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Multidrug-resistant *Klebsiella pneumoniae* from clinical isolates at dr. Soeradji Tirtonegoro central hospital Klaten

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ABSTRACT

Background: *Klebsiella pneumoniae* is a Gram-negative bacterium that often causes nosocomial infections. Use of broad-spectrum antibiotics as an empiric therapy has contributed to increases of *K. Pneumoniae* strains that are resistant to antibiotics. Therefore, a test on antibiotic susceptibility of *K. pneumoniae* is needed as a guide in treating a definitive therapy.
Objective: This study aimed to measure the percentages of multidrug-resistant (MDR) of *K. pneumoniae* and its susceptibility at dr. Soeradji Tirtonegoro Central Hospital, Klaten, Central Java in 2017.
Methods: This study was a descriptive study using secondary data at the Clinical Microbiology Laboratorium of dr. Soeradji Tirtonegoro Central Hospital, Klaten. The *K. pneumoniae* was isolated from patients hospitalized in the hospital from January 1, 2017, to December 31 2017. Identifications of the *K. pneumoniae* were conducted by a colony morphology observation, a gram staining, and a biochemical test. The test of antibiotics susceptibility used Kirby-Bauer method based on Clinical and Laboratory Standards Institute (CLSI). The data were analyzed by univariate analysis.
Results: In 2017, there were 213 *K. pneumoniae* isolates from various clinical samples. Among them, 122 isolates were MDR *K. pneumoniae* (57.28%). The majority of MDR *K. pneumoniae* were resistant to a wide range of antibiotics. The MDR *K. pneumoniae* had only a good sensitivity to meropenem (98.43%), amikacin (93.75%), nitrofurantoin (88.89%), and fosfomycin (88.89%). In contrast, all non-MDR *K. pneumoniae* had good sensitivity to all tested antibiotics, except to ampicillin.
Conclusion: The percentage of MDR *K. pneumoniae* isolates at the dr. Soeradji Tirtonegoro Cental in 2017 was 57%. MDR *K. pneumonia* clinical isolates showed good susceptibility to meropenem and amikacin.

Latar Belakang: Klebsiella pneumoniae *merupakan bakteri Gram negatif yang sering menyebabkan infeksi nosokomial. Penggunaan antibiotik spektrum luas sebagai terapi empirik menyebabkan meningkatnya strain K.* pneumoniae *yang resisten antibiotika. Oleh karena itu, diperlukan uji kepekaan terhadap antibiotik sebagai dasar pemberian terapi definitif dalam penanganan infeksi.*
Tujuan: *Untuk mengetahui persentase multidrug-resistant (MDR)* K. pneumoniae *dan pola kepekaannya terhadap berbagai antibiotika di RSUP dr. Soeradji Tirtonegoro, Klaten tahun 2017.*

Metode: *Penelitian ini merupakan penelitian deskriptif analitik menggunakan data sekunder di Laboratorium Mikrobiologi RSUP dr. Soeradji Tirtonegoro tahun 2017.* K. pneumoniae *diisolasi dari sampel pasien yang mondok di RSUP Soeradji Tirtonegoro antara 1 Januari – 31 Desember 2017. Identifikasi* K. pneumoniae *dilakukan dengan pengamatan morfologi koloni, pengecatan Gram dan uji biokimiawi. Uji kepekaan terhadap antibiotika dilakukan dengan metode Kirby Bauer berdasakan CLSI. Data dianalisis dengan univariat.*
Hasil: *Selama penelitian didapatkan 213 isolat* K. pneumoniae *dengan 122 isolat diantaranya adalah MDR* K. pneumoniae *(57.28%). Sebagian besar MDR* K. pneumoniae *telah resisten terhadap antibiotik yang diujikan. MDR* K. pneumoniae *hanya mempunyai sensitivitas yang tinggi terhadap meropenem (98.43%), amikacin (93.75%), nitrofurantoin (88.89%), dan fosfomisin (88.89%). Sebaliknya, semua isolat* K.pneumoniae *yang bukan MDR, masih mempunyai sensitivitas yang baik terhadap semua antibiotika yang diujikan, kecuali terhadap ampicillin.*
Kesimpulan: *Presentase infeksi oleh MDR* K. pneumoniae *di RSUP dr. Soeradji Tirtonegoro, Klaten tahun 2017 adalah 57.28%. MDR* K. pneumoniae *menunjukkan kepekaan yang baik terhadap meropenem dan amikasin*

