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Abstract

Typhoid fever is a global health problem, especially in developing countries, one of which is Indonesia. The incidence of resistance to the use of antibiotics in the treatment of typhoid fever can occur due to inappropriate use of antibiotics. This study aims to determine the impact of the application of clinical pathways on the quality and quantity of antibiotic use in typhoid therapy at FMC Bogor Hospital. This research is a descriptive analytic study conducted retrospectively which was analyzed using the Gyssens and ATC/DDD methods. The research data was taken from patient medical records for the period January-December 2018 and January-December 2020 which met the inclusion criteria. The results showed that from 115 medical records of typhoid fever patients, ceftriaxone was used as the most widely used antibiotic for typhoid therapy. The quality of antibiotic use as much as 40% was declared rational before the use of clinical pathways and as much as 57.3% after the use of clinical pathways (category 0), while the other 60% were irrational (categories I-VI) and after CP as much as 42.7% were included in category 0, the rest fall into the irrational category (Categories I-VI) which includes the use of antibiotics that are not appropriate for the administration interval, the use of antibiotics that are too long, the use of antibiotics that are too short, there are other antibiotics that are more effective, and there are other antibiotics that are less toxic /safer. The quantity of antibiotic use was stated to exceed WHO standards, namely the use of ceftriaxone by 81 DDD/100 patient days before the clinical pathway and 92.4 DDD/100 patient days after the clinical pathway. Based on the results of statistical tests, it was obtained 1) There were differences in the quality of antibiotic use between before and after the implementation of the clinical pathway in inpatients with typhoid fever at FMC Bogor Hospital; 2) There are differences in the quantity of antibiotic use between before and after the implementation of the clinical pathway in inpatients with typhoid fever at FMC Bogor Hospital. The results of this study are expected to be a consideration for the hospital as material for evaluation and improvement in order to increase the rationality of using antibiotics.

Keywords: Antibiotics, typhoid fever, Gyssens, ATC/DDD

INTRODUCTION

Typhoid fever occurs due to systemic infection of the bacterium Salmonella enterica serotype Typhi. The disease is characterized by fever and, in severe cases, gastrointestinal bleeding, altered mental status, intestinal perforation, and death. *United States Centers for Disease Control and Prevention, 2019*). This disease is also known as enteric fever and abdominal typhus. This disease can have severe clinical manifestations because of its complications and can cause carriers. This disease is closely related to the quality of clean and healthy living behavior, poor sanitation and environment (Ministry of Health of the Republic of Indonesia, 2013).

Data from Global Burden of Disease (GBD) on the concept of Disability-Adjusted Life Year (DALY) which is a description of health status (in principle, the greater the DALY, the worse the health status). In 2019 the data obtained showed an improvement in typhoid fever, indicated by a decrease in position to 12 with a value of 1251.52 DALYs per 100,000 (Maksura Ainil, 2020). The World Health Organization, namely the World Health Organization (WHO), said that in 2019 there were 11 to 21 million cases of typhoid fever in the world and 128,000 to 161,000 deaths (*United States Centers for Disease Control and Prevention, 2019*). Typhoid fever cases in Southeast Asia reached 1,414,400 people. The death rate due to this case in 2017 reached 116.00 and in Southeast Asia reached 12.000 people (Sutisna, N.S, 2020).

Typhoid fever in Indonesia is endemic and is a public health problem. The morbidity rate of typhoid fever in Indonesia was recorded in the 2008 World Health Organization (WHO) bulletin, namely 81.7 per 100,0005. Based on Indonesia's health profile in 2013, the prevalence of typhoid fever cases was 5.13% with a Case Fatality Rate of 0.67%. The 2014 National Basic Health Research showed that the prevalence of typhoid fever in Central Java was 1.61% which was spread across all districts with a different prevalence in each place (Ministry of Health of the Republic of Indonesia, 2006). Data from GBD for Indonesia based on gender in 2019, the value obtained for male patients was 187.06 DALYs per 100,000, while for female patients it was 122.99 DALYs per 100,000. Specifically for South Sulawesi Province, a value of 147.88 DALYs per 100,000 was obtained in 2019 (Maksura Ainil, 2019)

The proper treatment for typhoid fever is to use antibiotics. The choice of first-line antibiotics is chloramphenicol, ampicillin or amoxicillin (safe for patients who are pregnant), and trimethoprim sulfamethoxazole. If one of the first-line antibiotics is deemed ineffective, it can be replaced with another antibiotic or a second-line antibiotic such as ceftriaxone, cefixime, quinolone can be chosen. In Indonesia, chloramphenicol is still the drug of choice for typhoid fever because it is considered quite effective and the price of the drug is cheap, but the drawback of chloramphenicol is that it cannot prevent relapses or in carrier patients. Rampant, NH 2013.)

