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Carbapenem Susceptibility Rate Against Gram-Positive and Gram-Negative Bacteria and Its Correlation with Consumption

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ABSTRACT

Antibiotic susceptibility is significant in patient management and needs close monitoring. This study aims to evaluate the Carbapenem susceptibility profiles and correlation between Carbapenem consumption and susceptibility of the most frequent isolates from blood, sputum, and urine in 2020–2022 from the non-intensive inpatients. The proportion of males and females was 54% and 46%, with the median age group of males and females both being 65-74 years. Higher Meropenem susceptibility was shown in urine isolates of female patients. Lower susceptibility to Meropenem was shown in 2021 compared to 2020 and 2022. Lower susceptibility was shown in isolates from sputum compared to blood and urine. The three-year susceptibility of Carbapenem was decreased compared to 3 years before. The susceptibility of *E.coli* and *S.aureusto*. Meropenem showed relatively high proportions 95% and 88%, compared to *K.pneumoniae* (46%), *A.baumanii* (30%), *P.aeruginosa* (29%), and others. The susceptibility of isolates from non-intensive-care inpatients in 2020-2022 showed lower rates compared to the hospital-wide and the previous three years' rates. Meropenem consumption was highest compared to Imipenem with inhibitor and Doripenem. The susceptibility of Gram-negative rods to Meropenem showed higher proportions (58.9%) compared to Gram-positive cocci (26.2%). Carbapenem susceptibility was decreased, along with increased Carbapenem consumption but no significant statistical correlation between the susceptibility rates and the monthly defined daily dose.

Keywords: Carbapenem, susceptibility, consumption, defined daily dose, non-intensive inpatients

INTRODUCTION

The decrease in the susceptibility of antibiotics is related to their consumption.[1] The hospital antibiotic stewardship program application is a crucial factor in keeping high-susceptibility antibiotics for clinical effectiveness and economic value.[2] The antibiotic use procedure must be changed because it is essential to suppress antibiotic resistance development effectively.[3] Antimicrobial monitoring and stewardship programs are an effective way to regulate the suitability of the appropriate use of antimicrobials, including Carbapenems.[4]

Carbapenems are broad-spectrum antibiotics used to treat infections caused by multidrug-resistant organisms. Antimicrobial stewardship monitoring and intervention effectively improve the appropriateness of Carbapenem use.[5] The rate of Carbapenem resistance was reported to have been higher in several developing countries. In the ICU setting, the pressure of Carbapenem used to save a life may contribute to a decrease of its susceptibility. However, in non-intensive inpatients, more data is needed to evaluate the correlation between Carbapenem consumption and its susceptibility.

This study aims to evaluate the Carbapenem susceptibility profiles, trends, and correlation between Carbapenem consumption and susceptibility of the most frequent isolates from blood, sputum, and urine in 2020-2022.

METHODS

This was a descriptive-analytical research with a cross-sectional approach. Data collection came from medical records of inpatients at Medistra Hospital from January 2020 until December 2022, and complete data came from pharmacy and laboratory units. Data taken included total use of Carbapenem drugs, number of patient visits, length of stay, and Carbapenem susceptibility data from blood, sputum, and urine specimens from non-intensive inpatients. Antibiotic consumption data was processed using the Defined Daily Dose (DDD) formula established by WHO, using Python programming.[6]The Carbapenem susceptibility tests were performed in accordance with guidelines established by the Clinical and

Laboratory Standards Institute (CLSI), using automated microbial identification and antibiotic susceptibility testing Vitek 2 compact system (Biomerieux). Validated data from the Laboratory Information System (LIS) was exported to a text file, then imported to WHONet data file using the Baclink 2023 software and analyzed using WHONet 2023 software.[7] The data was analyzed for descriptive and correlational study using the JASP statistical software.[8]

The Ethics Committee of Medistra Hospital, approved this study protocol with letter no 002a/EA/KEPKM/2023.

RESULTS AND DISCUSSIONS

Figure 1 shows the distribution of patients by gender and age group.

