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Prevalence and Sensitivity Pattern of Gram-negative Bacilli Multidrug-Resistant (MDR) In Mohammad Hoesin Hospital Palembang

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Abstract

Antibiotic resistance is one of the most serious global health crisis and threats in human life today. Multidrug-resistant is a condition obtained when bacteria are resistant to at least one of the agents of 3 or more antimicrobial categories. Cases of multi-resistant gram-negative bacilli infection continue to increase so that the use of standard antibiotics is non-susceptible leading to increased morbidity and mortality. Therefore, this study aims to find out which antibiotics are still sensitive as empirical therapy. This retrospective descriptive research uses secondary data in the form of the status of patients infected with A. baumannii, P. aeruginosa, E. coli and K. pneumoniae at the Central Laboratory Installation of Mohammad Hoesin Hospital Palembang during the period January 2020 – June 2020. The samples in this study were all medical records of inpatients who met the inclusion criteria. Data is processed and analyzed univariately using Microsoft Excel 2020 and IBM SPSS Statistics Version 26 to determine the frequency distribution of each variable studied. Prevalence of MDR gram-negative bacilli at Mohammad Hoesin Hospital Palembang was MDR A. baumannii (66.5%), MDR P. aeruginosa (34.6%), ESBL-E. coli (61.3%), CRE-E. coli (2.7%), ESBL-K. pneumoniae (51.7%) and CRE-K. pneumoniae (20.1%). Based on the inpatient room, prevalence of MDR gram-negative bacilli is found in intensive care compared to non-intensive care rooms. Based on specimen type, MDR gram-negative bacilli isolates are often found in all types of specimens namely sputum, blood, pus, swab, others. Based on sensitivity patterns, Enterobacteriaceae producing ESBL isolates are sensitive to carbapenem, amikacin, tigecyclin and nitrofurantoin, while in CRE isolates are sensitive to tigecycline. MDR A. baumannii is sensitive to tigecycline and amikacin, but MDR P. aeruginosa is only sensitive to amikacin. The prevalence of MDR gram-negative bacilli is the highest in the intensive inpatient rooms and varies in specimen type. Antibiotics that are sensitive to the entire MDR gram negative bacilli is tigecycline, except MDR P. aeruginosa is sensitive to amikacin.

Keywords: gram-negative bacili, multidrug-resistance, prevalence, sensitivity

1. Introduction

Antibiotic resistance is one of the global health crises and the most serious threat in human life today. Based on the list of antibiotic-resistant bacteria published by WHO, gram-negative bacteria especially E. coli, K. pneumoniae, P. aeruginosa and A. baumannnii are the most multiresistant against some antibiotics[1].

Multidrug resistant is a condition obtained when bacteria are resistant to at least one of the agents of 3 or more antimicrobial categories. Organisms that are multidrug resistant are called MDRO (Multidrug Resistant Organism)[2]. MDRO has become a worldwide threat because it aggravates disease, increases mortality, increases medical costs and causes late treatments.[3] Some of the most common examples of gram-negative bacilli MDR are ESBL-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, MDR A.baumannii and MDR P.aeruginosa.[4]

Antibiotic is most widely used in ICU compared to other patient wards. The research stated that the use of antibiotics in the intensive inpatient room of Mohammad Hoesin Hospital Palembang reached 71%.30 Risk factors for antibiotic resistance include irrational antibiotic use, massive antibiotic use in endemic or pandemic cases, use of antibiotics with unclear indications and lack of public knowledge so use antibiotics without a prescription from doctor.[5]

While data on MDRO at Mohammad Hoesin Hospital Palembang has not been established, it is necessary to conduct research on the prevalence and sensitivity pattern of multidrug resistant (MDR) gram-negative bacilli at Mohammad Hoesin Hospital Palembang in the period January 2020 - June 2020 to be a guideline in making wise decisions on the use of appropriate antibiotics, safe and effective as empirical therapy and definitive therapy.

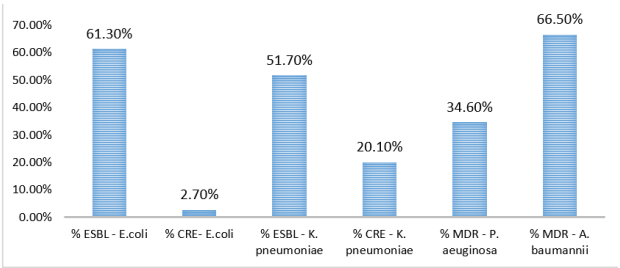
2. Method

This retrospective descriptive research uses secondary data in the form of the status of patients infected with A. baumannii, P. aeruginosa, E. coli and K. pneumoniae at the Central Laboratory Installation of Mohammad Hoesin Hospital Palembang during the period January 2020 – June 2020. The samples in this study were all medical records of inpatients who met the inclusion criteria. Data is processed and analyzed univariately using Microsoft Excel 2020 and IBM SPSS Statistics Version 26 to determine the frequency distribution of each variable studied.

