

DESCRIPTION OF ANTIBIOTIC USE PATTERNS IN TYPHOID FEVER PATIENTS IN INSTALLATIONS IN TOTO KABILA HOSPITAL IN 2019

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ABSTRACT

Typhoid fever is an acute systemic infectious disease caused by *Salmonella typhi*. Indonesia has a fairly high incidence with an increasing number of cases. It is estimated that there are 600,000 and 1.5 million cases of typhoid fever per year. Antibiotics are the main therapy for the treatment of typhoid fever patients. This study aims to describe the pattern of antibiotic use in typhoid fever patients in the inpatient installation of Toto Kabila Hospital in 2019.

The method in this study uses descriptive statistics with the type of observational research. Data collection was carried out retrospectively. The sample was taken from the medical records of adult patients with typhoid fever who were treated at the Toto Kabila Hospital in 2019. The subject selection technique used random sampling. The subjects in this study were adult patients with typhoid fever who were treated at the Toto Kabila Hospital in 2019. The total sample obtained was 44 typhoid fever patients.

The results showed that the class of antibiotics used was a third generation cephalosporin (84.1%) of the type of antibiotic ceftriaxone (72.7%) with a dose of 1 gram (72.7%) twice a day and given for 10-14 days. It can be concluded that the pattern of antibiotic use at the Toto Kabila Hospital, Gorontalo Province in 2019 was in accordance with the disease suffered.

Keywords: Typhoid Fever, Antibiotics, Ceftriaxone

INTRODUCTION

Typhoid fever is a systemic disorder caused by the presence of *Salmonella typhi* which infects the gastrointestinal tract to cause inflammation of the small intestine with the intestinal lumen [1].

Symptoms are characterized by prolonged fever and disturbances in the digestive tract. These disorders include infectious disorders that can be found in countries with tropical or sub-tropical climates [2].

The transmission of this disorder is through water and food infected with

Salmonella typhi. *Salmonella* germs can last a long time in food. With the presence of certain infections, it can be stated that food hygiene as well as personal hygiene plays a more important role when bacteria enter food [3].

The related impacts of typhoid fever are the practice of washing hands before eating, the practice of washing hands after defecation, the state of the garbage disposal, food management, eating habits outside the home, the respondent's occupation, and the income level of the family head [4].

World Health Organization (WHO) estimates that in 2012 the incidence of typhoid fever worldwide is around 17 million people per year. While the rate of death from typhoid fever is up to 600,000 with 70% of which are in Asia. Based on WHO the value of typhoid fever patients in Indonesia ranges from 81% per 100,000 population [5].

In Indonesia, the problem spreads evenly across all provinces in that the incidence in rural and urban areas is around 600,000 and 1.5 million cases per year [5].

Meanwhile, in Gorontalo City, based on the Health Observation and Development Agency (Balitbangkes) of Gorontalo Province, in 2011, 991 patients with typhoid fever, while based on information in 2012 there were 1,049 patients with typhoid fever. This is supported by information which reveals that the Gorontalo region is ranked the smallest province in implementing a Clean and Healthy Lifestyle (PHBS). PHBS standardization is 38.7% [6].

Irrational use of antibiotics will have negative effects such as increased treatment costs, increased drug resistance, increased toxicity, and increased the possibility of side effects from using antibiotics. Accuracy in the use of antibiotics is very important [7].

Choosing the appropriate treatment for typhoid fever caused by the bacteria *Salmonella typhi* is to use antibiotics. Inappropriate use of antibiotics can lead to an increase in the formation of bacteria that are resistant to antibiotics, including *Salmonella typhi*. Cases of resistance to *Salmonella typhi* in chloramphenicol were initially reported in 1974. Cases of bacterial resistance were also found in 1994 when several types of antibiotics were chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole, also known as Multi Drug Resistance [8].

The use of several kinds of antibiotics in a widespread manner that is not appropriate, due to the rapidity of obtaining certain drugs in the community, can lead to an increase in antibiotic-resistant bacteria (ABRB = Antibiotic Resistant Bacteria), including *Salmonella typhi* [8].

Based on data from the Toto Kabila Hospital, Gorontalo Province, where typhoid fever ranks 1st in the 10 highest inpatient disorders in 2016 in the number of patients, which ranges from 1,026 patients with outpatients as many as 19 patients.

