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Evaluation Of Antibiotic Use In Sepsis Patients In The ICU Treatment Room, Gatot Soebroto Rspad Period January 2020– December 2021

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ABSTRACT

Hypertension is Sepsis is a systemic inflammatory response syndrome caused by infection. Globally, the incidence of sepsis has increased with increasing mortality. Antibiotics used appropriately are considered to reduce mortality in sepsis. Destination of this study was to evaluate the use of antibiotics in septic patients in room care Gatot Army Hospital ICU Soebroto by qualitative with method old nor quantitative with method ATC / DDD. Method : Study this is study descriptive analytic and data collection is done retrospectively. The study was conducted by looking at the medical records of patients receiving antibiotic therapy who were treated at the hospital room Gatot Army Hospital ICU Soebroto period January 2020- December 2021. Results : Between 97 patient, 63 patient of them are male (64.9 %) and 34 patient Others are female (35.0 %). The highest age range is in the age of > 65 as many years (43.3 %). d result From the evaluation of the quality of antibiotics, it was found that the use of antibiotics was appropriate k (79%), possible appropriate (20.4%) and no exactly as much (0.52%). while the quantity of antibiotic use is obtained in total DDD/100 patient day take care as much 326.52 with antibiotics the most is usage meropenem 97.75 DDD/100 patient-day take care.

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INTRODUCTION

Sepsis is a clinical condition caused by the body's systemic response to infection. Infection is a disease condition resulting from the entry of pathogenic germs or other microorganisms into the body, causing symptoms. An infectious reaction in the body caused by the presence of this pathogen will enter the blood circulation. Globally, the incidence of sepsis is increasing with the death rate continuing to increase.

The incidence of sepsis in patients in hospitals, especially in referral hospitals, is quite high. This is because the patients who come are already characterized by various comorbid diseases or MODS (Multiorgan Dysfunction Syndrome). Usually, sepsis is often found in post-operative patients, patients on ventilators in the ICU (Intensive Care Unit) or patients

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using catheters. Sepsis can also occur in patients with a weak immune system, for example during chemotherapy treatment for cancer patients.

Based on a bulletin published by WHO (World Health Organization) in 2010, sepsis is the main cause of death in intensive care in developed countries, and its incidence is increasing. Every year there are 750,000 cases of sepsis in the United States. Things like this also happen in developing countries, where most of the world's population lives. Conditions such as malnutrition and germ infections will increase the incidence of sepsis.

The diagnosis of Sepsis itself is made based on the presence of symptoms of SIRS (Systemic Inflammation Response Syndrome) accompanied by infection of the organ that is the source of infection as a systemic inflammatory response. These symptoms can be characterized by 2 or more conditions including temperature > 38°C or < 36°C, heart frequency > 90 x/minute, respiratory frequency > 20 x/minute or PaCO2 < 32 mmHg, blood leukocytes > 12,000/mm3, < 4000 /mm3 or the presence of rod neutrophils >10% (2). Sepsis is most commonly caused by gram-negative bacteria (52% of sepsis cases), followed by gram-positive bacteria (37%) and the rest is caused by fungi or other microorganisms.

Providing appropriate antibiotics is one of the criteria in treating sepsis. Providing inappropriate/inappropriate antibiotic therapy and delays in administering appropriate antibiotics are two important factors in antimicrobial therapy related to the incidence of mortality in sepsis patients. There are several ways to analyze the appropriateness of antibiotic use, including the qualitative method, namely the Kunin method, and for quantitative studies using the defined daily dose (DDD) method.

The Kunin method is used to evaluate and ensure the rational use of antibiotics. The parameters assessed by the Kunin method are accuracy of indication, selection of antibiotics based on accuracy of dose, duration of treatment, route of administration, time of administration and duration of administration which are linked to culture results and germ patterns and adjusted to the sepsis management guidelines issued by the Ministry of Health, the surviving sepsis campaign guideline 2021, and sepsis clinical pathway at Gatot Soebroto Army Hospital, and Drug Information. The DDD method is a method for assessing antibiotic use using parameters for accuracy of drug use with the aim of improving the quality of drug use. There are comparisons carried out at other levels/places that require a standard classification, so WHO recommends classifying antibiotic use using the Anatomical Therapeutic Chemical (ATC) Classification.