Cases of resistance to chloramphenicol in typhoid fever patients were reported in the 1950s in Mexico. Resistance is increasingly developing to other antibiotics such as ampicillin, co-trimoxazole and quinolones (Multi Drug Resistance Salmonella Typhi / MDRST) (Rampengan, NH 2013). In 2017 it was reported that Salmonella typhi bacteria were resistant to ciprofloxacin by 74% in the United States, so that treatment with this antibiotic began to be limited (*United States Centers for Disease Control and Prevention, 2019*). This suggests

that treatment failure may occur among patients treated empirically with fluoroquinolones. The use of the antibiotics azithromycin and ceftriaxone to treat enteric fever is increasing until in 2015, there was only one Typhi isolate that was resistant to azithromycin and no Typhi isolates were resistant to ceftriaxone (Grace D. Appiah, Michael J. Hughes, Kevin Chatham-Stephens, 2020). The resistance of bacteria to antibiotics has become a health problem throughout the world, for this reason it is necessary to monitor and evaluate the use of antibiotics in hospitals in a systematic and standardized manner and to use antibiotics in a rational manner.Sukmawati, Jaya, et al, 2020).

Evaluation of antibiotic use aims to determine the quantity and quality of antibiotic use in hospitals in a systematic and standardized manner as well as being an indicator of the quality of hospital services. Evaluation of the quality of the use of antibiotics is carried out to find out the rationality of the use of antibiotics by assessing the accuracy of the use of antibiotics such as: accuracy of indications, accuracy of selection based on effectiveness, toxicity, price and spectrum, length of administration, dose, interval, route and time of administration. The Gyssens method is a tool for evaluating the quality of antibiotic use that has been widely used in various countries1. Quantitative evaluation of the use of antibiotics recommended by WHO uses the Anatomical Therapeutic Chemical method with Defined Daily Dose, also known as ATC/DDD.Ministry of Health of the Republic of Indonesia, 2015).

Hospital services must be able to carry out good clinical governance. To fulfill this clinical governance, the standard of health services provided to patients must be used as a reference in the implementation of health services in Indonesia in the form of a Clinical Practice Guideline (PPK) and contains a clinical pathway (Clinical Pathway)10. Clinical Pathway is an integrated service concept that summarizes every step given to patients based on evidence-based medical and nursing care services with measurable results and within a certain period of time while in hospital (Ministry of Health of the Republic of Indonesia, 2010).

Implementation of clinical pathways needs to be implemented to realize good governance (Good Clinical Governance) in improving service quality and reducing operational costs. Clinical pathway (CP) is one of the requirements in the Accreditation Standard version of the Hospital Accreditation Committee (KARS) 2012 and the 2017 National Hospital Accreditation Standard (SNARS) edition 1, so that every hospital is required to implement clinical pathways, especially in the high risk category, happens frequently, and is prone to problems.CP must be owned by the Hospital in meeting the 2012 KARS version of Hospital Accreditation Standards (Prih Sarnianto, et al, 2019).

FMC Hospital (Family Medical Center) received a hospital accreditation certificate from the Hospital Accreditation Commission (KARS) in 2019. In order to improve patient quality and safety, FMC hospitals must follow the provisions of KARS. The use of the Clinical Pathway in this hospital is one manifestation of the implementation of hospital accreditation (Hospital Accreditation Committee, 2017).

Typhoid fever is included in the top ten diseases at FMC Bogor Hospital, according to a source from the Medical Records section. This number illustrates that cases of typhoid fever at FMC Hospital are in the large category. Based on these data it is possible to increase the number of cases of typhoid fever at Bogor FMC Hospital. From the background above, the researchers wanted to know the impact of the application of the Clinical Pathway on the quality and quantity of antibiotic use and clinical outcomes in patients with typhoid fever who were hospitalized at FMC Bogor Hospital.

Typhoid fever is a disease caused by the bacterium Salmonella enterica serotype Typhi. This disease is also known as enteric fever and abdominal typhus. Typhoid fever is found in Indonesian people, who live in cities and villages. This disease is closely related to the quality of clean and healthy living behavior, sanitation and poor environment.

Based on data from medical records at the FMC Hospital, typhoid fever was in second place out of the top ten diseases in 2019. This is the background for researchers using typhoid fever as a case of the disease. Treatment therapy used to treat this disease is Antibiotics.

Various studies have found that around 40-62% of antibiotics are used inappropriately, among others, for diseases that actually do not require antibiotics. In research on the quality of antibiotic use in various parts of hospitals in Indonesia, it was found that 30% to 80% were not based on indications13. The incidence of Multi Drug Resistance Salmonella Typhi (MDRST) especially against ampicillin, chloramphenicol and co-trimoxazole is becoming a global problem at this time. MDRST is caused by the administration of antibiotics for irrational management (Nagshetty et al, 2010). In 2017 it was reported that Salmonella typhii bacteria were resistant to ciprofloxacin by 74% in the United States, so that treatment with this antibiotic began to be limited.