Therefore, based on the high cases of typhoid fever and the widespread use of antibiotics as the main treatment for typhoid fever, this research needs to be carried out to provide an overview of how the pattern of using antibiotics for typhoid fever sufferers is useful in improving public health services in the city which will ultimately provide treatment for patients with typhoid fever. typhoid fever hospitalization. So that patients with typhoid fever know the use of drugs from the type of antibiotics used, the dose of antibiotics and the frequency of the typhoid fever antibiotics used.

The results of the study will be seen in accordance with the guidelines for the administration of typhoid fever antibiotics with typhoid fever antibiotics at Toto Kabila Hospital.

RESEARCH METHODS

The research design used was descriptive observation, the results were taken in a retrospective manner from the medical records of adult patients with typhoid fever at the inpatient installation of the Toto Kabila Hospital in 2019.

The observation was carried out at the Toto Kabila Hospital, Gorontalo Province.

The collection of results is carried out in the period March-May 2021.

The population in the observation was all patients diagnosed with typhoid fever and undergoing treatment at the Toto Kabila Hospital installation, Gorontalo Province in 2019 with a total population of 602.

The sample for this observation was all patient data with a diagnosis of typhoid fever at the Toto Kabila Hospital installation in 2019 that met the inclusion criteria, namely 44 samples.

The observation tool used is the medical record of typhoid fever inpatients at the Toto Kabila Hospital, Gorontalo Province in 2019.

The observation material used was the contents through the recording of the Health Medical Record (RMK) of typhoid fever patients at the Toto Kabila Hospital, Gorontalo Province in 2019.

The sample collection was carried out in a retrospective manner, which was to observe backwards to examine secondary data. The data taken is from the medical record data of patients diagnosed with typhoid fever at the Toto Kabila Hospital installation in 2019.

The sampling technique used in these observations is random sampling. Before determining the sample, the sample must be separated in advance which sample will be taken and which will not be taken based on the inclusion and exclusion criteria. After the samples obtained meet the inclusion criteria, then they are analyzed using SPSS and the results are made in the form of a master table.

The inclusion characteristics of these observations are:

1. Inpatients diagnosed with typhoid fever
2. Patients without comorbidities
3. Positive patient Widal test for typhoid fever
4. Patient completes treatment until declared cured by the doctor

Research procedure

1. Preparation phase
2. Research stage
3. Sampling
4. Sample grouping

These observations use descriptive statistical procedures, in these procedures only provide information about the use of typhoid fever antibiotics in the hospital to be studied. Then the data obtained which contained medical records, then analyzed descriptively the data regarding age, gender, length of treatment, laboratory tests, names and types of antibiotics, antibiotic classes, frequency of antibiotics and doses of antibiotics given to patients with typhoid fever who were treated at the hospital using SPSS is then displayed in percentages, average prices and tables.

RESULTS AND DISCUSSION

The observation carried out at the Toto Kabila Hospital, Gorontalo Province, aims to determine the profile of antibiotic use for typhoid fever sufferers during 2019. The use of these antibiotics includes age, gender, length of hospitalization, laboratory examination data, types and classes of antibiotics, doses and frequency of drugs. antibiotics based on data from medical records of typhoid fever patients in all hospitalized patients through the period January to December 2019. The results were obtained through the medical record unit at the Toto Kabila Hospital, Gorontalo Province.

Medical record data that matched the inclusion characteristics were 44 patients through 165 patients. The details of these results obtained can be shown in the table including:

Table 1. Percentage of Patients by Gender

Gender	Number of patients	Percentage
Man	11	25%
Woman	33	75%
Total	44	100%

Source: Processed data (2021)

In accordance with the results of the percentage above, it shows that female patients are very high compared to male patients who were diagnosed with typhoid fever at the Toto Kabila Hospital, Gorontalo Province in 2019. In female patients, there were 33 patients or 75%. Compared with male patients about 11 patients or 25%.

In accordance with the percentage data that has been obtained, adult patients with typhoid fever are very often experienced by female patients compared to men. This is because based on the immune system, women are very likely to experience a very heavy influence or produce complications through typhoid [9].

One theory suggests that Salmonella typhi enters the liver cells, so the female hormone estrogen can work very hard because it gets two things at once [10].

Table 2. Percentage of Patients by Age

Age	Number of Patients	Percentage
18-40 Years	32	72.7%
41-60 Years	11	25%
>60 Years	1	2.3%
Total	44	100%

Source: Processed data (2021)

Based on the results of the percentage above, it shows that the highest patient diagnosed with typhoid fever was at the age of 18-40 years, namely as many as 32 patients or 72.7%. compared with patients aged 41-60 years and patients >60 years.