INTRODUCTION

Klebsiella pneumoniae is a Gram-negative and encapsulated bacterium that resides in mucosal surfaces of mammals and the environment such as soil, vegetation, and water. In humans, *K. pneumoniae* typically colonize the oropharynx and the gastrointestinal tract. It is also known as the most common cause of health-care-associated infection (HAIs) in the world. This bacterium can cause urinary tract infections, hospital-acquired pneumonia, ventilator-associated pneumonia, surgical wound infection, bacteraemia, and septicemia.[1] Children and patients with an immunocompromised immune system, such as patients in ICU, patients with malignancy, patients with HIV, patients with chemotherapy, or patients with diabetes, are more susceptible to a *K. pneumoniae* infection.[2]

Some studies reported increasing cases of HAIs caused by *K. Pneumoniae*.[3,4] Chung and collegues, who conducted a prospective surveillance study in 73 hospitals in 10 countries from 2008-2009, reported that the *K. pneumoniae* was one of the most frequent isolates from adults with hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP) in Asian countries.[3]

World Health Organization (WHO) has defined as a threat to global health because of increasing numbers of resistant strains.[5] Production of extended-spectrum beta-lactamases and other mechanisms of antibiotic resistance are favoured by a constant horizontal transfer of antimicrobial-resistant genes through mobile elements such as plasmids and transposons, which are essential factors for the *K. pneumoniae* to survive in hospital environments. The development of resistant bacteria has been increased due to frequent uses of broad-spectrum antibiotics for hospitalized patients, especially in ICU departments.[6] High incidences of *K. pneumoniae* resistance can cause a limited choice of antibiotics for infection treatments leading to increased morbidity, mortality and hospital costs.[5]

Prevalence of *K. pneumoniae* infection was 13% in the United States of America, 5% in Pakistan, 64.2 % in Nigeria, 33.9% in India, 17.4% in Denmark, and 14.1% in Singapore.[7] In Indonesia, an infection of ESBL-producing *K. pneumoniae* was 35.35% found in 297 inpatient isolates from January to April 2005 at dr. Soetomo Hospital, Surabaya.[8] Prevalence of ESBL-producing *K. pneumoniae* became 23% in January-June 2010, 50.28% in January-November 2011, 58% in July-December 2012, and 38.5% in October 2014-May 2015 at the dr. Soetomo Hospital.[9,10] At Kariadi Hospital Semarang, ESBL-producing *Enterobacteriaceae* was 37.64% from 85 isolates. Meanwhile, at Saiful Anwar Hospital, Malang, a number of Enterobacteriaceae found was 52% among 75 isolates.[11]

Most of *K. pneumoniae* was reported to be resistant to various antibiotics like ampicillin, cefazolin, and cefuroxime that was the least effective for *K. pneumonia*; meanwhile, amikacin,

piperacillin-tazobactam, and meropenem had the most favourable profile.[12] This report of *K. pneumonia* is supported by a study conducted by Madahiah founding that K. pneumoniae isolates were 100% resistant to ampicillin and 100% sensitive to amikacin.[13] Then ciprofloxacin and amoxicillin-clavulanic acid indicated 38.75% and 36.69% resistance, respectively. Results of the study are similar to a study of Cepas et al. reporting that 40% of K. pneumoniae strains were resistant to ciprofloxacin and amoxicillin-clavulanic acid.[14]

The antibiotic susceptibility pattern of *K. pneumoniae* can vary from time to time in a particular location. Thus, it is significant to conduct monitoring on multidrug-resistance (MDR) organisms as an antibiotic susceptibility test is needed by clinicians to determine an effective definitive therapy in managing infections.[15] Therefore this study was conducted to determine incidences of MDR *K. pneumoniae* infections and its susceptibility pattern to various antibiotics at dr. Soeradji Tirtonegoro Central Hospital, Klaten.