A 1 month observation in 2012 in the intensive care unit at Cipto Mangunkusumo Hospital (RSCM) Jakarta showed that severe sepsis and septic shock were found in 23 of 84 intensive care cases, with a mortality rate in 3 treatments reaching 47.8% in septic shock cases and the number mortality in the early phase of sepsis reached 34.7%. The very high mortality rate for sepsis is supported by various studies that have obtained similar results. Research at RSUP Prof. Dr. R. D. Kandou in 2017 obtained similar results where the sepsis mortality rate was much higher than the survival rate for sepsis patients in the ICU. Of the 35 patients, 23 people (65.7%) died. In another study, at Dr Soetomo General Hospital Surabaya in 2014, 14.58% were diagnosed with septic shock and 58.33% were diagnosed with sepsis.

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Gatot Soebroto Central Army Hospital (RSPAD) is a Type A Hospital where during the Covid pandemic there has been no specific research regarding the use of antibiotics in sepsis patients in the ICU considering that the high number of Covid patients during this pandemic does not rule out the possibility of creating a pattern of antibiotic administration. What is given may be different, especially for Covid patients with sepsis or non-Covid patients with sepsis related to the priority services for Covid patients. The aim of the research is to qualitatively assess the use of antibiotics in sepsis in the ICU (Intensive Care Unit) at the Gatot Soebroto Army Central Hospital using the Kunin method and quantitatively assess it using the ATC/DDD method.

METHOD

The type of research is Retrospective Cohort. This research was carried out from March to May 2022. The population in the study was all sepsis sufferers in the ICU Treatment Room at Gatot Soebroto Army Hospital for the period January 2020 – December 2021 who were included in the inclusion criteria. The population that met the inclusion criteria was 97 patients and the entire population was used as a sample. Data was obtained by looking at the patient's medical records and analyzed descriptively analytically and carried out bivariate statistical tests with the chi-square test at α=0.05. The method used for qualitative and quantitative analysis is the Kunin and DDD methods with sampling using the purposive sampling method, namely from the entire population based on the patient's medical records and the samples obtained are taken based on inclusion criteria and then analyzed.

RESULTS AND DISCUSSION

The characteristics of respondents can be seen as follows:

Characteristics	Category	N	%
Gender	Male	63	64.95
	Female	34	35.05
Age	17-25	2	2.06
	26-35	2	2.06
	36-45	8	8.25
	46-55	11	11.34
	56-65	32	32.99
	>65	42	43.29

The first respondent characteristics include age and gender. The research results showed that the respondents with the largest age were > 65 years, namely 42 people (43.29%). The majority of genders were men, namely 63 people (64.95%). This can be caused by the levels of the hormone estrogen which plays a role in the adaptive immune response in women being higher than in men. And at age that has begun to enter the criteria for elderly, organ systems will begin to decline and the formation of the immune system will decrease.

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Characteristics	Category	N	%
Length of Treatment	<10 day	32	32.98
	≥ 10 day	65	67.01
Concomitant Diseases	Without comorbidities	18	18.56
	With comorbidities	79	81.44
Number of Comorbidities	≥ 2	75	77.32
	< 2	42	43.29
Number of antibiotics received	1 – 2	21	21.65
	3 – 4	40	41.24
	≥ 5	36	37.11

Further characteristics of respondents include length of treatment, comorbidities, number of comorbidities and number of antibiotics received. The research results showed that respondents with a length of treatment ≥ 10 days were 65 patients (67.01%). The high percentage of length of stay may be related to the patient's condition having worsened, with comorbidities and the number of comorbidities, many patients have ≥ 2 comorbidities. These things can cause a patient's length of stay.

