Artikel Penelitian

Epidemiology of Children with Severe Dengue Infection in Dr. Soetomo General Hospital

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Abstract
Introduction: *Dengue infection is endemic to Indonesia and remains a public health problem. Severe dengue infection can cause rapid death, especially in children.*
Aim: *To determine the epidemiology of children with severe dengue infection in Dr. Soetomo Hospital.*
Method: *A cross-sectional study was conducted at the pediatric ward of Dr. Soetomo Hospital. Data were derived from medical records of children aged ≤18 years which hospitalized with severe dengue from March to April 2019.*
Result: *Of 135 children admitted with DHF, obtained 48 samples with characteristics >5–12 years old (72.9%), male (58.3%), residence Surabaya (89.6%), elementary school (60.3%), referral (81.3%), hospitalized ≤5 days (66.7%), day of illness ≥4 days (89.6%), moderate malnutrition (35.4%), had severe plasma leakage consisting of DHF grade III (73%) and IV (27%). Two patients died (4.2%). No patient with congenital disease and malignancy.*
Conclusion: *This study is not in line with the tendency of shifted dengue incidence to older age groups (>15 years old) in Indonesia. All patients had severe plasma leakage. No severe dengue patient with severe hemorrhage and organ impairment. Most patients were male, had moderate malnutrition, from referral, day of illness ≥4 days, hospitalized ≤5 days.*

Kata Kunci: *Severe dengue infection, children, Dengue Hemorrhagic Fever (DHF), Dengue Shock Syndrome (DSS).*

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Gambaran Epidemiologi Anak dengan Infeksi Dengue Berat di RSUD Dr. Soetomo

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Abstrak

Latar Belakang: *Infeksi virus dengue adalah penyakit endemik yang masih menjadi masalah kesehatan masyarakat Indonesia. Dengue berat dapat menyebabkan kematian yang cepat terutama pada anak.*

Tujuan: *Untuk menentukan gambaran epidemiologi anak dengan infeksi dengue berat di RSUD Dr. Soetomo.*

Metode: *Studi potong lintang dilakukan di bangsal anak RSUD Dr. Soetomo. Data diperoleh dari rekam medik anak berusia ≤18 tahun yang dirawat dengan infeksi dengue berat pada Maret–April 2019.*

Hasil: *Dari 135 penderita DBD, diperoleh 48 penderita dengue berat dengan karakteristik >5–12 tahun (72,9%), laki-laki (58,3%), tempat tinggal Surabaya (89,6%), sedang menempuh sekolah dasar (60,3%), dari rujukan (81,3%), dirawat ≤5 hari (66,7%), lama demam sebelum dirawat ≥4 hari (89,6%), berstatus malnutrisi sedang (35,4%), memiliki kebocoran plasma berat meliputi DBD derajat III (73%) dan IV (27%). Dua pasien meninggal (4,2%). Tidak terdapat pasien dengan penyakit bawaan dan keganasan.*

Kesimpulan: *Penelitian ini tidak sejalan dengan kecenderungan pergeseran insiden dengue ke kelompok usia yang lebih tua (>15 tahun) di Indonesia. Seluruh pasien mengalami kebocoran plasma berat. Tidak terdapat pasien dengue berat dengan perdarahan masif dan kerusakan organ. Mayoritas pasien adalah laki-laki, memiliki malnutrisi sedang, dari rujukan, lama demam sebelum dirawat ≥4 hari, dirawat selama ≤5 hari.*

Kata Kunci: *Infeksi dengue berat, anak, Demam Berdarah Dengue (DBD), Sindrom Syok Dengue (SSD).*

Introduction

A communicable disease that is still a problem for public health is dengue viral infection. The incidence of dengue infection has been on the rise in recent decades. Approximately, 50 million dengue infections occur worldwide annually. An estimated 500,000 *Dengue Hemorrhagic Fever* (DHF) patients require hospitalization each year, 90% of which are children less than five years old and about 2.5% of those affected died.[1] Since dengue infection cases in Indonesia were reported in 1968 in Jakarta and Surabaya, dengue infection has become a public health threat which causes morbidity and mortality.[2,3]

Aedes (Stegomyia) aegypti and A*edes (Stegomyia) albopictus* are the two most important vectors of dengue infection, which transmits the virus to humans in tropical and subtropical regions particularly in the urban and semi-urban area. The transmission of the dengue virus is affected by rainfall, temperature, and urbanization. Dengue infection is an acute fever caused by dengue virus that who has four serotypes (DENV-1, -2, -3, -4) which clinically vary in manifestation from asymptomatic to severe.[4]