The high prescription of antibiotics is the hope of the clinicians for antibiotics, especially to prevent secondary infections caused by bacteria. Inappropriate use of antibiotics results in ineffective treatment, increased patient morbidity or mortality and increased health care costs. One way to overcome this is by implementing an existing clinical pathway3. And

the next step is to evaluate the impact of applying a clinical pathway in the form of using antibiotics qualitatively and quantitatively in typhoid fever patients.

METHODS

This research is descriptive analytic in nature, to evaluate the impact of implementing a clinical pathway on quality and quantityuse of antibiotics in patientstyphoid fever. The cross-sectional research design is a study that studies the correlation between exposure or risk factors (independent) and effects or effects (dependent). Data collection was carried out retrospectively taken from medical records of typhoid fever patients in 2018 and 2020 who were treated at the hospital.FMC Bogor and meet the inclusion criteria, withusing a quantitative research method with an analytic descriptive design to determine the impact of the application of clinical pathways onquality and quantity of antibiotic use in typhoid fever patients.

The population is all elements or elements that are the object of research21. The population here is the whole of the research subjects who have certain characteristics determined by the researcher, which is X. The population in this study are patients diagnosed with typhoid fever who are taking antibiotic therapy inhospitalFMC Bogor and meet the 2018 and 2020 inclusion criteria.

The sample is part of the number and characteristics possessed by the population that are actually studied and conclusions are drawn23. Samples from the population of inpatients with typhoid feverhospitalFMC Bogor in 2018 and 2020 that meet the inclusion criteria. For Cross Sectional research the sample calculation formula used is to use two proportions (Imas Masturoh, Nauri Anggita, 2018). The number of samples is calculated using the following formula:

$$n=\frac{Z^2\ p(1-p)N}{d^2\ (N-1)+Z^2\ p(1-p)}$$

Information:

n = number of samples

N = total population

Z = degree of confidence (usually at the 95% level = 1.96)

P = population proportion the assumption of population diversity that is included in the calculation is P(1-P), where P = 0.5

d = percentage of tolerance for inaccuracy of the desired population and can still be tolerated is 5% (d = 0.05)

Total population of inpatients with typhoid feverhospitalFMC Bogor months from January to December 2018 who met the inclusion criteria were 164 people. The number of samples calculated using the formula of two proportions is 115 people.

$$n = \frac{1{,}96^2\ 0{,}5(1-0{,}5)\ x164}{0{,}05^2\ (164-1)+\ 1{,}96^2\ 0{,}5(1-0{,}5)}$$

$$=\frac{154{,}5056}{1{,}3679} = 115.14 \approx 115 \text{ people}$$

Total population of inpatients with typhoid feverhospitalFMC Bogor months from January to December 2020 who met the inclusion criteria were 151 people. The number of samples calculated using the formula of two proportions is 110 people.

$$n = \frac{1{,}96^2\ 0{,}5(1-0{,}5)\ x151}{0{,}05^2\ (151-1)+\ 1{,}96^2\ 0{,}5(1-0{,}5)}$$

