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The Quantitative and Qualitative Analysis of Antibiotic Use in Bone Fracture Patients in a Public Hospital in Indonesia

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A B S T R A K

Pendahuluan: Pemberian antibiotic profilaksis sebelum pembedahan berguna untuk mencegah terjadinya kolonisasi atau berkembangnya bakteri yang masuk ke jaringan target saat operasi berlangsung. Penggunaan antibiotik yang tidak tepat di rumah sakit akan meningkatkan biaya terapi dan kejadian infeksi nosokomial mikroorganisme infeksius. Antibiotik profilaksis pra operasi diyakini dapat mengurangi kejadian infeksi tempat pembedahan.
Tujuan: Penelitian ini bertujuan untuk mengetahui pola penggunaan antibiotik dan menganalisis penggunaan antibiotik secara kualitatif dengan metode Gyssen dan kuantitatif dengan metode *Anatomical Therapeutic Chemical (ATC)/Defined Daily Dose* dengan satuan *DDD/100 patient-days* pada pasien rawat inap dengan fraktur tulang di Rumah Sakit Umum Haji Surabaya, Indonesia.
Metode: Penelitian ini merupakan penelitian observasional deskriptif yang dilakukan terhadap 89 sampel. Data dikumpulkan secara retrospektif melalui rekam medis pada periode Januari-Desember 2019. Data penggunaan antibiotik kemudian dianalisis secara kualitatif dengan metode Gyssen dengan menilai menilai ketepatan penggunaan antibiotik meliputi ketepatan indikasi pemilihan obat berdasarkan efektivitas, toksisitas, harga dan spectrum, lama pemberian obat, dosis, interval, rute serta waktu pemberian. Data penggunaan antibiotik juga dianalisis secara kuantitatif dengan metode *Anatomical Therapeutic Chemical (ATC)/Defined Daily Dose* dengan satuan *DDD/100 patient-days* untuk menghitung jumlah penggunaan antibiotik sebagai dosis harian.
Hasil: Pada penelitian ini, antibiotik yang banyak digunakan sebagai antibiotik profilaksis dan terapeutik pada pasien fraktur tulang adalah seftriakson. Pada analisis kuantitatif menunjukkan bahwa nilai seftriakson adalah 45,6/100 patient-days dan sefazolin adalah 3,1/100 *patient-days*. Analisis penggunaan antibiotik pada pasien fraktur tulang dengan menggunakan metode Gyssen menunjukkan bahwa penggunaan antibiotik yang rasional sebanyak 84,3%, penggunaan antibiotik tidak tepat waktu sebanyak 4,5%, dan interval pemberian antibiotik tidak tepat sebanyak 11,2%.
Kesimpulan: penggunaan antibiotik pada pasien bedah fraktur sudah tergolong penggunaan antibiotik yang rasional. Seftriakson merupakan antibiotik dengan DDD tertinggi (45,6/100 *patient-days*) dan diikuti dengan sefazolin. Selanjutnya perlu dilakukan penelitian serupa dengan pengambilan data secara prospektif sehingga dapat mengamati kejadian infeksi luka operasi.

Keywords:
antibiotics, defined daily doses (DDD), Gyssen, fractures

A B S T R A C T

***Introduction**: prophylactic antibiotic administration before surgery is useful to prevent colonization or development of bacteria that enter the target tissue during surgery. Inappropriate use of antibiotics in hospitals will increase the cost of therapy and the incidence of nosocomial infections of infectious microorganisms. Preoperative prophylactic antibiotics are believed to reduce the incidence of surgical site infections.*
***Objective**: this study aims to determine the pattern of antibiotic use and analyze the use of antibiotics qualitatively with the Gyssen method and quantitatively with the Anatomical Therapeutic Chemical (ATC) method / Defined Daily Dose with DDD/100 patient-days units in inpatients with bone fractures at Haji General Hospital Surabaya, Indonesia.*
***Methods**: this study was a descriptive observational study conducted on 89 samples. Data were collected retrospectively through medical records in the period January-December 2019. Antibiotic use data were then analyzed qualitatively with the Gyssen method by assessing the appropriateness of antibiotic use including the appropriateness of indications for drug selection based on effectiveness, toxicity, price and spectrum, duration of drug administration, dose, interval, route and time of administration. Antibiotic use data was also analyzed quantitatively using the Anatomical Therapeutic Chemical (ATC)/Defined Daily Dose method with units of DDD/100 patient-days to calculate the amount of antibiotic use as a daily dose.*
***Results**: in this study, the antibiotic that was widely used as a prophylactic and therapeutic antibiotic in patients with bone*

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fractures was ceftriaxone. In quantitative analysis showed that the value of ceftriaxone was 45.6/100 patient-days and cefazoline was 3.1/100 patient-days. Analysis of antibiotic use in bone fracture patients using the Gyssen method showed that the rational use of antibiotics was 84.3%, the use of antibiotics was not timely as much as 4.5%, and the interval of antibiotic administration was not appropriate as much as 11.2%.

***Conclusion**:the use of antibiotics in fracture surgery patients is classified as rational antibiotic use. Ceftriaxone was the antibiotic with the highest DDD (45.6/100 patient-days), followed by cefazolin.*

1. Introduction

Nowadays, antibiotics are often prescribed for infectious diseases as they have the ability to kill or inhibit the growth of bacteria. This class of drugs, although useful, may become useless if used inappropriately. With an estimated population of 258 million people, Indonesia is the fourth most populous country in the world and is categorized as a lower-middle income country. Although there is no official estimate of its burden, antimicrobial resistance is thought to be high and on the rise in Indonesia (1,2). Antibiotic administration should take into account the antibiotic susceptibility profile present in each hospital and the risks and benefits posed to the patient so that rational use of antibiotics can be achieved. One of the biggest problems with inappropriate use of antibiotics is the emergence of antibiotic resistance. Common causes of problems in the emergence of antibiotic resistance are the use of the wrong type of antibiotic, improper dosage, and insufficient duration of use (3,4). Inappropriate use of antibiotics can have a negative impact on patients and related health services, including a decrease in patient quality of life, decreased patient safety, increased treatment costs, therapy failure, antibiotic resistance, decreased patient confidence in related health services, and the emergence of superinfection (5).

