JMU
Jurnal Medika Udayana
ISSN: 2597-8012 JURNAL MEDIKA UDAYANA, VOL. 13 NO.07, JULI, 2024
DOAJ DIRECTORY OF OPEN ACCESS JOURNALS
Accredited SINTA 3
Received: 2023-11-01 Revision: 2024-04-24 Accepted: 12-05-2024

LABORATORY EXAMINATION OF TYPHOID FEVER PATIENT AT PROF. NGOERAH GENERAL HOSPITAL IN 2020-2022

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ABSTRACT

Typhoid fever is systemic infection which is caused by *Salmonella typhi*. The gold standard of typhoid fever diagnosis is blood culture examination. Blood culture examination has a weakness, it could not be practically performed especially due to lack of laboratory facility. There are several others alternative examination including serology and hematology examination that could be used in supporting typhoid fever diagnosis. Therefore, investigation of hematology and serology examination results of typhoid fever patient is required. The type of research carried out was descriptive research with a cross-sectional design using secondary data from medical records of typhoid fever patients at Prof. Ngoerah General Hospital. A total of 52 patients with a diagnosis of typhoid fever as research subjects were taken using a total sampling technique. Following data were obtained: age, gender, serology and hematology examination result, type of antibiotics given, and complications found. Data processing was carried out using the SPSS ver. 26 with univariate analysis. This study found that typhoid fever patient at Prof. Ngoerah General Hospital tend to have normal hematological examination result including hemoglobin level, total count of leukocyte (neutrophile and lymphocyte) and thrombocyte. Widal test result of the patients showed the lowest titer value is 1/80 and the highest is 1/320 at O and H titers. Most of the patients have positive IgM anti-*Salmonella typhi* score of 4 and 6. 3 patients (5.8%) have negative IgM score of 2 and 11 patients (21.2%) did not have an IgM test. Most of the patients acquired antibiotic treatment with ceftriaxone become most used antibiotic. Complication is rarely occurred among the patients. Hepatomegaly is the most frequent complication occurred among the patients with complication.

Keywords: IgM anti *Salmonella typhi*., Typhoid fever.,Widal test ., Hematological examination

INTRODUCTION

Typhoid fever is systemic bacterial infection that caused by *Salmonella typhi.* The symptoms of *Salmonella typhi* infection are manifested as gastrointestinal symptoms to systemic infection and several complications[1]. Since this disease is transmitted through unhygienic food, lack of proper sanitation and clean water access contributed as risk factor of this disease morbidity and mortality [2].

World Health Organization (WHO) estimate about 128.000 – 161.000 death around the world are caused by typhoid fever every year. In developing countries including Africa, America, Southeast Asia, and West Pacific, this disease continues to be a public health problem (WHO, 2018). In Indonesia, typhoid fever is not found as endemic disease but is often found in big cities. Based on the research by the Health Research and Development Agency, the increase number of typhoid fever patients each year is around 500 per 100,000 population with 0.6 - 5% mortality rate [3].To establish the diagnosis of typhoid fever, it is necessary to do an anamnesis by looking at the clinical symptoms that appear, conducting physical examination, and perform laboratory examination[3]. There are several laboratory examinations that could be performed to establish diagnosis of typhoid fever including blood cultures, widal tests, IgM anti-*Salmonella typhi* test, and complete blood count. The current gold standard for typhoid fever diagnosis is blood culture examination [4]. Although designated as the gold standard, false-positive blood culture testing causes a large amount of cost in the examination. The estimated burden on hospitals in the United States for additional unnecessary diagnostic and avoidable hospitalizations due to false-positive blood cultures is $8.6 billion [5]. The false-positive patients received unnecessary broad-spectrum antibiotic treatment and received prolonged hospitalizations. Such unnecessary

antibiotics contribute to the global antibiotic resistance crisis [6]. In many developing countries where trained technicians and laboratory facilities are limited, this method of culture is not practical [7,8].Serology and hematology tests are fairly effective tests considering the limitations of laboratories in developing countries that make culture examination not entirely effective [7,9]. This study aims to determine the result of typhoid fever laboratory examination including serology and hematology test at Prof. Dr. dr. I Goesti Ngoerah Gde Ngoerah General Hospital Denpasar.

