

# Five years of antibiotic consumption for urinary tract infection patients in Indonesia's Provincial Public Hospital

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## Abstract

This retrospective study aimed to analyze antibiotic utilization and trends in urinary tract infection (UTI) patients without comorbidities at a Provincial Public Hospital in Indonesia. The data of 183 eligible patients who received antibiotics for UTI treatment from 2017 to 2021 were analyzed using the anatomical therapeutic chemical (ATC) classification system. Antibiotic utilization was measured in Defined Daily Dose (DDD) per 100 patient-days and Drug Utilization 90% (DU 90%) index. The study revealed fluctuating utilization, with 2018 (51.32 DDD/100 patient-days) and 2017 (37.22 DDD/100 patient-days) showing the highest and lowest antibiotic utilization, respectively. The most frequently prescribed antibiotics were ceftriaxone injection, cefixime oral, and levofloxacin injection, while ampicillin and amoxicillin oral were the least utilized. These findings provide valuable insights into antibiotic prescribing patterns for UTIs, highlighting fluctuating antibiotic utilization and the need for appropriate antibiotic stewardship strategies in primary care settings.

## Keywords

drug utilization study, antibiotic, ATC DDD, urinary tract infections, Indonesia

## Introduction

Urinary tract infections (UTIs) are common illnesses in primary care, and antibiotics are frequently prescribed by general practitioners to treat them (Plate et al. 2020). Antibiotics for UTIs have been shown to reduce the length of time that symptoms last and prevent repeat infections, but due to the difficulty in distinguishing between bacterial UTIs and self-limiting UTIs, a significant amount of over-

treatment is likely (Gágyor et al. 2016). The high frequency of antibiotic prescriptions for UTIs in general practice is associated with rising antimicrobial resistance, necessitating action (Sokhn et al. 2020). Globally, there are 222 million cases of urinary tract infections. In Indonesia, there are 90–100 UTI patients per 100,000 people, or 180,000 new cases every year (Hariati et al. 2019). Moreover, UTIs are the main indication for antibiotic prescribing in elderly patients. Thus, the scale and pattern of antibiotic use are

substantial factors in improving prescription practices for this highly susceptible population affected by infections. (Kusuma et al. 2022).

Antimicrobial resistance (AMR) poses a significant risk to human health. The ineffectiveness of antibiotic treatments occurs when microorganisms develop resistance to the medication, which might increase the risk of mortality (Melaku et al. 2021). Irrational use of antibiotics is a major contributing factor to this issue, leading to the rise and spread of antibiotic-resistant bacteria, which in turn can result in preventable adverse drug reactions, increased healthcare consumption, and rising healthcare costs (Ferri et al. 2017).

Evaluating national data on antibiotic consumption is crucial for a better understanding of global, provincial, and local patterns. Furthermore, it is critical to examine the relationship between the use of antibiotics and the development of resistance, considering the rising rates of antibiotic resistance (Metz-Gercek et al. 2009). The World Health Organization (WHO) recommends the Anatomical Therapeutic Chemical (ATC) Classification/Defined Daily Dose (DDD) System as a global benchmark for drug utilization studies (WHO 2021). This system provides a framework for presenting drug utilization research and improving the quality of drug use (WHO 2021). When a medicine is used for its primary indication in adults, DDD represents the expected average maintenance dose per day for a medication used. Only medications that have been given an ATC code are given the DDD designation. At every level of the healthcare system, these indicators can be highly helpful for assessing drug use (Patel et al. 2016).

To promote the appropriate use of antibiotics in the future, it is essential to conduct a study using the ATC/DDD methodology to compare antibiotic utilization in hospitals. Based on the findings, tailored strategies and interventions should be developed and implemented. This study aimed to assess the burden of UTI patients and the most frequently prescribed antibiotics at a Provincial Public Hospital in Central Java, Indonesia, between 2017 and 2021, utilizing the ATC/DDD and DU90% index for evaluation.

