al*., 2013a, Cheng *et al*., 2014, Tada *et al*., 2013, Le *et al*., 2016, Phu *et al*., 2016)
Unknown	3 (17.6)	(Wong *et al*., 2015, Kazmierczak *et al*., 2016, Apisarnthanarak *et al*., 2013)
Method for Identification		
MALDI-TOF	2 (11.8)	(Biedenbach *et al*., 2016, Kazmierczak *et al*., 2016)
API system (bioMérieux)	2 (11.8)	(Wong *et al*., 2015, Kor *et al*., 2013)
Biochemical	1 (5.9)	(Tran *et al*., 2017)
Molecular, PCR	8 (47.0)	(Karuniawati *et al*., 2013, Teo *et al*., 2015, Khuntayaporn *et al*., 2013, Kiddee *et al*., 2013, Biedenbach *et al*., 2014, Tada *et al*., 2016, Cheng *et al*., 2014, Tada *et al*., 2013)
Not mentioned	4 (23.5)	(Lim *et al*., 2013b, Le *et al*., 2016, Phu *et al*., 2016, Apisarnthanarak *et al*., 2013)
Method for AST		
Disk diffusion	5 (29.4)	(Karuniawati *et al*., 2013, Kor *et al*., 2013, Khuntayaporn *et al*., 2013, Kiddee *et al*., 2013, Tran *et al*., 2017)
Semi automatic	2 (11.8)	(Wong *et al*., 2015, Biedenbach *et al*., 2014)
Broth microdilution	4 (23.5)	(Biedenbach *et al*., 2016, Tada *et al*., 2016, Tada *et al*., 2013, Kazmierczak *et al*., 2016)
Not mentioned	5 (29.4)	(Teo *et al*., 2015, Lim *et al*., 2013a, Le *et al*., 2016, Phu *et al*., 2016, Apisarnthanarak *et al*., 2013)
Not performed	1 (5.9)	(Cheng *et al*., 2014)

Study characteristic

Population

Of the 17 articles included, 2013 was the year that has the most publications (Table 1). Vietnam and Thailand had most of the data (59%), Singapore, Malaysia, and Indonesia accounting for 35%, and there was one multinational study. Most of the articles had cross-sectional as their study design. Isolates were most commonly cultured from hospital-acquired infections of persons of all ages than solely from children or adults.

Laboratory methods

Method for identification used in the study from the highest number, respectively, were molecular, MALDI-TOF, API, and biochemically (Table 1). Disk diffusion was the most common method for AST used. Several studies did not mention their method of identification. They were a multicentre study that had followed the PPS methodology developed by ECDC and a review study. A study that did not mention their AST method was also a multicentre study and a molecular-based study. The multicentre study was following criteria from the Clinical and Laboratory Standards Institute guidelines (CLSI) and was enrolled in an external quality assurance program for microbiology.

Resistance rate

There were only Vietnam, Thailand, Indonesia, Singapore, and Malaysia that can be analyzed in this study regarding the resistance rate to different classes of antibiotics (Table 2). There were four studies from Vietnam, two studies from Thailand, and only one

Table 2. Overall resistance rate

Antibiotic	Vietnam (%R) (Biedenbach *et al.*, 2014, Biedenbach *et al.*, 2016, Tran *et al.*, 2017, Le *et al.*, 2016)	Thailand (%R) (Apisarnthanarak *et al.*, 2013, Kiddee *et al.*, 2013)	Indonesia (%R) (Karuniawati *et al.*, 2013)	Singapore (%R) (Lim *et al.*, 2013a)	Malaysia (%R) (Wong *et al.*, 2015)
Specimen size	614	50	[a]	55	84
Ceftazidime	42.9	88	-	-	2.4
Cefotaxime	-	100	-	-	-
Ceftriaxone	4.72	100	-	-	-
Cefepime	32.7	96	-	-	4.8
Piperacillin	-	70	-	-	-
Piperacillin-tazobactam	13.5	20	-	-	7.1
Ticarcillin	-	88	-	-	-
Ticarcillin/clavulanate	-	98	-	-	8.3
Cefoperazone	-	94	-	-	-
Cefoperazone/sulbactam	2.9	-	-	-	-
Carbapenem	3.9	14.4-15.5[a]	21.9	50	-
Imipenem	41.5	92	-	-	-
Meropenem	37.1	100	-	-	3.6
Doripenem	30.1	-	-	-	-
Aztreonam	-	90	-	-	8.3
Ciprofloxacin	40.5	90	-	-	4.8
Ofloxacin	-	92	-	-	-
Levofloxacin	41.3	92	-	-	-
Gentamicin	39.7	82	-	-	4.8
Tobramycin	35.8	-	-	-	4.8
Amikacin	18.24	62	-	-	2.4
Colistin	0.1	0	-	-	-