3. Result

From January to June 2020, 795 samples of MDR negative bacilli were obtained. Prevalence of gram-negative bacilli MDR (See Figure 1) shows MDR A. baumannii (66.5%) which occupies the highest position of gram-negative bacilli MDR. Then, followed by MDR P. aeruginosa (34.6%), ESBL-E. coli (61.3%), then CRE-E. coli (2.7 %). Prevalence of ESBL-K. pneumoniae (51.7%) and CRE-K. pneumoniae (20.1%).

Figure 1. Prevalence of negative gram bacilli MDR in RSUP Dr. Mohammad Hoesin Palembang



Based on the distribution of demographic characteristics (table 1), Gram-negative bacilli MDR is most found in the adult age category (26-45 years old) and seniors (46-65 years old). In gender distribution, gram-negative bacilli MDR is most found in males compared to females, except ESBL-E. coli and CRE-E. Coli.

In table 2, it can be seen that the prevalence of ESBL-E. coli (66.7%) and CRE-E. coli (3%), CRE-K. pneumoniae (34.4%) and MDR P. aeruginosa (47%) are highest in adult intensive inpatient room. Prevalence of ESBL-K. pneumoniae (80%) and MDR A. baumannii (85.7%) are highest in neonatal-child intensive inpatient rooms. Based on distribution of isolate, ESBL-E. coli and CRE-E. coli most comes from Komering room (medical room), while ESBL-K. Pneumoniae, CRE-K. pneumoniae, MDR A. baumannii and MDR P. aeruginosa mostly come from GICU room.

Table 3 presented data of gram-negative bacilli MDR based on specimen type. In other specimens (CVC, bronchial rinse, pleural fluid, peritoneal fluid, LCS) has a high prevalence in ESBL-E. coli (84.6%), CRE-E. coli (7.7%), MDR P. aeruginosa (70%). However, the prevalence of CRE-K. pneumoniae and MDR A. baumannii were high in ulcer swab specimens at 66.7% and 100% respectively. Prevalence of ESBL-K. pneumoniae is high in pus specimen (68.6%). Based on its isolate distribution, ESBL-K. Pneumoniae, CRE-K. pneumoniae, MDR A. baumannii and MDR P. aeruginosa are most commonly found in sputum, while ESBL-E. coli and CRE-E. coli is more found in urine specimens.

The sensitivity pattern of gram-negative bacilli MDR can be seen in figure 2. ESBL-E. coli and ESBL-K. pneumoniae is more sensitivite to meropenem (100%, 97%), ertapenem (98%,94%), amikacin (98%, 95%), tigecycline (100%, 87%). CRE-E. coli is more sensitive to meropenem antibiotics (100%), nitrofurantoin (86%), and tigecycline (100%), while CRE-K. pneumoniae is more sensitive only to tigecycline antibiotics (79%). MDR A. baumannii has good sensitivity to the antibiotic amikasin (80%) and tigesiklin (89%), while MDR P. aeruginosa is more sensitive to the amikacin (75%).

Table 1. Characteristics of Demographic

Karakteristik	Isolates					
	***E. coli* (N= 261)**		***K. pneumoniae* (N= 389)**		***P. aeruginosa* (N=205)**	***A. baumannii* (N= 418)**
	ESBL-*E. coli*	CRE-*E. coli*	ESBL-*K. pneumoniae*	CRE-*K. pneumoniae*	MDR *P. aeruginosa*	MDR *A. baumannii*
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
A. Age						
Child (<12 tahun)	24 (15)	1 (14.3)	32 (15.9)	15 (19.2)	5 (7)	35 (12.6)
Adolescents (12-25 tahun)	17 (10.6)	1 (14.3)	18 (9)	9 (11.5)	3 (4.2)	24 (55.8)
Adults (26-45 tahun)	36 (22.5)	4 (57.1)	45 (22.4)	13 (16.7)	19 (26.8)	66 (64.1)
Seniors (46-65 tahun)	66 (41.3)	1 (14.3)	71 (35.3)	23 (29.5)	34 (47.9)	117 (67.2)
Geriatric (> 65 tahun)	17 (10.6)	0 (0)	35 (17.4)	18 (23.1)	10 (14.1)	36 (72)
Total	160 (100)	7 (100)	201 (100)	78 (100)	71 (100)	278 (100)
B. Sex						
Male	71 (44.4)	0 (0)	113 (56.2)	44 (56.4)	44 (62)	139 (50)
Female	89 (55.6)	7 (100)	88 (43.8)	34 (43.6)	27 (38)	139 (50)
Total	160 (100)	7 (100)	201 (100)	78 (100)	71 (100)	278 (100)

