

Evaluation Of Antibiotic Use With Quantitative Methods at Sultan Agung Semarang Hospital

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ABSTRACT

Antimicrobial Resistant in Indonesia estimates that the data of deaths due to Antimicrobial Resistant in 2018 is around 700,000 people and this number will continue to increase to 10 million people by 2050. It is necessary to control antibiotic resistance by evaluating the use of antibiotics. The purpose of this study was to determine the quantity of antibiotic use at RSI Sultan Agung Semarang period July-December 2021. This research is observational with a descriptive research design and retrospective data collection. The population used was all medical record data of inpatients in the internal medicine ward who used antibiotics. There were 394 medical records that met the inclusion criteria. Data calculated using the ATC/DDD method is described descriptively and presented in the form of percentages and tables, percentages and tables. The results showed the total DDD value of the antibiotic was 81.56 DDD/100 patient days with a total Length of Stay (LOS) of 2,588 days. Antibiotics with the highest DDD value are Levofloxacin parenteral with a value of every 100 days of hospitalization 20.38 patients received the treatment with a dose of 0.5 grams every day. While antibiotics that enter the 90% DU segment are Levofloxacin (P), Ceftriaxone (P), Moxifloxacin, Cefoperazone Sulbactam (P), Ampicillin Sulbactam (P), Meropenem (P), Metronidazole (P), Cefixime (O), Azitromycin (O), Levofloxacin (O), dan Cefotaxime (P). As a consequence of the possibility of antibiotic resistance, its use should be strictly controlled.

Keywords : Antibiotics, Defined Daily Dose, Drug Utilization 90%, Infectious Disease

INTRODUCTION

Infectious diseases represent a significant concern in Indonesia. Treatment might be a provided with antimicrobial agents, such as antibacterial, antifungal, antiviral, and antiprotozoal drugs. Antibiotics are the most widely used drug therapy in the treatment of bacterial infections. The high use of antibiotics can lead to resistance which is a global threat (Permenkes, 2021). When antibiotic are used, bacteria might evolve to evade the effect of antibiotics through a variety of mechanism.

Observation at the WHO report on Surveillance of Antibiotics Consumption at 2022 showed increase in AMR rates by more than 15% in 2020 compared with 2017 for meropenem and third-generation cephalosporin resistance in bloodstream *E. coli* BCIs, ciprofloxacin resistance in *Salmonella* spp. bloodstream BCIs, and azithromycin resistance in gonorrhoea BCIs. Based on Antimicrobial

Resistant in Indonesia (AMRIN) data in 2018, it is estimated that deaths due to Antimicrobial Resistant (AMR) are around 700,000 people. This data is predicted to continue to increase, until in 2050 it reaches 10 million people per year (Octavianty *et al.*, 2021).

The high mortality rate causes the need to monitor the use of antibiotics in all health care facilities, one of which is the hospital. Inappropriate use of antibiotics will lead to resistance. Therefore, antibiotic utilization studies need to be conducted in healthcare facilities, including hospitals. Antibiotic resistance, or the ability of germs to withstand harmful drugs, is one of today's most serious global public health concerns. Hospital is one of the main health facilities, where in clinical pharmacy services such as evaluation of drug use (EPO), antibiotic. The evaluation evaluates the use of drugs qualitatively and quantitatively (Octavianty *et al.*, 2021; WHO,

2024; Rachmawati *et al.*, 2020; Sovia *et al.*, 2023; Permenkes, 2016).

WHO recommends the classification quantitatively of antibiotic use by Anatomical Therapeutic Chemical (ATC) and measuring the amount of antibiotic use with Defined Daily Dose (DDD)/100 patient-days to obtain standardized data and can be compared with data in other hospitals. DDD is an assumption of the average dose per day in the use of antibiotics with certain indications in adults for the main indication. In addition to the ATC/DDD method, an assessment of drugs included in the 90% segment was also carried out using the 90% Drug Utilization (DU) method. The DU 90% method is a method that explains the pattern of drug consumption that is most widely used and is useful in terms of drug evaluation, control, and planning. This method is widely used in the implementation of antibiotic utilization evaluation in hospitals (Lestari *et al.*, 2019; Permenkes, 2015; Ridwan *et al.*, 2019; WHO, 2021).