Bone fracture is one of the indications for orthopedic surgery. Fracture is a break in the continuity of the bone. An open fracture is a condition when the fracture penetrates the skin or body cavity. Meanwhile, a closed fracture is when the fracture part is still covered with intact skin (6). In open fractures, there is a higher risk of infection which may not only contribute to wound healing problems, but may also play an important role in the subsequent development of nonunion and continued bone instability (7). The incidence of infection in closed fractures is 2-4%, which is lower than the incidence of infection in open fractures, which reaches 11-13% (8–11). Gram-positive bacteria such as Stretococcus and Staphylococcus were identified as the most common bacteria in Gustilo type I and II fractures. In addition, there are several strategies which surgeons use in order to minimize infection, including timely wound irrigation and debridement, timely fracture stabilization, and early administration of systemic antibiotics or prophylactic antibiotics befor surgery (12,13).

Prophylactic antibiotics are given prior to surgical procedures, especially for clean and clean contaminated surgery. Prophylactic antibiotic administration before surgery is useful to prevent colonization or development of bacteria that enter the target tissue during surgery. Although the timing of antibiotic administration varies, the goal of preoperative systemic prophylaxis of antibiotics is to achieve the highest tissue concentrations at the beginning and during surgery. Prophylactic antibiotics are given at least 30 minutes and no more than 60 minutes before skin incision, considering the optimal timing for administration of the most commonly used preoperative antibiotics. Antibiotics used in contaminated and dirty surgical procedures are classified as therapeutic antibiotics, so no prophylactic antibiotics are needed. (5).

Surgical site infection (SSI) is an infection which occurs within 30 days after surgery. The incidence of SSI remains a major cause of postoperative morbidity and mortality, prolonging hospital stays and increasing health care costs in surgical departments. Furthermore, appropriate prophylactic antibiotics before surgery and appropriate postoperative antibiotic therapy can reduce the incidence of SSI (14,15). Male gender, previous hospitalization, prescription of antibiotics in hospital before perioperative antibiotic prophylaxis, and postoperative length of stay >15 days were associated with risk factors for surgical site infection in orthopedic surgery (16).

Based on a study conducted in two private hospitals in Surabaya, East Java, out of 24 antibiotics given as prophylactic antibiotics, ceftriaxone was the most commonly used in both hospitals. There was a clear difference between the daily practice in both hospitals and the recommendations in the guidelines (17). Approximately 11.2% and 18.0% of the total antibiotic DDD at Rafidia and Thabet hospitals were given to patients with clean surgeries where antibiotic prophylaxis was not indicated (18). Research conducted by Anand et al. related to the use of prophylactic antibiotics in tertiary hospitals in India stated that 50% of cases of prophylactic

antibiotics were inappropriate while 73.07% of antibiotic treatment failed to comply with guidelines (19).

In Indonesia, research on the use of prophylactic antibiotics in surgery is still limited. This study aims to analyse the pattern of antibiotic use, the quantity of antibiotic use by using Anatomical Therapeutic Chemical (ATC)/Defined Daily Dose (ATC/DDD) method, and the quality of antibiotic use of bone fracture patients in orthopedic surgery inpatients in hospitals in Indonesia by using the Gyssens method. It is expected that research related to the quantity and quality of antibiotic use can be taken into consideration in the preparation of guidelines for the use of prophylactic and therapeutic antibiotics; besides, can help clinical pharmacists in order to monitor and evaluate the use of antibiotics wisely.

2. Methods

This study was an observational descriptive study with data collection conducted retrospectively which based on patient's medical record data. The analysis is performed using Gyssen method for qualitative analysis and ATC/DDD method for quantitative analysis. This study involved all adult orthopedic surgery patients with open or closed fractures who received antibiotic therapy at Haji General Hospital Surapaya who met the inclusion criteria in the period January-December 2019. In addition, the inclusion criteria of this study were (i) patients aged 18-65 years, (ii) received antibiotic therapy, and (iii) patients with closed fractures and open fracture. Patients with discontinuation of antibiotic therapy that was not clinically considered by the doctor (forced discharge, death or referral to another hospital) would be excluded from the study.

Restrospective data was taken from the medical records of patients undergoing hospitalization in surgical inpatient installation of Haji General Hospital Surabaya which were adjusted to the inclusion and exclusion criteria during the period January-December 2019. Data collected included patient demographics (age, gender, diagnosis), length of stay, and data on antibiotics used (antibiotic name, indication, dosage, route, frequency of administration, and duration of antibiotic administration). The pattern of antibiotic use includes the type, dose, frequency, route and duration of use and antibiotics .

Qualitative analysis of the use of antibiotics in this study used the Gyssen category, which this assessment was recommended by the Ministry of Health of the Republic of Indonesia for a qualitative audit of antibiotic use in hospitals. The quality of antibiotic use can be assessed by looking at the records of antibiotic administration and patient medical records. There are seven categories in Gyssen categories. In the analysis, the evaluation starts from reviewing the completeness of the patient's medical record data, the presence or absence of indications for use, the effectiveness of antibiotics in terms of selection, price and toxicity, accuracy of dosing, route and interval of antibiotics, and timeliness of administration (5,20–22).