METHODS

A cross-sectional study was conducted using secondary data in the Clinical Microbiology Laboratory of dr. Soeradji Tirtonegoro Central Hospital, Klaten. Subjects of this study were *K. pneumoniae* isolates obtained from various clinical samples of hospitalized patients at the hospital, from January–December 2017. Identification of *K. pneumoniae* was organized by culturing on Mc Conkey agar, microscopic examinations with Gram staining and biochemical test using Microbact™ GNB 24E (Oxoid, UK).

Antibiotic susceptibility tests were conducted by the Kirby Bauer method based on the Clinical and Laboratory Standards Institute (CLSI). The used antibiotics included ampicillin (10μg), gentamicin (10μg), ceftriaxone (30μg), trimethoprim-sulfamethoxazole (25μg), cefuroxime (30μg), ciprofloxacin (5μg), cephazolin (30μg), nitrofurantoin (100μg), amikacin (30μg), meropenem (10μg), levofloxacin (5μg), tobramycin (10μg), and piperacillin-tazobactam (100/10μg). The antibiotics were tested according to agreements of the Indonesian Society for Clinical Microbiologist (PAMKI) 2015 based on CLSI references.[16] The *K. pneumoniae* was classified as a multidrug-resistant (MDR) *K. pneumoniae* if the isolates were resistant to three or more different classes of antimicrobials.[17]

This study was approved by the Ethical Committee, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia by a number: KE/FK/0862/EC/2017.

RESULTS

A During the period of January-December 2017, there were 213 *K. pneumoniae* isolates from 1,105 (19.28%) total clinical bacterial isolates at dr. Soeradji Tirtonegoro Central Hospital. The *K. pneumoniae* isolates were obtained mostly from male patients (54.46%). Based on age, the isolates mostly were from patients by 18-64 years old (47.89%). Most of the isolates were obtained from Melati Ward (20.66%) and intensive care unit (ICU) (19.72%). In addition, they were mostly obtained from respiratory specimens (61.97%) that consisted of sputum, bronchial washing, tracheal aspirate, and bronchoalveolar lavage fluid (Table 1).

During the period of study, there were 122 MDR *K. pneumoniae* isolates (57.28%). The *K. pneumoniae* was classified as an MDR *K. pneumoniae* if the isolates were resistant to three or more different classes of antimicrobials.[17]

Most of MDR *K. pneumoniae* were resistant to a wide range of antibiotics. Antibiotic sensitivity could be called good if it had ≥ 80% sensitivity.[18] Then it had only a good sensitivity to meropenem (98.43%), amikacin (93.75%), nitrofurantoin (88.89%), and fosfomycin (88.89%) (Table 2). In contrast, all non-MDR *K. pneumoniae* had good sensitivity to all tested antibiotics, except to Ampicillin.

Table 1. Clinical characteristics of patients with *K. pneumoniae* isolates

Characteristics		Total	
		n	%
Sex	Male	116	54.46
	Female	86	40.38
	Unknown	11	5.16
	Total	213	100
Age (year)	< 18	42	19.72
	18 – 64	102	47.89
	≥ 65	60	28.17
	Unknown	9	4.23
	Total	213	100
Sampling Location	Melati ward	44	20.66
	ICU	42	19.72
	Dahlia ward	25	11.74
	Edelweis ward	25	11.74
	PICU	15	7.04
	HCU	10	4.69
	Menur ward	10	4.69
	Outpatient	10	4.69
	Perinatology ward	7	3.29
	Mawar ward	5	2.35
	Teratai ward	5	2.35
	Kenanga ward	4	1.88
	NICU	3	1.41
	Aster ward	2	0.94
	ICCU	2	0.94
	Unknown	4	1.88
	Total	213	100
Clinical Specimen	Respiratory	132	61.97
	Wound	48	22.54
	Blood	20	9.39
	Urine	13	6.10
	Total	213	100