Sultan Agung Islamic Hospital Semarang is one of the referral hospital centers in Semarang city and surrounding areas. The use of antibiotics in the hospital ranged from 45%-60% in 2020. This result when compared to the WHO standard value of rational drug use indicators which should be <22.70%, shows a result that is still quite high. The higher the use of antibiotics, the higher the potential for resistance. Infection that often occurs in hospitals is in cases of internal medicine. Cases that occur include the respiratory tract, urinary tract, digestion, and infections due to the using of catheters. Therapy using antibiotics is needed to overcome these cases of infection.

AMRIN research conducted at Dr. Soetomo Hospital and Dr. Kariadi Hospital showed the use of antibiotics in internal medicine cases reached 67% (Ridwan *et al.*, 2019). Based on this explanation, the researcher intends to conduct research related to evaluation of antibiotic use at Sultan Agung Islamic Hospital Semarang to determine the amount of antibiotic use in hospitalized patients in the internal medicine ward, using the ATC /DD method. The results of this study are expected to be one of the evaluation materials related to the use of antibiotics to optimize the control of antimicrobial resistance in hospitals.

RESEARCH METHOD

This study was conducted descriptively observational with retrospective data collection. Data

were obtained from the hospital during the period July-December 2021. This research passed the ethical review by KEPK RSI Sultan Agung Semarang with number: 143/KEPK-RSISA/X/2022. The samples in this study were all medical records of inpatients in the internal, which inclusion criteria, namely patient medical records were complete and easy to read (age, gender, diagnosis, length of hospitalization and drug data in the form, doses, duration of administration, and route of administration) and there was antibiotic use included in the ATC classification and had a standard DDD value. Meanwhile, the exclusion criteria were incomplete medical records of patients in the internal medicine ward, discharged from the hospital at their own request, referred to another hospital, or died and antibiotics that did not have standard DDD values, such as antibiotics for topical and ophthalmic use.

Data analysis was carried out by calculating the quantity of antibiotic use using the ATC/DDD method were viewed through the website (<http://www.whocc.no/atc-ddd-in-dex/>) and determining DU 90% by dividing the DDD/100 patient days hospitalization value of an antibiotic by the total DDD/100 patient days hospitalization of all antibiotics multiplied by 100%. The DDD/100 patient days value is calculated by dividing the number of grams of each type of antibiotic used by the patient, with the standard set by WHO in grams. Then multiplied by one hundred and divided by the total Length of Stay (LOS). Then accumulated and sorted from the highest percentage to the lowest percentage.

RESULT AND DISCUSSION

The research was conducted by looking at patient characteristics based on the distribution of age and gender. Patient characteristics (age, gender) are used to determine the distribution of patients. Data obtained from medical records of patients hospitalized in the internal medicine ward of RSI Sultan Agung Semarang during the period July-December 2021 showed that there were 1,186 patients and 394 medical records with inclusion criteria (Figure 1).

The results of patient characteristics based on gender show the same ratio between male and female (50%:50%), both of the patients have the potential to experience cases of infection that require treatment with antibiotic therapy.

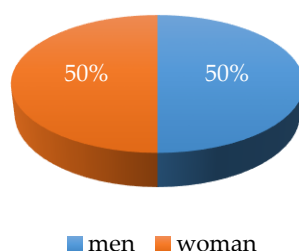


Figure 1. Characteristics Of Gender Patient

These results are different from research at Dr. Margono Soekarjo Purwokerto Hospital which states that male patients are more susceptible to infections than female patients with a percentage of 56% to 44% so that male patients are prescribed more antibiotic (Lestari *et al.*, 2019).

The 46-65 years range distribution showed high values, because in the elderly are a combination of disorders arising from disease. A sign of the onset of the process is the gradual loss of tissue's ability to repair or replace itself and maintain its normal structure and function, making it unable to defend against including infection (Rahmasari, V &Lestari, K, 2016) .

Incidence of coronavirus infection disease is

in the first position with the number of patients amount to 109 (27.67%) showed at Table I. This is directly proportional to the Covid-19 infection cases which also increased in 2021. According to the Covid-19 statistical report in Central Java province, 21.26% of Covid-19 cases came from Semarang City, Banyumas Regency, and Klaten Regency. Semarang City has the highest number of confirmed and suspected Covid-19 patients at 52,049 cases. Meanwhile, Banyumas Regency had 26.810 cases and Klaten Regency had 24,630 cases (Kemenkes, 2021). Researchers also conducted other antibiotic use studies, looking at several wards. Where the most use of antibiotics was also found in respiratory cases, for example in pediatric wards 26.38%.