The age of patients affected by typhoid fever is very often in the age range of 18 to 40 years. This age is related to poor sanitation in the community and also often doing activities outside the home.

However, the data is different from the observations carried out by Jahja (2011) where the results obtained are at the age of 41-60 years due to factors at that age the patient begins to experience a decrease in endurance and physical function.

Table 3. Percentage of Patients According to Length of Hospitalization

Number of Hospitalization Days	Number of Patients	Percentage
1-3 Days	12	27.3%
4-6 Days	29	65.9%
7-9 Days	3	6.8%
Total	44	100%

Source: Processed data (2021)

Based on the results of the percentage above, it shows that the length of hospitalization is very large, up to 4-6 days as many as 29 patients or 65.9%. compared with patients for 1-3 days about 12 patients or 27.3% and hospitalized patients for 7-9 days, namely 3 patients or 6.8%.

Adult patients with typhoid fever can ideally get a clinical change in 3 to 7 days [9], but treating typhoid fever takes an average of 5 to 14 days depending on the type of antibiotic used [10]. In these observations, the duration of antibiotic treatment in the treatment of typhoid fever was within 4 to 6 days (65.9%) which was more than 3 days (27.3%) (table 3). This matter can be called natural because treating cases of typhoid fever are mainly treated within 3 to 7 days [11], when the duration of antibiotic treatment is appropriate in changing microbiological data, patient conditions and other clinical results [11].

Table 4. Percentage of Patients According to Laboratory examination

Widal	Titer O		Titer H	
	J	%	J	%
1/40	4	9.1%	2	4.5%
1/80	7	15.9%	8	18.2%
1/160	13	29.5%	9	20.5%
1/320	18	40.9%	10	22.7%

1/640	2	4.5%	12	27.3%
1/1280	-	-	3	6.8%
Total	44	100%	44	100%

Source: Processed data (2021)

Based on the percentage results above, it shows that from the 44 samples examined there are several differences in the agglutinin O and H titers in the Widal test. The Widal test carried out on the most typhoid fever patients was in the O titer, there were 1/320 18 samples (40.9%). Compared to the H titer, there were 1/640 12 samples (27.3%).

The interpretation of the Widal test data include [12]:

- 1) A high O titer (≥ 160) indicates an acute infection
- 2) A high H titer (≥ 160) indicates that it has been immunized or has had an infection.

In the Widal test, it is possible to examine the reaction in agglutinine antibodies in the serum of patients who have received different dilutions of somatic antigen (O) with flagella (H) which are added in appropriate amounts until agglutination is formed. The largest dilution that persists with agglutination shows the serum antibody titer [13].

In these observations, there were 12 patients in the Widal test data for Salmonella typhi H to a titer of 1/640, for example, the Widal test data were patients who had experienced Salmonella typhi infection, so that IgG in Salmonella typhi could be detected. Compared to the Widal test data for Salmonella typhi O with a titer of 1/320, there were 18 patients, the data for this kind of Widal test were patients with acute infection with typhoid fever.

Widal is a serological procedure to assist in the diagnosis of typhoid fever. The examination is in accordance with the presence of agglutinine antibodies in the serum of infected patients on H (flagel)

and O (somatic) antigens of Salmonella typhi bacteria. Positive Widal test data can add to the index of suspicion of typhoid fever in an agglutinin titer of 1/320 [14].

Positive data on the Widal examination can be caused by several types of things, where the patient being examined has indications of acute typhoid fever infection or has been infected with typhoid fever initially, initial immunization with Salmonella typhi antigen, cross-reaction against non-typhoid Salmonella, variability and poor standardization of commercial antigens, malaria and Enterobacteriaceae infections and other disorders such as dengue fever. Negative data on Widal examination can be caused by the absence of infection by Salmonella typhi bacteria, carriers, bacterial antigens that are not strong in host cells in inducing antibody formation, errors when carrying out the examination and having received antibiotic treatment at first [15].

Table 5. Percentage by group, types and dosage of antibiotics

Antibiotic Group	Qty	%	Types of Antibiotics	Dose	Qty	%
Third generation cephalosporin	37	84.1%	CTX	1 gr	32	72.7%
			CFX	200 mg	5	11.4%
Fluoroquinolones	4	9.1%	CLS	500 mg	2	4.5%
			LVS	500 mg	2	4.5%
Chloramphenicol	2	4.5%	TFL	500 mg	2	4.5%
Macrolides	1	2.3%	AZR	500 mg	1	2.3%
Total	44	100%	Total		44	100%

Source: Processed data (2021)

Based on the percentage results above, it shows where the profile of antibiotic use that is very often used at Toto Kabila Hospital in 2019 is the third generation cephalosporin group of 84.1% for its type, namely ceftriaxone 72.7% at a dose of 1 gram and cefixime 11.4% at a dose of 200 mg. compared to the

fluoroquinolone group of about 9.1% for the ciprofloxacin and levofloxacin types 4.5% and the macrolide group about 2.3% with each dose of 500 mg.