Ministry of Health reported 68,407 DHF cases with Incidence Rate (IR) 26.12 in 100,000 populations in Indonesia. East Java is the province with the highest mortality of DHF in 2017 with 105 deaths.[5] Mortality due to shock accompanied by severe gastrointestinal bleeding and encephalopathy remains high.[6] Meanwhile, the prevalence of DHF with shock in various hospital in Indonesia vary between 11.2–42%.[7]

DHF is more prevalent in children less than 15 years who live in hyperendemic areas that have recurrent dengue infection.[1] *World Health Organization* (WHO) classified dengue infection into dengue and severe dengue infection according to dengue guidelines issued in 2009. Severe dengue infection is characterized by one or more criteria: severe plasma leakage, severe hemorrhage, and organ impairment. Severe plasma leakage will

cause shock, followed by death.[8]
Children are believed to have complex immune system response and thus they usually have a more severe manifestation of dengue infection than adults.[9] Severe dengue can cause rapid death especially in children if not detected early and managed properly.[10] This condition potentially leads to significant morbidity and mortality. Studying epidemiology of children with severe dengue infection is important to anticipate and manage the potential of deterioration in children with dengue infection, but until now the reports are limited. The research aims to determine the epidemiology of children with severe dengue infection in Dr. Soetomo Hospital.

Method

This is a descriptive observational study with a cross-sectional design using medical records of children with severe dengue infection admitted from March to April 2019 in the pediatric ward of Dr. Soetomo Hospital, Surabaya. Inclusion criteria in this study were children aged ≤18 years; diagnosed with severe dengue infection; hospitalized in the pediatric ward of Dr. Soetomo Hospital. Patients with non-severe dengue were excluded according to World Health Organization (2009).[8]
The definition of severe dengue infection includes the clinical manifestation of non-severe dengue infection, with one or more of the following manifestations:[8]

1. Severe plasma leakage, characterized by high or progressively rising hematocrit (≥20% of the basal average for age and gender); pleural effusions or ascites; circulatory compromise or shock (tachycardia, cold and clammy extremities, prolonged capillary refill time, weak or undetectable pulse, narrow pulse pressure, or undetectable blood pressure observed in late shock).
2. Severe hemorrhage, represented by gastrointestinal bleeding (epistaxis, hematemesis, melena) followed with anemia and evidenced by hematocrit changes; bleeding with blood transfusion therapy.
3. Severe organ impairment, such as hepatitis dengue (AST/ALT >1000 unit/L), encephalitis dengue (altered mental status and neurologic disturbances), myocarditis dengue (abnormal ECG); nephritis dengue (abnormal blood urea nitrogen and creatinine level).

Diagnosis of the patients with severe dengue infection in this study was established according to WHO guideline issued in 2009. However, diagnosis of dengue infection in Dr. Soetomo Hospital is using WHO SEARO guideline issued in 2011. Therefore, there are some adjustments in terms of diagnosing. DF, DHF grade I, and DHF grade II are considered as non-severe dengue in WHO guideline issued in 2009. DHF grade III and IV are the term for severe plasma leakage in severe dengue infection.[1,8]
The sample size was calculated based on a cross-sectional formula study, in which the α was 0.05 ($Z\alpha$=1.96); the expected proportion (P) and alternative proportion (Q) was 0.5; deviation towards population (d) was 0.15; correction factor was 1.1. The minimum subjects required were 48 children.
Data was determined through purposive sampling and collected in a dummy table. Variables studied in this study included age, sex, residence, education level, duration of hospitalization, day of illness (length of fever before admission), nutritional status, referral status from other health services, diagnosis of severe dengue infection, and outcome when discharged from hospital. The duration of hospitalization was determined since the patient was admitted to the hospital until discharged.
Nutritional status was assessed using weight for height/length cut off z-scores of WHO Growth Chart (2006) for children aged 0–5 years. Children aged 5–18 years were assessed using ideal body weight percentage according to Waterlow criteria with reference CDC Chart (2000). Height and weight data of patient from medical records were plotted in weight for height chart based on age and type of chart (WHO or CDC chart).[11]
Given that only two cases had confirmatory serology, the diagnosis was made based on consistent clinical manifestation from hospital admission until the end of the treatment period. All patients had a discharge diagnosis as a dengue infection. Univariate analysis was conducted using Microsoft Excel 2016 version. This study complied with the institutional proceedings and requirements in health research, in which the Ethics Committee of Dr. Soetomo Hospital had already approved.