Table 1. Patient Characteristics Based on Disease Pattern

No.	Diagnosis	Persentase (%)
1	Coronavirus infection	27.67
2	Uncomplicated non-insulin-dependent diabetes mellitus	6.85
3	Gastroenteritis and colitis of	6.60
4	Congestive heart failure	3.55
5	Non-insulin dependent diabetes mellitus with peripheral circulatory complications	3.05
6	Chronic kidney disease, stage 5	2.79
7	Kidney disease with hypertension	2.28
8	Bronchopneumonia	1.78
9	Urinary tract infection	1.78
10	Typhoid fever	1.52
11	Others	57.61
Total		100

Diabetes mellitus cases are the second most common diagnosis given antibiotic therapy. Antibiotic therapy is given because patients with diabetes mellitus are highly associated with infection, complications associated come from peripheral blood system disorders, so there is a high risk of diabetic foot wounds, cellulitis, and gangrene (Octaviany *et al.*, 2021).

The next most common diagnosis was gastroenteritis. Acute gastroenteritis can afflict anyone at any moment, but it can be prevented by having adequate food safety protocols in place. There

are several pathogens detected to cause acute gastroenteritis disease other than those routinely tested in public hospitals. According to the study, the pathogens identified in this study that caused the illness included, *Salmonella*, *Shigella*, *Norovirus*, *Rotavirus*, *Campylobacter*, *Clostridium difficile*, *E.coli*, *Adenovirus*, and *Sapovirus*. Therapeutic management in gastroenteritis for causal therapy is by administering antibiotics according to the causative pathogen (Lakhan *et al.*, 2022).

Pneumonia is one of the diseases with the highest risk of death in Indonesia. The first line of pneumonia treatment is antibiotic therapy, antibiotic control that can be done is to evaluate the use of antibiotics quantitatively and evaluate the appropriateness of antibiotics. The most used antibiotics for pneumonia patients in RSUD Bangil based on DDD/100 patient days are fluoroquinolone and cephalosporin with the LOS 1-5 days (Rahmasari, V & Lestari, K, 2016; Zavira *et al.*, 2021).

The other most common disease diagnosis is kidney disease or kidney failure with clinical condition characterized by an irreversible decline in kidney function to a certain degree and requires permanent kidney replacement therapy, kidney transplant or dialysis. Patients with chronic renal failure have low immunity so they tend to be more prone to infectious diseases such as pneumonia, urinary tract infections, and sepsis. It is necessary to give antibiotic treatment by considering the factors of pharmacokinetics, pharmacodynamics, and drug toxicity as well as the degree of decline in kidney function. When infections in patients with kidney failure are not treated first, it will worsen the kidney failure disease itself and can even cause death (Sinaga CR & Tjitrosantoso H, 2017).

Typhoid fever cases were also one of the most common diagnoses in this study. Typhoid fever is an acute febrile diseases caused by *Salmonella typhi* bacterial infection, that can be treated with antibiotics such as ciprofloxacin, cefixime, chloramphenicol, thiamfenicol, azithromycin, and ceftriaxone (Rahmasari, V & Lestari, K, 2016; Zavira *et al.*, 2021).

There are several types of antibiotics used by inpatients in the internal medicine ward at the

hospital. The antibiotics consisted of 10 classes of antibiotics and 28 types of antibiotics and one antiprotozoal class. Metronidazole given orally with ATC code J01XD01 is included in the classification and calculation in this study because it is included in the therapeutic drugs given to patients. The most common antibiotic group is the quinolone group (39.00%) with the most common type of antibiotic is levofloxacin parenteral route (14.71%).

This is in line with the high number of Covid-19 cases, where pharmacological therapy for the treatment of Covid-19 based on the Covid-19 Management Guidelines Edition 3th, one of which is using azithromycin, levofloxacin or ceftriaxone (PDPI, 2020).

Similar research has been conducted in one of the private hospitals in Bandung City which shows that quinolone is the most widely used antibiotic in the hospital with a percentage value of 67.54% and levofloxacin parenteral route is the most widely used type of antibiotic at 48.80%. The high use of levofloxacin is because this antibiotic has a broad spectrum antibacterial effect which means it is active against gram-positive bacteria, such as *streptococcus pneumoniae* or gram-negative bacteria, such as *haemophilus influenzae*, as well as atypical bacteria such as *chlamydia pneumoniae*, *mycoplasma pneumoniae* and *legionella* spp by inhibiting DNA gyrase and topoisomerase IV enzymes used by bacteria in the replication process (Hanifah *et al.*, 2022).