The proportion of males and females was 54% and 46%. The median age group of males and females were 65-74 years and 65-74 years, respectively. The age distribution skewed more frequently to more than 50 years of age.

The urine, blood and sputum specimen proportion were 20.2%, 19.5% and 7.8%, respectively (Table 1). *Klebsiella pneumoniae* was the most common pathogen in blood and respiratory specimens, while *E.coli* was the most common in urine with more Meropenem susceptibility. More susceptibility of Gram-Positive Cocci (GPC) to Imipenem compared to Meropenem showed while inverse situation showed in the case of Gram-Negative Rods (GNR) (Table 2).

Less susceptibility was shown to Meropenem in 2021 compared to 2020 and 2022, while Imipenem

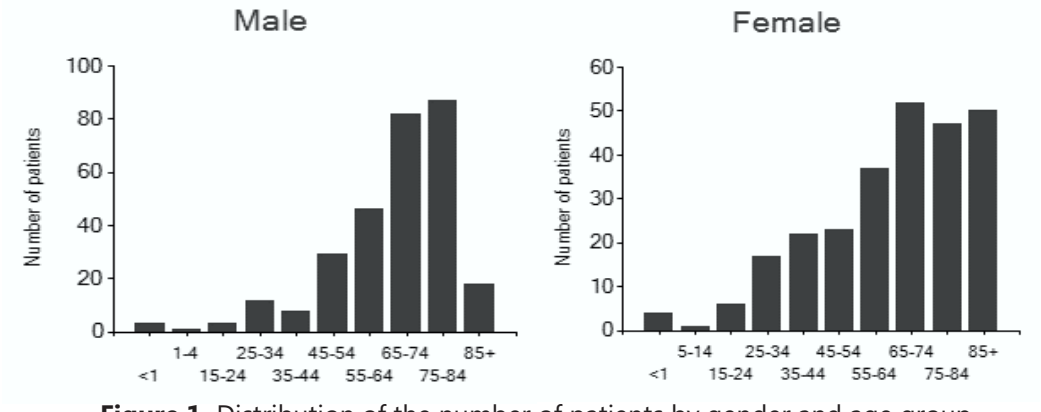

Figure 1. Distribution of the number of patients by gender and age group

Table 1. Sources of clinical isolates

Specimen	2020	2021	2022	Total	%
Urine	79	82	110	271	20.2
Blood	63	84	114	261	19.5
Sputum	29	41	35	105	7.8
etc.	228	233	243	704	52.5
Total	**399**	**440**	**502**	**1341**	**100.0**

Table 2. Carbapenem susceptible rate in Gram-positive cocci and Gram-negative rods bacteria during the year of 2020 to 2022

	n	Meropenem		n	Imipenem	
		(%S)	95%CI		(%S)	95%CI
Gram-positive cocci						
2020	29	31.0	16.0-51.0	36	44.4	28.3-61.7
2021	29	20.7	8.7-40.3	46	50.0	35.1-64.9
2022	29	31.0	16.0-51.0	42	52.4	36.6-67.7
Gram-negative rods						
2020	124	66.1	57.0-74.2	123	61.8	52.6-70.3
2021	143	49.0	40.6-57.4	128	52.3	43.4-61.2
2022	196	62.2	55.0-69.0	186	52.2	44.7-59.5

susceptibility kept increasing in GPC and GNR. Carbapenem susceptibility in 2020-2022 decreased compared to 3 years before. From hospital-wide isolates, Meropenem, Imipenem with inhibitor, and Doripenem susceptibility were 58%, 52%, and 48% compared to the previous three years, 62%, 57%, and 53%, respectively.

