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Research Article

Drug Utilization 90% Profile of Antibiotics Use during the Period of 2013 – 2017 at a Private Teaching Hospital in Yogyakarta

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ABSTRACT

Evaluation of antibiotics use plays an important role in antimicrobial stewardship programs to support the rational use of antibiotics at all healthcare facilities. This study aimed to describe the profile of drug utilization 90% (DU90%) of antibiotics use for hospitalized patients at a private teaching hospital in Yogyakarta over period of 2013 – 2017. Aggregate data of all systemic antibiotics having an anatomic therapeutic chemical (ATC) code and used for hospitalized patients during 2013 – 2017 were included in this study. Quantity of antibiotics use was expressed in defined daily dose (DDD) and final quantity was expressed in DDD/100 bed days. DU90% profile was obtained by calculating the cumulative use of antibiotics from the highest to the lowest percentage. There were 44 antibiotic agents used each year over the period of 2013 – 2017. However, there were only 10 – 12 agents within the DU90% segment. Cephalosporins group was identified as the most used antibiotics consistently over the period and the top three antibiotics that were consistently prescribed were: ceftriaxone, levofloxacin, and cefixime. It can be concluded that only about a quarter of the total antibiotic agents used in hospitals are within the DU90% segment and those antibiotic agents are relatively consistent, especially for the top three of the highest used antibiotics.

INTRODUCTION

The development of bacterial resistance to antibiotics is one of the major problems in the health sector faced by all countries worldwide (Shallcross *et al.*, 2015). Given the urgency for serious action to tackle the growing problem of antibiotics resistance, the World Health Organization (WHO) has compiled recommendations on global action plans to be implemented in all countries at all levels of healthcare facilities (WHO, 2015). Optimizing the use of antibiotics in infection management is one of those recommendations and is also one of the pillars in the implementation of antibiotic stewardship recommended by various research centers and policy makers related to infectious diseases (Barlam *et al.*, 2016; Dyar *et al.*, 2017; WHO, 2015).

One of the important activities to optimize the use of antibiotics is continuous evaluation both quantitatively and qualitatively to determine the profile and quality of antibiotics use (WHO, 2015). Results from those evaluations can be further considered for policy improvement on the use of antibiotics in healthcare facilities to increase the rationality of antibiotics use. Pharmacists and hospital pharmacy departments play an important role as one of the pillars in the implementation of antimicrobial stewardship policies to increase effectiveness and minimize the adverse effects of antibiotics (Gallagher *et al.*, 2018; Wang *et al.*, 2019).

In conducting quantitative drug use evaluation at various levels of healthcare facilities, the WHO recommends the use of anatomical therapeutic chemical/defined daily

dose (ATC/DDD) with the aim that the results from the evaluation can be compared among healthcare facilities, regions, and even among countries globally (Sözen *et al*., 2013). To assess the profiles of drug use, the ATC/DDD method is usually combined with other methods, including the drug utilization 90% (DU90%) method which has been shown to be a good method to assess the profile of drug use (Bergman *et al*., 1998).

This study was conducted with the aim of describing the profile of antibiotic use for hospitalized patients at a private teaching hospital in Yogyakarta with the main focus on the antibiotic agents used and their quantity of use. The quantity of antibiotic use in this study was calculated in DDD units and the profile focused on the DU90% profile which describes a list of antibiotics in which the quantity of use is within the 90% segment of cumulative use.

METHODS

This study collected data from the hospital pharmacy department (HPD) of one of the private teaching hospitals in Yogyakarta and has received a research permit with number 0564/PI.24.2/III/2018. This descriptive study used retrospective aggregate data on antibiotics use for all hospitalized patients during the period 2013 - 2017. All systemic antibiotics having ATC code and coded with J01 in the ATC classification system were included in this study. This study also collected data from the medical record department (MRD) to obtain the number of hospitalized patients and the average length of stay each year during the study period.