Table 2. Distribution of Gram-negative Bacilli MDR based on Inpatient Room

Inpatient Room		Isolat									
		E. coli			*K. pneumoniae*			*P. aeuginosa*		*A. baumannii*	
		N	ESBL	CRE	N	ESBL	CRE	N	MDR	N	MDR
			n (%)	n (%)		n (%)	n (%)		n (%)		n (%)
A. Intensive room	**Neonatus-child**	**6**	**3 (1.9)**	**0 (0)**	**30**	**24 (12)**	**6 (7.7)**	**10**	**4 (5.6)**	**35**	**30 (10.8)**
	NICU	0	0 (0)	0 (0)	16	13 (6.5)	4 (5.1)	3	3 (4.2)	19	18 (6.5)
	PICU	6	3 (1.9)	0 (0)	14	11 (5.5)	2 (2.6)	7	1 (1.4)	16	12 (4.3)
	Adults	**33**	**22 (13.8)**	**1 (14.3)**	**143**	**65 (32.4)**	**49 (62.8)**	**68**	**32 (45.1)**	**162**	**121 (43.6)**
	GICU	26	19 (11.9)	0 (0)	113	51 (25.4)	39 (50)	60	31 (43.7)	141	103 (37.1)
	BHC	7	3 (1.9)	1 (14.3)	30	14 (7)	10 (12.8)	8	1 (1.4)	21	18 (6.5)
B. Non-Intensive room	**Neonatus-Child**	**46**	**25 (15.6)**	**1 (14.3)**	**33**	**12 (6)**	**10 (12.8)**	**11**	**1 (1.4)**	**20**	**10 (7.6)**
	Selincah Room	44	24 (15)	1 (14.3)	28	9 (4.5)	9 (11.5)	11	1 (1.4)	16	7 (6.5)
	Neonatus Room	2	1 (0.6)	0 (0)	5	3 (1.5)	1 (1.3)	0	0 (0)	4	3 (1.1)
	Adults	**176**	**110 (68.7)**	**5 (71.4)**	**183**	**100 (49.6)**	**13 (16.7)**	**116**	**34 (47.9)**	**201**	**117 (38.3)**
	Enim Room	15	3 (1.9)	0 (0)	7	2 (1)	0 (0)	1	0 (0)	4	1 (0.4)
	Borang Room	0	0 (0)	0 (0)	2	1 (0.5)	0 (0)	2	1 (1.4)	6	4 (1.4)
	Kelingi Room	4	3 (1.9)	0 (0)	20	14 (7)	3 (3.8)	19	4 (5.6)	11	4 (1.4)
	Komering Room	47	35 (21.9)	4 (57.1)	48	27 (13.4)	1 (1.3)	31	10 (14.1)	75	45 (16.2)
	Lakitan Room	32	18 (11.3)	0 (0)	22	9 (4.5)	3 (3.8)	16	4 (5.6)	18	13 (4.7)
	Lematang Room	14	12 (7.5)	0 (0)	15	10 (5)	0 (0)	7	2 (2.8)	14	10 (3.6)
	Musi Room	13	10 (6.3)	0 (0)	13	8 (4)	1 (1.3)	8	0 (0)	7	3 (1.1)
	Ogan Room	9	7 (4.4)	0 (0)	12	6 (3)	2 (2.6)	2	2 (2.8)	8	4 (1.4)
	Rambang Room	11	5 (3.1)	0 (0)	6	4 (2)	1 (1.3)	1	0 (0)	8	6 (2.2)
	Rawas Room	15	8 (5)	0 (0)	25	9 (4.5)	0 (0)	12	4 (5.6)	25	18 (6.5)
	Rupit Room	16	9 (5.6)	1 (14.3)	13	10 (5)	2 (2.6)	17	7 (9.9)	25	9 (3.2)
Total		**261**	**160 (100)**	**7 (100)**	**389**	**201 (100)**	**78 (100)**	**205**	**71 (100)**	**418**	**278 (100)**