$$= \frac{145{,}0204}{1{,}3354} = 108.59 \approx 110 \text{ people}$$

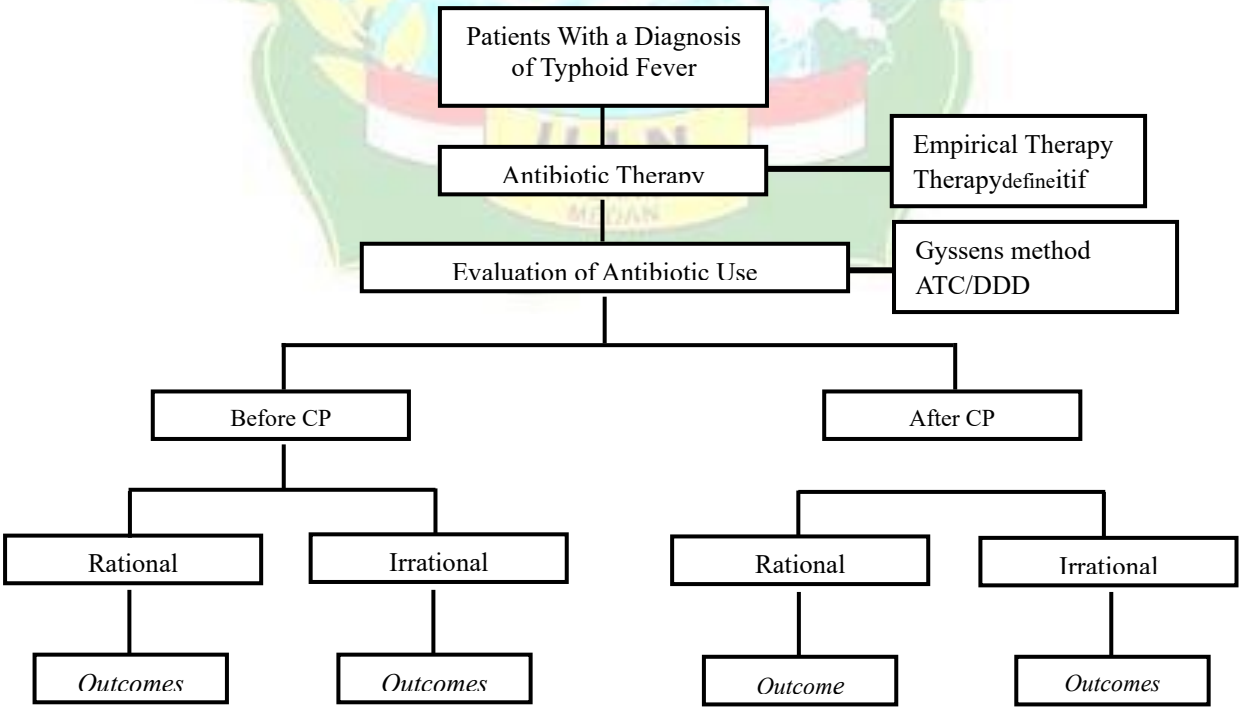

Figure III.1 Research Concept Framework

RESULTS AND DISCUSSION

This research was conducted on 225 medical records of typhoid fever patients who met the inclusion criteria, namely 115 medical records for 2018 and 110 medical records for 2020 at FMC Bogor Hospital respectively.

A. Socio-Demographic Characteristics of Patients

Characteristics of typhoid fever patients used as samples were obtained from the results of recording data collection sheets carried out by researchers based on medical record data. Characteristics of research patient subjects based on gender conditions.

Table V.1.

Socio-Demography of inpatients with Typhoid Fever at Bogor FMC Hospital

Characteristics	before CP (2018)		after CP (2020)		P-values
Gender	(N=115)		(N=110)		
Man	56	49%	42	37%	0.112
Woman	59	51%	68	59%	
Age Group	(N=115)		(N=110)		P-values
18-24 years	29	25%	35	30%	0.241
25-31 years	30	26%	24	21%	
32-38 years	30	26%	18	16%	
39-45 years	12	10%	16	14%	
46-52 years	9	8%	10	9%	
53-59 years	5	4%	7	6%	

Note: Chi-Square Test

From the data table V.1. The distribution of the sex of the patients before the clinical pathway was 115 patients, based on the sex of the patients, there were 56 patients (49%) who were male and 59 patients (51%) who were female. The sex of the patients after the clinical pathway was 42 patients(37%)male and 68 patients(59%)female. This suggests that male patients are more likely to suffer from typhoid fever than female patients. Based on Etikasari's 2012 study, it was explained that gender is not a risk factor because men and women have the

same chance of getting typhoid fever25. Results of chi-square analysis (appendix 5) on gender in 2018 and 2020 with a P-value = 0.112 > 0.05. In conclusion, there is no sex difference before and after CP, so Ho is accepted.

In table V.1. The age group of patients before the clinical pathway in the 18-24 year age group was 29 patients (25%), the 25-31 year age group was 30 patients (26%), the 32-38 year age group was 30 patients (26%), the 39-45 year age group had 12 patients (10%), the 46-52 year age group had 9 patients (8%) and the 53-59 year age group had 5 patients (4%). Then in the age group of patients after the clinical pathway in the 18-24 year age group there were 35 patients (30%), the 25-31 year age group were 24 patients (21%), the 32-38 year age group were 18 patients (16%) , the 39-45 year age group had 16 patients (14%), the 46-52 year age group had 10 patients (9%) and the 53-59 year age group had 7 patients (6%).

Based on the table above, most typhoid fever patients are in the age range of 25-38 years before CP and 18-24 years after CP. This is because at this age the activities carried out by individuals are more numerous and during this period they often consume food from outside so that the risk factor for being infected with Salmonella typhi bacteria is greater6. Approximately 85% of carriers of typhoid fever are found in women over 50 years. In general, the incidence of typhoid fever is reported to be 75% found at the age of less than 30 years. It can be concluded that the age group of 18-24 years both before and after the Clinical Pathway were diagnosed with typhoid fever more than the other age ranges.

Results of chi-square analysis (appendix 6) in the age group before the implementation of CP in 2018 and after the implementation of CP in 2020 with a P-value = 0.241 > 0.05. In conclusion, there is no relationship between the age groups before the implementation of CP 2018 and after the implementation of CP 2020, then Ho is accepted.

