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Antimicrobial Susceptibility of Gram-negative Organisms from Southeast Asia

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SENTRY ANTIMICROBIAL SURVEILLANCE

Introduction

- The SENTRY Antimicrobial Surveillance Program monitors the occurrence frequency and antimicrobial susceptibility of organisms from various infection types worldwide.
- Gram-negative pathogens can cause serious bloodstream infections, pneumonia, and urinary tract infections. Increasing antimicrobial resistance remains a concern among *Enterobacterales* as well as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Monitoring resistance trends of empirical antimicrobial therapy as well as novel agents is crucial to reduce morbidity and mortality of patients with infections caused by these organisms.
- We evaluated the susceptibility results for Gram-negative bacteria from hospitals in Southeast Asia during 2017–2020.

Materials and Methods

Bacterial isolates

- A total of 2,366 Gram-negative bacilli were consecutively collected (1/patient) in 2017–2020 from 4 hospitals located in Malaysia (n=584), Philippines (n=748), Thailand (n=667), and Vietnam (n=367).
- Organisms were mainly from patients with pneumonia (n=652), urinary tract infection (n=555), and bloodstream infection (n=497).
- Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in the program.

Susceptibility testing

- Organisms were tested for susceptibility by broth microdilution method in a central laboratory (JMI Laboratories).
- Results were interpreted using CLSI breakpoint criteria, except for colistin where EUCAST criteria was applied.
- Carbapenem-resistant *Enterobacterales* (CRE) were defined as *Enterobacterales* with MIC values at ≥4 mg/L for imipenem (except *Proteeae*), meropenem, and/or doripenem. These qualified isolates were screened for carbapenemase (CPE) genes by whole genome sequencing.
- Isolates were categorized as multidrug-resistant (MDR) according to criteria published by Magiorakos *et al.* (2012), i.e., nonsusceptibility to ≥1 agent in ≥3 antimicrobial classes. The antimicrobial classes and drug representatives used in the analysis were: antipseudomonal cephalosporins (ceftazidime and cefepime), carbapenems (imipenem and meropenem), broad-spectrum penicillins combined with a β-lactamase-inhibitor (piperacillin-tazobactam), fluoroquinolones (ciprofloxacin and levofloxacin), aminoglycosides (gentamicin, tobramycin, and amikacin), and a polymyxin (colistin) for *P. aeruginosa*.

Results

- Ceftazidime-avibactam ($MIC_{50/90}$, 0.12/1 mg/L; 92.0%S overall) was the most active β-lactam agent against *Enterobacterales* (n=1,633), followed by meropenem ($MIC_{50/90}$, 0.03/16 mg/L; 88.0%S) and colistin ($MIC_{50/90}$, 0.12/>8 mg/L; 87.3%S per EUCAST criteria; Table 1).
- CRE rates varied from 9.1% (Malaysia) to 23.1% (Vietnam) and were 11.9% overall (Figure 1).
- Ceftazidime-avibactam activity against CRE varied from 47.8% (Vietnam) to 0.0% (Malaysia) and were 32.5% overall (Table 1).
- The most active agent against CRE was amikacin ($MIC_{50/90}$, 4/32 mg/L), with susceptibility rates ranging from 69.6% (Vietnam) to 93.7% (Philippines; Table 1).
- A carbapenemase was identified in 165 of 194 CRE isolates (85.1%), including NDM-type (123 isolates; 63.4% of CREs), OXA-type (39; 20.1% of CREs), KPC-type (33; 17.0% of CREs), and ≥2 CPEs (29; 14.9% of CREs; Table 2).
- The most active agents against *P. aeruginosa* (n=460) after colistin ($MIC_{50/90}$, 1/1 mg/L; 100.0%S) were ceftazidime-avibactam ($MIC_{50/90}$, 2/16 mg/L; 88.2%S), ceftolozane-tazobactam ($MIC_{50/90}$, 0.5/16 mg/L; 88.9%S), and tobramycin ($MIC_{50/90}$, 0.5/>16 mg/L; 87.2%S; Table 1).
- Only 21.2% of *A. baumannii* (from 14.7% [Malaysia] to 46.0% [Philippines]) were meropenem-susceptible and 32.2% of *A. baumannii* (from 20.0% [Vietnam] to 50.0% [Philippines]) were amikacin-susceptible (Table 1).
- Yearly frequency of selected resistance phenotypes for all countries combined are shown in Figure 2.

Figure 1. Prevalence of key resistance phenotypes stratified by country (2017–2020)

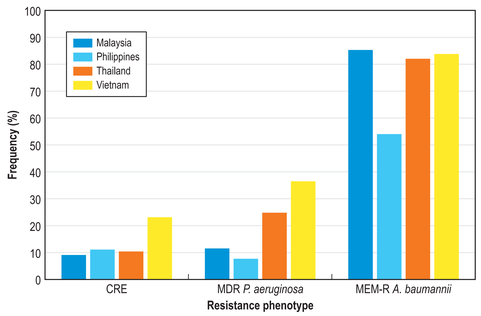

Figure 2. Yearly frequency of key resistance phenotype for all countries combined