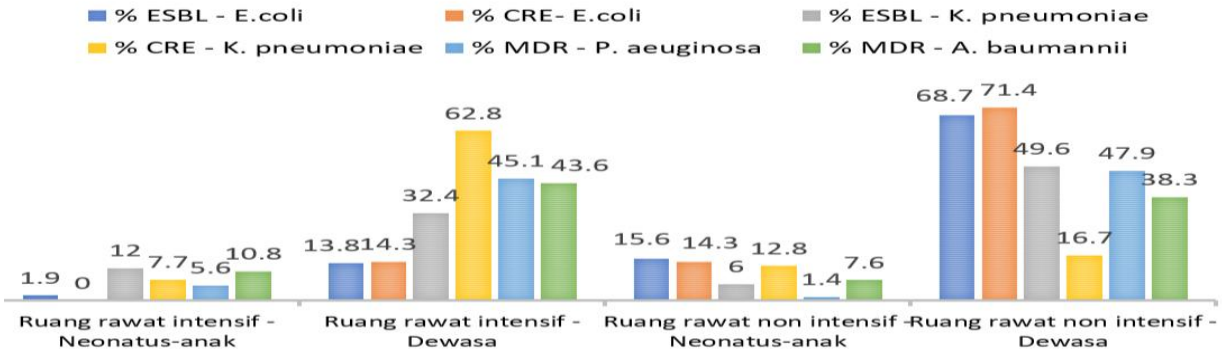


Table 3. Distributions Gram-negative Bacilli MDR based on Specimen Type

Specimen Type	Isolates									
	E. coli			*K. pneumoniae*			*P. aeruginosa*		*A. baumannii*	
	N	ESBL	CRE	N	ESBL	CRE	N	MDR	N	MDR
		n (%)	n (%)		n (%)	n (%)		n (%)		n (%)
Sputum	29	20 (12.5)	0 (0)	215	116 (57.7)	39 (50)	105	36 (50.7)	234	148 (53.2)
Blood	17	12 (7.5)	0 (0)	32	19 (9.5)	8 (10.3)	4	1 (1.4)	35	26 (9.4)
Urine	93	57 (35.6)	5 (71.4)	48	21 (10.4)	14 (17.9)	15	5 (7)	27	17 (6.1)
Pus	83	48 (30)	1 (14.3)	35	24 (11.9)	3 (3.8)	41	13 (18.3)	61	52 (18.7)
Ulcer Swabs	6	4 (2.5)	0 (0)	3	0 (0)	2 (2.6)	9	4 (5.6)	15	15 (5.4)
Other Swabs	20	8 (5)	0 (0)	41	14 (7)	6 (7.7)	21	5 (7)	33	9 (3.2)
Others*	13	11 (6.9)	1 (14.3)	15	7 (3.5)	6 (7.7)	10	7 (9.9)	13	11 (4)
Total	**261**	**160 (100)**	**7 (100)**	**389**	**201 (100)**	**78 (100)**	**205**	**71 (100)**	**418**	**278 (100)**