## Methods

### Research design and settings

This study was a retrospective, descriptive, cross-sectional study performed in the Provincial Public Hospital, Central Java, Indonesia, for 5 years (2017–2021). The study was conducted from March 15 to April 15, 2022. The data on antibiotics consumption in UTI patients were analyzed according to the anatomical therapeutic chemical (ATC) classification system defined by the World Health Organization (WHO), version 2022 (WHO 2021). The use of systemic antibacterials (ATC: J01) was measured as a defined daily dose (DDD) per 100-bed days and using Drug Utilization 90% (DU 90%) method. DDD values are the

assumed average maintenance dose per day for a drug used for its main indication for an average adult. DDD per 100 bed-days was used as a measurement unit for analyzing the consumption of antibiotics use. It was calculated by using the following equation (WHO 2021):

$$\text{DDDper100days} = \frac{\text{number of antibiotics(gram)}}{\text{standard DDD WHO(gram)}} \times \frac{100}{\text{total LOS}}$$

The Drug Utilization 90% (DU90%) indicator has been proposed as a measure to identify the most commonly used drugs. This indicator measures the number of drugs accounting for 90% of the use in DDDs. Products are ranked in order of DDDs, and the number of drugs accounting for 90% of use is the DU90%. The focus was on the drugs that account for 90% of the volume and adherence to treatment guidelines within this 90%. The adherence to guidelines could then be calculated as the number of DDDs that were in the treatment guidelines over all DDDs within 90% (Bergman et al. 1998).

The inclusion criteria in this study were hospitalized UTI patients who were aged  $\geq 18$  years old, received antibiotics, and had a complete and clear medical record, including information such as the patient's age, gender, name of prescribed antibiotic, dosage form, dosage strength, and the number of preparations. Exclusion criteria included patients with comorbidities or other infectious diseases, surgical patients, pregnant and nursing mothers, chemotherapy patients, and emergency cases.

### Description of databases

Data on antibacterial use was obtained from the medical record and electronic data retrieval in the Management Information Systems (MIS) taken manually from January 2017 to December 2021. The database in Provincial Public Hospital contains records of all dispensed prescriptions issued by general practitioners (GPs) or specialists. A data collection form was utilized to gather relevant information, including the registration number, patient name, age, prescribed antibiotics, dosage, route of administration, dosage form, admission and discharge date, and duration of antibiotics prescribed for each patient.

### Data statistics

Microsoft Office Excel 2019 software was used for statistical analysis to calculate DDD/100 Patient-days and Drug Utilization 90% from 2017 to 2021 antibiotics use a database, and visualization was conducted using the R package (version 4.1.2).

### Ethical considerations

Ethical approval was not required. This article does not contain any studies with human participants performed by any of the authors; no active intervention was introduced and had official approval from the hospital management.

## Results

### Background characteristics of study participants

During the five years observed, the number of patients diagnosed with UTIs was 3,743 patients, among them 183 patients (4.89%) were selected according to the inclusion criteria. Among the eligible patients, there were 51.60% females, and more than 40% were in the range of 18–25 years old (Table 1). Almost 80% of the patients were hospitalized for one to five days. The most prevalent cases were found in 2017 with the number of patients was 72 (39% of total cases).

**Table 1.** Patient characteristics.

Patient characteristics	Number of patients	Percentage (%)
<b>Gender</b>		
Male	86	48.40%
Female	97	51.60%
<b>Age</b>		
18–25	42	23.00%
26–35	36	19.70%
36–45	28	15.30%
46–55	29	15.80%
56–65	27	14.80%
> 65	21	11.50%
<b>Length of Stay (LOS)</b>		
1–5 day	144	78.70%
6–10 day	38	20.80%
11–15 days	1	0.50%
<b>Number of Patients Per Year</b>		
2017	72	39%
2018	50	27%
2019	30	16%
2020	18	10%
2021	13	7%