In this study, the author used the CLSI M100-S25 document as a reference method for antibiotic susceptibility test based on the Indonesian Association of Clinical Microbiologists in terms of specimen origins, which differentiate panels of antibiotics tested to each specimen based on its origins. Since the authors included various specimen sources,

Table 2. Antibiotic susceptibility patterns of MDR-*K. pneumoniae* and non-MDR-*K. pneumoniae* isolates

No	Antibiotics	Number tested	MDR				Non-MDR			
			Sensitive		Resistant		Sensitive		Resistant	
			n	%	n	%	n	%	n	%
1	Amikacin	217	120	93.75	8	6.25	89	100.00	0	0.00
2	Amoxicillin	203	29	25.89	83	74.11	90	98.90	1	1.10
3	Ampicillin	194	2	1.75	112	98.25	2	2.50	78	97.50
4	Gentamicin	163	40	43.48	52	56.52	70	98.59	1	1.41
5	Meropenem	220	125	98.43	2	1.57	93	100.00	0	0.00
6	Levofloxacin	227	77	59.23	53	40.77	97	100.00	0	0.00
7	Ceftriaxone	186	17	15.74	91	84.26	78	100.00	0	0.00
8	Trimethoprim sulfamethoxazole	203	22	20	88	80.00	87	93.55	6	6.45
9	Cefuroxime	221	14	11.02	113	88.98	93	98.94	1	1.06
10	Ciprofloxacin	99	21	35.99	38	64.01	37	92.50	3	7.50
11	Tobramycin	227	37	28.46	93	71.54	94	96.91	3	3.09
12	Piperacilin-Tazobactam	154	65	75.81	21	24.19	68	100.00	0	0.00
13	Cefazoline	171	5	5.05	94	94.95	68	94.44	4	5.56
14	Nitrofurantoin	12	8	88.89	88.89	88.89	3	100.00	0	0.00
15	Fosfomycin	12	8	88.89	88.89	88.89	3	100.00	0	0.00

a number of antibiotics tested to each isolate was different, depending on its specimen origin (Table 3, Table 4).[16]

The MDR *K. pneumoniae* isolated from respiratory specimens only had good sensitivity to meropenem (98.63%) and amikacin (98.63%). For MDR *K. pneumoniae* isolated from wound specimens, sensitivity to meropenem, amikacin and piperacillin-tazobactam were good with 100%, 90.48%, and 80% respectively. All non-MDR K. pneumoniae isolated from respiratory and wound specimens had good sensitivity to all tested antibiotics, except to ampicillin (Table 3).

MDR *K. pneumoniae* isolated from blood specimens had the highest sensitivity to meropenem (100%), followed by amikacin (93.75%). All of non-MDR *K. pneumoniae* isolates obtained from blood were sensitive to amikacin, gentamicin, meropenem, levofloxacin, ceftriaxone, tobramycin, and piperacillin-tazobactam. The sensitivity of non-MDR *K. pneumoniae* isolates obtained from blood to ciprofloxacin, cefuroxime, and ampicillin was 75%, 75%, and 0%, respectively (Table 4)

Resistance rates of MDR *K. pneumoniae* isolated from urine specimens to meropenem, amikacin, piperacillin-tazobactam, nitrofurantoin, and fosfomycin were 100%; 100%; 100%; 88,89%; and 88,89% respectively. In contrast, all non-MDR *K. pneumoniae* isolated from urine specimens had good sensitivity to all tested antibiotics, except to ampicillin (Table 4).

Table 3A. Antibiotic susceptibility patterns of MDR K. *pneumoniae* and non-MDR *K. pneumoniae* isolated from respiratory specimens