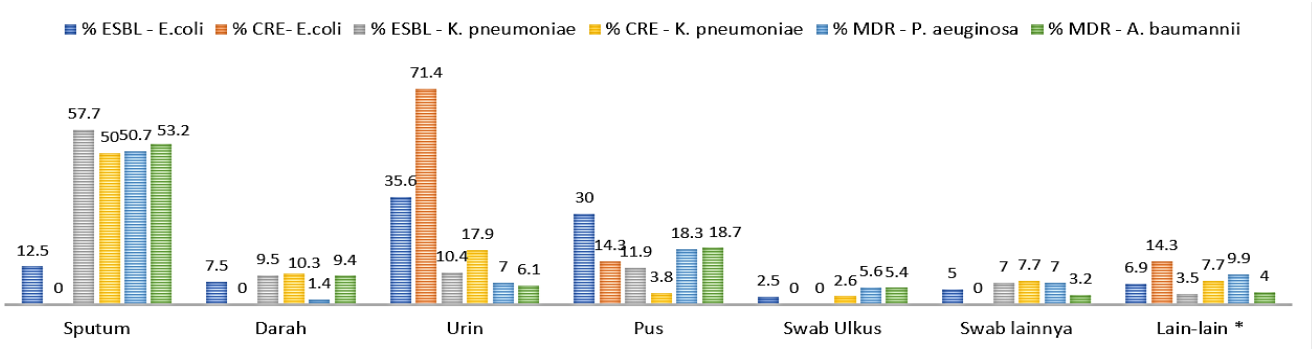


Figure 2. Gram-negative bacilli multridrug-resistance sensitivity pattern

Organism	N	Antibiotics (%S)															
		AMP	SAM	TZP	FEP	CZ	CAZ	CRO	AZT	MEM	ATP	AK	CIP	GN	NIT	TGN	SXT
ESBL- *E. coli*	160	0	26	79	59	0	34	1	11	100	98	98	9	45	86	100	33
CRE-*E. coli*	7	0	0	0	0	0	0	0	0	100	0	57	0	0	86	100	29
ESBL-*K. pneumoniae*	201	0	7	61	69	0	11	0	3	97	94	95	29	50	29	87	53
CRE-*K. pneumoniae*	78	0	1	8	15	0	1	1	0	8	3	56	9	10	27	79	55
MDR *A. baumannii*	278	-	15	1	1	0	1	0	-	14	-	80	4	6	-	89	28
MDR *P. aeruginosa*	71	-	-	20	16	0	11	-	13	16	-	75	28	42	-	1	-

Descriptions : AMP: Ampicilin; SAM : Ampicilin/ Sulbactam; TZP : Piperacilin/ Tazobactam; FEP : Cefepim; CZ : Cefazolin; CAZ : Ceftazidime; CRO : Ceftriaxon; AZT : Aztreonam; MEM : Meropenem; ATP : Ertapenem; AK : Amikacin; CIP : Ciprofloxacin; GN : Gentamicin; NIT : Nitrofurantoin; TGN : Tigecycline; SXT: Sulfametoxazol/ Trimetroprim.

Based on sensitivity of hospital germ patterns to antibiotic use (Dahesihdewi, 2018):

1. Use of Antibiotics that have sensitivity < 40% (Not recommended)
2. Use of Antibiotics that have sensitivity < 40-80% (Can be considered for use)
3. The use of antibiotics that have a sensitivity > 80% is highly recommended.
4. Antibiotics not tested

4. Discussion

The results of this study conducted at Mohammad Hoesin Hospital Palembang showed the highest prevalence of gram-negative bacilli MDR is MDR A. baumannii (66.5%). This is due to the spread of resistance genes associated with excessive use of broad-spectrum antibiotics, cross-infection among hospitalized patients, patients with comorbidity, invasive procedures and therapeutics.[6] This result is lower than the research conducted on inpatients at Dr. Soeradji Tirtonegoro Klaten Hospital in 2016-2018, namely 81.11% (in 2016), 70.77% (in 2017) and 71.74% (in 2018)26. In other studies, also found a very high prevalence of MDR A. baumannii which is 91%.[1] The highest prevalence of MDR A. baumannii is most likely caused by the spread of resistance genes and the ability of these bacteria to live in hospital environment.[1]

In this study, 71 out of 120 isolates of P. aeruginosa (34.6%) that have been multidrug-resistant. The results of this study are in accordance with the research on the prevalence of MDR P. aeruginosa conducted at Dr.M Djamil Padang Hospital which is 36%.[7] On the contrary, the prevalence of MDR P. aeruginosa in Arifin Achmad Hospital is higher by 45.5% because the bacteria had intrinsic resistance and can obtain resistance to other antibiotics during therapy.[8] The use of carbapenem and floroquininolone antibiotics is the main cause in increasing cases of MDR P. aeruginosa.[7]

Throughout January-June 2020, the prevalence of ESBL-E. coli and ESBL-K. pneumoniae at Mohammad Hoesin Hospital in Palembang at 61.3% and 51.7% respectively. In previous survey, the prevalence of ESBL-E. coli and ESBL-K. pneumoniae in 2018 at Mohammad Hoesin Hospital Palembang at 66% and 55% respectively. This indicates that there is a decrease in the prevalence of ESBL-E. coli from 66% to 61.3% and ESBL-E. coli from 55% to 51.7% which means the antimicrobial resistance control program at Mohammad Hoesin Hospital Palembang is running well. However, the results of this study are still quite high when compared to surveillance reports from several referral hospitals in Indonesia, the prevalence of ESBL-E. coli (21%) and prevalence of ESBL-K. pneumoniae (17%).[2] Prevalence of ESBL-K. pneumoniae and ESBL-E. coli at Dr.M Djamil Hospital in Padang were higher than the results of this study which was 70.9% and 75.7%.[9] The high prevalence of ESBL-E. coli and ESBL-K. pneumoniae at Dr.M Djamil Hospital in Padang was influenced by the condition of treated patients such as patients with long-treated comorbids and patients using invasive tools (urinary catheters, nasogastric tube tubes, endotracheal tube, CVP) thus increasing the risk of colonization of these bacteria.[9]