From the results of this study in table 5 classes of antibiotics used in the treatment of adult patients with typhoid fever at the Toto Kabila Hospital in 2019 are third-generation cephalosporin antibiotics with fluoroquinolones. Antibiotics of the third generation cephalosporin group and fluoroquinolones are the choice because now the chloramphenicol group which is designated for initial line drugs has not been used for first-line drugs because of the close relationship in the high rate of recurrence with side effects produced. There are various side effects that can be caused by the use of chloramphenicol for adults and children, namely bone marrow suppression, gray baby syndrome, optic neuritis in children, candida life in the gastrointestinal tract with the appearance of a rash [16].

The third generation cephalosporins such as ceftriaxone were chosen because they are faster in lowering body temperature, short administration period, can be used as a single dose and are quite safe for use in adults and children. Antibiotics of the third generation cephalosporin group include the broadest spectrum antibiotics in excess of gram-negative sensitivity until they can be used for the eradication of *Salmonella typhi* infection [14].

The fluoroquinolone group is ciprofloxacin and levofloxacin. Levofloxacin, like other fluoroquinolone drugs, has the broadest spectrum of effectiveness against gram-negative and gram-positive bacteria, works by preventing the action of the enzyme DNA gyrase, causing DNA replication to stop. The antibiotic levofloxacin has the highest sensitivity to the inhibition of the life of *Salmonella typhi* bacteria [14]. In

addition, the fluoroquinolone group also achieved better tissue penetration and was able to eradicate *Salmonella typhi* bacteria in its intracellular stationary stage in monocytes/macrophages by reaching a very large active level in the gallbladder compared to other drugs [17]. Through observational data carried out until now, levofloxacin is known to be optimal in curing typhoid fever in adults, including Toto Kabila Hospital, Gorontalo Province. The percentage of antibiotic use at the Toto Kabila Hospital, Gorontalo Province for typhoid fever is indeed not the same in all antibiotic groups.

Dosage includes the size of the drug administration in providing this effect in all drug administration. In Table 5 it is shown that the sequential antibiotic doses from the highest were 72.7% ceftriaxone 1 g injection and 11.4% cefixime 200 mg tablet, 4.5% each for ciprofloxacin injection, levofloxacin injection, thiamphenicol 500 mg tablet and 2.3% azithromycin 500 mg injection. . It can be seen through the acquisition of certain results, the route of administration of antibiotics used in these observations is very often intravenously. Oral administration of antibiotics should be the initial choice in the treatment of infections [17], but for patients who experience loss of appetite, constipation or diarrhea, oral administration has not been able to provide optimal impact, to moderate infection when the weight of intravenous antibiotics can be taken into account [18].

In these observations, the most frequently used dose of third-generation cephalosporin antibiotics was ceftriaxone 1 g injection and followed by cefixime 200 mg tablets. This allows for a comparison of the state of infection experienced by the patient and the severity of the signs with the complaints experienced, related to the comparison of the body's immunity when responding to *salmonella typhi* bacterial infection.

Management of typhoid fever 2010, it is recommended the use of levofloxacin, both in mild or severe problems. In mild cases, levofloxacin 500 mg/day is administered orally for up to 7 days, but in severe cases, levofloxacin 500 mg intravenously is administered for up to 3–5 days [16].

Several studies have been carried out in assessing the effectiveness of fluoroquinolones and a fluoroquinolone which has now been observed to have corresponding effectiveness is levofloxacin. A comparative, randomized, single-blind study was carried out on levofloxacin with the standard drug ciprofloxacin in the treatment of uncomplicated typhoid fever, levofloxacin was produced in a dose of 500 mg, once daily with ciprofloxacin produced in a dose of 500 mg twice daily every up to 7 days. The conclusion from this study is that currently levofloxacin is very useful compared to ciprofloxacin in terms of reducing fever, microbiological data in a significant way have very few side effects compared to ciprofloxacin. Besides that, in an open study of the efficacy and safety of levofloxacin in the treatment of uncomplicated typhoid fever, levofloxacin was administered in a dose of 500 mg, once daily for up to 7 days [19]. The clinical efficacy found in the study was 100% with minimal side effects. Through this study, there is also a comparison table for the average duration of fever reduction in several types of fluoroquinolones that are widespread in Indonesia when the fever reduction in levofloxacin is very short, which is 2-4 days. A meta-analysis published in 2010 concluded that when enteric fever is mature, fluoroquinolones are more suitable than chloramphenicol in treating relapse. Patients with persistent vomiting, severe diarrhea, abdominal distension,