Antibiotic-related data collected from HPD included the name of the antibiotic agents, dosage form and dosage strength, and the quantity of use each year during the study period. The quantity of use of each antibiotic was then calculated in DDD units by dividing the total use of each antibiotic in grams by the definitive DDD obtained from the WHO website page (WHO Collaborating Centre for Drug Statistics Methodology, 2021). The final unit used to express the quantity of antibiotic use in this study is DDD/100 bed days (DDD/100 BD) as a unit commonly used to express the quantity of drug use for hospitalized patients. To obtain a DU90% profile of antibiotic use per year, the quantity of each antibiotic is converted into a percentage by dividing the quantity of each antibiotic by the total quantity of all antibiotics used over the year. All antibiotics were then sorted according to the percentage of use from the highest to the lowest and a DU90% was obtained by looking at the list of antibiotics which quantity of use was in the 90% segment of cumulative use. The R^2 values that resulted from linear regression were used to identify antibiotic agents showing consistent increase or decrease in terms of utilization during the study period.

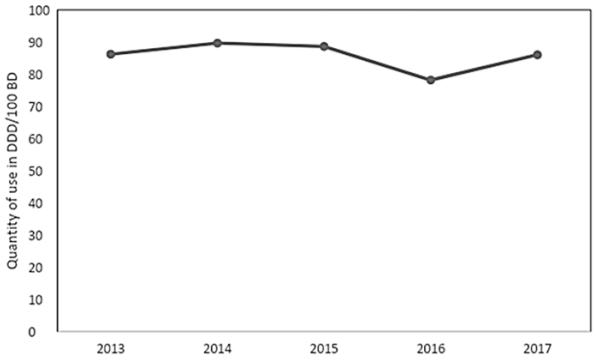


Figure 1. Total quantity of antibiotics used at the hospital each year over five-year-period of 2013 – 2017

Table 1. Numbers of antibiotics agents used at the hospital based on pharmacological subgroup according to ATC classification system

ATC Code (3rd level)	Pharmacological subgroup (4th level in ATC classification)	Number of antibiotics agents used in the hospital
J01A	Tetracyclines	1
J01B	Amphenicols	2
J01C	Beta-lactam (Penicillins)	6
J01D	Other beta-lactams	15
J01F	Macrolides, lincosamides and streptogramins	7
J01G	Aminoglycosides	4
J01M	Quinolones	5
J01X	Other antibacterials	4
Total of antibiotic agents used in the hospital		**44**

ATC, anatomic therapeutic chemical.

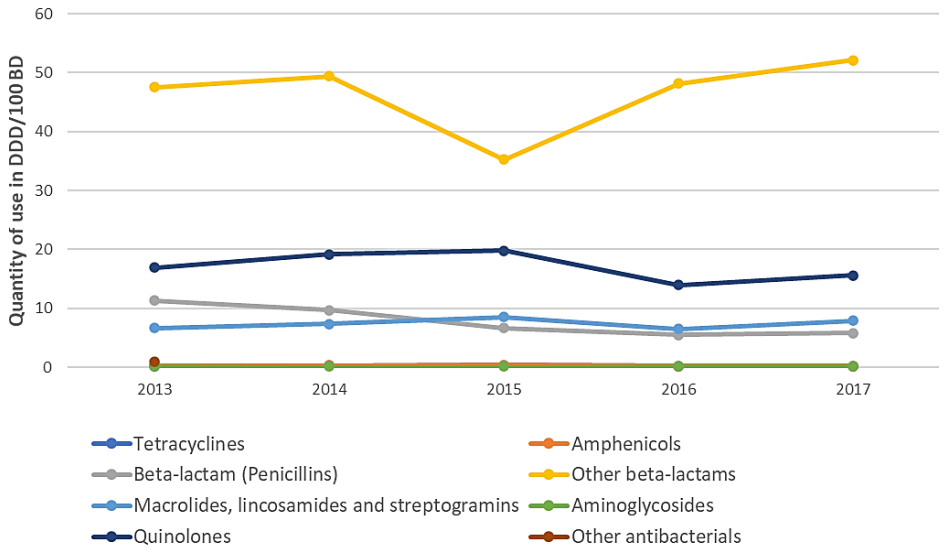


Figure 2. Quantity of antibiotic use at the hospital expressed in DDD/100BD during the period 2013-2017 based on pharmacological group according to ATC classification system