Sofa Score

Score SOFA	Mortality				Total	
	Yes		No			
	N	%	N	%	N	%
< 7	11	11.34	24	24.74	35	36.08
≥ 7	57	58.76	5	5.15	62	63.91
Total	68	70.10	29	29.89	97	100

Organ dysfunction conditions are represented by an increase in the total SOFA score value ≥ 2. Sepsis conditions are usually characterized by a SOFA score value ≥ 2 and the higher the SOFA score value increases the risk of mortality. The SOFA score calculated when a patient is newly admitted to the intensive care unit, and changes in the SOFA score calculated on days 1-7 are associated with patient mortality in the intensive care unit at the hospital.

The results of the study showed that the SOFA score < 7 was 35 patients (36.08%) with a death rate of 11 patients (11.34%) while for a SOFA score ≥ 7 it was 62 patients (63.91%) with a death rate of 57 patients (58.76%). SOFA ≥ 7 is more at risk of mortality and SOFA scores < 7 are more likely to experience improvement. Patients with an initial SOFA score < 7 have a mortality rate of 56% and this will increase to 70% in patients with a SOFA score of 8-15. This score can be reviewed after 48 hours. The result is that patients with a SOFA score of <7 have a mortality rate of more than 52% and this increases to 88% with a SOFA score of 8-15.

Although the SOFA score is used to describe and measure the function of the body's organs, and is not intended to predict outcome, previous studies have stated that there is a

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relationship between the occurrence of organ dysfunction and patient mortality. Because the higher the SOFA score, the higher the number and severity of the patient's organs.

Cultural Results

Types of Microorganisms	N	%
Sterile (no microorganisms found)	4	8.5
(Gram negative bacteria)	26	55.31
Acinetobacter baumannii	6	12.76
Acinetobacter haemolyticus	3	6.38
Escherichia coli	2	4.25
Klebsiella pneumoniae	9	19.15
Klebsiella oxytoca	1	2.13
Pseudomonas aeruginosa	4	8.51
Burkholderia cepacia	1	2.13
(gram positive bacteria)	17	36.17
Aeococcus viridans	1	2.13
Staphylococcus aureus	7	14.89
Staphylococcus epidermis	2	4.25
Staphylococcus haemolyticus	3	6.38
Staphylococcus hominis	3	6.38
Enterococcus faecalis	1	2.13
(Fungal spores)	0	0
Candida albicans	0	0
Candida sp	0	0

The groups of germs that cause sepsis in the ICU Room at Gatot Soebroto Army Hospital from highest to lowest number are 26 (55.31%) Gram negative bacteria, 17 (36.17%) Gram positive bacteria, 0 (0%) fungi. This is in accordance with the statement that in developing countries the main cause of sepsis is Gram negative bacteria. The most common bacteria found in sepsis were Klebsiella pneumoniae (19.15%), Staphylococcus aureus (14.89%) and Acinetobacter baumannii (12.76%).

Antibiotic Use Profile

Types of antibiotic therapy	Number (N) of patients	Percentage (%)
Empirik	72	74.22
Definitif	25	25.77
Total	97	100

The empirical antibiotics used by patients consisted of 17 types of antibiotics, with the highest use of antibiotics being ceftriaxone, either in the form of single or combination therapy, namely 49 people (45.4%). This can be caused because ceftriaxone is a cephalosporin III class antibiotic with a broad spectrum against bacteria, has a long half-life so it can be given once a day and is cheap compared to other types of antibiotics. Profile of antibiotic use from 97 patients, the most frequently used was combination antibiotic

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therapy in 84 patients (88.65%) and single therapy in 11 patients (11.34%). This is related to the main diagnosis of sepsis at Gatot Soebroto Army Hospital is pneumonia, and based on the treatment of pneumonia therapy is the administration of the antibiotic levofloxacin with a combination of beta lactam antibiotics.

Types of Antibiotic Therapy	Regimen Antibiotik			
	Empiris		Definitif	
	N	%	N	%
Single therapy	15	9.80	10	6.53
Combination therapy	113	73.85	15	9.80
Total	128	100	25	100

The empirical antibiotics used in this study were β-lactams (cephalosporin and penicillin), fluoroquinolones, aminoglycosides and carbapenems. According to the literature, it is also stated that this group is suitable for sepsis treatment management.