In category VI, the medical record data taken are complete and meet the requirements for study; such as, patient data, clinical and laboratory data of patients, there is information about antibiotics and their regimens, patient's medical history, history and physical examination, and there is no missing medical record sheet. Meanwhile, in category V, the indications for the use of prophylactic antibiotics are based on the surgery class which is clean and clean-contaminated surgical procedures. Prophylactic antibiotic is indicated for clean and clean-contaminated surgery. Therapeutic antibiotic is indicated for contaminated and dirty. The presence or absence of indications of bacterial infection can also be identified through the presence of systemic inflammatory response syndromes (SIRS) signs; such as, an increase/decrease in body temperature, tachypnea, tachycardia, leukocytosis, high erythrocyte sedimentation rate, and high neutrophil stem levels. For category IV, there are four types, namely IVA (there are antibiotics that are more effective), IVB (there are other antibiotics that are less toxic), IVC (there are antibiotics that are less costly), and IVD (there are antibiotics with a narrower spectrum. In category III, there are IIIA (duration of antibiotics is too long) and IIIB (duration of antibiotics is too short antibiotics) categories. Furthermore, in category II, there are three categories, namely category IIA (inappropriate dose), category IIB (inappropriate interval of administration), and category IIC (inappropriate route of administration). Moreover, category I shows the timeliness of antibiotic administration, from the time of administration after indicated infection and the time of giving antibiotics every day. If the assessment does not end in category VI-I, the antibiotics used fall into category 0, indicating that the antibiotics used are appropriate (5,20–22).

Qualitative analysis was conducted together with clinicians, discussions were held regarding the therapy which had been given based on the guidelines used by clinicians (guideline that clinicians use to determine antibiotic therapy, e.g. The National Health Service Antimicrobial Guideline and The South Australian expert Advisory Group on Antimicrobial Resistance Guideline) in order to determine the quality category of antibiotic use. The reviewer team was more than one from Antimicrobial Stewardship Team at Haji General Hospital Surabaya.

When there was a significant difference between the reviewers' assessment, a panel discussion for each case may be held.

In addition, quantitative analysis of antibiotic use was conducted by collecting the total length of stay of patients and calculating the number of doses of antibiotics in each patient during treatment (in grams). Quantitative analysis of antibiotic use using Anatomical Therapeutic Chemical (ATC)/Defined Daily Dose and then calculated using DDD/100 patient-days units. ATC/DDD is a drug classification and measurement system used to improve the quality of drug use. The defined daily dose (DDD) of antibiotics is the average daily dose of antibiotics used in adults for their primary indication. The dose for each patient is determined by the patient's condition. WHO assigns a DDD value to each antibiotic based on the average maintenance dose for the main indication in a 70 kg adult (23). The calculation of DDD/100 patient days with the formula:

$$Amount\ of\ antibiotic\ consumption\ (in\ DDD) = \frac{amount\ of\ antibiotic\ consumed\ in\ Gram}{DDD\ antibiotics\ in\ grams}$$

$$DDD\ per\ 100\ patient\ days = \frac{total\ DDD}{total\ number\ of\ days - patients}\ x\ 100$$

3. Results and Discussion

This study was conducted at the Surgical Inpatient Installation of Haji Hospital Surabaya and it has obtained a permit for written research on August 25, 2020 with the number 070/132/03.2/2020. In this study, medical records were collected. from January 1, 2019 to December 31, 2019. During the study period, there were 155 orthopedic surgery patients, 96 of whom were orthopedic surgery patients with fractures. Of these 96 patients, 89 met the inclusion criteria and were included in the study, while seven were excluded.

Table 1 shows data on patient characteristics including gender, age, length of hospitalization, and indications for antibiotics, and the type of surgical diagnosis. Furthermore, there were 48 male patients (53.9%) and 41 female patients (46.1%) who were included in the study sample with the highest age range being 18-29 years (34.8%) as many as 31 people. The prevalence of male patients is higher than female patients. The high prevalence in age and gender categories is related to high mobility and activities; such as, driving which lead to an increased risk of injury. Bone fractures are more common in men than women. Men are 2.9 times more likely to have a fracture than women at the age of 15-49 years (24).

Based on the length of stay of patients in the hospital, there were 27 patients (30.34%) who were hospitalized for three days and 19 patients (21.34%) who were hospitalized for five days. The longest recorded hospitalization time was 8 days with 4 patients (4.5%). There is an association between infection rates and length of stay, hospitalized patients are at high risk of developing nosocomial infections and often microorganisms resistant to antibiotics. In addition, appropriate use of antibiotics is associated with a shorter length of stay and it has a positive impact on patient outcomes and costs of care (25,26).

When it comes to antibiotics, there are two types that surgical patients received: prophylactic antibiotics and therapeutic antibiotics. Prophylactic antibiotics are recommended for both clean and contaminated surgery. According to the Ministry of Health of the Republic of Indonesia, surgical prophylactic antibiotics are the use of antibiotics before, during, and for up to 24 hours after surgery in cases where there are no clinical signs of infection in order to prevent surgical wound infection. The goal of prophylactic antibiotic administration is to prevent the occurrence of postoperative infectious complications in the surgical area, as well as the associated consequences such as increased hospitalization time, treatment costs, the need for additional actions to overcome complications, decreased patient performance due to infectious complications, and increased mortality. Antibiotic administration in contaminated and dirty surgical procedures is classified as therapeutic, so no prophylactic antibiotics are required (5). During the study, 85 patients received prophylactic antibiotics and 72 patients received therapeutic antibiotics. One patient could receive more than one antibiotic indication, such as prophylactic antibiotics before surgery and therapeutic antibiotics after 24 hours post-surgery. Antibiotics used in this study can be seen in **Table 2.**

Table 1. Characteristics of patients with bone fracture receiving antibiotics

Patient characteristics	Number of patients	%
Gender		
Male	48	53,9
Female	41	46,1
Age (years)		
18-29	31	34,8
30-39	16	17,9
40-49	19	21,4
50-59	16	17,9
60-65	7	7,9
Length of stay		
2 days	5	5,6
3 days	27	30,3
4 days	16	18
5 days	19	21,3
6 days	13	14,6

7 days	5	5,6
8 days	4	4,5
Antibiotic indication		
Prohylactic antibiotics	85*	95,5
Therapeutic antibiotics	72*	80,9
Surgical diagnose		
Open fractur	19	21,3
Closed fracture	58	65,2
Non union	1	1,1
Mal union	1	1,1
Union	2	2,2
Implant falure	1	1,1
Near amputation	1	1,1
Post orif	6	6,7

* Note: one patient might have more than one antibiotic indication.