MATERIAL AND METHOD

The study was conducted using an observational analytic method with a cross-sectional design, where each respondent was only collected data once. The population of this study were typhoid fever patient at Prof. Dr. dr. I Goesti Ngoerah Gde Ngoerah General Hospital in 2020-2022.The data were collected from medical record. Following data were extracted from medical record: patient age and gender, serology and hematological test result, type of antibiotics given, and complications. Data were processed using univariate analysis with SPSS ver. 26 software.

RESULTS

A total of 52 patients who met the inclusion and exclusion criteria were collected. Sample characteristic including age and gender is presented in table 1 and 2 respectively. The higher percentage of patient is in the age range of 25-44 years old. The percentage of male patients is higher than female patient.

Table 1. Patient age distribution

Age (years)	Frequency	Percentage (%)
0-10	6	11.5
10-19	6	11.5
20-24	7	13.5
25-44	16	30.8
44-60	9	17.3
60-75	7	13.5
75-90	1	1.9
Total	**52**	**100.0**

Table 2. Patient gender distribution

Gender	Frequency	Percentage (%)
Male	29	55.8
Female	23	44.2
Total	**52**	**100.0**

Type of serology examination was used is IgM Anti-*Salmonella typhi* and widal test. Widal test result of the patients is presented on table 3. Widal test was performed only on 44.2% of total patient. Highest percentage and of tested patient has 1/80 titer O and H value.

Table 3. Patient widal test result

Widal Test	Frequency	Percentage (%)
Titer O value	**23**	**44,2**
1/80	13	25.0
1/160	2	3.8
1/320	8	15.4
Titer H value	**23**	**44,2**
1/80	10	19.2
1/160	4	7.7
1/320	9	17.3
Not tested	**29**	**55.8**
Total	**52**	**100.0**

IgM anti-*Salmonella typhi* test is presented on table 4. The test was conducted in 78.8% of patients, only 21.2% of patients were not tested with IgM anti-*Salmonella typhi* test. The majority of patients had a total positive score of 4 and 6 for IgM anti-*Salmonella typhi*. There are 5.8% patients had a negative IgM anti-*Salmonella typhi* score of 2.

Table 4. Patient IgM anti-*Salmonella typhi* test result

IgM Score	Frequency	Percentage (%)
Not tested	11	21.2
2	3	5.8
4	19	36.5
6	19	36.5
Total	**52**	**100.0**

Blood examination result is presented on table 5-6. Total 48.1% patients have decreased hemoglobin level. Majority of patient have normal leucocyte level. Same as leucocyte level, majority of patients have normal neutrophile level. Majority of patients also have normal lymphocyte level. Majority of patients also have normal level thrombocyte. Average level of all performed hematology examination is presented on table 6.

Table 5. Patient distribution based on hemoglobin concentration, leucocyte, neutrophile, lymphocyte and thrombocyte count

Hemoglobin	Frequency	Percentage (%)
Anemia (<13g/dl)	25	48.1
Normal (13-17g/dl)	27	51.9
Leucocyte	**Frequency**	**Percentage (%)**
Leucopenia (<4000/µl)	10	19.2
Normal (4000-10000/µl)	28	53.8
Leukocytosis (>10000/µl)	14	26.9
Neutrophile	**Frequency**	**Percentage (%)**
Neutropenia (< 2500/µl)	15	28.8
Normal (2500-8000/µl)	29	55.8
Neutrocytosis (> 8000/µl)	8	15.4
Lymphocyte	**Frequency**	**Percentage (%)**
Lymphocytopenia (< 1000/µl)	16	30.8
Normal (1000-4000/µl)	32	61.5
Lymphocytosis (> 4000/µl)	4	7.7
Total	52	100.0
Thrombocyte	**Frequency**	**Percentage (%)**
Thrombocytopenia (<150000/µl)	16	30.8
Normal (150000-450000/µl)	29	55.8
Thrombocytosis (>450000/µl)	7	13.5