No.	Types of Antibiotics	Empiris		Definitif		Amount	
		N	%	N	%	N	%
1	Ceftriaxon	6	24	1	4	7	28
2	Ceftazidime	1	4	0	0	1	4
3	Levofloxacin	2	8	2	8	4	16
4	Gentamisin	1	4	0	0	1	4
5	Meropenem	2	8	3	12	5	20
6	Amikasin	1	4	1	4	2	8
7	Cefaperazon	2	8	0	0	2	8
8	Tygecil	0	0	2	8	2	8
9	Vancomisin	0	0	1	4	1	4
	Total	15	100	10	100	25	100

The antibiotics most widely used for single therapy in sepsis patients in the ICU ward of Gatot Soebroto Army Hospital for empiric and definitive therapy are the β-lactam cephalosporin group, namely Ceftriaxon (28%), Cefoperazone (8%); the fluoroquinolone group, namely Levofloxacin (16%); and the carbapenem group, namely meropenem (20%). The research results showed that the first single antibiotic that is widely used is ceftriaxone. Ceftriaxone is a third generation cephalosporin which has a broader spectrum of activity compared to class II cephalosporins.

Antibiotik	Empiris		Definitif		Amount	
	N	(%)	N	(%)	N	%
Ceftriaxon-Levofloxacin	21	16.40	0	0	21	16.40
Meropenem-Levofloksasin	18	14.06	1	0.7824	19	14.84
Ceftazidime – Levofloksasin	6	4.69	1	0.78	7	3.21
Amikasin – Levofloksasin	1	0.78	2	1.56	3	2.34
Metronidazole – Levofloksasin	1	0.78	0	0	1	0.78
Cefoperazone – Levofloksasin	8	6.25	0	0	8	6.25

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Antibiotik	Empiris		Definitif		Amount	
	N	(%)	N	(%)	N	%
Piperacillin – Levofloksasin	0	0	1	0.78	1	0.78
Moxifloksasin – Meropenem	3	2.34	0	0	3	2.34
Amikasin – Meropenem	3	2.34	2	1.56	5	3.90
Metronidazole – Meropenem	3	2.34	0	0	3	2.34
Ceftazidime – Meropenem	1	0.78	0	0	1	1.78
Tigecycline – Meropenem	3	2.34	0	0	3	2.34
Ciprofloksasin – Meropenem	2	1,56	0	0	2	1.56
Ceftriaksone – Meropenem	1	0.78	0	0	1	0.78
Tigecycline – Amikasin	5	3.90	1	0.78	6	4.68
Moxifloksasin – Amikasin	1	0.78	0	0	1	0.78
Ampicillin Sulbactam – Amikasin	2	1.56	0	0	2	1.56
Ceftazidime – Amikasin	4	3.12	2	1.56	6	4.68
Ciprofloksasin – Amikasin	0	0	2	1.56	2	1.56
Piperacillin – Amikasin	2	1.56	0	0	2	1.56
Ceftriaxsone – Amikasin	0	0	2	1.56	2	1.56
Cefoperazone – Amikasin	1	0.78	0	0	1	0.78
Ceftazidime – Metronidazole	1	0.78	0	0	1	0.78
Ceftriaxsone – Metronidazole	1	0.78	0	0	1	0.78
Cefoperazone – Gentamisin	1	0.78	0	0	1	0.78
Tigecycline – Gentamisin	1	0.78	1	0.78	1	0.78
Ceftazidime – Gentamisin	2	1.56	0	0	1	0.78
Ciprofloksasin – Gentamisin	1	0.78	0	0	1	0.78
Cefoperazone – Moxifloksasin	1	0.78	0	0	1	0.78
Streptomycin – Moxifloksasin	1	0.78	0	0	1	0.78
Azitromisin – Ceftazidime	1	0.78	0	0	1	0.78
Ceftazidime – Levofloksasin – Metronidazole	4	3.12	0	0	4	3.12
Ceftriaxsone – Levofloksasin – Metronidazole	1	0.78	0	0	1	0.78
Meropenem – Levofloksasin – Metronidazole	2	1.56	0	0	2	1.56
Meropenem – Amikasin – Levofloksasin	1	0.78	0	0	1	0.78
Meropenem – Amikasin – Vancomisin	1	0.78	0	0	1	0.78
Meropenem – Amikasin – Metronidazole	1	0.78	0	0	1	0.78
Meropenem – Gentamisin – Fosfomisin	1	0.78	0	0	1	0.78
Meropenem – Amikasin – ceftazidime	1	0.78	0	0	1	0.78
Meropenem – Metronidazole – Ampicilin Sulbactam	1	0.78	0	0	1	0.78
Ceftriaksone – Ciprofloksasin – Levofloksasin	1	0.78	0	0	1	0.78
Tigecycline – Gentamisin – Amikasin	1	0.78	0	0		0.78
Ceftazidime – Metronidazole – Lincomisin	1	0.78	0	0		0.78
Levofloksasin – Tigecycline -Cotrimoksazol	1	0.78	0	0		0.78
Total	113		15			