Table 2. Distribution of prophylactic antibiotics use in patients with bone fracture

No	Type of antibiotics	Route of administration	Amount	%
1.	Ceftriaxone 2 gram	parenteral	79	92,94
	- Dirty surgery		2	
	- Clean-contaminated surgery		2	
	- Clean surgery		75	
2	Cefazolin 2 gram	parenteral	6	7,06
	- Clean surgery		6	
	Total		85	100

Ceftriaxone was the most commonly used prophylactic antibiotic in this study, with 79 patients (92,24%) patients, followed by cefazolin.in six patients (7,06%). Seen from the classification of surgery, patients who received cefazolin prophylactic antibiotics are included in the clean surgery category. Meanwhile, patients who received ceftriaxone prophylactic antibiotics were included in the dirty surgery category as many as two patients, clean-contaminated surgery as many as two patients, and the most dominant was clean surgery as many as 75 patients. These results are in line with the study on the use of prophylactic antibiotics in orthopedic surgery which had conducted at a tertiary hospital in Jakarta, Indonesia, where the most widely used prophylactic antibiotic for orthopedic surgery is ceftriaxone with a percentage of 87.8% (14). This result is in contrast to a similar study conducted at a tertiary hospital in Surabaya, Indonesia which showed that cefazolin is the prophylactic antibiotic which is widely used in this study (27). Furthermore, another study reported that prophylactic use of antibiotics in proximal femoral surgery and closed long bone fractures, single-dose ceftriaxone can significantly reduce the risk of surgical site infection (SSI) and its use has been shown to have reduced treatment costs (28). The use of prophylactic antibiotics helps reduce the rate of SSI which leads to reduced hospitalization time and costs (29). A study from Salomon conducted on fracture patients found that there was no difference between prophylactic antibiotic administration of cefazolin and ceftriaxone in terms of superficial surgical site infection (SSI), deep SSI, osteomyelitis, re-operation after index hospital visit, re-admission due to prior injury, limb loss, and death (30). According to Kigera, administration of ceftriaxone as prophylaxis in fracture patients is because ceftriaxone is widely available and more cost-effective (31).

In the administration of therapeutic antibiotics, patients could get single antibiotics or combination antibiotics. Seventy-two patients (80,90%) received therapeutic antibiotics in this study. On the pattern of the use of therapeutic antibiotics in patients with fractures, the dominant single therapeutic antibiotics used were ceftriaxone 1 gram twice daily as many as 49 patients (68%) and ceftriaxone 1 gram once daily as many as 14 patients (19.45%) (Table 3). It was because patients with ceftriaxone dose 1 gram once daily regiment whose condition had improved and it was recommended by doctors to be discharged from the hospital. Meanwhile, patients who received ceftriaxone 1 gram twice daily still need improvement, including therapy.

Empirical antibiotics are assigned based on microbial patterns and local antibiotic susceptibility (5). Causes of surgical site infection include Staphylococcus aureus, Coagulase-negative Staphylococci aureus or S. Epidermitis, Escherichia coli, Enterobacter spp, Klebsiella spp., Pseudomonas aeruginosa, Acinetobacter baumanii. The dominant species found in surgical site infections are Gram-negative bacteria. The most common pathogen reported among studies is Escherichia coli which reaches 6.7-50% of the general incidence of orthopedic surgery, cardiothoracic surgery, and caesarean surgery (29).

There were combination therapeutic antibiotics in this study that were ceftriaxone and metronidazole, cefazolin and metronidazole as well as ceftriaxone and gentamicin. In general, the greater the damage to bone and soft tissue so that the greater the risk of infection (6). Furthermore, the administration of combination antibiotics aims to increase the activity of antibiotics in specific infections (synergistic effect) or broadening the spectrum of antibiotics in treating infections due to the presence of polymicrobials (17,32) besides, slowing and reducing the risk of developing resistant bacteria. Combination antibiotic therapy has also been shown to be more effective than single antibiotic therapy in the treatment of infections caused by resistant microorganisms (33).

Anaerobic bacteria are common organisms which infect wounds and antibiotics that can inhibit the growth of anaerobic bacteria are needed. Therefore azithromycin or

metronidazole may be added to suppress these organisms (17,32). Gentamicin is an aminoglycoside antibiotic which is often used in synergistic combinations with other classes of antibiotics; such as, the beta-lactam group which produces a bactericidal effect (34).

In this study, duration of therapeutic antibiotic ranges from 24 hours - 72 hours. The profile of the duration of antibiotic administration is dominated by the highest duration of 0-24 hours of administration, with a total of 42 patients, followed by the duration of administration of 24-48 hours which is 23 patients. There are differences in the dose regimen for ceftriaxone, namely ceftriaxone 1 gram twice daily intravenously as many as 25 patients and ceftriaxone 1 gram once daily intravenously in 14 patients. It is because patients with regimented doses of ceftriaxone 1 gram once daily have improved conditions and it is recommended by doctors to be discharged from the hospital. Furthermore, research which had conducted by Ahmed et al. related to the use of prophylactic antibiotics in public hospitals in Saudi Arabia showed that most patients receive antibiotics for seven days or for five days, and only 1.08% of patients received antibiotics appropriately for a maximum of one day (35). In addition, Shadmehr et al. reported that surgery performed in a hospital in Iran, contain 86.7% of surgery whose antibiotics were continued for more than 24 hours after surgery (36). The duration of antibiotic administration affects the qualitative analysis of antibiotics, where the administration of antibiotics is too long without a review of clinical data and laboratory can result in overuse and lead to resistance. Meanwhile, the administration of antibiotics which are too short without a review of clinical and laboratory data can result in patient relapse and resistance. Avoiding unnecessary use of antibiotic therapy in the postoperative period can have important implications for health care costs and patient outcomes (37).

