The relationship between antibiotics treatment with length of stay and the daily temperature fluctuation of child patients infected by dengue at UNS Hospital

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Abstract. Dengue fever is infectious disease caused by dengue virus. Climate change, especially warming temperature is associated with the spread of Aedes aegypti which is the main vector for dengue virus. Antibiotics for dengue infection are used to prevent secondary infection. Thus, hospitalized patients treated with antibiotics are suspected to be associated with days reduction of hospitalization. It is important to monitor the patients’ temperature as it becomes the sign of worseness or recovery. This study aims to determine whether there is relationship between antibiotic treatment with length of stay and daily temperature of child patients infected by dengue. The study was conducted at UNS Hospital Indonesia. A total data of 180 children hospitalized with dengue infection since 2019 to 2020 were analyzed. Confirmation to parents was done when needed. Data were analyzed using Mann-Whitney and Fisher's test. There was insignificant relationship between antibiotics treatment with length of stay (p-value = 0.48) and daily temperature (p-value = 0.078) of child patients infected by dengue at UNS Hospital. There was no significant relationship between antibiotic treatment with length of stay and daily temperature fluctuation. Further study to investigate other factors which affect the length of stay and daily temperature fluctuation is needed.

1. Introduction
Dengue fever is an infectious disease found in most tropical and subtropical regions, especially Southeast Asia, Central America, America, and the Caribbean [1]. Dengue fever is caused by dengue virus infection which is transmitted by Aedes aegypti mosquito as a vector [2]. Climate change, especially warming temperature is associated with the spread of the Aedes aegypti [3]. Warming temperature plays an important role in the reproduction, development, and longevity of mosquito [4]. Thus, warming temperature is potentially cause an increase of dengue outbreaks [5]. Indonesia is the second country with highest cases of dengue fever out of 30 endemic countries [6]. There are approximately 50 million get infected of dengue virus every year, where 500,000 of them require hospitalization. There are about 90% of hospitalized patients are children [7].

There is no specific therapy of dengue fever. The treatments are supportive therapy and fluid therapy [8]. However, research conducted by Adrizain et al. [9] states that as many as 537 out of 3078 cases of dengue infection or 17.5% received antibiotic therapy. Meanwhile, Kumar et al. [10], states that the use of antibiotics in patients with self-limiting diseases such as dengue is used to prevent hospital-acquired infection.
Length of stay (LOS) is defined as the length of hospitalization for patients [11]. LOS in patients with suspected infection at least 48 hours before hospitalization is defined as the day between starting antibiotic therapy and discharging from the hospital [12]. A study shows that hospitalized patients treated with antibiotics for suspected bacterial infection coinciding with 4 days in LOS as well as higher reports of appropriate antibiotic use reduce 1 day from LOS [12]. However, there are no studies that mention the relationship of giving antibiotics to LOS in patients infected by viruses, especially the dengue virus.

Daily temperature monitoring in patients infected with dengue is important to prevent death. Ranjit and Kissoon [13] state that the temperature pattern of dengue patients is a saddle back pattern or horse saddle. Dengue fever is divided into 3 phases after the virus incubation period, namely the fever phase (Febril phase), the critical phase, and the recovery phase [14]. The phase occurs for 1-3 days were on the third day, the body temperature drops to 37.5 °C or 38 °C. Then, a plasma leakage occurs which can result in organ failure [14]. Currently, there are no studies that mention the relationship between antibiotic use and temperature fluctuation in child patients infected with dengue. The purpose of this study is to know the relationship between antibiotic treatment with length of stay and daily temperature fluctuation of child patients infected by dengue at UNS Hospital.

2. Materials and methods
An analytic observational study with a cross-sectional approach was conducted at UNS Hospital from September to October 2020. The population was patients aged 0-18 years with a diagnosis of dengue infection, namely Dengue Fever (DF) or Dengue Hemorrhagic Fever (DHF) grade I or Dengue Hemorrhagic Fever (DHF) grade II in 2018-2019.