The susceptibility of GNR towards Meropenem showed higher proportions (58.9%) compared to GPC (26.2%). The susceptibility of *E. coli* and *S. aureus* towards meropenem showed relatively high proportions i.e., 95.0% and 87.5% compared to *K.pneumoniae* (46.1%), *A.baumanii* (30.3%), *P.aeruginosa* (28.6%) and others (Table 3). The susceptibility rates of isolates from non-intensive inpatients in 2020-2022 showed a lower proportion compared to the hospital-wide proportion and the previous three years susceptibility proportion of the hospital-wide isolates. The *K.pneumoniae* Meropenem susceptibility in 2020-2022 was 46.1%, compared to 51% of the hospital-wide proportion and 54% in the previous three years.

The Meropenem consumption was highest compared to Imipenem with inhibitor and Doripenem. The monthly Meropenem DDD was 146 in 2020 and increased in 2021 and 2020 to 155 and 160 (Table 4). Using JASP statistical software, correlation analysis showed no significant correlation ($p>0.05$) between the susceptibility rates and the DDD from the monthly non-intensive inpatient data. The increase of yearly consumption also showed no visual correlation to the susceptibility (Figure 2).

Antimicrobial resistance is a fast-growing public health issue over shadowing modern medicine.[9] Compared to years before, the decreasing

Table 3. Meropenem susceptibility of clinical isolates of Gram-positive cocci and Gram-negative rods

Microorganism	2020		2021		2022		Total	
	n	%S	n	%S	n	%S	n	%S
Gram -positive cocci								
Staphylococcus aureus	5	80.0	4	100.0	7	85.7	16	87.5
Staphylococcus epidermidis	5	20.0	11	9.1	7	14.3	23	13.0
Staphylococcus epidermidis - MRSE (+)	7	0.0	5	0.0	1	0.0	13	0.0
Staphylococcus haemolyticus	10	20.0	9	11.1	13	15.4	32	15.6
Total	27	25.9	29	20.7	28	32.1	84	26.2
Gram -negative rods								
Klebsiella pneumoniae ssp.pneumoniae	48	58.3	54	31.5	91	48.4	193	46.1
Escherichia coli	37	100.0	44	88.6	58	96.6	139	95.0
Pseudomonas aeruginosa	22	22.7	27	22.2	14	50.0	63	28.6
Acinetobacter baumannii	7	57.1	12	33.3	14	14.3	33	30.3
Proteus mirabilis	2	100.0	3	66.7	5	100.0	10	90.0
Total	116	65.5	140	48.6	182	62.6	438	58.9

Table 4. Monthly Carbapenem consumption (DDD) 2020-2022

	Meropenem			Imipenem + inhibitor			Doripenem		
Month	2020	2021	2022	2020	2021	2022	2020	2021	2022
Jan	8.01	10.8	11.7	1.59	0.78	0.02	0.29	0.72	0.49
Feb	9.49	12.4	13.2	1.16	2.39	1.36	0.46	1.29	0.05
Mar	14.3	14.8	15.6	0.33	0.96	1.26	0.37	0.57	1.08
Apr	13.4	12.4	16.2	0.31	0.58	0.96	1.32	0.59	0.97
May	10.0	16.5	13.2	1.07	0.85	1.13	0.35	0.74	0
Jun	9.49	12.3	11.7	0.25	3.21	0.21	0.58	0.51	1.36
Jul	12.6	13.4	13	0.69	1.4	3.17	0.88	0.09	0.24
Aug	11.3	9.53	12.1	0.76	1.12	0.8	1.61	0.25	0.4
Sep	18.2	12.3	14.2	3.12	1.11	0.97	0.43	0.45	0.88
Oct	16.7	11.5	14.8	2.69	1.49	0.99	0.41	1.89	1.76
Nov	10.9	14.5	11.3	1.47	1	0	0.75	1.28	0.55
Dec	11.4	14.8	13.1	1.48	2.16	1.19	0.22	1.96	0.26
Total	146	155	160	14.9	17.1	12	7.67	10.3	8.04