Table 3. Type of therapeutic antibiotic and duration of therapeutic antibiotic administration in patients with bone fractures

No	Type of antibiotics	Duration of antibiotic administration (hours)				Amount	%
		0-24	24-48	48-72	>72		
Single therapy							
1	Ceftriaxone 1 gram three times a day		1			1	1,4
	Ceftriaxone 1 gram twice daily	25	21	2	1	49	68
	Ceftriaxone 1 gram once daily	14	14			14	19,451
	Cefazolin 1 gram three times a day		1	1		2	2,78
	Cefazolin 1 gram twice daily	3				3	4,17
Combination therapy							
2	Ceftriaxone 1 gram twice daily + Metronidazol 1 gram three times a day				1	1	1,4
	Ceftriaxone 1 gram twice daily + Gentamicin 80 mg twice daily				1	1	1,4
	Cefazolin 1 gram twice daily + Metronidazol 500 mg three times a day			1		1	1,4
	Total	42	23	4	3	72	100%

Table 4. The results of qualitative analysis of antibiotic use in patients with bone fractures using the Gyssen method.

Categories		Amount	%
0	Appropriate use of antibiotics	75	84,3
I	Antibiotice use is not timely	4	4,5
IIA	Inappropriate antibiotic dosage	0	0
IIB	Inappropriate antibiotic administration interval	10	11,2%
IIC	Inappropriate antibiotic administration method/route	0	0
IIIA	Duration of antibiotic use is too long	0	0
IIIB	Duration of antibiotic use is too long	0	0
IVA	There are other antibiotics that are more effective	0	0
IVB	There are other antibiotics that are less toxic	0	0
IVC	There are other antibiotics that are less costly	0	0
IVD	There are other antibiotics with a narrower antibacterial spectrum	0	0
V	There is no indication for antibiotic use	0	0
VI	Medical record data is incomplete and cannot be evaluated	0	0
Total		89	100

Qualitative analysis of the use of antibiotics in this study used the Gyssen classification, which method is recommended by the Ministry of Health of the Republic of Indonesia for a qualitative analysis of antibiotic use in hospitals. The assessment was conducted by considering the appropriateness of antibiotic use including the appropriateness of indications for drug selection based on effectiveness, toxicity, price and spectrum, duration of drug

administration, dose, interval, route and time of administration (5,20).

Of the results of this study, there were no antibiotic prescriptions that ended at category VI, implying that no medical records were incomplete. Furthermore, there are no antibiotic prescriptions in categories V to III, indicating that the use of antibiotics was appropriate in selecting drugs based on effectiveness, toxicity, price and spectrum, and duration of drug administration. In category II, no antibiotics were included in IIA or IIC, but 10 (11.2%) were included in IIB. In IIB, the antibiotic interval was not appropriate where the time interval exceeds the recommended time. Four cases (4.5%) were classified as category I, indicating inappropriate timing of antibiotic administration. From this study, the results of the analysis grouped with the category of appropriate antibiotic administration (Category 0) were 75 cases (84.3%). The results of the qualitative analysis using the Gyssen method can be seen in **Table 4**.

A similar study which had conducted at a tertiary hospital in Semarang, Indonesia showed that the number of antibiotics used in category I reached 45.3% and the number of inappropriate antibiotic use (categories IIIa, IVD, and V) reached 53.3%. In addition, the study shows that ceftriaxone was an antibiotic which is widely used for orthopedic surgery cases on the basis of unclear indications (Category V) by 42% (38). In the study which had conducted by Radji et al., showed that of the total patients who received prophylactic antibiotics before orthopedic surgery, 4.9% of patients experienced SSI. The appropriateness of prescribing prophylactic antibiotics in the selection of antibiotics was 6.1% (14). In addition, another study at a referral hospital in Indonesia showed that the level of adherence to prophylactic antibiotics in Indonesia from 2013 to 2016 was 48.3%. The compliance includes the selection of antibiotics, the dose of administration, the method of administration, the time of administration, and the route of administration (27). Research which had conducted in hospital in Turkey and Indonesia showed that the level of use of antibiotics which were not properly indicated would lead to an increase in costs and increase in the number of nosocomial infections with resistant species (17,39).

The timing and duration of antibiotic administration is one indicator of inappropriate antibiotic use.. The addition of postoperative antibiotics prophylactic to the standard preoperative and/or perioperative antibiotic regimen does not show a significant difference in the risk of surgical site infection. One study does not support the routine use of postoperative antibiotics prophylactic in patients with maxillofacial fractures. Avoiding unnecessary use of antibiotic therapy in the postoperative period has important implications for health care costs (37,40). Perioperative antibiotics prophylactic should usually be discontinued within 24 hours of completion of surgery (5). The short duration of prophylactic antibiotics facilitates early rehabilitation of patients and reduces the burden on healthcare workers (36,41). Long-term administration of antibiotics after surgery without evidence of secondary infection or SSI may pose a risk of drug toxicity and superinfection. Meanwhile, long-term prophylaxis is associated with an increased risk of antimicrobial resistance compared to short-term prophylaxis (36,41). In a randomized controlled trial with 1.121 patients undergoing orthopedic surgery shows that the duration of prophylactic antibiotics in orthopedic surgery extended to 48 hours has no difference in the prevention of healthcare association infection (HAI) within 30 days after clean orthopedic surgery compared preventing HAI with no more than 24 hours (41).

Inappropriate administration of surgical prophylactic antibiotics can be caused by low awareness in adhering to guidelines. There are no comprehensive institutional guidelines, access to antibiotic use which is not too strict, and doctors' preferences in the use of antibiotics and to reduce the risk of infection. It is undeniable that there are concerns of surgeons in orthopedic surgery regards to the use of antibiotics; such as, the possible higher risk of SSI when the duration of prophylactic antibiotics is too short. In addition, the presence of fever, inflammation, installation of drains, colored and thick secretions and overall postoperative morbidity are the reasons for doctors to give antibiotics after surgery (36,41,42).