This study used total sampling technique with a total sample of 180 patients. The independent variable in this study was the antibiotics treatment of child patients infected by dengue aged 0-18 years who fulfilled the criteria. The variable was measured by nominal scale with the classification of got antibiotics treatment and did not get antibiotics treatment. Meanwhile, the dependent variable in this study was the length of stay (LOS) and daily temperature fluctuation. The length of stay was defined as the number of days the patient was admitted to the hospital from being registered as a hospitalized patient until discharged from the hospital. This variable was measured by a numerical scale. Daily temperature fluctuation was defined as an assessment of daily temperature stability of dengue patients during hospitalization. The data measurement scale was stated in nominal scale with the classification of stable and unstable. Temperature fluctuation is said to be stable when it is in the range 36.5°C-37.5°C.

The data was obtained from patient medical records. The data analysis was performed using the IBM Statistical Package for the Social Sciences (SPSS) computer program version 26 which consisted of univariate and bivariate analyses. The univariate analysis consisted of the percentage or proportion frequency distribution for the variable of antibiotic treatment, daily temperature fluctuation, and the size of data concentration for the length of stay variable. Mann-Whitney test or Fisher’s exact test was used to determine the relationship between antibiotic treatment, LOS and daily temperature fluctuation.

3. Result
Based on the research on the medical record of child patients infected by dengue in 2018-2019, a sample of 180 patients was obtained which met the inclusion and exclusion criteria. The characteristics of the sample in this study are seen from their age and clinical diagnosis which can be seen in the Table 1. Based on Table 1, most of the patients were 6-18 years old (84.4%). Meanwhile, there were only 28 patients aged 0-5 years (15.6%). Based on clinical diagnosis, the majority of patients had DHF (148; 82.2%).
The univariate analysis explained the distribution of each variable, namely length of stay and daily temperature fluctuation as the dependent variable, while antibiotic administration as the independent variable.

**Table 1. Characteristics of subjects.**

| Characteristics      | Total (%) |
|----------------------|-----------|
| Age (years)          |           |
| 0-5                  | 28 (15.6) |
| 6-18                 | 152 (84.4)|
| Clinical Diagnosis   |           |
| DF                   | 32 (17.8) |
| DHF                  | 148 (82.2)|

Based on Table 2, most patients (83.3%) received antibiotics treatment, while 16.7% did not receive antibiotics treatment. The unstable temperature patient group consisted of 164 patients (91.1%), while the patients with stable temperature were only 16 patients (8.9%). The types of antibiotics that are widely used are ceftriaxone, cefixime, and metronidazole.

**Table 2. Distribution of antibiotics treatment and daily temperature fluctuation in child patients infected by dengue.**

| Groups                        | Total (%) |
|-------------------------------|-----------|
| Antibiotics Treatment         |           |
| Yes                           | 150 (83.3)|
| No                            | 30 (16.7) |
| Daily Temperature Fluctuation |           |
| Stable                        | 16 (8.9)  |
| Not Stable                    | 164 (91.1)|

Based on Table 3, from 180 subjects, the mean length of stay (LOS) of the patients was 4.1. Bivariate analysis was carried out by examining the relationship between the dependent variable (length of stay and daily temperature fluctuation) and the independent variable (antibiotics treatment). To fulfill the parametric test requirements, a normality test was carried out to assess whether the data was normally distributed. The normality test was carried out using the Kolmogorov-Smirnov test on the length of stay variable.

Based on the Kolmogorov-Smirnov test, it was found that the data were not normally distributed as indicated by the value of $p = 0.000$ ($p < 0.05$) in the group with antibiotics treatment and $p = 0.000$ ($p <0.05$) in the group without antibiotics treatment. Thus a parametric test could not be performed. Since the data were not normally distributed, a non-parametric Mann-Whitney test would be performed as an alternative to test the relationship between antibiotics and LOS.