**Table 2.** Total DDD per 100 patient-days from 2017–2021.

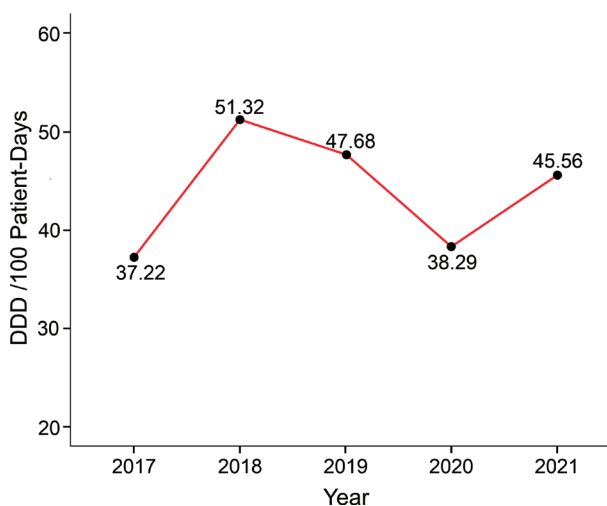
Antibiotic classification	Antibacterial for systemic use	ATC	DDD/100 patients-days					Cumulative DDD per 100 patient-days
			2017	2018	2019	2020	2021	
Penicillin	Ampicillin oral	J01CA01	0.37	–	–	–	–	0.37
	Amoxicillin oral	J01CA04	0.49	–	–	–	–	0.49
Cephalosporins	Cefazolin inj.	J01DB04	–	2.00	–	0.71	2.13	4.84
	Cefadroxil oral	J01DB05	–	0.30	–	–	0.27	0.57
	Cefotaxime inj.	J01DD01	1.14	0.45	–	–	–	1.59
	Ceftazidime inj.	J01DD02	0.49	1.50	–	0.54	–	2.53
	Ceftriaxone inj.	J01DD04	26.29	31.08	45.10	15.59	28.19	146.25
Carbapenems	Cefixime oral	J01DD08	3.07	6.43	0.49	4.03	13.56	27.58
	Meropenem inj.	J01DH02	–	1.00	–	3.23	1.41	5.64
Macrolides	Azithromycin inj.	J01FA10	–	0.60	–	–	–	0.60
Aminoglycosides	Gentamicin inj.	J01GB03	0.82	–	–	–	–	0.82
Quinolones	Ciprofloxacin oral	J01MA02	1.35	1.20	2.09	1.29	–	5.93
	Ciprofloxacin inj.	J01MA02	1.47	0.15	–	–	–	1.62
	Levofloxacin inj.	J01MA12	0.49	–	–	10.75	–	11.24
Other Quinolones (pyridopyrimidine)	Pipemidic acid oral	J01MB04	1.23	5.41	–	2.15	–	8.78
Imidazole	Metronidazole inj.	J01XD01	–	1.20	–	–	–	1.20
<b>Total DDD per 100 patient-days each year</b>			37.22	51.32	47.68	38.29	45.56	
<b>Total DDD per 100 patient-days from 2017–2021</b>								220.07