Table 6. Range value and mean of blood count examination

Variable	Range Value	Mean
Hemoglobin	4.14 - 16.94 g/dl	12.8 g/dl
Leucocyte	2.44 x 10^3/µl -28.69 x 10^3/µl	8.3 x 10^3/µl
Neutrophile	0.20 x 10^3/µl - 23.39 x 10^3/µl	5.1 x 10^3/µl
Lymphocyte	0.41 x 10^3/µl - 7.30 x 10^3/µl	1.87 x 10^3/µl
Trombocyte	32.00 x 10^3/µl - 952.00 x 10^3/µl	240.2 x 10^3/µl

Table 7 shows the distribution of patients that treated with antibiotic. Most of the patients is treated with antibiotic. There was administration of more than one type of antibiotic in some patients. Therefore, table 8 shows proportion of antibiotic type that used for treat typhoid fever patients. There are some antibiotic combination that used for A combination of antibiotics was also found, namely ceftriaxone with azithromycin in 1 patient, ceftriaxone with erythromycin in 1 patient, ceftriaxone with levofloxacin in 7 patient, ceftriaxone with fefixime in 1 patient.

Table 7. Patient distribution based on antibiotic treatment

Antibiotic treatment	Frequency	Percentage (%)
Without antibiotic treatment	5	9.6
With antibiotic treatment	47	90.4
Total	**52**	**100.0**

Table 8. Proportion of antibiotic type usage

Antibiotic treatment	Frequency	Percentage (%)
Ciprofloxacin	2	3.8
Ceftriaxone	38	64.0
Levofloxacin	16	27.1
Azithromycin	1	1.7
Cefixime	1	1.7
Erythromycin	1	1.7
Total	**59**	**100.0**

Most of patients did not shows any complication (Table 9). Only 26.9% of patients were found to have complications. More than one complication was found in some patients. Therefore, table 10 shows the proportion of types of complications found in patients. Hepatomegaly is the most frequent complication.

Table 9. Patient distribution based on present of complication

Present of complication	Frequency	Percentage (%)
Without complication	38	73.1
With complication	14	26.9
Total	**52**	**100.0**

Table 10. Type of complication proportion

Complication	Frequency	Percentage (%)
Sepsis	3	16.7
Hepatomegaly	6	33.3
Splenomegaly	2	11.1
Pneumonia	4	22.2
Acute pulmonary tract infection	2	11.1
Myocarditis	1	5.6
Total	**18**	**100.0**

DISCUSSION

This study shows the highest frequency of typhoid fever cases occurs in young adults (25-44 years). The reason for the high cases in young adults is likely due to their unhygienic lifestyles and the increasing number of social gatherings [10]. Based on gender, this study shows that there are more male patients compared to female patients. The reason why the trend of cases was found more in male compared to female in this study is not yet known. Previous research suggested typhoid fever was independent of gender [10].

The results of hemoglobin examination in typhoid fever patients showed anemia results (<13 g / dl) in 25 patients (48.1%) and normal results (13-17 g / dl) in 27 patients (51.9%). Bone marrow depression due to toxins produced by *Salmonella typhi* bacteria can be the cause of anemia [11,12]. Previous study reported similar result, Hameedullah et al found majority of typhoid fever patient have normal hemoglobin level and 32% have low hemoglobin level (<12 g/dl) [11]. The results of varied hemoglobin concentrations in different studies are common. This difference is caused by hemoglobin concentrations are found to be normal in the early stages of the disease, but decrease slowly as the disease progresses [11].