Carbapenem is a class of beta- lactam antibiotics that bind to penicilin binding proteins and inhibit the synthesis of cell walls.[10] In this study, Enterobacteriaceae (E. coli and K. pneumoniae) were tested with 2 antibiotic agents from carbapenem namely ertapenem and meropenem. The results of this study show the prevalence of CRE-E. coli is lower than the prevalence of CRE-K. pneumoniae. Prevalence of CRE-E. coli and CRE-K. pneumoniae in this study were 2.7% and 20.1%. In the study at Dr. Mohammad Hoesin Hospital in 2019 showed the prevalence of CRE-Enterobacteriaceae is 12.7% with CRE-K. pneumoniae (55.7%) and CRE-E. coli (19.3%). Reduction cases in CRE-E. coli and CRE-K. pneumoniae caused by the control of antimicrobial resistance program at RSUP Dr. Mohammad Hoesin has been running well. The results of this study are lower than the research in India, the prevalence of CRE-E. coli and CRE-K, pneumoniae in India is 15.6% and 53.6%.[11] Prevalence CRE-K pneumoniae and CRE-E. coli lower in this study compared to other studies due to high variations of

Enterobacteriaceae were studied in other studies.[12]

Gram-negative bacilli MDR is more commonly found in the adult-elderly age category and in the male gender than females. Literature study mentioned that the distribution of age and gender in cases of gram-negative bacilli MDR is evenly distributed at all ages.[13] Cases of gram-negative bacilli MDR that increase in the adult-elderly age range are likely associated with a highly vulnerable productive age with various infections.[1] In this studies and other studies also showed a higher group of men in cases of gram-negative bacilli which is likely caused by a spectrum of more infectious diseases in men. Several other studies have also mentioned that there is no significant link between sex and cases of gram-negative bacilli multidrug-resistant.[14] However, ESBL-E. coli and CRE-E. coli research is not in accordance with previous research. This distribution difference is due to the study of E. coli isolates found more in urine specimens that are likely caused by urinary tract infections that affect more common in women than men.

In this study, gram-negative bacilli MDR had a higher prevalence in intensive inpatient rooms than non-intensive. Based on the distribution of isolates, most isolates are found in the room of medical room surgery room and GICU. The results of this study are also in accordance with the research at Arifin Achmad Pekanbaru Hospital which also found that the prevalence of ESBL-E. coli and ESBL¬-K. pneumoniae are highest in children's intensive care.[15] Prevalence of ESBL-E. coli in this study is different from other studies. Singh's research showed that the highest prevalence of ESBL-E. coli was found in children's intensive care compared to other intensively inpatient rooms.[16] High risk factors for ESBL-E. coli infection in intensive inpatient rooms were long-term antibiotic use, chronic disease patients, invasive procedures, and permanent use of urinary catheters.[16] Hospitalization was also one of the risk factors for ESBL-E. coli and ESBL-K. pneumoniae infections due to genes that encode ESBL can be carried by plasmids that are easily spread throughout infected bacteria in inpatients.[14]

These results are in line with research in Turkey which states that CRE-Enterobacteriaceae is most commonly found in ICU.[17] Study of CRE-Enterobacteriaceae in Thailand stated that the distribution of CRE-E. coli and CRE-K. pneumoniae is most common in medical room.[9] CRE can colonize medical devices, such as ventilators, intravenous catheters, urinary catheters, trauma wounds or surgery and can be transmitted by contact from person to person.[18] This causes high cases of CRE in adult intensive inpatient rooms because the use of medical devices in this room is very high.

The results of this study are in accordance with research in Nepal which shows that MDR A. baumannii is found in intensive care.[1] Research in Saudi Arabia states that the ICU room is the highest place where cases of MDR A. baumannii are found and are closely related to ventilator-associated pneumoniae.[6] The results of this study are in accordance with Aloush's research, which states that adult intensive inpatient rooms are significantly related to cases of MDR P. aeruginosa infection.[19] In intensive care, there are patients with comorbids, immunocompromized patients, long-term hospitalization, long-term antibiotic use and invasive procedures with medical devices that are risk factors for infection of MDR A. baumannii and MDR P. aeruginosa.[1]

Based on the type of specimen, MDR gram-negative bacilli has a varied distribution. In this study, the prevalence of ESBL-E. coli is more commonly found in other specimens (CVC, pleural fluid, peritoneal fluid, LCS, bronchial rinse) and its isolate distribution is found in urine specimens (35.6%). The results of this study are different from the survey at Mohammad Hoesin Hospital Palembang in 2018 which

showed that the prevalence of ESBL-E. coli is the highest in urine specimens. The difference between results of this study and the others was due to a study at Mohammad Hoesin Hospital Palembang in 2018 only divided the specimen type into 5 groups namely sputum, blood, pus, swab and urine. Based on distribution isolates, ESBL-E coli according to previous research was more common found in many urine specimens.