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The most frequently used antibiotic combinations were the combination Ceftriaxon-Levofloxacin (16.40%), Meropenem – Levofloxacin (14.84%), cefoperazone – Levofloxacin (6.25%), Tigecyclin – Amikacin (4.68%) and Ceftazidime – Amikacin (4.68%). Based on the number of sepsis patients who were given antibiotics in this study, lung infection (pneumonia) was the most common cause of sepsis, so the administration of antibiotics between levofloxacin - ceftriaxone is an antibiotic intended for sepsis patients with lung infections.

Quantitative Evaluation Of The Ddd Method

Antibiotic Name	Code ATC	Rute	DDD Standart WHO (gram)	Calculation DDD	DDD/100 care day
Ceftriaxone	J01DD04	P	2	1040	36.5
Levofloxacin	J01MA12	P	0,5	225.36	31.6
Meropenem	J01DH02	P	3	8376	97.7
Moxifloksasin	J01MA14	P	0,4	9.44	1.6
Metronidazole	J01XD01	P	1,5	420.38	19.6
Ceftazidime	J01DD02	P	4	1552	27.2
Gentamisin	J01GB03	P	0,24	6.26	1.8
Cefaperazone	J01DD12	P	4	1520	26.6
Ciprofloksasin	J01MA02	P	0,8	80	7.0
Amikasin	J01GB06	P	1	351	24.6
Streptomicin	J01GA01	P	1	27.75	1.9
Ampisilin Sulbaktam	J01CR01	P	6	2196	25.6
Piperacillin	J01CA12	P	14	4347	21.7
Doripenem	J01DH04	P	1,5	37.5	1.8
Vancomycin	J01XA01	P	2	24	0.8
Lincomisin	J01FF02	P	1,8	8.1	0.3
Fosfomicin	J01XX01	P	8	16	0.1
Total DDD/100 patient-days admitted					326.5

In this study, the total DDD/100 patient days of care for antibiotic use was 326.52 DDD/100 patient days of care. The greater the total value of DDD use/100 patient days of hospitalization indicates the magnitude or number of antibiotics used in 100 days of hospitalization.

The highest use of antibiotics is the carbapenem group, namely parenteral meropenem, amounting to 97.75 DDD/100 patient days of stay, which means that there are 97-98 patients who receive parenteral meropenem therapy according to the daily dose of empirical antibiotics, with a total length of stay (LOS) of 1428 days of stay. Meropenem is a broad spectrum antibiotic that has bactericidal properties and is stable against hydrolysis and beta-lactamase enzymes so it is often used as a drug of choice in conditions of severe infections.

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Qualitative Evaluation Of The Kunin Method

core SOFA	Appropriate therapy						Therapy may be appropriate						Inappropriate therapy			
	I		II		Sub total		III		IV		Sub total		V		Sub total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
< 7	58	15.18	79	20.68	137	35.86	19	4.97	9	2.35	28	7.32	0	0	0	0
≥ 7	77	20.15	88	23.03	165	43.19	34	8.9	16	4.18	50	13.08	2	0.52	2	0.52
Total	135	35.34	167	43.71	302	79.05	53	13.87	25	6.54	78	20.41	2	0.52	2	0.52

The category of appropriate therapy consists of criterion I, namely agreeing with the use of antimicrobial therapy and the protocol (selection, route, duration, dose) is appropriate. Criterion I in sepsis includes 135 antibiotic regimens. The next category of appropriate therapy is criterion II, namely agreeing with the use of antimicrobial therapy, the protocol (selection, route, duration, dose) is likely to be appropriate, in the event that the patient's microbiological data is not found or is incomplete, so it cannot be evaluated completely. Criterion II in sepsis patients is 167 antibiotic regimens.