[a] Specimen size unknown

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Table 3. Genetic analysis

Resistance genes	Country of isolation	Isolate number	Reference
β-lactamase			
bla$_{\text{IMP-1}}$	Indonesia	4	(Karuniawati *et al*., 2013)
	Malaysia	1	(Kazmierczak *et al*., 2016)
	Phillipines	1	(Kazmierczak *et al*., 2016)
	Thailand	2	(Kazmierczak *et al*., 2016)
bla$_{\text{IMP-7}}$	Thailand	1	(Kazmierczak *et al*., 2016)
bla$_{\text{IMP-14}}$	Thailand	1	(Kazmierczak *et al*., 2016)
bla$_{\text{IMP-15}}$	Vietnam	10	(Tada *et al*., 2016)
bla$_{\text{IMP-26}}$	Vietnam	12	(Tada *et al*., 2016)
	Phillipines	10	(Kazmierczak *et al*., 2016)
bla$_{\text{IMP-48}}$	Thailand	6	(Kazmierczak *et al*., 2016)
bla$_{\text{IMP-51}}$	Vietnam	3	(Tada *et al*., 2016)
bla$_{\text{VIM-2}}$	Phillipines	21	(Kazmierczak *et al*., 2016)
	Thailand	3	(Kazmierczak *et al*., 2016)
bla$_{\text{VIM-5}}$	Thailand	2	(Kazmierczak *et al*., 2016)
bla$_{\text{VIM-6}}$	Malaysia	1	(Kazmierczak *et al*., 2016)
bla$_{\text{VIM-45}}$	Thailand	2	(Kazmierczak *et al*., 2016)
bla$_{\text{VEB-1}}$	Vietnam	5	(Tada *et al*., 2016)
	Singapore	3	(Cheng *et al*., 2014)
bla$_{\text{VEB-2}}$	Thailand	1	(Kiddee *et al*., 2013)
bla$_{\text{NDM-1}}$	Vietnam	1	(Tada *et al*., 2016)
	Phillipines	13	(Kazmierczak *et al*., 2016)
	Thailand	4	(Kazmierczak *et al*., 2016)
	Singapore	3	(Teo *et al*., 2015)
bla$_{\text{OXA-10}}$	Thailand	1	(Kiddee *et al*., 2013)
bla$_{\text{PER-1}}$	Vietnam	2	(Tada *et al*., 2016)
bla$_{\text{PSE-1}}$	Vietnam	12	(Tada *et al*., 2016)
	Thailand	2	(Kiddee *et al*., 2013)
OprD	Thailand	118	(Khuntayaporn *et al*., 2013)
AmpC cephalosporinase	Thailand	5	(Khuntayaporn *et al*., 2013)
Aminoglycoside			
aac (3’’)-Ia	Vietnam	7	(Tada *et al*., 2016)
aac (3)-Ic	Thailand	10	(Kiddee *et al*., 2013)
aac (6’)-Ib	Vietnam	20	(Tada *et al*., 2016)
	Thailand	5	
aacA4	Malaysia	1	(Kor *et al*., 2013)
aacA7	Thailand	10	(Kiddee *et al*., 2013)
aacA37	Vietnam	12	(Tada *et al*., 2016)
aacC3	Malaysia	5	(Kor *et al*., 2013)
aadA1	Vietnam	7	(Tada *et al*., 2016)
	Thailand	1	(Kiddee *et al*., 2013)
	Malaysia	1	(Kor *et al*., 2013)
aadA2	Thailand	2	(Kiddee *et al*., 2013)
aadA6	Thailand	25	(Kiddee *et al*., 2013)

	Malaysia	8	(Kor *et al.*, 2013)
aadA11	Vietnam	27	(Tada *et al.*, 2016)
aadA15	Thailand	1	(Kiddee *et al.*, 2013)
aadB	Vietnam	6	(Tada *et al.*, 2016)
	Thailand	9	(Kiddee *et al.*, 2013)
aph (3')-Via	Vietnam	2	(Tada *et al.*, 2016)
Arr	Thailand	1	(Kiddee *et al.*, 2013)
cmlA5	Thailand	11	(Kiddee *et al.*, 2013)
	Malaysia	5	(Kor *et al.*, 2013)
cmlA6	Thailand	1	(Kiddee *et al.*, 2013)
orfD	Thailand	25	(Kiddee *et al.*, 2013)
	Malaysia	8	(Kor *et al.*, 2013)
rmtB	Vietnam	13	(Tada *et al.*, 2016)
		2	(Tada *et al.*, 2013)
Smr	Thailand	10	(Kiddee *et al.*, 2013)
tnpA	Thailand	1	(Kiddee *et al.*, 2013)

study from Malaysia, Singapore, and Indonesia. This study calculated all the isolates numbers found in the articles into one specimen size for each country to be used as a numerator. Vietnam had the biggest isolates numbers, and others had less than 100 isolates. There was no specimen size found in the Indonesian study.