Patients referred to the hospital generally required treatment for moderate to severe illnesses, consequently, this parenteral route is the most widely utilised (64%). The high number of Covid-19 cases that occurred during this study are patients who need immediate treatment because they are included in moderate to severe cases of infection (Figure 2).

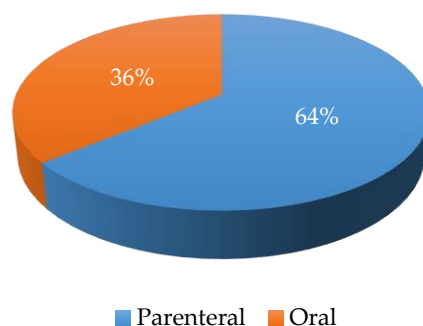


Figure 2. Route Of Administration And Dosage Forms

Meanwhile, the oral route is an alternative for treating minor category infections. The parenteral route was chosen due of its swifter onset and increased absorption. So that it will optimize the efficacy of antibiotic action in suppressing or

eradicating microorganisms that cause infection. (Permenkes, 2021; Rachmawati, 2020; PDPI, 2020).

The rules of use determine the frequency of antibiotic use in a day. The high frequency of antibiotic use will affect the increase in the number of

doses (grams) of antibiotics received by the patient. The increase in the number of antibiotic doses (**Table II**) will eventually affect the DDD value which also increases (WHO, 2021).

Antibiotics with a 1 x 1 frequency in this study include azithromycin, levofloxacin, and moxifloxacin with the total 42.86%. Levofloxacin is the most widely used in this study, given once a day at a dose of 500 mg -750 mg. Antibiotics with a 2 x 1 are cefixime, ceftriaxone, and cefoperazone. While antibiotics with a 3 x 1 are metronidazole, amoxicillin, and ampicillin.

The duration of antibiotic use shows at Figure 3. The length of antibiotic use is mostly in the range of 1-3 days (64.71%), where levofloxacin which are included in the broad spectrum are the most widely used types of antibiotic.

This result is in accordance with the explanation of the Indonesian Ministry of Health, which states that empirical therapy of broad spectrum antibiotics is two to three days. This is directly proportional to the Covid-19 infection cases which also increased in 2021. According to the Covid-19 statistical report in Central Java province, 21.26% of Covid-19 cases came from Semarang City, Banyumas Regency, and Klaten Regency. Semarang City has the highest number of confirmed and suspected Covid-19 patients at 52,049 cases. Meanwhile, Banyumas Regency had 26,810 cases and Klaten Regency had 24,630 cases (Kemenkes, 2021).

Researchers also conducted other antibiotic use studies, looking at several wards. Where the most use of antibiotics was also found in respiratory cases, for example in pediatric wards 26.38%.

Rules of Use	Percentage (%)
1 x 1	42.86
2 x 1	33.00
3 x 1	17.71
1 x 2	3.71
2 x 2	1.86
4 x 1	0.57
1 x ½	0.29
Total	100

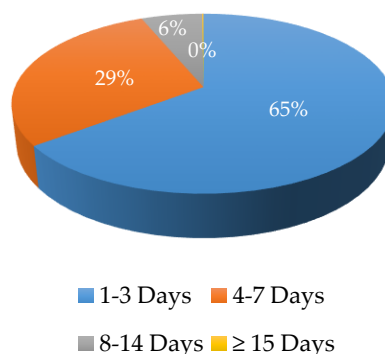


Figure 3. Patient characteristics based on duration of antibiotic use

Baitul Izzah 1 room is a class III inpatient room and is the room with the largest percentage of antibiotic use, namely 21.32%. This result is related to the type of health insurance used by patients, where the number of patients who use the National Health Insurance (JKN) both as Contribution Assistance Recipients (PBI) and Non PBI respectively amounted to 76 and 170 patients. When totaled, it amounts to 246 patients and is the type of health insurance most widely used in this study (Figure 4).

During the July-December 2021 period, the total Length Of Stay (LOS) value of 394 patients was 2,588 days as shown in bar chart (Figure 5). The

average total LOS value was 6.57, which illustrates that patients hospitalized in the internal medicine ward had an average hospitalization of 6-7 days.