In addition to the study on the qualitative analysis of antibiotics, a qualitative analysis of antibiotics was also conducted. Quantitative analysis of antibiotics by using the DDD method with the results of the DDD value of each type of antibiotic describes the quantity of use of each type of antibiotic.

Table 5. The results of quantitative analysis of antibiotic use in patients with bone fractures using the DDD/100 patient days method.

No	Type of antibiotics	Rute of administration	ATC code	DDD standard WHO (gram)	DDD/100 patient days
1	Ceftriaxone	Parenteral	J01DD04	2	45,6
2	Cefazolin	Parenteral	J01DB04	3	3,1
3	Cefixime	Peroral	J01DD08	0,4	1,5
4	Metronidazole	Parenteral	J01XD01	1,5	1,2
5	Gentamicin	Parenteral	J01GB03	0,24	1,1

Quantitative evaluation was conducted to evaluate the type and amount of antibiotics used by using the

ATC/DDD method with units of DDD/100 patient-days. The results of the qualitative study can be seen in **Table 5**. DDD is the assumption of the average daily dose of antibiotics for a particular indication. The DDD value is expressed in units of DDD/100 patient days (22). In this study, there are 5 types of antibiotics which have ATC codes and WHO standard DDD values. The antibiotics are ceftriaxone (parenteral), cefazolin (parenteral), cefixime (peroral), metronidazole (parenteral) and gentamicin (parenteral).

Intravenous ceftriaxone had the highest quantity value of antibiotics, with a DDD/100 patient-days value of 45.6, which means that for every 100 days of patient hospitalization, 45.6 (rounded 47) patients received ceftriaxone antibiotics according to the WHO standard DDD, namely teo grams. Following that, intravenous cefazolin with a DDD/100 patient-days value of 3.1, which means that for every 100 days of hospitalization, 3 patients received cefazolin antibiotics based on the WHO standard DDD, namely three grams. Cefixime (oral), metronidazole (intravenously), and gentamicin (intravenously) had DDD/100 patient-days values of 1.5, 1.2, and 1.2, respectively, implying that for every 100 days of hospitalization, one patient received these antibiotics in accordance with the WHO standard DDD. It is in line with the research which had conducted by Herawati et al. who stated that of the 24 antibiotics given as prophylactic antibiotics, ceftriaxone is the most commonly used in the study (17). In another study, ceftriaxone was the most commonly used antibiotic for orthopedic surgery patients in a hospital in Samarinda City, Indonesia, with an ATC/DDD value of 20.21 DDD/100 patient-days (43). A similar study was also conducted in a government hospital in East Java, Indonesia, which revealed that ceftriaxone was the most commonly used antibiotic in orthopedic surgery patients, with a value of 34.57 DDD/100 patients (11). Cetriaxone was the therapeutic antibiotic with the highest DDD value among other antibiotics, with a value of 53.64/100 patient-days, according to research on antibiotic use in surgical patients at an Indonesian teaching hospital (44).

Fundamental improvements are needed in the use of prophylactic antibiotics in hospitals in Indonesia. Furthermore, there is an urgent need for every hospital to publish guidelines for the use of antibiotics or clinical guidelines for every type of surgery, including complicated surgeries and other infectious diseases. Antibiotics should be chosen more precisely dosing frequency and route. It is recommended to administer a single dose of narrow-spectrum antibiotics in a period of not more than 24 hours for surgical prophylaxis in order to prevent the emergence of microbial resistance. In Asia, the use of antibiotic stewardship programs (ASPs) can reduce antibiotic consumption in hospitals and clinics and it does not worsen clinical outcomes. These findings strongly support the widespread implementation of antimicrobial surveillance interventions in hospitals and clinics in Asia (45). Moreover, the existence of ASP can be a strategy to prevent antibiotic resistance and reduce the burden of treatment costs. Reducing antibiotic consumption can also increase patient satisfaction and reduce medical costs imposed on patients (25,46). Policies in the use of antibiotics wisely are very important in controlling antibiotic resistance. These policies are generally spelled out by restricting the use of antibiotics for certain indications and within a certain time limit. The policy on the use of antibiotics can be stated in the guidelines for the use of antibiotics in a hospital (5).

In practice, the ASP Team consists of multidisciplinary health workers and there should be at least one infectious disease doctor and clinical pharmacist. Clinical pharmacists can play a role in improving the quality of antibiotic prescribing since clinical pharmacists have knowledge in pharmacology and know about optimization of antibiotic doses, appropriate administration routes, adverse drug effects of a drug, and have experience in auditing the use of anti-infectives. Meanwhile, in general, the clinical pharmacist on the ASP team is responsible for the design, implementation, and compliance with the formulary and pre-authorization requirements. In addition, clinical pharmacists are responsible for processing antimicrobial consumption and cost data for surveillance and benchmarking (pharmacoeconomics) purposes (46).

The limitation of this study is that data collection is conducted retrospectively so that it has potential to cause errors in conducting medical records. It is necessary to conduct similar research with prospective data collection in order to minimize errors in conducting medical record data so that re-examinations related to prophylactic antibiotics can be conducted between drug administration records, SSI surveillance forms, surgical preoperative assessments and drug sales reports so that it can be known with certainty the type, dose and time of administration of antibiotics used.

4. Conclusions

Based on the analysis of the use of antibiotics in hospitalized fracture patients, ceftriaxone was the antibiotic with the highest DDD (45.6/100 patient-days), followed by cefazolin (3.1/100 patient-days). In addition, the result of the qualitative analysis by using the Gyssen method shows that most of the antibiotics are given appropriately to bone fracture patients at Haji General Hospital, Surabaya.

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6. **Konflik Kepentingan**

Tidak ada konflik kepentingan selama penelitian atau publikasi.

7. **Conflict of Interest**

The authors have no conflicts of interest regarding this investigation.