There was a variable P. aeruginosa resistance rate among countries for different classes of antibiotics. Thailand had the complete data of antibiotic resistance and had the highest resistance rate of almost all antibiotics listed (Table 2), except for carbapenem. Overall, Singapore had the highest resistance to carbapenem. But, if we look at individual data, one study from Vietnam had a 71% resistance rate on carbapenem (Le et al., 2016). Colistin had the lowest resistance rate among all antibiotics.

Genetic Analysis

Reports from Malaysia and Thailand showed the possibility of drug-resistant Pseudomonas aeruginosa harboring integron spreading (Kor et al., 2013, Kiddee et al., 2013). Integrons are mostly located on transposon, with class 1 integrons are the most commonly found in antibiotic-resistant Pseudomonas aeruginosa (Kiddee et al., 2013, Kor et al., 2013) Sequence analysis from class 1 integron in Northern Thailand revealed resistance to aminoglycoside (aac, aad and aph), chloramphenicol (cmlA), β-lactams (blaPSE, blaOXA and blaVEB) and rifampicin (arr) (Kiddee et al., 2013) Study in Malaysia also found class 2 integrons from MDR Pseudomonas aeruginosa, although in small number of isolate, and the most common gene cassettes were those encoding resistance to trimethoprim (dfr), and aminoglycosides (aad) (Kor et al., 2013)

DISCUSSION

In this study, we found that in Southeast Asia, most P.aeruginosa was still sensitive to colistin. A similar result was found in Germany; from ten year period, researchers found that both MDR and non-MDR P.aeruginosa was still susceptible to colistin (Yayan et al., 2015).

Our study shows that P.aeruginosa resistance to antibiotic were endemic in almost all antibiotics. Class A ESBLs deliver resistance to expanded-spectrum cephalosporins and are inhibited in vitro by β-lactamase combination agents (Potron et al., 2015) Two isolates of blaPER-1, the first ESBL identified, was found in Vietnam (Tada et al., 2016)

Class B β-lactamases hydrolyze carbapenems and other-lactams and not inhibited in vitro by β-lactamase combination agents (Potron et al., 2015) Resistance to carbapenems in P.aeruginosa is caused by reduced antibiotic permeability, includes a nontransmissible porin deficiency (reduction of OprD protein expression), efflux pump; and modification of antibiotics by overproducing β-lactamases (AmpC cephalosporinase) and metallo-β-lactamases (primarily IMP and VIM) (Apisarnthanarak et al., 2013, Khuntayaporn et al., 2013) Reduction in oprD transcription, mexAB-oprM mRNA overproduction and mexXY mRNA overproduction are the most prevalent resistance mechanisms, whereas AmpC overexpression is the least prevalent among Thailand carbapenem resistant P. aeruginosa clinical isolates (Khuntayaporn et al., 2013) In Southeast Asia, most carbapenemases-producer P.aeruginosa harbor blaIMP and blaVIM gene (Karuniawati et al., 2013) (Kazmierczak et al., 2016) Three case of blaNDM-1 producer P.aeruginosa has been found in surgical intensive care unit in Singapore, suggested a transmission event (Teo et al., 2015)

The resistance mechanism of Pseudomonas aeruginosa to aminoglycoside are due to enzymatic modification and the methylation of 16S rRNA. Eight plasmid-associated 16sRNA methylase genes are armA, rmtA, rmtB, rmtC, rmtD, rmtE, rmtF and npmA. rmtB was found in hospitals in Vietnam (Tada et al., 2013). Resistance P. aeruginosa to colistin remains unclear, with the linkage between genes PmrAB, PhoPQ, ParRS and CprRS (Bialvaei and Samadi Kafil, 2015).

We only used PubMed as a search engine, and that limits our data. We suggest further study using various search engine that is readily accessible to extend the number of the included articles. Experiencing difficulties in gathering the data, we also suggest researchers focusing on antimicrobial resistance to explicitly provide detail data both in the method and result section.

CONCLUSIONS

Colistin had the lowest resistance rate among all antibiotics. Another study with more extensive data should be done to validate this study. Future research should explicitly provide detail data results for antimicrobial resistance analyses.

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