Meanwhile, the results obtained at the Toto Kabila Hospital were that

levofloxacin was given by injection for 5 to 9 days in adults at a dose of 500 mg twice a day and in the administration of ciprofloxacin, it was given by injection for up to 1 to 4 days for adults in a dose of 500 mg twice a day. This indicates that the use of levofloxacin and ciprofloxacin in RSUD Toto Kabila is not appropriate in terms of duration of administration and frequency.

Table 6. Antibiotic therapy for typhoid fever

Antibiotics	Antibiotic Therapy
Ceftriaxone	IV 2-8 days Adults: 1 g twice a day
Cefixime	PO 3-7 days Adults: 200 mg twice daily
Ciprofloxacin	IV 1-4 days Adults: 500 mg twice daily
Levofloxacin	IV 5-9 days Adults: 500 mg twice daily
thiamphenicol	PO 4-5 days Adults: 500 mg twice daily
Azithromycin	IV 5 days Adults: 500 mg twice daily

Source: Processed data (2021)

In the frequency of administration of antibiotics, ceftriaxone is most often given twice a day, this is because ceftriaxone has a half-life of 6.5-8.6 hours in adults, so it can be given twice a day. When the drug has a frequency of twice a day, it shows that the drug does not work in a long onset so it is hoped that patients with typhoid fever who are suspected of getting

supportive therapy using several other drugs so that patients do not take drugs that are given repeatedly and many other drugs [21].

And the results that have been obtained at the Toto Kabila Hospital on the administration of ceftriaxone in the Toto Kabila Hospital are given by injection for 2 to 8 days in adults with a dose of 1 gram twice a day, this indicates that the use of ceftriaxone in the Toto Kabila Hospital is appropriate.

The use of drugs for typhoid fever patients at Toto Kabila Hospital which has been given to typhoid fever patients, namely ceftriaxone is in accordance with the illness. The right dose is the benefit of the drug given to the patient based on the diagnosis, complaints and also laboratory data.

Drug interactions include two or more drugs taken together that produce an effect without affecting each other or interacting frequently. The use of typhoid fever drugs in Toto Kabila Hospital did not occur interactions between drugs that had been prescribed more than one antibiotic.

The use of each drug can provide adverse side effects or toxic effects from the drug and the data obtained did not occur unexpected side effects from the treatment of typhoid fever at the Toto Kabila Hospital.

CONCLUSION

Through observational data carried out by researchers at the Inpatient Installation of Toto Kabila Hospital, it can be concluded that the pattern of antibiotic use in typhoid fever patients is in accordance with established guidelines.

1. Antibiotics that are very often used are the third generation cephalosporin group (84.1%) of the ceftriaxone type (72.7%).
2. The most dose of antibiotics given was 1 gram (72.7%).

3. The frequency of administration of antibiotics is twice a day with a healing time of 10-14 days depending on the severity.

Institutions should always carry out further observations on the use of antibiotics in patients with typhoid fever and pay attention to the duration of antibiotic treatment in patients with typhoid fever.

For agencies, it is recommended that Toto Kabila Hospital pay more attention to the duration of antibiotic use and evaluate drug prescriptions, especially antibiotic drugs in a routine way. And for the next observer to pay attention to the description of the prescription and treatment of antibiotics that have been determined.