B. Distribution of Patient Length of Stay

Table V.2. Distribution of Length of Stay Inpatients with Typhoid Fever at Bogor FMC Hospital

Length of Treatment	(N=115)		(N=110)		P-values
1-3 days	91	79.1%	80	72.7%	0.261
4-6 days	24	20.9%	30	27.3%	
7-9 days	0	0%	0	0%	

Note: Chi-Square Test

Length of Stay(LOS) is the length of time the patient stays in the hospital to get treatment at the hospital to get treatment for the illness until the patient is discharged from the hospital (Sukmawati, Jaya, et al, 2020). The total LOS in this study was 345 days before CP application and 356 days after CP application with an average length of patient stay of 3 to 4 days. Table V.2 shows the results of the number of LOS inpatients with Typhoid Fever at Bogor FMC Hospital, where in the 1-3 day long stay category there were 91 (79.1%) in 2018 and 80 (72.7%) in 2018. 2020. A small number of others require LOS for 1-3 days. Adult category of typhoid fever patients will ideally experience clinical improvement within 3-7 days. LOS can be influenced by several clinical factors from the patient including side effects of drug use, the severity of the disease and the possibility that the patient has taken the drug before entering the hospital. A short LOS can be caused because the patient has difficulty with treatment and obtains good nutrition, thereby accelerating the patient's length of stay in the hospital. The longer the patient is treated, the more vulnerable the patient is to the risk of nosocomial infection. So the costs incurred for maintenance are increasing (Enjelina S, Adam MR, Erwin S, 2021).

The results of the chi-square analysis (appendix 7) in the LOS group before implementing CP in 2018 and after implementing CP in 2020 with a P-value = 0.261 > 0.05. In conclusion, there is no relationship between the LOS group before the implementation of CP 2018 and after the implementation of CP 2020, then Ho is accepted.

C. Patterns of Antibiotic Use

The antibiotic therapy given is definitive, namely the use of antibiotics in cases of infection where the type of bacteria that causes it and its sensitivity pattern are known. Typhoid fever isacute disease caused by the bacterium Salmonella typhii.

Table V.3. Patterns of Antibiotic Use in Inpatients with Typhoid Fever at Bogor FMC Hospital

Characteristics	**before CP (2018)**		**after CP (2020)**	
Types of Antibiotics	**(N=115)**		**(N=110)**	
Ceftriaxone	95	82.6%	76	69.1%
Cefotaxime	9	7.8%	0	0.0%
Levofloxacin	7	6.1%	10	9.1%

Ceftazidime	4	3.5%	2	1.8%
Ceftizoxime	0	0.0%	4	3.6%
Cefuroxime	0	0.0%	18	16.4%

In Table V.3. The pattern of antibiotic use in inpatients with typhoid fever can be seen that ceftriaxone is the type of antibiotic that has the highest percentage in this study, namely 82.6% before using CP and 69.1% after using CP. Ceftriaxone has strong gram-negative antibacterial activity, so it has the ability to inhibit Salmonella typhi cell wall synthesis. The third generation cephalosporin, namely ceftriaxone, is an alternative use for cases such as multi-drug resistance (resistance to chloramphenicol, amoxicillin, and co-trimoxazole) (Vani R., Keri L., 2018).

D. Evaluation of the Quality of Antibiotic Use

Table V.4. Evaluation of the Quality of Antibiotic Use in Inpatients with Typhoid Fever using the Gyssens Method

Category	**before CP (2018)**		**after CP (2020)**	
Gyssens	**(N=115)**		**(N=110)**	
0	44	40.0%	63	57.3%
I	0	0	0	0
IIA	0	0	0	0
IIB	0	0	0	0
IIC	0	0	0	0
IIIA	0	0.0%	1	0.9%
IIIB	43	39.1%	12	10.9%
IVAs	4	3.6%	24	21.8%
IVB	0	0	0	0
IVC	24	21.8%	10	9.1%
IVD	0	0	0	0
V	0	0	0	0

VI	0	0	0	0

The results of evaluating the quality of antibiotic use using the Gyssens method found that antibiotic therapy in patients with typhoid fever was 40% before the application of CP and 57.3% after the application of CP which was classified as rational use (category 0). The irrational use of antibiotics was dominated by Category IIIA as much as 0.9% after the application of CP because there were prescriptions for antibiotics with durations of use that exceeded the guidelines used. Category IIIB was 39.1% before the application of CP and 10.9% after the application of CP, due to the prescription of antibiotics with a duration of use that was less than the guidelines used. This also affects the irrational use of antibiotics which is in the IVA category as much as 3.6% before the application of CP and 21.8% after the application of CP. This is due to the use of antibiotics used not in accordance with the guidelines or CP. In the IVC category it was 21.8% before the application of CP and 9.1% after the application of CP. This is due to the use of antibiotics that are used in accordance with the guidelines and CP but the types of drugs use trade names.