No	Antibiotics	Number tested	Respiratory							
			MDR				Non-MDR			
			Sensitive		Resistant		Sensitive		Resistant	
			n	%	n	%	n	%	n	%
1	Amikacin	126	70	94.59	4	5.41	52	100.00	0	0.00
2	Amoxicillin	130	17	22.97	57	77.03	55	98.21	1	1.79
3	Ampicillin	113	1	1.52	65	98.48	1	2.13	46	97.87
4	Gentamicin	96	23	40.35	34	59.65	39	100.00	0	0.00
5	Meropenem	126	72	98.63	1	1.37	53	100.00	0	0.00
6	Levofloxacin	130	51	68.92	23	31.08	56	100.00	0	0.00
7	Ceftriaxone	106	8	13.11	53	86.89	45	100.00	0	0.00
8	Trimethoprim sulfamethoxazole	126	13	18.57	57	81.43	52	92.86	4	7.14
9	Cefuroxime	125	9	12.68	62	87.32	53	98.15	1	1.85
10	Tobramycin	130	24	32.43	50	67.57	55	98.21	1	1.79
11	Tazobactam	91	40	72.73	15	27.27	36	100.00	0	0.00
12	Cefazolin	113	3	4.48	64	95.52	43	93.48	3	6.52
13	Ciprofloxacin	-	-	-			-	-	0	0.00

Table 3B. Antibiotic susceptibility patterns of MDR K. *pneumoniae* and non-MDR *K. pneumoniae* isolated from wound specimens

No	Antibiotics	Number tested	Wound							
			MDR				Non-MDR			
			Sensitive		Resistant		Sensitive		Resistant	
			n	%	n	%	n	%	n	%
1	Amikacin	42	19	90.48	2	9.52	21	100.00	0	0.00
2	Amoxicillin	43	9	42.86	12	57.14	22	100.00	0	0.00
3	Ampicillin	40	1	5.00	19	95.00	0	0.00	20	100.00
4	Gentamicin	34	6	40.00	9	60.00	19	100.00	0	0.00
5	Meropenem	44	22	100.00	0	0.00	22	100.00	0	0.00
6	Levofloxacin	45	8	36.36	14	63.64	23	100.00	0	0.00
7	Ceftriaxone	39	4	21.05	15	78.95	20	100.00	0	0.00
8	Trimethoprim sulfamethoxazole	45	4	18.18	18	81.82	22	95.65	1	4.35
9	Cefuroxime	45	1	4.55	21	95.45	23	100.00	0	0.00
10	Tobramycin	46	7	30.43	16	69.57	22	95.65	1	4.35
11	Tazobactam	34	12	80.00	3	20.00	19	100.00	0	0.00
12	Cefazolin	38	2	10.00	18	90.00	18	100.00	0	0.00
13	Ciprofloxacin	46	5	21.74	18	78.26	23	100.00	0	0.00

Table 4. Antibiotic susceptibility patterns of MDR K. pneumoniae and non-MDR K. pneumoniae isolated from blood and urine specimens

No	Antibiotics	Blood								Urine							
		Number tested	MDR				Non-MDR				Number tested	MDR				Non-MDR			
			Sensitive		Resistant		Sensitive		Resistant			Sensitive		Resistant		Sensitive		Resistant	
			n	%	n	%	n	%	n	%		n	%	n	%	n	%	n	%
1	Amikacin	18	15	93.75	1	6.25	2	100.00	0	0.00	13	9	100.00	0	0.00	4	100.00	0	0.00
2	Amoxicilin	-	-	-	-	-	-	-	-	-	13	2	22.22	7	77.78	4	100.00	0	0.00
3	Ampicillin	16	0	0.00	14	100.00	0	0.00	2	100.00	9	0	0.00	7	100.00	1	50.00	1	50.00
4	Gentamicin	9	3	42.86	4	57.14	2	100.00	0	0.00	9	4	57.14	3	42.86	2	100.00	0	0.00
5	Meropenem	19	15	100.00	0	0.00	4	100.00	0	0.00	13	9	100.00	0	0.00	4	100.00	0	0.00
6	Levofloxacin	20	10	62.50	6	37.50	4	100.00	0	0.00	13	3	33.33	6	66.67	4	100.00	0	0.00
7	Ceftriaxone	16	0	0.00	14	100.00	2	100.00	0	0.00	8	2	28.57	5	71.43	1	100.00	0	0.00
8	Trimethoprim sulfamethoxazole	-	-	-	-	-	-	-	-	-	12	2	22.22	7	77.78	3	100.00	0	0.00
9	Cefuroxime	20	0	0.00	16	100.00	3	75.00	1	25.00	13	2	22.22	7	77.78	4	100.00	0	0.00
10	Tobramycin	20	2	12.50	14	87.50	4	100.00	0	0.00	13	3	33.33	6	66.67	4	100.00	0	0.00
11	Tazobactam	8	4	66.67	2	33.33	2	100.00	0	0.00	8	6	100.00	0	0.00	2	100.00	0	0.00
12	Cefazolin	-	-	-	-	-	-	-	-	-	9	0	0.00	7	100.00	2	100.00	0	0.00
13	Ciprofloxacin	20	10	62.50	6	37.50	3	75.00	1	25.00	13	2	22.22	7	77.78	4	100.00	0	0.00
14	Nitrofurantoin	-	-	-	-	-	-	-	-	-	12	8	88.89	1	11.11	3	100.00	0	0.00
15	Fosfomycin	-	-	-	-	-	-	-	-	-	12	8	88.89	1	11.11	3	100.00	0	0.00