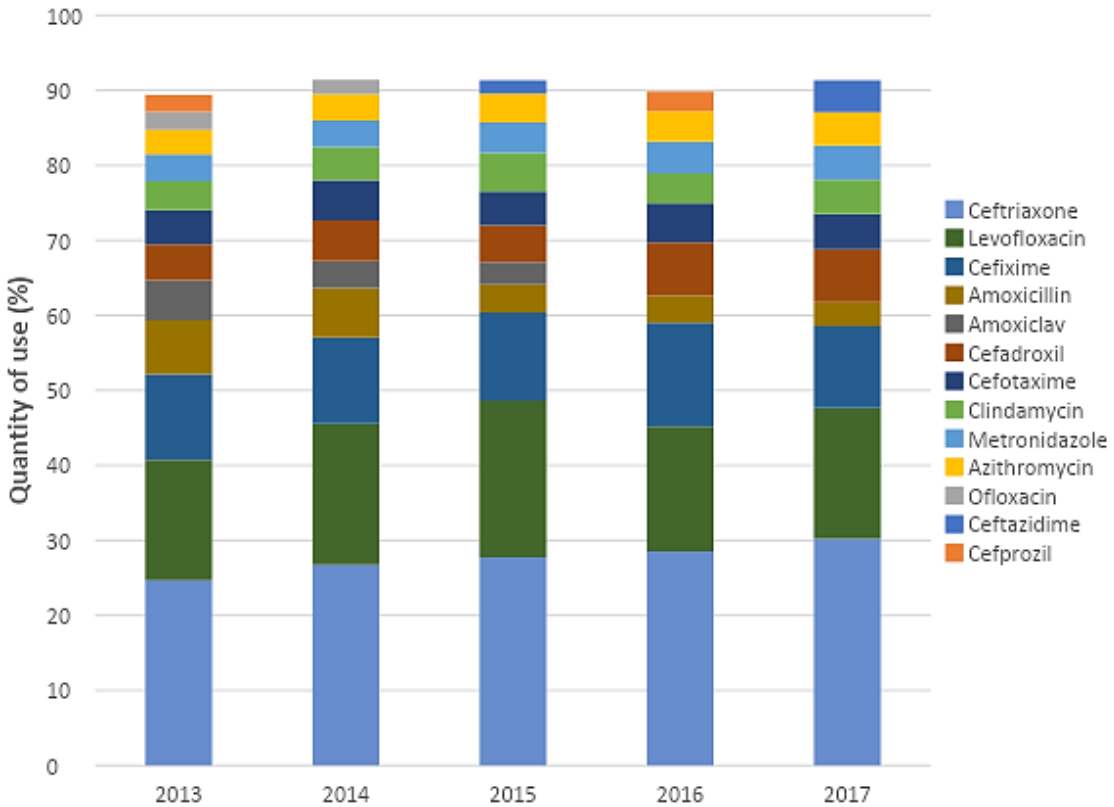


Figure 3. DU90% profiles of antibiotics use at the hospital each year during the period of 2013-2017

RESULTS AND DISCUSSION

This study found that there were 44 antibiotic agents used for hospitalized patients at the hospital based on the generic name of the antibiotics. Table 1 lists the number of antibiotic agents used at the hospital based on pharmacological subgroups following the ATC classification system in which 8 pharmacological subgroups of antibiotics were used. Antibiotic agents from other beta-lactams subgroups which include cephalosporins, monobactam and carbapenem are the most used antibiotics during the study period of 2013-2017. Fourteen out of 15 antibiotic agents within other beta-lactams

subgroups used in the hospital are cephalosporins, consisting of the first, second and third generation of cephalosporins. Among the cephalosporins found in this study, the third generation cephalosporins were the most widely used (57%). While the level of bacterial resistance to antibiotics from the third generation cephalosporins is reported to be increasing worldwide due to the extensive development of extended spectrum beta-lactamase-producing bacteria, those antibiotics are still the most widely used antibiotics in hospitals for the treatment of various infections until now (Kim *et al*., 2020; Plüss-Suard *et al*., 2011; Qu *et al*., 2018).