REFERENCES

- [1] Alam, A. 2011. Resistance Pattern of Salmonella enterica Typhi Serotype, Department of Child Health, RSHS 2006-2010. Sari Pediatrics. Vol 12(5):296-301.
- [2] Anna, Y. 2015. Sensitivity Test of Levofloxacin Antibiotics on the Market Against Salmonella thyphosa ATCC 2401. Thesis. Pharmacy Study Program, Bakti Tunas Husada College of Health Sciences.
- [3] Ministry of Health of the Republic of Indonesia. 2011. General Guidelines for the Use of Antibiotics. Regulation of the Minister of Health of the Republic of Indonesia. Indonesian Ministry of Health.
- [4] Ministry of Health of the Republic of Indonesia. 2013. Indonesian Health Profile. Indonesian Ministry of Health. Jakarta
- [5] Ministry of Health of the Republic of Indonesia. 2016. Guidelines for Typhoid Fever Control. Indonesian Ministry of Health.
- [6] Goddess LA. 2018. Evaluation of Antibiotic Use in Inpatient Typhoid

- Fever at the Klaten Islamic Hospital in 2017. Thesis. Faculty of Pharmacy, Setia Budi University, Surakarta.
- [7] Etikasari, R., Andayani, TM, and Mukti, AG, 2012, Cost Analysis and Suitability of Antibiotic Use in Typhoid Fever in RSUD Kota Yogyakarta. *J. Manaj. And Farm Services. (JMPF) J. Manag. Pharm.Pract.* 2.147-153
- [8] Fatmawati, R. 2011. Diagnostic Tests of Widal Serology Tests Compared with Blood Cultures as the Gold Standard for the Diagnosis of Typhoid Fever in Children at Dr. RSUP. Kariadi Semarang. Thesis. Diponegoro University.
- [9] Hidayati, H. 2011. Recent developments in the treatment of typhoid fever. *Medika Indonesian Medical Journal* [online series]. Available from: URL:<http://www.jurnalmedika.com/edis-tahun-2011/edisi-no-09-vol-xxxvii2011/363-activity/727-latest-development-therapeutic-typhoid-fever>.
- [10] Jahja, Yudrik. 2011. *Developmental Psychology*. Prenada Media. Jakarta.
- [11] Kusuma, BF, Saleh, I., Selviana. 2015. Occurrence Risk Factors Associated with Typhoid Fever Incidence in Children in the Work Area of Sui Kakap Health Center and Sui Durian Health Center. *JUMANTIK (Journal of Students and Scientific Research)*, 2(1): 41-53
- [12] Maghfiroh, AE, Siwiendrayanti, A. 2016. Relationship of Hand Washing, Trash Cans, Ownership of SPAL, Food Sanitation with Typhoid Fever. *Medical Pen Journal*, 6(1): 34-45
- [13] Nelwan, RHH 2012. Current management of typhoid fever. *Continuing Medical Education*, 39(4): 247-250.
- [14] Patattan, S. 2017. Evaluation of Antibiotic Use in Inpatients of Typhoid Fever Stella Maris Makassar in 2016. Thesis. Sanata Dharma University. Yogyakarta.
- [15] Pramitasari, OP 2013. Risk Factors for Typhoid Fever In Patients Treated At Ungaran Hospital. *Journal of Public Health* 2 : 1-10
- [16] Satwika, A. and Lestari, A. 2015. Diagnostic Test of Widal Serology Test Compared with Anti-Salmonella Typhi IgM Test as the Gold Standard in Patients Suspected of Typhoid Fever at Surya Husadha Hospital from January to December 2013. *E-Jurnal Medika Udayana*, 4 (8): 1-12.
- [17] Stoesser, N., Eyre D., Basnyat B. & Parry C. 2013. Treatment of enteric fever (thypoid and paratyphoid fever) with third and fourth generation cephalosporins. *Cochrane Database of Systematic Reviews*.
- [18] Sucipta, AAM 2015. The Gold Standard for Laboratory Examination of Typhoid Fever in Children. *Husada Scale Journal*, 12(1), 22–26.
- [19] Thompson, CN, Abhilasha K., Sabina D., Amit A., Marcel W., Thomas D., Jeremy JF, et al. 2017. Treatment Response in Enteric Fever in an Era of Increasing Antimicrobial Resistance. An Individual Patient Data Analysis of 2092 Participants Enrolled into 4 Randomized Controlled Trials in Nepal. *Clinical Infectious Disease*, 64(1) :1522-1531.
- [20] Prayoga DK., Fatmawati ND. Identification of Salmonella sp in feces of food handlers at RJ chicken slaughterhouse by culture method. *Medical Science Digest*. 2018. 9(3). DOI: 10.15562/ism.v9i3.287.
- [21] WHO. 2013. Background document: The diagnosis, treatment, and prevention of typhoid fever/https://www.glowm.com/pdf/WHO_CustomLicense.pdf. Retrieved May 5, 2020.

- [22] Willke, Widal Test in Diagnosis of Typhoid Fever in Turkey, Clinical and Diagnostic Immunology. 2002. Laboratory