1. Category VI

Category VI means that the data needed for evaluation is not completely available so that further evaluation cannot be carried out. Complete data on typhoid fever patients, including name, age, gender, length of stay, laboratory examination data, dose, antibiotic drug and amount of antibiotic drug. In this study, 225 samples passed category VI because they entered the inclusion criteria by having complete data.

2. Category V

Category V if there is no clear indication for antibiotics. Giving antibiotics is only based on clinical symptoms such as fever without any laboratory tests that support the diagnosis of infection. In this study, a total of 225 samples passed category V because the results of the evaluation in this study found no cases of prescribing antibiotics without indications.

3. IVA category

Category IVA, namely there are other antibiotic options that are more effective if the antibiotics given are not first-line or recommended antibiotics. The use of ineffective antibiotics causes antibiotic resistance resulting in increased morbidity, mortality and more expensive treatment costs. Antibiotics included in the IVA category in this study were 3.6% before CP application and 21.8% after CP application. Typhoid fever patients in 2018 who are included in the IVA category are patients with medical records 896, 3866, 3695, and 9735 attached in Appendix 1.

Typhoid fever patients in 2020 who are included in the IVA category are patients with medical records4584, 9389, 3028, 8948, 456, 6504, 166, 3177, 5139, 289, 1645, 7127, 3950, 6783, 871, 4719, 9664, 8261, 9162, 7566, 9164, 32147, 32247, 32247, 32247, 3264 and 3264 Appendix 2. The reason for being included in the IVA category is because aThe prescribed antibiotics are not in the RI Ministry of Health's Typhoid Fever Control Guidelines 2013 and FMC hospital Clinical Pathway 2020.

1. Category IVB

Category IVB, namely the selected antibiotic has the highest toxicity and there are other alternative antibiotics that have lower toxicity. In this study, 225 samples passed the IVB category because the results of the evaluation in this study found no cases of prescribing antibiotics with safer toxicity.

2. IVC category

The IVC category means that there are other, cheaper antibiotic options. The price of antibiotics using the price of drugs from the hospital. Prescribing antibiotics using patent brands or with trade names even though generic antibiotics are available. Antibiotics included in the IVC category in this study were 21.8% before CP application and 9.1% after CP application. Typhoid fever patients in 2018 are included in the IVC category, namely patients with medical records9953, 5062, 4067, 67, 3032, 2261, 6684, 6167, 1853, 9943, 3831, 6405, 7112, 4884, 6928, 6612, 3515, 5554, 6277, 5369, 5802, 58085 and 34 attached attached 1. Typhoid fever patients in 2020 who are included in the IVC category are patients with medical records 635, 5906, 4816, 6720, 1968, 9562, 2513, 4967, 6224 and 1528. The use of drugs with patent brands or trade names has been approved by the parties patient.

3. IVD category

The IVD category is an antibiotic with a broad spectrum, while the alternatives are with a narrower spectrum. Selection of antibiotics with a narrower spectrum is based on culture results or from the pattern of antibiotic sensitivity. In certain circumstances, giving broad-spectrum antibiotics is still justified, but after obtaining the results of bacterial culture, adjustments and evaluations need to be made. Evaluation results based on the Gyssens method found no cases of prescribing antibiotics for the IVD category.

4. Category IIIA

Category IIIA is if the time for giving antibiotics is too long compared to the time of therapy that should be. The use of antibiotics with doses that are too long is one of the causes of antibiotic resistance. Antibiotics included in category IIIA in this study were 0.9% after the

application of CP because there were prescriptions for antibiotics with a duration of use that exceeded the guidelines used. In a previous study at a government hospital in the Province of Bali in 2019, 40% were in the category of using antibiotics for too long8. Patients who fall into category IIIA are patients with 7395 medical records, the reason is that the administration of ceftriaxone is too long from the guidelines.*Clinical Pathways*FMC Hospital.

5. Category IIIB

Category IIIB is if the time for giving antibiotics is too short compared to the time of therapy that should be. The use of antibiotics with too short a dose can reduce the effectiveness of antibiotics as a bacteria killer and can also increase the risk of causing antibiotic resistance. Antibiotics included in category IIIB in this study were 39.1% before the implementation of CP and 10.9% due to antibiotic prescriptions with a duration of use that was too short based on the guidelines used. In a previous study at the Bali Provincial Government Hospital in 2019, 5% were included in the category of using antibiotics for too long. Typhoid fever patients in 2018 who are included in category IIB are with medical records 8693, 3270, 7319, 7802, 1693, 8477, 6855, 4927, 8666, 297, 5012,8902, 6119, 2611, 5303, 4680, 7499, 6667, 6794, 9490, 8836, 3342 and 3205.