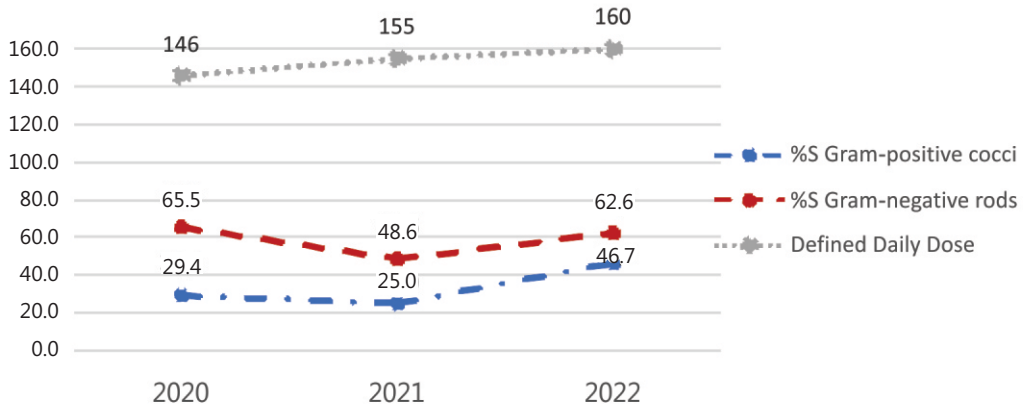

Figure 2. Meropenem susceptibility of Gram-negative rods and Gram-positive cocci had no correlation to DDD of respective years

susceptibility rates of Meropenem, Imipenem with inhibitors, and Doripenem have been a common trend worldwide.[10,11]

The susceptibility rates of *E.coli*, *K.pneumoniae*, *P.aeruginosa* and *A.baumanii* isolates in this study were quite low as the susceptibility rate in type B Hospitals in Indonesia in 2018 was reported to be 96%, 89%,73%, and 75% for blood specimen while for sputum specimen were 91%, 90%, 66% and 64%, respectively.[12] Possible aspects were the different study situations as this study population is in a large city with a more aged but wealthy population, which may have more consumption of antibiotics compared to Indonesia's general population.

Interestingly, there was no significant correlation between the monthly Carbapenem DDD and susceptibility. Further studies may be needed to confirm these findings as we need a relatively low number of data for this analysis. Wang *et al*. reported several correlations and no correlations between antimicrobial susceptibilities and consumption. However, they confirmed that proper management of antibiotics can decelerate or even reverse bacterial resistance.[13] In this study, a possible explanation was that the Carbapenem microbial resistance of this specific population was not strongly affected by the amount of Carbapenem consumption. The non-intensive patients had relatively short hospital days compared to the intensive-care patients. This data suggests possible non-hospital factors as the cause of Carbapenem susceptibility in this study. In a wider aspect, hospital antimicrobial use is not the only factor that can cause increasing antimicrobial resistance. There were increasing studies related to the non-human use of antibiotics.[14] As antibiotics have been used in animals, food-producing animals are reservoirs of bacterial pathogens. They may be vectors for the transfer of resistant bacteria and antimicrobial resistance genes to humans.[15] The first report of carbapenemase-producing isolates from livestock was made in 2012 in dairy cattle in France where *Acinetobacter spp*. from rectal swabs was described to harbor the blaOXA-23 carbapenemase gene. There was also a study reporting similar findings in the United States.[16] More studies may be needed regarding why the non-intensive patients in Jakarta already had relatively low Carbapenem susceptibility.

CONCLUSIONS AND SUGGESTIONS

The Carbapenem susceptibility profile showed decreased rates compared to previous years, with lower susceptibility shown in 2021 compared to 2020 and 2022. The susceptibility of GNR to Meropenem showed a higher proportion (58.9%) compared to GPC (26.2%). There was higher Meropenem susceptibility in urine isolates. Isolates of sputum showed lower susceptibility compared to blood and urine. The Carbapenems susceptibility was decreased, along with increased Carbapenems consumption but there was no statistically significant correlation between the susceptibility rates and the monthly DDD.

Strengthening of prudent antimicrobial stewardship practices obviously suggested in order to prevent further decreased of Carbapenems susceptibility. Further study is needed to determine the correlation between susceptibility rates and DDD over a longer period.

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