Patterns of infectious diseases and policies on antibiotics can influence the selection of classes and types of antibiotics used in hospitals. Figure 1 depicts the total quantity of antibiotics use each year during the study period of 2013 – 2017. Overall, the total quantity of antibiotics used each year during the study period is relatively constant with average of 83.75 DDD/100 BD which is much higher when compared to the results from studies in hospitals in China, but slightly lower when compared to the results of similar studies in Korea (Kim *et al*., 2020; Qu *et al*., 2018; Versporten *et al*., 2018). Meanwhile, Figure 2 indicates the quantity of antibiotics used based on pharmacological subgroup showing that in addition to being the most used based on the number of antibiotic agents within the subgroup, other beta-lactams antibiotics also become the subgroup that consistently used with highest quantity each year during the study period with average use of close to 50 DDD/100BD. Of the total quantity of cephalosporin antibiotics, 57% are third generation cephalosporins consisting of cefotaxime, ceftazidime, ceftriaxone, ceftizoxime, cefixime, cefoperazone and cefditoren. The cephalosporin antibiotics as the most widely used antibiotic have been reported by many studies both in Indonesia and in other countries (Versporten *et al*., 2018).

Following the subgroup of other beta-lactams, quinolone subgroup is also consistently ranked second in terms of quantity with an average quantity of use of 17 DDD/100BD. There are 5 antibiotic agents within the quinolone subgroup used at the hospital in which levofloxacin is the most widely used. Antibiotic subgroups other than the other beta-lactams and quinolones were used with a significantly low quantity of use with an average annual use of less than 5 DDD/100BD with the lowest quantity of antibiotics used were from the aminoglycoside subgroup. Vancomycin is the only antibiotic in the glycopeptide class that was used and its very low use compared to other antibiotics can be understood because vancomycin is an antibiotic whose use is very limited in order to maintain its effectiveness in overcoming infections caused by Methicillin Resistant *Staphylococcus aureus* (MRSA) bacteria (Álvarez *et al*., 2016).

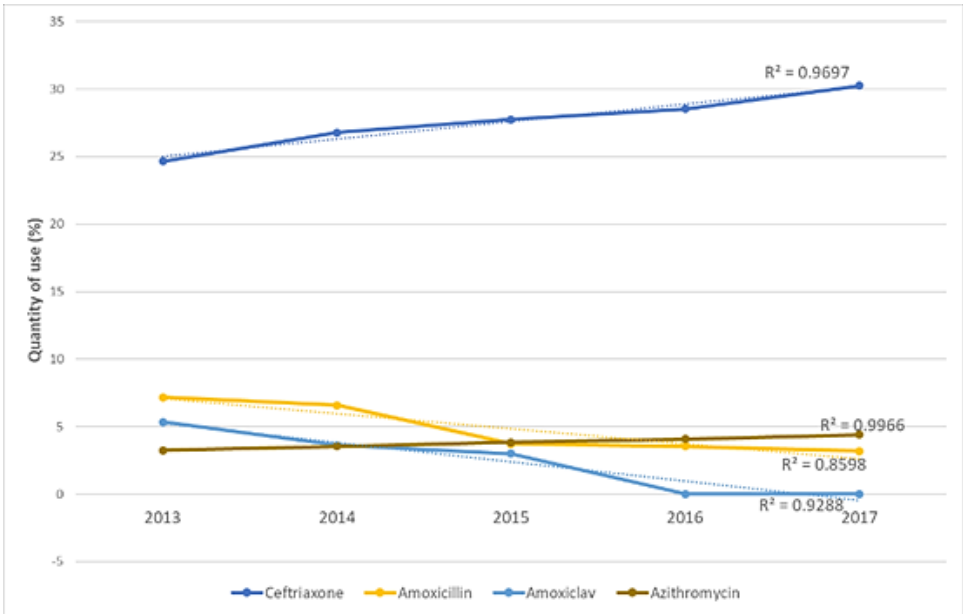


Figure 4. Antibiotics agents with consistent increase or decrease over the five-year-period of 2013 – 2017

DU90% profiles of antibiotics use each year during the study period are shown in Figure 3 which shows that although there are 44 antibiotic agents used in the hospital, only 10-12 out of those 44 agents have the quantity of use within the area of 90% of use. These data mean that around 70% of the antibiotic agents were used within the rest of the 10% quantity. Apart from being remarkable as a clinical review, these profiles can also be reviewed in more depth from the administration and management aspects to evaluate the efficiency and effectiveness of drug management.