6. Category IIA

Category IIA is the administration of antibiotics that are not in the right dose than they should. Inappropriate dosage of antibiotics is caused by giving too low or too high a dose. A dose that is too low will result in the minimum effective level not being reached, but if the dose given is too high, it is feared that it can cause toxicity. Evaluation results based on the Gyssens method found no cases of prescribing category IIA antibiotics

7. Category IIB

Category IIB is the administration of antibiotics with inappropriate intervals than they should. Evaluation results based on the Gyssens method found no cases of prescribing category IIB antibiotics.

8. IIC category

Category IIC is a route of administration of antibiotics with an inappropriate route of administration, not according to the recommended route or not in accordance with the patient's condition. The route of drug administration is mainly determined by the nature and purpose of drug use so that it can provide the right therapeutic effect. Evaluation results based on the Gyssens method found no cases of prescribing category IIC antibiotics

9. Category I

Category I is the use of antibiotics is considered not timely if the time is not right every day. Evaluation results based on the Gyssens method found no cases of prescribing category I antibiotics

10. Category 0

Proper use of antibiotics, namely the use of antibiotics with a narrow spectrum, under strict conditions with adequate doses, intervals and the right duration of administration. The results of evaluating the quality of antibiotic use using the Gyssens method found that antibiotic therapy in patients with typhoid fever was 40% before the application of CP and 57.3% after the application of CP which was classified as rational use (category 0). In a previous study at the Bali Provincial Government Hospital in 2019, 40% were included in the category of rational antibiotic use.

Table V.5. Relationship Between Quality of Antibiotics before and After CP Use

***Outcomes*Clinical**	**before CP (2018)**	**after CP (2020)**	**P-Value**
Irrational	71	47	0.004
Rational	44	63	

The results of the Pearson Test showed that the P-value was 0.004 <0.05. It was concluded that there was a difference between rationality before and after the achievement, then Ho was rejected.

In the medical record documents before the existence of a clinical pathway, there were several actions that had not been implemented before, namely the absence of liver function tests and widal examinations. And there are other tests, namely urine and faeces. This condition affects the quality of the antibiotics given. After the clinical pathway was implemented, the rationale number increased to 63 or around 75% compared to before the clinical pathway was implemented. This is similar to the results of research by Adiwisastra et althe application of CP can increase the rationality of antibiotics, reduce the quantity of antibiotics used and reduce the length of stay without affecting clinical outcomes.

*Clinical Pathways*describeAthe method or instrument used in the diagnosis and treatment of patients which includes the sequence of activities and time carried out by doctors, nurses and all medical personnel. This method has been widely used in hospitals throughout the United

States, Australia and the United Kingdom.*Clinical Pathways*created through the collaborative efforts of doctors, nurses, pharmacists, physiotherapists and other related health professionals with the aim of improving the quality of patient care.*Clinical Pathways*has been shown to reduce unnecessary variation in patient care, reduce discharge delays through more efficient discharge planning, and increase the cost-effectiveness of clinical services. The clinical path approach and goals are consistent with total quality management and continuous quality improvement, and are essentially the application of these principles at the patient's bedside.

E. Evaluation of the Quantity of Antibiotic Use

Table V.5.*Evaluation of the Quantity of Antibiotic Use in Inpatients with Typhoid Fever using the ATC/DDD Method before the Clinical Pathway*

Types of Antibiotics	ATC code*)	route	Total Usage (grams)	DDD WHO*) (grams/patient)	DDD Usage (patient)**)	Total Length of Stay	DDD/100 Patient days***)
Ceftriaxone	J01DD04	P	559	2	279.5	345	81.0
Cefotaxime	J01DD01	P	44	4	11	345	3.2
Levofloxacin	J01MA12	P	12	0.5	24	345	7.0
Ceftazidime	J01DD02	P	28	4	7	345	2.0
Ceftizoxime	J01DD07	P	0	4	0	345	0.0
Cefuroxime	J01DC02	P	0	3	0	345	0.0

Information :

P: Parenteral *) obtained from WHO guideline 2021 **) Total usage/WHO DDD ***) DDD usage x 100/LOS

Table V.6*. Evaluation of the Quantity of Antibiotic Use in Inpatients with Typhoid Fever using the ATC/DDD Method after the Clinical Pathway*

Types of Antibiotics	ATC code*)	route	Total Usage (grams)	DDD WHO*) (grams/patient)	DDD Usage (patient)**)	Total Length of Stay	DDD/100 Patient days***)
Ceftriaxone	J01DD04	P	658	2	329	356	92.4

Cefotaxime	J01DD01	P	0	4	0	356	0.0
Levofloxacin	J01MA12	P	17	0.5	34	356	9.6
Ceftazidime	J01DD02	P	5	4	1.25	356	0.4
Ceftizoxime	J01DD07	P	17	4	4.25	356	1.2
Cefuroxime	J01DC02	P	61	3	20.3	356	5.7