Based on the standards set by the Ministry of Health of the Republic of Indonesia, these results are in accordance with the range of average LOS values of 6-9 days. LOS is the length of time that each patient is hospitalized, which is obtained by dividing the number of days of stay by the number of patients. The LOS is calculated from the time the patient enters the treatment room until leaves. If the patient's condition improved, the patient was transferred to the inpatient room and

antibiotics were administered according to the clinical pathway of the patient's diagnosis. In general, patients with bacterial infections are hospitalized for

7–10 days, but this depends on comorbidities, the development of complications, and the severity of the disease (Nasution *et al.*, 2023).

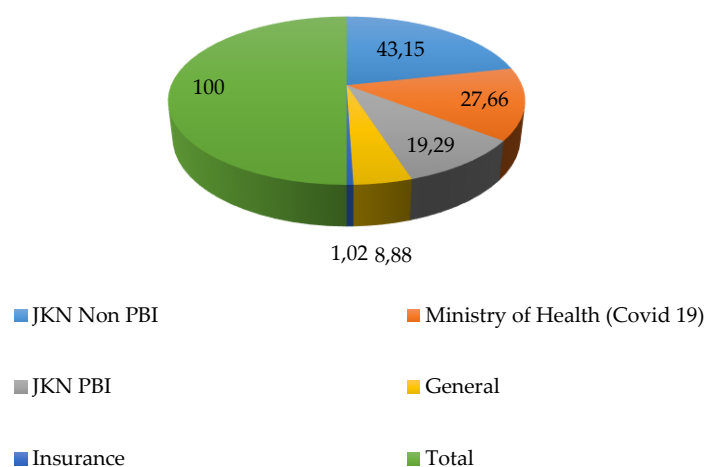


Figure 4. Type Of Health Insurance

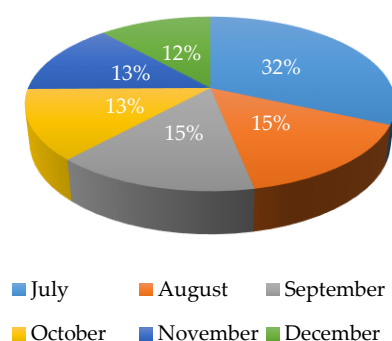


Figure 5. Length Of Stay

The total LOS (Length of Stay) value is used as a divisor in the DDD calculation along with the standard DDD value from WHO. A high DDD value for antibiotics, higher than the WHO standard suggest a potential for irrational antibiotic use. The smaller the DDD value, the more selective the use of antibiotics. Non-selective prescription and use of antibiotics may lead to inappropriate prescribing, contributing to irrational antibiotic use (Efendi & Evelin, 2019).

The results of the DDD calculation showed a total DDD value of 81.56 DDD/100 patient days. This result provides a rough estimate that in every 100 days of hospitalization, the average patient gets 81.56 DDD of antibiotics every day. The total DDD value in this study was lower than the total DDD value of research in the internal medicine ward of Dr. H. Abdul Moeloek Lampung Hospital in the July-December 2017 period which amounted to 118.57 DDD/100 patient days. Meanwhile, when compared

to the total DDD value in a study in the internal medicine ward of Bangil Hospital, Pasuruan Regency in 2017 which amounted to 77.57 DDD/100 patient days, the total DDD value in this study was higher. The greater the value of total DDD/100 patient days means that it shows the high level of antibiotic use in every 100 days of hospitalization (Rachmawati *et al.*, 2020; Lestari *et al.*, 2019; Dirga *et al.*, 2021; Sari&Safitri, 2016).

Based on the results of the calculation of the DDD value, the highest DDD value in this study was the use of levofloxacin parenterally, which amounted to 20.38 DDD/100 patient days. This explains that every 100 days of hospitalization there are as many as 20.38 (rounded up to 20) patients getting levofloxacin parenterally at a dose of 0.5 grams every day. While the lowest DDD value in this study was the use of pyrazinamid antibiotics perorally, which amounted to 0.04 DDD/100 patient days. The high use of levofloxacin given parenterally in this study which

amounted to 20.38 DDD/100 patient days is in line with the results of research conducted in the internal medicine ward in one of the private hospitals in Bandung. The study showed that the highest antibiotic use was levofloxacin given parenterally with a value of 40.34 DDD/100 patient days. These results are much higher when compared to the DDD value of levofloxacin parenterally in this study (Hanifah *et al.*, 2022).