Figure 3 also shows that ceftriaxone, levofloxacin and cefixime consistently were the three highest used antibiotics each year during the period of 2013-2017. Results from this study are almost the same as the results of other studies related to the use of antibiotics which also found ceftriaxone to be the most widely used antibiotic in hospitals (Kim *et al*., 2020; Sözen *et al*., 2013). Ceftriaxone's broad-spectrum antibacterial properties have made it widely chosen as an empirical therapy in the treatment of various infections. In addition, the pharmacokinetic characteristics possessed by ceftriaxone which allow it to be used with a frequency of 1-2 times a day and the availability of quite diverse branded products at affordable prices make ceftriaxone a popular choice (Fauziyah *et al*., 2011). However, the high use of ceftriaxone should receive more attention in terms of its effectiveness (Krockow *et al*., 2019) as well as the risk in causing the development of extended spectrum beta lactamases-producing bacteria (Krockow *et al*., 2019; Paterson *et al*., 2001).

Levofloxacin and other quinolone antibiotics have also been reported by other studies as being widely used in hospitals (Vu *et al*., 2019; Yang *et al*., 2020). Fluoroquinolone antibiotics generally have a broad spectrum and especially levofloxacin has excellent activity against streptococcus bacteria as the main bacteria causing infections in the respiratory tract. Its availability in an oral dosage form with an effectiveness almost equivalent to that of third generation cephalosporins also makes fluoroquinolone antibiotics used widely (Cheng *et al*., 2012). However, the use of fluoroquinolone antibiotics also needs to be continuously evaluated given the increasing prevalence of fluoroquinolone resistant Enterobacteriaceae infections (Cheng *et al*., 2012; Kim *et al*., 2018; Klein *et al*., 2018).

Cefixime is the only third generation cephalosporin antibiotic that can be used orally and has a relatively broad spectrum. Its effectiveness in fighting infection-causing bacteria in the respiratory tract makes cefixime widely used as a follow-up therapy in inpatients who experience respiratory infections and previously received parenteral therapy with third-generation cephalosporin antibiotics (Dreshaj *et al*., 2011). In addition to respiratory infections, cefixime is also one of the antibiotics of choice for the treatment of infections related to sexually transmitted diseases (Tanvir *et al*., 2018).

In addition to focusing on DU90% profiles, this study identified antibiotics agents showing significant trends either increased or decreased in use. These trends were identified using R^2 measures resulting from linear regression analysis. Antibiotic agents with R^2 value of 0.8 or higher are considered as having significant trends in this study. Figure 4 shows that the quantity ceftriaxone and azithromycin use tended to increase over the study period with R^2 values of 0.9687 and 0.9966, respectively. In contrast, the quantity of use of amoxicillin and amoxiclav tended to decrease during the study period with R^2 value of 0.8598 and 0.9288, respectively.

Results from this study are remarkable and require further follow-up from both the clinical and management points of view. Further research from a clinical point of view is needed to ensure that those antibiotics with a high quantity of use are used rationally and achieve higher benefits in terms of expected therapeutic outcomes compared to the risk of adverse effects and the development of bacterial resistance (Cusini *et al*., 2010; Davey *et al*., 2017; Krockow *et al*., 2019). Further research from the management point of view is very important to ensure that the more antibiotic agents are used, even with very low quantities, they do not reduce the efficiency and effectiveness of the drug management processes.

CONCLUSIONS

It can be concluded that the DU90% segments of antibiotics over the five years of the study period consisted only of about a quarter of the total antibiotic agents used in the hospital. In addition, the antibiotic agents that are within the DU90% segments are relatively unchanged during the study period between 2013-2017, in which ceftriaxone, levofloxacin and cefixime have consistently been the top three antibiotics with the highest use.

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