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DIAGNOSIS AND MANAGEMENT OF TYPHOID FEVER IN ROYAL PRIMA HOSPITAL MEDAN IN 2019

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Abstract

Typhoid fever is an infectious disease caused by negative-gram bacteria, *Salmonella typhi*. The gold standard study for typhoid fever is blood culture, however blood culture has several limitations including high costs, long time requirement, and sometimes lead to negative result if the patient has taken antibiotics. Widal test is a serological test for diagnostic tests that is relatively inexpensive, fast and easy and it is still widely used in laboratories for the diagnosis of typhoid fever, however diagnosing typhoid fever from widal test alone will lead to less accurate result, due to the large number of false negative and positive results. The purpose of this study was to illustrate antibiotic management in pediatric typhoid fever in Royal Prima Hospital in 2019. This study was an experimental study with the post-test only control group design. The samples were blood drawn from 25 children. Culture was carried out for isolation and identification using Kirby Bower method. Of the 25 patients with typhoid fever, six patient were found to be resistant to ampicillin and erythromicin antibiotics. On the other hand, they were found to be sensitive to ciprofloxacin, amikacin and chloramphenicol.

Keywords: ***Typhoid Fever, Salmonella typhi, ampicillin, eritromicin.***

INTRODUCTION

Typhoid fever is one of the several diseases in the world with unclear surveillance value due to its wide range of clinical spectrum. The incidence of typhoid fever reported by World Health Organization (WHO) was 17 million cases with around 600,000 cases of death worldwide in 2003. About 95% of typhoid fever was reported from developing countries on an outpatient basis. The mortality rate in Indonesia reached 20,000 from 900,000 cases of typhoid fever.

In 2007, the Indonesia Basic Health Research (RISKESDAS) stated that typhoid fever was one of the leading causes of death with a percentage of 1.6% (MOH, 2009). The incidence rate of typhoid fever was 180 / 100,000 cases per year and the prevalence rate was up to 61/1000 cases, commonly affected children who are vulnerable, around the age of 5 to 15 years (Ochiai, 2008).

Typhoid fever is widely spread through the provinces in Indonesia with an incidence rate of 1,100 / 100,000 population and a mortality rate of 3-10%. From the MOH data, typhoid fever was the second most common cause of death in urban areas in 5-14 years old group, in which 90% of the typhoid fever affected 3-19 years old age group (Irawati&Hanriko, 2016).

Each year, the incidence of typhoid fever has a 500 / 100,000 increased cases in hospital and the mortality rate is about 0.6 to 5.0%. Typhoid fever is one of the ten most common causes of hospitalization as reported by the Directorate General of Community Health Efforts with an incidence around 41,081 (Setiati et al., 2014).

Based on the data from the Ministry of Health and surveys of various hospitals in Indonesia, increased cases are observed every year. Cases of typhoid fever in 1981 to 1986 had an increased of 35.8% from 19.596 and to 26.06, while in 1990-1994 there was an increase from 9.2 cases per 10,000 population to 15.4 cases per 10,000 population (Sudoyo et al, 2009).

Inadequate supply of clean water and waste disposal management that does not meet environmental health criteria lead to an incidence gap of typhoid fever in various regions. In rural areas, the incidence rate of typhoid fever is 157 / 100,000 population, while in urban areas the incidence rate is in the range of 760-810 / 100,000 (Sudoyo et al, 2009).

Clinical manifestations include gastrointestinal symptoms such as constipation, diarrhea, and whitish plaque on the tongue with reddish edges. When fever is high, altered consciousness (delirium, apathy, coma) is observed. Fever often fluctuates and usually rises in the afternoon towards the evening (Putra, 2015).

Blood tests of patients with typhoid fever may exhibits leukopenia and leukocytosis. However, leukocytosis is associated with fever and toxicity (endotoxins and endogenous mediators) that cause bone marrow depression. Leukopenia (2,500 / μm3) is observed after a week or two and leukocytosis (20,000-25,000 / μm3) is observed when pyogenic abscesses occur (Nelson, 2015; Rosinta et al., 2014).