Prevalence of ESBL-K. the highest pneumoniae was found in pus specimens (68.6%) and its distribution is most commonly found in sputum specimens (57.7%). The results of this study are in accordance with the survey at Mohammad Hoesin Hospital Palembang in 2018 which showed that ESBL-K. pneumoniae is most commonly found in specimens of sputum. ESBL-K. pneumoniae in Arifin Achmad Pekanbaru Hospital is most commonly found in sputum specimens.[15] Research at Dr. Soeradji Tirtonegoro Klaten Hospital also states that ESBL-K. pneumoniae is most commonly found in specimens of sputum.[20] K. pneumoniae often causes pneumonia, sepsis, urinary tract infections and wound infections. This leads to ESBL-K. pneumoniae is found in many specimens of sputum and pus. In Anggraini's research stated that there is no meaningful difference in the prevalence of ESBL-E. coli and ESBL-K. pneumoniae by specimen type.[15]

Carbapenem such as meropenem and ertapenem are recommended as first line medications for patients with severe infection Enterobacteriaceae that produces ESBL. Irrational use of antibiotics leads to increased cases of resistance. The study found that CRE-E. coli was most found in urine specimens were 71.4% and CRE-K. pneumoniae was most common in sulcers/wounds swab (66.7%). The results of this study are in accordance with research at Mohammad Hoesin Hospital Palembang last year which found the most isolated CRE-Enterobacteriaceae isolates in specimens of sputum, urine, pus and wounds/ulcers swab.[12] The results of this study are also in accordance with the study at Cipto Mangunkusomo Hospital in 2011.[11]

In this study, the prevalence of MDR A. baumannii was found in ulcer swabs (100%) and its isolate distribution is found in sputum specimens (53.2%). The results of this study are in accordance with the research in Nepal that showed MDR A. baumannii is found in many sputum specimens compared to other specimens.[1] Research in Saudi Arabia shows that there is a relationship between the use of ventilators and increasing cases of MDR A. baumannii.[6] This is due to the ability of A. baumannii in forming biofilms that are closely related to cases of resistance to antibiotics and can live well in dry environments so that the conbinded environment can become a reservoir of the spread of MDR A. baumannii.[6]

MDR P. aeruginosa infections attacks many patients with weak immune systems such as neutropenia, chemotherapy and burns.[21] The results of research at Mohammad Hoesin Hospital Palembang stated that the prevalence of MDR P. aeruginosa is the highest in other specimens (CVC, pleural fluid, peritonitis fluid, LCS, bronchial rinse) by 70%, while the distribution of isolates is more found in sputum specimens (50.7%) than others. The results of this study are in accordance with research in Padang which states that MDR P. aeruginosa is most commonly found in sputum and swab specimens.[7] Research at Arifin Achmad Pekanbaru Hospital also obtained MDR P. aeruginosa much isolated in sputum and pus specimens.[8] In some studies showed that no significant association between the incidence of MDR P. aeruginosa with specimen types so that MDR P. aeruginosa can be found in all types of specimens.

Cases of gram-negative bacilli are influenced by selection pressures closely related to irrational antibiotic use and the spread of resistant bacteria. Therefore, each hospital has a PPRA committee that conducts surveillance of antibiotic use and is displayed

in the form of an antibiogram aimed at controlling antimicrobial resistance in hospitals.[22] This antibiogram will display a profile of bacterial sensitivity to antibiotics aimed at assisting clinicians in determining empirical therapy.[23] Based on recommendations from CLSI M39A4 in the manufacture of sensitivity patterns, the number of bacterial isolates is at least 30 and antibiotic sensitivity results are divided into 3 categories namely <40% is not recommended, <40%-80% can be considered and >80% is highly recommended as empirical therapy.[23]

In this study, it was found that E. coli has good sensitivity in piperacilin/ tazobactam, ertapenem, meropenem, amikacin, tigecycline and nitrofurantoin. Sensitivity ESBL-E. coli at Arifin Achmad Hospital in accordance with the results of this study.[15] Meanwhile, research at M Djamil Padang Hospital obtained the best sensitivity to ESBL-E. coli is only 2 antibiotics namely amikacin and meropenem.[9] According to the results of PDS Patklin surveillance, carbapenem group (meropenem, ertapenem, doripenem, imipenem), tigecycline and amikacin are highly recommended as empirical therapy in ESBL-E. coli infections.[2]