8. **References**

1. Parathon H, Kuntaman K, Widiastoety TH, Muliawan BT, Karuniawati A, Qibtiyah M, et al. Progress towards antimicrobial resistance containment and control in Indonesia. BMJ. 2017 Sep 1;358:j3808.
2. Aslam B, Wang W, Arshad MI, Khurshid M, Muzammil S, Rasool MH, et al. Antibiotic resistance: a rundown of a global crisis. Infect Drug Resist. 2018 Oct;Volume 11:1645–58.
3. Romandini A, Pani A, Schenardi PA, Pattarino GAC, De Giacomo C, Scaglione F. Antibiotic Resistance in Pediatric Infections: Global Emerging Threats, Predicting the Near Future. Antibiotics. 2021 Apr 6;10(4):393.
4. Putra ON, Saputro ID, Nurhalisa HD, Yuliana E. Surveilans Retrospektif Penggunaan Antibiotik Pada Pasien Anak Dengan Luka Bakar. Pharm J Indones. 2021 Dec 1;7(1):21–8.
5. Kementerian Kesehatan Republik Indonesia. Peraturan Menteri Kesehatan Republik Indonesia Nomor 28 Tahun 2021 tentang Pedoman Penggunaan Antibiotik. Kementerian Kesehatan Republik Indonesia; 2021.
6. Sop JL, Sop A. Open Fracture Management [Internet]. StatPearls [Internet]. StatPearls Publishing; 2022 [cited 2022 Nov 13]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448083/
7. Chang Y, Bhandari M, Zhu KL, Mirza RD, Ren M, Kennedy SA, et al. Antibiotic Prophylaxis in the Management of Open Fractures: A Systematic Survey of Current Practice and Recommendations. JBJS Rev. 2019 Feb;7(2):e1–e1.
8. Tornetta P, Della Rocca GJ, Morshed S, Jones C, Heels-Ansdell D, Sprague S, et al. Risk Factors Associated With Infection in Open Fractures of the Upper and Lower Extremities. JAAOS Glob Res Rev. 2020 Dec;4(12):e20.00188.
9. Kamat AS. Infection Rates in Open Fractures of the Tibia: Is the 6-Hour Rule Fact or Fiction? Adv Orthop. 2011;2011:1–4.
10. Fernandes M de C, Peres LR, Queiroz Neto AC de, Lima Neto JQ, Turíbio FM, Matsumoto MH. Open fractures and the incidence of infection in the surgical debridement 6 hours after trauma. Acta Ortopédica Bras. 2015 Feb;23(1):38–42.
11. Firdaus YV, Jaelani AK, Herawati F, Yulia R. Evaluasi penggunaan antibiotik profilaksis pada pasien bedah ortopedi di Rumah Sakit Bangil. Intisari Sains Medis. 2021 Jun 1;12(2):407.
12. Bhandari M, Tornetta, Sprague S, Najibi S, Petrisor B, Griffith L, et al. Predictors of Reoperation Following Operative Management of Fractures of the Tibial Shaft. J Orthop Trauma. 2003 May;17(5):353–61.
13. Khatod M, Botte MJ, Hoyt DB, Meyer RS, Smith JM, Akeson WH. Outcomes in Open Tibia Fractures: Relationship between Delay in Treatment and Infection: J Trauma Inj Infect Crit Care. 2003 Nov;55(5):949–54.
14. Radji M, Aini F, Fauziyah S. Evaluation of antibiotic prophylaxis administration at the orthopedic surgery clinic of tertiary hospital in Jakarta, Indonesia. Asian Pac J Trop Dis. 2014 Jun;4(3):190–3.