In developing countries, typhoid fever is still become the main focus of the health issues. The WHO re-

port stated that there are 900,000 new cases in Indonesia each year with a mortality rate of 20,000 (Surya et al., 2006).

One of the clinical features of typhoid fever is fever, but it is not a typical symptom. Several tests are used to confirm the diagnosis of typhoid fever include blood smears, microbiological examination, serology tests (widal test, anti *S. typhi* IgM test of IMBI method, and rapid test), and bacterial molecular tests (Osman &Mulyantari, 2014).

The gold standard examination for typhoid fever is blood culture, but the examination has the disadvantage of being quite expensive and may exhibit negative results if the patient has taken antibiotics (Satwika& Lestari, 2015).

Widal test is a serological for diagnosis at an affordable price, fast and easy to do and is still widely used in laboratories for the diagnosis of typhoid fever, however diagnosing typhoid fever from widal test alone will lead to less accurate result, due to the large number of false negative and positive results (Satwika& Lestari, 2015).

Study by Musnelina (2004) exhibited that chloramenicol is the treatment of choice for *S. Typhi* with typhoid fever at Famawwati Hospital, Jakarta. In addition, ceftriaxone as alternative antibiotic is effective for the management of typhoid fever in children (Musnelina et al, 2004).

From the background mentioned above, the authors aimed to study the management of antibiotics in typhoid fever im the Royal Prima General Hospital in 2019.

METHODS

This study is an experimental study. The tools used consist of bunsenbuner, test tubes, tube rack, blender, needle loop, ring loop, petri dish, incubator, erienmeyer, a durham tubes, beaker glasses, volume pipettes, droppers, cottons, glass objects, a marker, stirring rod, scales, and autoclave.

The media used were: glucose, lactose, mannite, maltose, saccharose, indol, methyl red, vogesproskauer, semi solid simon citrate, TSI.

The reagents used were: 70% alcohol, kovaka, 5% ala naphthol, 10% KOH, 0.02% methyl red, 0.5% gentian violet arbol, 1% lugol, 96% alcohol, 0.5% carbol fuchsin.

Procedure of samples preparation:

- Sample containers made of plastic boxes were disinfected with 70% alcohol
- Put the samples inside of it after it is dry, then cover.
- Sample Processing:

  Blood samples were obtained aseptically by a measuring pipette and then cultured on Salmonella enrichment media to multiply germs.

- Samples were incubated for 24 hours at 37^0C
- The second day

  After being cultured on the media, the samples were then cultured on solid media, namely *Salmonella Shigella* agar (SSA) solid media in zig zag manner, then incubated for 24 hours at 37^0C.
- The third day

  After 24 hours at the incubator, the colony growth was seen on the solid media.
- From each Salmonella Shigella Agar (SSA) media overgrown by rein colonies (separate), specific *salmonella sp*, gram staining and biochemical culture were conducted.
- Gram staining

  After being incubated for 24 hours, the colony was taken and gram-stained:
- The colony from each of *Salmonella Shigella* Agar (SSA) was taken by using a ring loop, then being placed on the surface of the glass object, being dried afterward.
- Fixation was performed it was dry on a Bunsen burner
- 0.5% gentin violet carbol was dropped, left for 3-5 minutes
- Washed using running water slowly
- Lugol was dropped for 2-3 minutes
- Washed again with running water slowly.
- 90% alcohol was dropped
- Washed again using running water slowly.
- 0.5% Carbol Fuchsin was dropped, left for 1-2 minutes.
- Washed again with running water slowly.
- Dried at room temperature.
- Then oil immersion was dropped, and samples were observed using a microscope at 100x magnification.

Biochemical culture

- After being inoculated for 24 hours, *Salmonella sp* colonies were obtained from SSA media and then cultured biochemically:
- Biochemical reaction media

  Procedure:
- Germ colony was obtained from the agar medium using a sterile needle loop.
- Afterward it was cultured into sugar media (glucose, lactose, mannite, maltose, maccharose) by mixing until homogeneous.
- It was covered tightly with small gauze and put in an incubator at 37^0C for 24 hours.