**Notes: Abbreviations:** inj., injection; ATC, anatomical therapeutical chemical; DDD, Defined Daily Dose.

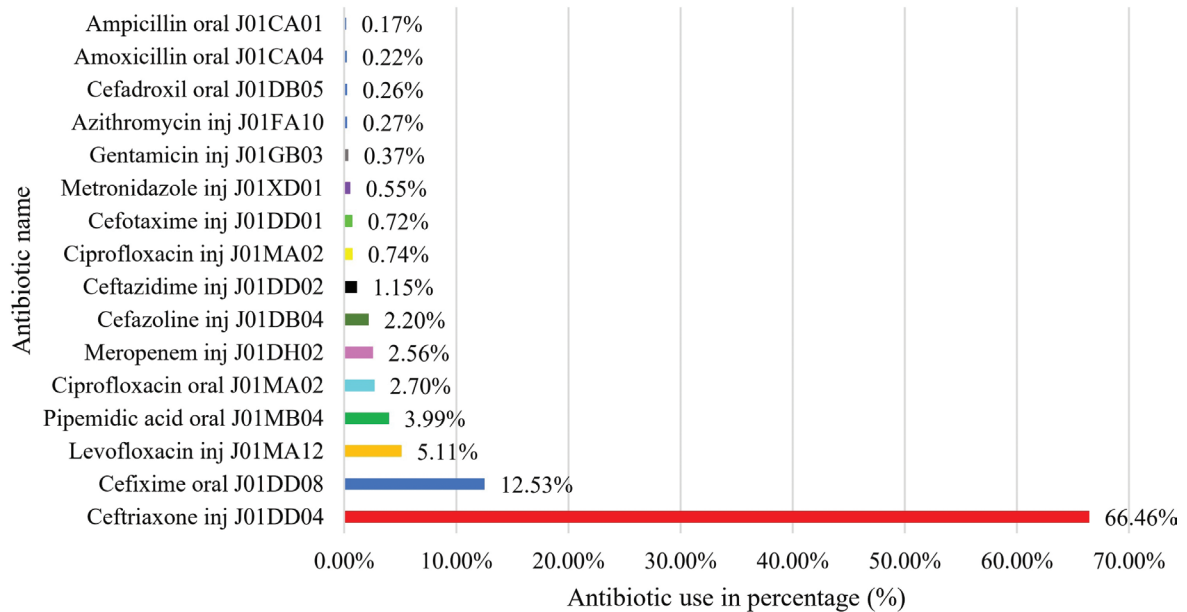
### Antibiotics consumption

Data on the use of antibiotics for UTI patients at Provincial Public Hospital for the period of January 1, 2017 – December 31, 2021, was presented in Fig. 1. It illustrates DDD per 100 patient-days each year from 2017 to 2021 i.e., 37.22, 51.32, 47.68, 38.29 and 45.56, respectively. Overall, the use of antibiotics during 2017–2021 fluctuated, reaching a peak of antibiotic use at 51.32 DDD/100 patient days in 2018 and the lowest value of 37.22 DDD/100-patient days in 2017. The average number of DDD for antibiotics consumption was 44.01 DDD/100-patient days with 220.07 DDD/100-patient days in total (Fig. 1).

The most frequently used antibiotic based on DDD/100 patient-days was ceftriaxone inj. (J01DD04) with 146.25 DDD/100 patient-days (Table 2). Beta lactam antibiotics



**Figure 1.** DDD/100 patients-days from 2017 to 2021.



**Figure 2.** Antibiotic Consumption based on the DU90% Segment from 2017–2021.

such as ampicillin oral and amoxicillin oral, and aminoglycosides (Gentamicin inj.) were only used in 2017. Metronidazole and azithromycin inj. were used only in 2018. UTI treatment more often uses injection than oral administration.

Fig. 2 shows the top list of antibiotics used ranked based on DU 90% segment. Ceftriaxone inj. (J01DD04), cefixime oral (J01DD08), and levofloxacin inj. (J01MA12), were responsible for 66.46%, 12.53%, and 5.11% of antibiotic use in UTI patients, respectively (Fig. 2).