15. Vessal G, Namazi S, Davarpanah MA, Foroughinia F. Evaluation of prophylactic antibiotic administration at the surgical ward of a major referral hospital, Islamic Republic of Iran. East Mediterr Health J. 2011 Aug 1;17(08):663–8.
16. Skender K, Machowska A, Singh V, Goel V, Marothi Y, Lundborg CS, et al. Antibiotic Use, Incidence and Risk Factors for Orthopedic Surgical Site Infections in a Teaching Hospital in Madhya Pradesh, India. In: ECA 2022 [Internet]. MDPI; 2022 [cited 2022 Nov 21]. p. 2. Available from: https://www.mdpi.com/2673-9992/12/1/2
17. Herawati F, Yulia R, Hak E, Hartono AH, Michiels T, Woerdenbag HJ, et al. A Retrospective Surveillance of the Antibiotics Prophylactic Use of Surgical Procedures in Private Hospitals in Indonesia. Hosp Pharm. 2019 Oct;54(5):323–9.
18. Sweileh WM, Adas SO, Sawalha AF, Abu Taha AS. Utilization and cost of antibacterial drugs in 2 general surgery units in Palestine measured using anatomical therapeutic chemical classification and defined daily dose methodology. East Mediterr Health J. 2012 Jun 1;18(6):641–7.
19. Priyanka Anand TV, Sree SK, S. Pavani P, Bhargavi GM, Gupta SB. Assessment of Rational use of Antibiotics in Orthopedic Surgery Procedures. J Young Pharm. 2020 Aug 10;12(2s):s102–7.
20. Gyssens IC. Audits for Monitoring the Quality of Antimicrobial Prescriptions. In: Gould IM, van der Meer JWM, editors. Antibiotic Policies: Theory and Practice [Internet]. Boston, MA: Springer US; 2005 [cited 2022 Nov 13]. p. 197–226. Available from: https://doi.org/10.1007/0-387-22852-7_12
21. van der Meer JWM, Gyssens IC. Quality of antimicrobial drug prescription in hospital. Clin Microbiol Infect. 2001 Dec;7:12–5.
22. Kementerian Kesehatan Republik Indonesia. Pedoman Umum Penggunaan Antibiotik. Kementerian Kesehatan Republik Indonesia; 2013.
23. World Health Organization. Guidelines for ATC classification and DDD assignment. Oslo; 2018.
24. Noorisa R, Apriliwati D, Aziz A, Bayusentono S. THE CHARACTERISTIC OF PATIENTS WITH FEMORAL FRACTURE IN DEPARTMENT OF ORTHOPAEDIC AND TRAUMATOLOGY RSUD DR. SOETOMO SURABAYA 2013 – 2016. Jt J Orthop Traumatol Surabaya. 2019 Dec 9;6(1):1.
25. Damayanti AAIASS, Maharjana IBN, Nurwahyuni A. Antimicrobial Stewardship Strategy to reduce Length of Stay and Cost of Antibiotic Consumption: A Systematic Review. Proc Int Conf Appl Sci Health. 4:346–59.
26. van den Bosch CMA, Hulscher MEJL, Akkermans RP, Wille J, Geerlings SE, Prins JM. Appropriate antibiotic use reduces length of hospital stay. J Antimicrob Chemother. 2016 Dec 20;dkw469.
27. Setiawati Y, Farhadi A. The Use of Prophylactic Antibiotics on Orthopaedic Procedures in an Academic Hospital in Indonesia. Int Islam Med J. 2021 Jul 28;2(2):88–94.
28. Gillespie WJ, Walenkamp GH. Antibiotic prophylaxis for surgery for proximal femoral and other closed long bone fractures. Cochrane Bone, Joint and Muscle Trauma Group, editor. Cochrane Database Syst Rev [Internet]. 2010 Mar 17 [cited 2022 Nov 13]; Available from: https://doi.wiley.com/10.1002/14651858.CD000244.pub2
29. Purba AKR, Setiawan D, Bathoorn E, Postma MJ, Dik JWH, Friedrich AW. Prevention of Surgical Site Infections: A Systematic Review of Cost Analyses in the Use of Prophylactic Antibiotics. Front Pharmacol. 2018 Jul 18;9:776.
30. Salomon B, Griffard J, Patel J, Wideman M, Mcgee T, Corbitt N, et al. Efficacy of Cefazolin versus Ceftriaxone for Extremity Open Fracture Management at a Level 1 Trauma Center. Surg Infect [Internet]. 2022 Aug 26 [cited 2022 Dec 8]; Available from: https://www.liebertpub.com/doi/10.1089/sur.2022.049
31. Jwm K. Audit of prophylactic antibiotic use in orthopaedic surgery in Mulago Hospital. :3.
32. Leekha S, Terrell CL, Edson RS. General Principles of Antimicrobial Therapy. Mayo Clin Proc. 2011 Feb;86(2):156–67.
33. Tängdén T. Combination antibiotic therapy for multidrug-resistant Gram-negative bacteria. Ups J Med Sci. 2014 May;119(2):149–53.
34. Chaves BJ, Tadi P. Gentamicin [Internet]. StatPearls [Internet]. StatPearls Publishing; 2022 [cited 2022 Nov 13]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557550/
35. Ahmed N, Balaha M, Haseeb A, Khan A. Antibiotic Usage in Surgical Prophylaxis: A Retrospective Study in the Surgical Ward of a Governmental Hospital in Riyadh Region. Healthcare. 2022 Feb 18;10(2):387.
36. Shadmehr MB, Aleen Z, Baniasadi S. Adherence to American Society of Health-System Pharmacists guidelines for antibiotic prophylaxis in thoracic surgery: a prospective observational study. J Pharm Pract Res. 2019;
37. Habib AM, Wong AD, Schreiner GC, Satti KF, Riblet NB, Johnson HA, et al. Postoperative prophylactic antibiotics for facial fractures: A systematic review and meta-analysis: Prophylactic Antibiotics for Facial Fractures. The Laryngoscope. 2019 Jan;129(1):82–95.
38. Waridiarto DS, Priambodo A, Lestari ES. KUALITAS PENGGUNAAN ANTIBIOTIK PADA KASUS BEDAH ORTHOPEDI DI BANGSAL BEDAH RSUP Dr. KARIADI. 2015;4(4):8.
39. Sözen H, Gönen I, Sözen A, Kutlucan A, Kalemci S, Sahan M. Application of ATC/DDD methodology to eveluate of antibiotic use in a general hospital in Turkey. Ann Clin Microbiol Antimicrob. 2013 Dec;12(1):23.
40. Mousavi S, Zamani E, Bahrami F. An audit of perioperative antimicrobial prophylaxis: Compliance with the international guidelines. J Res Pharm Pract. 2017;6(2):126.
41. Nagata K, Yamada K, Shinozaki T, Miyazaki T, Tokimura F, Tajiri Y, et al. Effect of Antimicrobial Prophylaxis Duration on Health Care–Associated Infections After Clean Orthopedic Surgery: A Cluster Randomized Trial. JAMA Netw Open. 2022 Apr 12;5(4):e226095.
42. Anggraini AB, Syachroni S. Penggunaan Antibiotik Profilaksis pada Bedah Bersih di Rumah Sakit

di Jakarta. J Penelit Dan Pengemb Pelayanan Kesehat. 2020 May 7;7–12.
43. Fitriyani, Ramadhan AM, Mahmudah F. Studi Penggunaan Antibiotik Berdasarkan ATC/DDD Pada Pasien Bedah Orthopedi Di RSUD Abdul Wahab Sjahranie Samarinda. Proceeding Mulawarman Pharm Conf. 2018 Dec 31;8:207–13.
44. Pratama NYI, Suprapti B, Ardhiansyah AO, Shinta DW. Analisis Penggunaan Antibiotik pada Pasien Rawat Inap Bedah dengan Menggunakan Defined Daily Dose dan Drug Utilization 90% di Rumah Sakit Universitas Airlangga. Indones J Clin Pharm. 2019 Dec 29;8(4):256.
45. Lee CF, Cowling BJ, Feng S, Aso H, Wu P, Fukuda K, et al. Impact of antibiotic stewardship programmes in Asia: a systematic review and meta-analysis. J Antimicrob Chemother. 2018 Apr 1;73(4):844–51.
46. de With K, Allerberger F, Amann S, Apfalter P, Brodt HR, Eckmanns T, et al. Strategies to enhance rational use of antibiotics in hospital: a guideline by the German Society for Infectious Diseases. Infection. 2016 Jun;44(3):395–439.