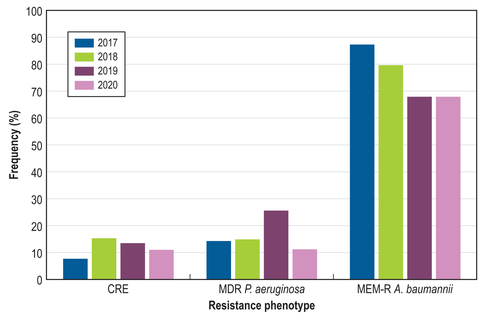

Table 1. Antimicrobial susceptibility of *Enterobacterales*, *P. aeruginosa*, and *A. baumannii* from countries in Southeast Asia (2017–2020)

Organism/antimicrobial	All countries combined (no. of isolates)			% Susceptible[a] (no. of isolates)			
	MIC_{50}	MIC_{90}	% Susceptible[a]	Malaysia	Philippines	Thailand	Vietnam
Enterobacterales			(1,633)	(386)	(568)	(480)	(199)
Ceftazidime	0.5	>32	59.7	71.8	59.5	57.5	42.2
Ceftriaxone	0.25	>8	55.0	66.1	57.9	51.5	33.7
Piperacillin-tazobactam	4	>128	76.9	83.9	75.4	76.9	67.5
Ceftolozane-tazobactam	0.25	>16	81.9	85.7	83.0	81.7	71.7
Ceftazidime-avibactam	0.12	1	92.0	90.9	93.5	92.7	87.9
Meropenem	0.03	16	88.0	90.9	88.9	89.4	76.4
Imipenem	≤0.12	8	85.2	86.0	85.4	88.3	75.9
Levofloxacin	0.5	>16	54.1	68.2	51.3	53.3	36.7
Gentamicin	0.5	>16	75.2	83.7	73.2	73.1	69.8
Amikacin	2	8	97.6	98.2	98.8	97.7	92.5
Colistin	0.12	>8	87.3	88.3	86.0	85.7	92.9
CRE			(194)	(35)	(63)	(50)	(46)
Ceftazidime-avibactam	>32	>32	32.5	0.0	41.3	30.0	47.8
Levofloxacin	>16	>16	6.2	20.0	4.8	2.0	2.2
Gentamicin	1	>16	59.8	60.0	46.0	74.0	63.0
Amikacin	4	32	85.6	88.6	93.7	88.0	69.6
Colistin	0.12	>8	86.0	91.4	98.4	64.0	89.1
P. aeruginosa			(460)	(130)	(130)	(137)	(63)
Ceftazidime	2	>32	82.6	86.9	91.5	75.7	69.8
Piperacillin-tazobactam	4	64	81.4	83.8	87.6	76.5	74.6
Ceftolozane-tazobactam	0.5	16	88.9	93.1	97.7	83.9	73.0
Ceftazidime-avibactam	2	16	88.2	92.3	96.9	82.4	74.6
Levofloxacin	0.5	>16	71.0	79.2	76.2	64.0	58.7
Meropenem	0.5	32	79.7	82.3	91.5	72.1	66.7
Tobramycin	0.5	>16	87.2	93.1	95.4	84.7	63.5
Colistin	1	1	100.0	100.0	100.0	100.0	100.0
A. baumanni			(273)	(68)	(50)	(50)	(105)
Amikacin	>32	>32	32.2	33.8	50.0	38.0	20.0
Ceftazidime	>32	>32	19.4	11.8	44.0	16.0	14.3
Ampicillin-sulbactam	64	>64	20.9	14.7	48.0	14.0	15.2
Meropenem	>32	>32	21.2	14.7	46.0	18.0	15.2
Minocycline	2	32	63.1	62.7	92.0	53.1	54.3
Levofloxacin	16	>16	20.1	20.6	36.0	14.0	15.2
Tobramycin	>16	>16	30.0	33.8	50.0	30.0	18.1
Colistin	0.25	0.5	97.1	98.5	98.0	94.0	97.1

[a] Per CLSI criteria.

Table 2. List of carbapenemases produced stratified by country

β-Lactamase	No. of isolates per country (% of CRE isolates)				
	Malaysia	Philippines	Thailand	Vietnam	Total
NDM-type	35 (100.0%)	39 (61.9%)	35 (70.0%)	14 (30.4%)	123 (63.4%)
NDM-1	16	8	30	6	60
NDM-4	9	—	1	1	11
NDM-5	10	4	4	6	24
NDM-7	—	27	—	—	—
OXA-type	—	—	34 (68.0%)	5 (10.9%)	39 (20.1%)
OXA-48	—	—	1	3	3
OXA-181	—	—	2	2	5
OXA-232	—	—	31	—	31
KPC-2	—	23 (36.5%)	—	10 (21.7%)	33 (17.0%)
	—	—	—	—	—
NDM + OXA	—	—	23	2	—
NDM + KPC-2	—	1	—	2	—
NDM + OXA + KPC-2	—	—	—	—	1
Total isolates with CPE	35 (100.0%)	61 (96.8%)	46 (92.0%)	23 (50.0%)	165 (85.1%)
Total CRE isolates	35	63	50	46	194

Abbreviations: CPE, carbapenemase; CRE, carbapenem-resistant *Enterobacterales*.

Conclusions

- Gram-negative bacilli from Southeast Asia showed high rates of resistance.
- The production of metallo-β-lactamase (NDM-type) represented the main mechanism of resistance to carbapenems among *Enterobacterales*; the NDM-type was observed in 63.4% of Southeast Asian CREs.
- The results of this investigation emphasize the importance of continued surveillance in the region.

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