DISCUSSION

This study showed high incidences of MDR *K. pneumoniae* infections at dr. Soeradji Tirtonegoro Central Hospital, Klaten, in 2017. This result was in line with several studies. Setyati and Murni reported that *K. pneumoniae* was common causative agents in patients admitted to PICU of dr. Sardjito Central Hospital.[19] Another study, Manikandan and Amsath also reported about *K. pneumoniae* infections in Tamil Nadu, India.[20] The high incidences of *K. pneumoniae* infections could correlate with a decreasing immune system function. Patients with diabetes or malignancy more susceptible to get *K. pneumoniae* infection. Use of an invasive medical instrument such as a catheter or an endotracheal tube for a long time contribute to incidences of *K. pneumoniae* infections as well.[21]

K. pneumoniae could colonize nasopharynx and gastrointestinal tracts. The bacteria could also be found on the skin as transient bacteria. Before infections happened, 80% of patients infected by ESBL-producing *K. pneumoniae* had the same bacteria colony in their gastrointestinal tracts.[22] Nasopharynx colonization also could be related to alcohol consumption. Alcohol could change mucosal immunity due to normal flora changing in mucosal surfaces.[23] High Klebsiella colonization could be related to a broad spectrum and antibiotic combination exposures.[24] Risk factors of *K. pneumoniae* infections could include uses of a catheter, prior colonization, severe illness, length of inpatient care, invasive treatment, length of antibiotic use, poor personal and environmental hygiene, and poor immunity.[7,25]

Based on the sex characteristics, *K. pneumoniae* isolates were mostly obtained from male patients. This result was concordant with other studies. Even though showing different results, most of the studies reported that *K. pneumoniae* isolates were obtained mostly from male patients. However, there was no statistical significance between males and female. [26,27]

K. pneumoniae in this study were mostly obtained from adult patients by age between 18-64 years of age. This result was in concordance with a study conducted by Osagie and collegues, who collected samples from 5 primary health cares in Nigeria.[27] The adult group productive ages as they will be exposed directly to their surroundings.[27] Increasing age also could lead to a higher risk of *K. pneumoniae* infection due to increasing incidences of comorbid illness.

In this study, *K. pneumoniae* mostly isolated from Melati Ward which was for internal medicine patients provided five beds in one room. Because of its density, it could be spread easily from one patient to the others. The high incidences of *K. pneumoniae* infections also happened in the ICU department. This might be caused by exposures toward invasive procedures, such as intubation, mechanical ventilation, urine catheterization, artery catheterization, or central vein catheterization. Duration of care in the ICU would determine the incidence of infection as well.[28,29]

Based on the source of the specimens, *K. pneumoniae* isolates were mostly found in the respiratory specimen. This was because *K. pneumoniae* was primary bacteria that usually could cause infection in the respiratory tracts, which could be manifested as pneumonia, sinusitis, or even otitis.[30] Other studies supported these findings, as well.[30,31] Some of the *K. pneumoniae* isolates were obtained from the wound specimens. Infection in a wound usually was obtained when the patients received care in a hospital after trauma, burn injury, or surgical procedure.[32] The infection of the wound might cause sepsis, longer hospital stay, and increasing healthcare cost, and it also might affect the morbidity and mortality of an individual.[33] Other studies also showed similar results as findings in this study.[34,35]