**Table 3. Overview of length of stay in child patients infected by dengue.**

| Variable | Mean | Median | Modus | Min | Max |
|----------|------|--------|-------|-----|-----|
| Length of stay | 4.1  | 4      | 4     | 2   | 12  |

**Table 4. Bivariate test results of relationship between antibiotics treatment with LOS and daily temperature fluctuation.**

| Antibiotics Treatment | Nilai p |
|-----------------------|---------|
| LOS                   | 0.481   |
| Daily Temperature Fluctuations | 0.078   |
Table 4 shows that based on the Mann-Whitney test, there was no significant difference in LOS between groups with antibiotics treatment and without antibiotics treatment, as indicated by p-value = 0.481 (p > 0.05). Based on Fisher’s test, the value of p = 0.078 (p > 0.05) was obtained, which indicated that there was no statistically significant relationship between antibiotic treatment and daily temperature fluctuation.

4. Discussion

Based on the results in Table 4, there was no significant relationship between antibiotic administration and length of stay (p = 0.481; p > 0.05) in child patients infected by dengue at UNS Hospital. This is supported by Bosch et. al. (2016) who states that a significant relationship between the use of appropriate antibiotics and LOS occurs only in patients infected by bacteria, namely a 1 day reduction from LOS [12]. Meanwhile, dengue is a disease caused by a viral infection, not bacteria. Another study by Daalen et al. (2017) by using a Randomized Control Trial (RCT) model states that antibiotics treatment does not result in a shorter length of stay (LOS) [15].

The use of antibiotics in diseases that are self-limiting and caused by viral infections such as dengue is carried out if there is a bacterial co-infection [16]. Table 2 explains that the majority of patients received antibiotics treatment, which indicated that some patients were infected by dengue accompanied by a concurrent bacterial infection.

In general, the use of antibiotics is used to prevent hospital-acquired infections [10]. The factors that cause prolonged length of patient care or LOS in dengue patients are the occurrence of MOD (Multiple organ dysfunction), hypertension, increased alkaline phosphatase (ALP), and prolonged Prothrombin Time (PT) and activated Partial Thromboplastin Time (aPTT) [11].

DHF patients who are accompanied by MOD, hypertension, coagulopathy, and elevated ALP have more severe clinical manifestations that have the potential to have higher morbidity resulting in prolonged length of hospital stay [11]. PT and PTT that are prolonged are associated with disruption of the coagulation cascade so that it is one of the factors that aggravate dengue with bleeding [17]. Another study by Khalil et. al. (2014) stated that other factors such as secondary infection, comorbidity, acute renal failure (AKI), increased aspartate aminotransferase (AST), and hematocrit >20% were also found in dengue patients with long hospitalization. AKI in dengue patients occurs due to hypoperfusion and hypoxia due to shock caused by vascular leakage and coagulopathy in patients infected by dengue [18]. Older age can also increase the likelihood of prolonged LOS and the incidence of mortality [19]. Patients with older age will have other comorbidities and have rehabilitation problems that may complicate the healing process and tend to have longer length of stay [18].

The results of the study listed in Table 4 also show that there is no significant relationship between antibiotic treatment and daily temperature fluctuation in child patients infected by dengue at UNS Hospital (p = 0.078; p > 0.05).

These results contradict the research conducted by Bowers et. al. (2014) which states that the use of antibiotics can reduce core body temperature in experiments using mice infected by bacteria [20]. Another study by Duong et. al. (2020) states that there is a finding of a decrease in temperature to hypothermia on the use of the combination of amoxicillin antibiotics and sulbactam [21]. The temperature returns to normal after stopping treatment.

The limitation of this study is that the authors did not examine confounding factors that could affect LOS, such as comorbidity and secondary infection. In addition, the authors did not carry out analyses related to the location of temperature measurement. The limited data available in medical records can also be a bias in this study.

5. Conclusion

Climate change causes an increase of dengue cases and it is related to increase the incidence of other infections. Thus, antibiotics are one of the option for dengue therapy. The importance of knowing the relationship between dengue and length of stay is to determinants of hospital capacity management.
Based on the research that has been conducted, there is no significant relationship between antibiotic treatment with length of stay and daily temperature fluctuation in child patients infected by dengue at UNS hospital. Based on the conclusion above, the authors suggest that further research can look for other factors that affect the length of stay and daily temperature fluctuation in child patients infected by dengue, such as secondary infection or comorbidity. In addition, indications for giving antibiotics treatment to child patients infected by dengue such as concomitant bacterial infection and prevention of nosocomial infections are listed and further explained in the study.

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