Information :

P: Parenteral *) obtained from WHO guideline 2021 **) Total usage/WHO DDD ***) DDD usage x 100/LOS

OnTables V.5 and V.6 concerning the evaluation of the quantity of antibiotic use using the ATC/DDD method show that the use of ceftriaxone has a valueThe highest DDD/100 Patient days both before and after the implementation of CP. Where in 2018 there were 81, meaning that out of 100 patients every day there were 81 patients, and in 2020 there were 92.4, which means that out of 100 patients every day there were 92-93 patients who received 2 grams of ceftriaxone per day. The quantity data on the use of antibiotics states that the greater the value of DDD/100 patient days, the greater the use of antibiotics.

Quantitythe use of ceftriaxone antibiotics has a high value, in accordance with research conducted by Sukmawati in 2020 at the Bali provincial government hospital showing ceftriaxone was the most widely used antibiotic for typhoid therapy with a value of 83.80 DDD/100 Patients8. Based on research conducted by Enjelina in 2021 it is also known that the antibiotic ceftriaxone is most widely used in Samarinda government hospitals with a DDD/100 Patient day value of 81.21.

Excessive use of antibiotics can cause high DDD values and is influenced by the large number of gram values of antibiotics used. Several factors are thought to influence the quantity of antibiotic use, including the high frequency of use of antibiotics and the duration of use of antibiotics that exceeds the standard guideline for use of antibiotics.

Table V.7. Analysis of Antibiotic Types with DDD results/100 patient days before CP and accordinglyalready CP

Types of Antibiotics	ATC code	before CP (2018)	P-values	after CP (2020)	P-values

		DDD/100 Patient days		**DDD/100 Patient days**	
Ceftriaxone	J01DD04	81.01	0.011	92.4	0.000
Cefotaxime	J01DD01	3.19		0.0	
Levofloxacin	J01MA12	6.96		9.6	
Ceftazidime	J01DD02	2.03		0.4	
Ceftizoxime	J01DD07	0.00		1.2	
Cefuroxime	J01DC02	0		5.7	

Table V.8 Analysis of DDD/100 patient days before CP and after CP (Relationship Between Antibiotic Quantities before and After CP Use)

DDD/100 Patient days	N	Means	P-values
2018 year	115	103.07	0.019
2020 year	110	123.38	

OntableV.7AnalysisDDD/100 patient days before CP and after CP, an independent T test was performed with the condition that the data were normally distributed and homogeneous. The results of the normality test using the Kolmogorov-Smirnov Test obtained valuesP-values= 0.001 <0.05 which means the data is normally distributed. Then the homogeneous test was tested and the value was obtainedP-values= 0.000 <0.05 which means the data is not homogeneous. Because the data is normally distributed and not homogeneous, the independent T test requirements are not met, so the alternative is to use the Man Whitney test in table V.8.

The results of the analysis in appendix 8 show a p-value of 0.019 <0.05, which means that there is a difference between the DDD/100 patient day values before and after the application of the clinical pathway, then Ho is rejected (appendix 4). This means that the DDD/100 patient days in 2020 will increase by 123.38 if the DDD/100 patient days in 2018 increase every one year. This value shows that the use of DDD/100 patient days each year increases, which should not have happened. Excessive use of antibiotics can cause high DDD

values and is influenced by the large number of gram values of antibiotics used22. The impact of the application of clinical pathways on the quantity of antibiotic use is very significant with implementation in the field.

CONCLUSIONS

Based on the results of evaluating the quality of the use of antibiotics with the Gyssens method, the following conclusions can be drawn:

1. There are differences in the quality of the use of antibiotics between before and after the implementation of clinical pathways in inpatients with typhoid fever at FMC Bogor Hospital. This can be explained as follows.
    a. Administration of antibiotics at the FMC Bogor hospital in 2018 before CP was as much as 60% rational use of antibiotics (category 0) and as much as 43.7% fell into the irrational category (Categories I-VI) which was dominated by categories IIIA, IIB, IVA, and IVC.
    b. Giving antibiotics at the FMC Bogor hospital in 2020 after CP as much as 40% of the use of antibiotics is rational (category 0) and as much as 57.3% falls into the irrational category (Categories I-VI) which is dominated by categories IIIA, IIB, IVA, and IVC.
2. There are differences in the quantity of antibiotic use between before and after the implementation of clinical pathways in inpatients with typhoid fever at FMC Bogor Hospital. This can be explained as follows
    a. Average quantity of antibiotic used before implementation*clinical pathways*(year 2018)DDD/100 patient daysis as big103.07
    b. Average quantity of antibiotic use after application*clinical pathways*(2020 year)DDD/100 patient daysis as big123.38.

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