The DDD/100 patient days values of levofloxacin and ceftriaxone are the most widely used types of antibiotics in the results of this study. The DDD/100 patient days value of levofloxacin is 20.38 DDD/100 patient days and ceftriaxone are 11.79 DDD/100 patient days. These results are in accordance with the Covid-19 Management Guidelines Edition 3th which explains that patients with confirmed Covid-19 with moderate and severe symptoms/crisis are given pharmacological therapy, one of which is the administration of azithromycin, levofloxacin or ceftriaxone and combination with antiviral. Levofloxacin is given if a bacterial infection is suspected at a dose of 750 mg/24 hours parenterally or orally for 5-7 days. Ceftriaxone is given at a dose of 50-100 mg/kgBB/24 hours in cases of community pneumonia or suspected co-infection with bacteria for pediatric patients (PDPI, 2020).

The results in this study are also in line with research that has been conducted related to antibiotic administration patterns in the Covid-19 pandemic era at Diponegoro Semarang National Hospital. According to the results, the highest use of antibiotics was azithromycin, levofloxacin and ceftriaxone. The DDD/100 patient days value of each antibiotic is azithromycin as much as 48.12 DDD/100 patient days, levofloxacin as much as 44.01 DDD/100 patient days and ceftriaxone as much as 21.13 DDD/100 patient days. These values are higher than the DDD/100 patient days of levofloxacin and ceftriaxone in this study (Putra *et al.*, 2021).

The administration of levofloxacin and ceftriaxone antibiotics in the management of Covid-19 cases in this study is not an indication that these antibiotics are the genuine therapeutic therapy for coronavirus infection. Coronavirus is a disease caused by microorganisms in the form of viruses and for treatment, of course, requires antiviral drug therapy. While antibiotic drugs are basically drugs indicated to treat cases of infection caused by bacteria, not by viruses.

Consequently, Levofloxacin antibiotics were not included as one of the medication alternatives in the Covid-19 Management Guidelines in the subsequent versions, namely, the subsequent edition,

in preparation. (PDPI, 2020). In addition to being a pharmacological therapies for Covid-19 cases in 2021, levofloxacin antibiotics are also a treatment for other cases of infectious diseases, such as pneumonia, prostatitis, urinary tract infections, skin infections, and as prophylactic antibiotics

Similarly, Ceftriaxone antibiotics have therapeutic effects for various types of bacteria such as in cases of pneumonia, bone infections, abdominal infections, skin and soft tissue infections, urinary tract infections, central nervous system infections, and for prophylactic indications. Meanwhile, other types of antibiotics such as rifampicin, isoniazid, and pyrazinamid are used to treat Tuberculosis (TB) disease. These three drugs are available in the form of a combination of one drug preparation with a standard dose called the Fixed Dose Combination (FDC) preparation and are the first-line drugs used for TB cases (Podder & Sadiq, 2019; Ayele *et al.*, 2018; Prabowo *et al.*, 2012).

The DDD (Defined Daily Dose) value reflects the amount of antibiotics administered. A reduced DDD suggests that antibiotic prescribing has become more selective, aligning with the concept of appropriate drug use. Conversely, a high DDD may indicate irrational or excessive antibiotic use. For the DDD calculation to be more accurate, it should encompass the entire antibiotic use within the hospital, including all wards (Sari & Safitri, 2016; Mahmudah & Sumiwi, 2016).

CONCLUSION

Evaluation of antibiotic use with the ATC/DDD method obtained a total DDD value 1 of 81.56 DDD/100 patient days, and antibiotics with the highest DDD value were levofloxacin antibiotics parenterally, which was 20.38 DDD/100 patient/days.

Antibiotics included in the 90% DU segment were levofloxacin(P) 24.99%; ceftriaxone(P) 14.45%; moxifloxacin(P) 12.65%; cefoperazone sulbactam(P) 6.85%; ampicillin sulbactam(P) 6.31%; meropenem(P) 4.64%; metronidazole(P) 4.45%; cefixime(O) 4.36%; azithromycin(O) 4.03%; levofloxacin(O) 3.39%; and cefotaxime(P) 3.10%. These medicines constitute a category of antibiotics that are 90% frequently utilised in hospitals.

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