The results of this study showed that K. pneumoniae and ESBL-K. pneumoniae has good sensitivity to ertapenem, meropenem, amikacin and tigecycline. This study in accordance with the research at Soeradji Tirtonegoro Klaten Hospital which has good sensitivity to antibiotics meropenem, amikacin, nitrofurantoin, tigecycline and phosphomisin.[20] Research at Arifin Achmad Hospital also has the same research results.[15] Differences in the results of this study are closely related to antibiotic resistance control programs, germ patterns of each hospital, and what antibiotics are tested. The main therapeutic options in Enterobacteriaceae infections (E. coli and K. pneumoniae) that produce ESBL are carbapenem groups (meropenem, doripenem, ertapenem, imipenem). Many studies state that carbapenem is still very sensitive in ESBL-producing bacteria. Aminoglycosides such as amikacin can be used as an empirical therapy option in addition to carbapenem group in case of ESBL-producing bacterial infection.[9] The resistance mechanism in ESBL-producing bacteria is located in plasmids that carry resistant genes causing other antibiotics tested to experience resistance. Phosphomisin, cholistin and tigecycline are other therapeutic options for ESBL-producing bacteria.[15]

Excessive use of carbapenem-type antibiotics in cases of Enterobacteriaceae (E. coli and K. pneumoniae) infections producing ESBL can trigger selection pressures that cause Carbapenem-resistant Enterobacteriaceae (CRE). In this study, CRE-E. coli was obtained that have good sensitivity to antibiotics meropenem, tigecycline and nitrofurantoin. The results of this study are in accordance with research in Saudi Arabia which shows that CRE-K. pneumoniae has 90-100% resistance to carbapenem, fluoroquininolon and cephalosporins.[24] Carbapenem is subjected to resistance caused by several factors, consists of excessive expression of chromosomal cephalosporinase, loss of porin, acquisition of carbapenem genes through plasmids.[25] Therapy in CRE-Enterobacteriaceae should be based on examination of sensitivity tests, sources, the severity of infections and data from clinical research.[9] Based on the literature that has been submitted, CRE-Enterobacteriaceae therapy can be given to antibiotics polymycin, tigecycline and phosphomisin.

The results of this study, it was found that A. baumannii and MDR A. baumannii have good sensitivity in only 2 antibiotics namely amikacin and tigecycline. However, the sensitivity of MDR A. baumannii is lower than the isolate of A. baumannii. MDR A. baumannii has experienced resistance in meropenem, cephalosporins and gentamisin. The results of this study are in accordance with the research at Zainoel Abidin Hospital namely MDR A. baumannii has a good sensitivity to antibiotics amikasin compared

to all antibiotics tested.[26] Research at Soetomo Hospital Surabaya is also in accordance with this study.[27] Amikacin is one of the antibiotic agents of the aminoglycoside group that has nephroxicity effects so that its use should be monitored. The mechanism of resistance A. baumannii to antibiotics is an enzyme that activates antibiotics, decreases access to bacterial targets through decreased permeability resulting from loss of porin, and mutation of target or cell function through PBPs.[28]

In this study, it was found that isolates P. aeruginosa and MDR P. aeruginosa have a good sensitivity to the antibiotic amikasin. Of all the antibiotics tested, P. aeruginosa was resistant. The results of this study are in accordance with research in Padang that shows that only amikasin antibiotics have the best sensitivity compared to other antibiotics tested.[7] On the contrary, the study at Arifin Achmad Hospital found that all antibiotics tested on MDR P. aeruginosa have experienced resistance and amikacin already has a sensitivity of < 80% meaning it cannot be used as empirical therapy. The resistance mechanism in P. aeruginosa is the loss of porin OprD, excessive regulation of the eflux pump, and the production of enzyme (beta-lactamase and carbapenemase).[29] Combination therapy provides the possibility that one or both agents are synergistic actively fighting pathogens infecting patients. Recommended combination therapy in MDR P. aeruginosa are seftazidime/avibaktam and seftolozane/ tazobaktam.[30]

5. Conclusion

Gram-negative bacilli MDR was most found in male and adult-elderly age categories. The prevalence of gram-negative bacilli MDR is higher in intensively inpatient rooms than non-intensive. The distribution of gram-negative bacilli MDR isolates based on specimen types varies. Antibiotics that are sensitive to the entire gram-negative bacilli MDR is tigesiklin, except MDR P. aeruginosa is only sensitive to amikacin.

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