Based on this study, generally, amikacin and meropenem were highly effective against MDR *K. pneumoniae* infections. In contrast, MDR *K. pneumoniae* was found to be resistant against ampicillin, gentamicin, ceftriaxone, trimethoprim-sulfamethoxazole, cefuroxime, ciprofloxacin, cefazolin, levofloxacin, and tobramycin.

Another study held in dr. Kariadi Central

Hospital Semarang also showed high sensitivity to meropenem.[36] Meropenem usually could be the third antibiotic used in the management of *K. pneumoniae* infection, so the exposure of *K. pneumoniae* toward this antibiotic could be infrequent. This might cause susceptibility rates of *K. pneumoniae* toward meropenem to be still high.[37]

In this study, the authors found a high number of MDR *K. pneumoniae* isolates (57.28%).[38] A study conducted in India also showed a high number of MDR *K. pneumoniae* isolates. A study conducted in Iran showed that 46.6% of *K. pneumoniae* were MDR, with a high rate of resistance toward ampicillin, cephalosporin 3rd generation, and also aminoglycoside (especially gentamycin).[39] The high number of MDR *K. pneumoniae* isolates might be affected by history and duration of inpatient care in the hospital, history of antibiotic use, and also a history of health care obtained in the wards.[39] The use of the invasive device in the hospital for a long term was also a significant risk factor.[40]

Managing infections caused by MDR *K. pneumoniae* could become a challenge for clinicians. A combination of antibiotics using colistin is a drug of choice, which can be colistin-meropenem, colistin-meropenem-tigecycline, colistin-tigecycline, colistin-gentamycin, and colistin-vancomycin. Nevertheless, these combinations of antibiotics may have a certain effect, such as nephrotoxicity.[41] A study showed that therapy using a combination of antibiotics could prevent the emergence of new resistant strains during the therapy process, so its use in the management of MDR *K. pneumoniae* was highly recommended.[42]

In the dr. Soeradji Tirtonegoro Central Hospital, antibiotic usage was controlled by a team called *Tim Program Pengendalian Resistensi Antibiotik* (PPRA), a team to manage antibiotic resistance. In general, antibiotic usage should be based on the clinical microbiology result. Collecting clinical samples before antibiotic administration was a significant point. The result of the antibiotic sensitivity test would be analyzed to make an antibiogram. The antibiogram could be used as a guide for empirical therapy and a monitor for antimicrobial-resistant trends in the hospital. In addition, the appropriateness of prophylaxis antibiotics and de-escalation of definitive antibiotics have not yet audited, which might give impact to the presence of multi-resistant phenotypes.

Based on this study, it could be seen that MDR *K. pneumoniae* isolates in the dr. Soeradji Tirtonegoro Central Hospital was high. Therefore, it is very important to conduct control of hospital infection and antibiotic stewardship effectively. A hospital needs to have an antibiotic guidance or stewardship program based on the most accurate microbiological data. In conjunction with the guidance, a continuous effort in hospital pathogen surveillance, infection control, and clinical audits should be conducted to fight against rapid development of antibiotic-resistant pathogens.

This study had limitations due to a limited number of *K. pneumoniae* isolated from blood and urine specimens. The result of the antibiotic sensitivity test could be analyzed to make an antibiogram that could be used for empirical therapy and a monitor for antimicrobial resistance trends. To do this, at least 30 clinically isolates should be collected for their analysis.

CONCLUSION

The prevalence of MDR *K. pneumoniae* isolates in RSUP dr. Soeradji Tirtonegoro, Klaten was high. Most of them were resistant to various antibiotics. MDR *K. pneumoniae* clinical isolates showed good susceptibility against meropenem and amikacin.

CONFLICT OF INTEREST

There was no conflict of interest.

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