Based on leucocyte level, normal leucocyte level group has highest frequency. Based on other studies, Leukocyte counts tend to be found normal in typhoid fever patients [11,12]. The pathogenesis mechanism of *Salmonella typhi* infection underlie why leucocyte count of typhoid fever patients tend to be normal. *Salmonella typhi* penetrates into the intestinal mucosa layer, it will be phagocytosed by phagocytic cells. These bacteria have capability to survive inside phagocytic cell. Phagocytic cells provide protection for bacteria to spread throughout the body and protect them from antibodies and antimicrobial agents. Therefore, there is no antibody response to increase the number of leukocytes [13].

Majority of patients on this study also have normal number of neutrophile. Previous study showed the number of neutrophile on typhoid fever patients tend to be normal [9]. However, neutrophilic leukocytosis and neutropenia could be occurred on typhoid fever patients. The condition of neutropenia in typhoid fever is caused by increased margination and granulopoeisis damage. Meanwhile neutrophilic leukocytosis could occur during short-term infections or acute infections where the types of cells that tend to increase are polymorphonuclear leukocyte cells or granulocytes, namely neutrophils, eosinophils and basophils [14]. Study by Paul and Bandyopadhyay also found similar result [15].

This study also found that majority of patients have normal number of lymphocytes. This finding is similar to previous study which is also showed that lymphocyte count of typhoid patients tend to be normal [9]. Same as neutrophile level on typhoid fever patient, lymphocytopenia and lymphocytosis could occur on typhoid patients. Lymphocytosis can be caused because the infection experienced is a long-term infection or chronic infection where what tends to increase is mononuclear leukocyte cells or agranulocytes, one of which is lymphocytes, while lymphocytopenia can be caused because the infection experienced is an acute infection. In this study, patients with lymphocytopenia are more frequent than patients with lymphocytosis. This finding corresponds with previous study [14].

This study also found that number of thrombocytes on typhoid fever patient tend to be normal. Previous studies also found that majority of typhoid patients have normal of thrombocytes [16,11]. However, this study found that thrombocytopenia and thrombocytosis could possibly occurs on

typhoid fever patients. Number of patients with thrombocytopenia is more frequent than patients with thrombocytosis. This result is matched with previous study [17]. *Salmonella typhi* produces endotoxins that stimulate macrophages to secrete their cytokines and mediators such as histamine, bradykinin, and serotine. The products released by macrophages and suppress the bone marrow. This process also reduces platelet production and platelet maturation process [18]. Meanwhile thrombocytosis can be caused by the presence of abnormal cells in the bone marrow, which is where myelopoiesis occurs. Thrombocytosis is known to be an indicator of typhoid fever severity. Its presence indicates that the individual is at risk of various complications [19].

This study shows the lowest titer value which is 1/80 and the highest is 1/320 at O and H titers. This causes a discrepancy in the titer value standard which strengthens the diagnosis of typhoid fever in a typical clinical picture, which is > 1/320 at the O titer or > 1/160 at the H titer [20]. However, another study in India, O and H titer values at 1/80 were considered to be diagnosed with typhoid fever [21]. There is also a stipulation of its own laboratory guidelines for the interpretation of widal O agglutinin titers of 1/80 and H 1/80 in India [22]. This proves the absence of conformity regarding the agglutination value standard which is said to be positive [20]. Titer value in a population depend on background levels of *Salmonella typhi* antibodies and typhoid fever vaccination, which can vary over time. Widal test could be negative even blood culture shows positive result. This can occur due to differences in the background of antibody levels in an endemic region or several individuals and decreased antibody response with early administration of antibiotics [21]. A negative widal test result does not always rule out a diagnosis of typhoid fever in patients with signs and symptoms of the disease. Negative widal test result can be found at early phase phase of the disease [23].

The most frequent widal test results in this study were found at a value of 1/80 at titers O and H. Previous studies also showed the same result [21,23]. However, in another areas, Sharma et al found that the most frequent value of titers O and H were 1/40. These findings prove that differences in background of antibody values would affect widal test results [22].