- SIM

  Procedure:

- The germ colony was obtained the SSA media using a sterile needle loop.
- It was cultivated on the SIM media perpendicularly to the bottom of the media.
- It was covered tightly with sterile cotton and put in an incubator at 37^0C for 24 hours.
- Methyl Red

  Procedure:

- Germ colonies was obtained from SS media using a sterile needle loop
- It was embedded into methyl red by mixing it until homogeneous, methyl red media was provided as a control.
- The sample was covered tightly with sterile cotton and put in an incubator at 37^0C for 24 hours.

Voges Proskauer

Procedure:

- Germ colonies was obtained from the SS media using a sterile needle loop
- It was embedded onto Vogaes Proskauer's media by mixing it until homogeneous, Voges Proskauer's media was provided as control.
- The sample was covered tightly with sterile cotton and put in an incubator at 37^0C for 24 hours.

Simon Citrate

- Procedure:
- Germ colonies was obtained from SS media using a sterile needle loop
- It was embedded onto the Simon Citrat media by mixing it until homogeneous, Simon Citrat media was provided as a control
- The sample was covered tightly with sterile cotton and put in an incubator at 37^0C for 24 hours.

TSI (Triple Sugar Iron)

Procedure:

- Germ colonies was obtained from SS media using a sterile needle loop
- It was embedded onto the TSI media by using needle loop in perpendicular position until the bottom and the slanted part was sliced in zigzag manner, TSI media was provided as a control.
- The sample was covered tightly with sterile cotton and put in an incubator at 37^0C for 24 hours.

The fourth day

Reading the results using the biochemical reaction table.

Data collection was carried out at the Regional Health Laboratory in Medan City and began in June

2019 and in September 2019 at UNPRI Laboratory. The samples were blood drawn from 25 children. Culture was carried out for isolation and identification by Kirby Bower period. From the collected and reviewed data, results can be concluded as below.

RESULT AND DISCUSSION

Below is the frequency distribution of characteristics of patients with typhoid fever according to age and sex in Royal Prima Hospital, Medan.

Table 1. Baseline characteristics of typhoid fever patients in Royal Prima Hospital of Medan according to age and sex.

Variables	Frequency	Percentage
Age (year)		
1-10	19	76
11-20	6	24
Total	25	100
Sex		
Female	14	56
Male	11	44
Total	25	100

Patients diagnosed with typhoid fever at the age of 1-10 years were 19 children (76%) and at the aged 11-20 year were 6 people (24%). Based on gender, female were found to be predominant, 14 (56%) children compared to 11 (44%) male children.

Typhoid fever cases with antibiotics resistance

Patients of typhoid fever that were resistant and sensitive to several antibiotics are illustrated as follows:

Table 2. Typhoid Fever Patients with Antibiotics Resistance

Age (year)	Sex	Resistance	Sensitive
7	Female	Ampisilin, Eritromicin	Ciprofloxacin, Amikacin, Cloramphenikol
10	Male	Ampisilin, Eritromicin	Ciprofloxacin, Amikacin, Cloramphenikol
13	Male	Ampisilin, Eritromicin	Ciprofloxacin, Amikacin, Cloramphenikol
11	Female	Ampisilin, Eritromicin	Ciprofloxacin, Amikacin, Cloramphenikol
8	Female	Ampisilin, Eritromicin	Ciprofloxacin, Amikacin,

			Cloramphenikol
9	Male	Ampisilin, Eritromicin	Ciprofloxacin, Amikacin, Cloramphenikol

Of the 25 patients with typhoid fever, six patients were resistant to ampicillin and erythromicin. In addition, they were also sensitive to ciprofloxacin, amikacin and chloramphenicol.

Discussion

Children at the age range of 3 to 19 year more often experience typhoid fever with mild symptoms compared to adults. The disease is commonly asymptomatic or exhibits atypical symptoms. However, patients may have high fever and gastrointestinal disorders (Etikasari et al., 2012).