The next category is the category of therapy that may be appropriate (has shortcomings) consisting of criterion III, namely agreeing with the use of antimicrobial therapy, but the use of a different antimicrobial is preferable (cheaper, less toxic, narrow spectrum, other combinations). Criterion III consists of 53 antibiotic regimens. The next category of therapy that may be appropriate is criterion IV, namely agreeing with the use of antimicrobial therapy but modifying the dose, interval, duration, route of use is more recommended. The IV criteria in this study were 25 antibiotic regimens. The category of inappropriate therapy in the Kunin method is criterion V regarding not agreeing with the use of antimicrobial therapy, its use cannot be justified. In the data there are 2 patients who fall into this category.

Patient Clinical Outcomes

No.	*Outcome Klinik*	N	%
1	Improved	29	29.89
2	Not getting better	68	70.10
	Total		100

In this study, clinical outcomes of 29 patients (29.89%) improved and clinical outcomes worsened for 68 patients (70.10%). Rational use of antibiotics is expected to provide good clinical outcomes. From the results of research on 97 patients with 392 antibiotic regimens, 391 antibiotic regimens met the rational criteria but only 29 patients (29.89%) experienced improved outcomes. This may be caused by the body's ability to respond to antibiotics, the patient's clinical condition, age, and the patient's comorbid diseases. Apart from that, patients who enter the ICU are patients transferred from other treatment rooms who have experienced worsening conditions caused by comorbidities.

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The Relationship Of The Kunin Method With Outcomes

Kunin Method Category	Outcome				Total		Bivariate analysis (p-value)
	Improved		Die				
	n	%	N	%	n	%	
Appropriate	91	23.21	215	54.84	306	78.06	
Maybe Exactly	15	3.83	69	17.60	84	21.43	0.100
Not exactly	0	0	2	0.51	2	0.5	

The results of the analysis of the relationship between Kunin method categories and patient clinical outcomes (Table V.6) have a p-value >0.05 (p=0.100), meaning there is no significant relationship. This could be because it is not only the appropriateness of antibiotics that affects patient outcomes, there are other factors that cause patient outcomes to not improve, namely irrational supportive therapy so that the patient's symptoms are not resolved or there are comorbidities that make the patient's condition worse.

The Relationship Of The Kunin Method With Length Of Treatment

Kunin Method Category	Length of Treatment				Total		Bivariate analysis (p-value)
	<10 days		≥ 10 days				
	n	%	N	%	n	%	
Appropriate	72	35.64	53	26.23	125	61.88	
Maybe Exactly	4	1.88	81	40.09	85	42.07	
Not exactly	0	0	2	0.9	2	0.99	0.000

In contrast, the relationship between the Kunin method category and patient length of stay has a p-value <0.05, meaning there is a significant relationship. This can illustrate that the more appropriate the antibiotics given, the shorter the patient's hospital stay.

CONCLUSION

The use of antibiotics reviewed using the ancient method of appropriate therapy was 307 antibiotic regimens consisting of criteria I and Criterion II, then there were 83 possible appropriate therapy regimens consisting of criteria III and criteria IV and there was inappropriate therapy consisting of criterion V, namely a total of 2 antibiotic regimens. The Kunin method did not have a significant relationship with clinical outcomes. Shows that it is not only rational use of antibiotics that influences clinical outcomes. Meanwhile, the number of days of treatment has a relationship which shows that the higher the accuracy of antibiotics using the Kunin method, the shorter the length of treatment. Evaluation of the quantity of antibiotic use using the ATC/DDD method showed that the total DDD/100 patient-days of care was 326.52. The highest use of antibiotics is the use of meropenem with ATC code J01DH02 with a DDD value/100 patient days admitted to 97.75.

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