The study showed the highest frequency of IgM anti-*Salmonella typhi* was found at scores of 4 (36.5%) and 6 (36.5%) and the lowest frequency at scores of 2 (5.8%). These results correspond with results of previous study. Munir et al also found that the highest frequency of typhoid fever patients serum that tested with IgM anti-*Salmonella typhi* were found at score of 4 and 6 [34]. An IgM anti-salmonella typhi result with a score of 2 could be caused by the test being carried out when the antibody titer in the serum was still low [13].

Based on antibiotic treatment, this study shows that most of typhoid fever patients at Prof. Ngoerah General Hospital were treated with antibiotic with no blood cultures results. This finding does not correspond to Clinical and Laboratory Standards Institute (CLSI) recommendations where antibiotics should be given after proving positive blood cultures of *Salmonella typhi* [25]. On the other hand, physicians in developing countries are often faced with the challenge of making treatment decisions based on appropriate clinical symptoms or a combination of clinical symptoms and widal test results obtained from a single acute phase [26]. Delay in antibiotic administration can increase the risk of complications in typhoid fever patients [27].

Ceftriaxone is the most frequent type of antibiotic that used for treat typhoid fever patients at Prof. Ngoerah General Hospital. This finding corresponds with typhoid fever management recommendations in previous studies. Ceftriaxone is most recommended antibiotic for the treatment of typhoid fever [4,28]. The use of ceftriaxone also combined with levofloxacin. This shows the suitability of previous studies. Combination antibiotics (mostly cephalosporins and fluroquinolones) are the most commonly used classes of antibiotics for the treatment of typhoid fever. Combination antibiotics are the main choice for adult patients while cephalosporins are the main choice in children and young patients (up to the age of 20 years) [29]. Antibiotic combination needs to be done in patients with critical conditions who have been given empiric antibiotic therapy before blood culture evidence, infections caused by more than one organism, and for the prevention of antibiotic resistance [30].

Only 26.9% of patients have complication. Previous study reported that complication could occurs on 26.3% of typhoid fever patients [31]. The most frequent type of complication in this study is hepatomegaly. According to a meta-analysis, liver infection is one of common typhoid fever complication [32].

Sepsis is the second most frequent typhoid fever complication in this study. Sepsis complication is rare among typhoid fever patients [17]. Pneumonia was found 3 times and acute respiratory tract infections 2 times in this study. Previous study has shown that respiratory complications can occur in 1-6% of typhoid fever patients. It is thought to be caused by *Salmonella typhi* regularly entering the lungs through pulmonary circulation in patients with bacteremia [33].

CONCLUSION

Based on hematologic examination, typhoid fever patients at Prof. Ngoerah General Hospital tend to have normal level of hemoglobin, leukocyte, neutrophile, lymphocyte, and thrombocyte. Based on widal test, this study shows the lowest value is 1/80 and the highest is 1/320 at titers O and H. The highest frequency in the widal test was found at 1/80 which was 13 patients (25.0%) and the lowest was found at 1/160 which was 2 patients (3.8%) at titers O and H. Widal test was carried out on 23 patients (44.2%) and not carried out on 29 patients (55.8%). IgM anti-*Salmonella typhi* was carried out on 41 patients (78.8%) and not carried out on 11 patients (21.2%). The majority of patients had a total positive score of 4 and 6 for IgM anti-Salmonella typhi. There are 5.8% patients had a negative IgM anti-Salmonella typhi score of 2.

Most of typhoid fever patients at Prof. Ngoerah General Hospital were treated with antibiotic. Ceftriaxone is the most common antibiotic that used for typhoid fever treatment.

Majority of typhoid fever patients at Prof. Ngoerah General hospital did not have complication. Only 26.9% of patients have

complication. Hepatomegaly is the most frequent complication occurred.

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