The essential management of typhoid fever cases is the administration of antibiotics. Common antibiotics administered are ampicillin / amoxicillin, chloramphenicol or cotrimoxazole. Long-term use of chloramphenicol may lead to multidrug resistant *Salmonella typhi* (MDRST). However, the antibiotic is quite effective at low prices and is not difficult to obtain (Pudjiadi et al., 2009; Sidabutar and Satari, 2010).

Based on Saputri's study (2016) in Adi Soemarmo Hospital, the most common prescribed antibiotics to hospitalized patients was ceftriaxone (30.56%) with a prescription accuracy of 100%, recovery percentage of 88.9%, and therapy accuracy of 41.67%. The study did not explain the doses of prescribed drugs (Saputri, 2016).

Study Widodo (2016) exhibited that prescription accuracy of antibiotics prescription in typhoid fever cases was 100% from goal accuracy, recovery rate was 82.5%, therapy accuracy was 67.5%, and doses accuracy was 27.5%. Analysis of its effectiveness showed 100% effectiveness (Widodo, 2016).

Study by Hapsari (2019) exhibited that the most widely used drugs to treat this disease were ceftriaxone (45.24%), clorampenicole (23.81%), ciprofloxacin (9.52%), cefotaxim and ampicillin (both 7.14%), cotrimoxazole (4.76%), and azithromycin (2.38%). Assessment of antibiotic exhibited goal accuracy of 100%, recovery rate of 100%, therapy accuracy of 97.62%, and doses accuracy of 36.58% (Hapsari, 2019).

Typhoid fever may occur due to lack of personal hygiene, poor sanitation in the surrounding environment, and transmission through oral-fecal or from bacterial contamination of food and drink (WHO, 2015). Therefore typhoid fever warrants specific and appropriate attention from the community and the government, because this disease is an endemic disease that is very dangerous and threatens the health of all individuals (Purba et al, 2016). The inaccuracy of antibiotics prescription leads to increase in bacterial antibiotic resistance (Nature, 2011). According to WHO (2013), as many as 23,000 people died and 2,049,442 cases of illness arising from antibiotic resistance. The occurrence of antibiotic resistance may aggravate this case, and will compli-

cate therapeutic and preventive trials of this disease (MOH, 2006).

Antibiotic is the appropriate management of typhoid fever. The drug aims to terminate bacterial infections (Ministry of Health, Republic of Indonesia, 2011). Clinical pathways of Dr. Soetijono General Hospital for antibiotic therapy for this entity consist of chloramphenicol, tiamphenicol, cotrimoxazol, ceftriaxone, cefotaxime, cefoperazone, quinolone class drugs (norfluxacin, ofluxacin, pfloxacin, ceftriaxone, cefotaxime, cefoperazone, quinolone drugs (norfluxacin, ofluxacin, pfloxacin, floroxacin, cipotaxime, ciprofloxicillin, amoproxicillin, ciprofloxicillin, amoproxicillin, ampoulin). On the other hand, first-line antibiotics therapies according to the Indonesian Ministry of Health (2006) were chloramphenicol, ampicillin or amoxicilin, and trimethoprim-sulfamethoxazole. Second-line antibiotic therapies were ceftriaxone, cefixime, and quinolone.

Study by Sidabutar and Satari (2010), ceftriaxone was the drug of choice that had been studied for this entity. It had a faster effect compared to chlorampenicole that requires a long-term administration. Ceftriaxone also has a small adverse effects and resistance with a fine drug interaction for reducing fever.

Typhoid fever is a health issue in developing countries including Indonesia. The incidence rate of typhoid fever increases every year, hence prompt diagnosis and proper antibiotic administration are both essential.

CONCLUSION

The present study concluded that predominant age was 1-10 year group. The patients were predominantly female. Of the 25 patients with typhoid fever, six children were resistant to ampicillin and erythromicin antibiotics. Moreover, they were also sensitive to ciprofloxacin, amikacin and chloramphenicol.

Future studies are expected to better define the most effective treatment as well as probable complications for this disease.

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