## Discussion

UTIs pose a significant financial burden on the healthcare system due to the high prevalence of infections in the community and hospital settings, and the surveillance of antibiotics use in its treatment is an essential step in identifying problem areas and developing interventions (Medina and Castillo-Pino 2019). This study highlights the widespread use of broad-spectrum antimicrobial agents, such as third generation cephalosporins, carbapenems, and quinolones, in UTIs treatment in the Indonesian setting. The study revealed a slightly higher incidence of UTIs in females than males. Several predisposing factors might contribute to this increase in UTIs among women (Eriksson et al. 2010). Previous studies suggest that vaginal colonization with pathogens and sexual activity have been identified as risk factors for UTI in women (Haque et al. 2015; Abou Heidar et al. 2019). Besides, the prevalence of UTI was also high in postmenopausal women. This phenomenon might be a result of genito-urinary atrophy and vaginal prolapse after menopause, which alters the vaginal pH, decreasing the normal vaginal flora. Gram-negative bacteria can grow as uropathogens under these conditions (Muhammad et al. 2020).

In the present study, the most frequent antibiotics used from 2017 to 2021 were cephalosporins; particularly ceftriaxone (CRO) injection being the most used. CRO injection has a broad spectrum of activity, favorable safety, and tolerability profile, and is currently the recommended empiric treatment for complicated UTIs in the inpatient setting (Wells et al. 2004; Gupta et al. 2011). Due to its long half-life, IV potency, and a similar percentage of urinary secretion compared to first-line oral agents for UTIs, a short course (i.e., 3-day) of CRO injection therapy is more efficacious in the treatment of UTIs (Bach et al. 1973; Pollock et al. 1982). Norrby et al. also discovered that oral beta-lactam antibiotics had higher rates of failure than CRO (Norrby 1990). Cefixime was the second most commonly used antibiotic in this study. According to V. Fanos & L. Cataldi, cefixime has the same effects as other usual treatments with low side effects in non-complicated UTIs (Fanos and Cataldi 2001).

Treatment recommendations for lower UTIs varied among European countries. Heterogeneity was found in the classification of patient subgroups. For example, no male UTIs were classified as acute cystitis or lower UTIs in France, and in the Dutch guidelines, some of the recommendations were restricted by patient age, the presence of complicating factors, and local resistance levels. Nitrofurantoin was the most frequently recommended antibiotic for female patients with UTIs and was listed as a first-line option for uncomplicated cystitis, followed by pivmecillinam and fosfomycin. Recommendations for male lower UTIs patients were made in twelve countries, and they recommended most often ciprofloxacin, nitrofurantoin, and pivmecillinam (Malmros et al. 2019). Based on this information, despite numerous studies demonstrating the efficacy of third generation cephalosporins in treating UTIs, this broad-spectrum class of drugs necessitates prudent use.

According to our study, beta-lactam antibiotics such as ampicillin and amoxicillin were only discovered in 2017 for treating UTIs, while metronidazole was only used in 2018. Gram-negative bacteria were the main pathogens found in patients with UTIs, with *Escherichia coli*, *Enterococcus faecalis*, and *Monilia albicans* being the most common Gram-negative bacteria (Cui 2021). *Escherichia coli* and *Klebsiella pneumoniae* were the most resistant to ampicillin, while imipenem was the least resistant (Cui 2021). Moreover, the drug ampicillin has been largely abandoned because most UTIs are now resistant to it (Shah et al. 2018). It may be one of the reasons why penicillin was no longer used in 2018–2021, but meropenem was still used until 2021 in our study.

We recognize several limitations in our study due to a lack of clinical data. Though the distribution of uropathogens is somewhat consistent across settings, rising antibiotics resistance to bacteria that cause UTIs is a major concern around the world, but especially in developing and emerging countries.

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## Conclusion

The total use of antibiotics in treatment of UTIs fluctuated from 2017 to 2021. The most widely used antibiotic over the years were ceftriaxone inj. (J01DD04) at 146.25 DDD/100 patient-days. Meanwhile, the least used antibiotic was ampicillin oral (J01CA01) at 0.37 DDD/100 patient-days. Antibiotics that are always in the DU segment 90% are ceftriaxone inj. (66.46%), cefixime oral (12.53%), and fluoroquinolone levofloxacin inj. (5.11%). Finally, a comprehensive survey and research on antibiotic resistance are required to analyze this disastrous national situation and develop management solutions.

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