Result

Of 135 children with DHF, forty-eight children aged ≤18 years who were admitted from March to April 2019 in Dr. Soetomo Hospital with severe dengue infection were studied. Univariate analyses were performed to determine the epidemiology of children with severe

dengue infection in Dr. Soetomo Hospital. Distribution and frequency of inpatients with severe dengue infection based on sociodemographic characteristics are shown in Table 1.

Table 1. Sociodemographic Characteristics of the Subject

Sociodemographic Characteristics	Number	%
Age (years)		
0–1	1	2.1
>1–5	1	2.1
>5–12	35	72.9
>12–18	11	22.9
Gender		
Male	28	58.3
Female	20	41.7
Residence		
Surabaya	43	89.6
Outside Surabaya	5	10.4
Level of Education		
Preschool	1	2.1
Kindergarten	8	16.7
Elementary school	29	60.3
Junior high school	8	16.7
Senior high school	2	4.2

The majority of the cases (72.9%) were in a group of >5–12 years and followed with >12–18 years (22.9%). Severe dengue was most common in males (58.3%), although the difference is slight compared to the number of cases in females (41.7%). Patients from Surabaya (89.6%) dominated the sample population. Most patients were elementary school students (60.3%), followed by kindergarten and junior high school. Senior high school students were observed as the least (4.2%).

Distribution and frequency of subjects based on the patient's profile are shown in Table 2. All patients were diagnosed with severe plasma leakage which consisted of DHF grade III (73%) and IV (27%). No severe dengue patients found with severe hemorrhage and organ impairment. The majority of the patient was admitted to hospital with the day of illness four days or more (89.6%). Meanwhile, abnormal nutritional status was observed in most patients, in which moderate malnutrition was found in 17 patients (35.4%) and obese in 13 patients (27.1%). Well-nourished patients were only observed in 12 children (25%). The frequency of patients who came from other health services referral was greater (81.3%) than who comes directly to Dr. Soetomo Hospital (18.7%). Most patients were hospitalized for ≤5 days (66.7%).

Of the deaths (4.2%), all were from other health services and admitted to Dr. Soetomo Hospital late in the course of the disease. Patients who died had multiple complications which lead to systemic failure. The authors reported no malignancy and congenital disease found in any patients.

Table 2. Patient's Profile Related to Severe Dengue

Patient's Profile	Number	%
Severe dengue diagnosis		
DHF grade III	35	73.0
DHF grade IV	13	27.0
Day of illness		
<4 days	5	10.4
≥4 days	43	89.6
Nutritional status		
Obese	13	27.1
Overweight	6	12.5
Normal	12	25.0
Moderate malnutrition	17	35.4
Referral		
Yes	39	81.3
No	9	18.7
Duration of hospitalization		
≤5 days	32	66.7
>5 days	16	33.3
Outcome		
Live	46	95.8
Died	2	4.2

Discussion

World Health Organization estimates 50–100 million dengue infections occurred every year globally along with thirty fold increased cases observed in the last 50 years.[12] Asia bears 70% of the dengue burden in the world.[13] In forty-five years (1968–2013), DHF incidence in Indonesia increased rapidly along with decreased mortality.[14] Case fatality rate of dengue infection in East Java in 2017 was 1.34%, which was still relatively high.[5] From October 2008 to April 2009, Dr. Soetomo Hospital reported a total of 23 patients of DHF grade III and IV (Dengue Shock Syndrome/ DSS).[15]

Of 135 children admitted with DHF in two

months, researchers examined 48 children with severe dengue infection. All patients were diagnosed with severe plasma leakage (DHF grade III and IV. Cases were dominated by children >5–12 years old. A similar result was also found in two studies conducted in Yogyakarta and Brazil.[16,17] Both reported DSS patients were dominated by children aged less than 15 years. In Indonesia, decreased DHF trend in children aged 5–14 years (the age group with the highest incidence of DHF historically) occurred from 1993, while the incidence in children aged over 15 years increased steadily and decreased incidence in younger children since 1999. The fact that majority of the participants were from a younger age group in this study (>5–12 years) shows that is not in line with the tendency of shifted dengue incidence to older age groups in Indonesia.[14] Knowledge of group vulnerable to DSS is essential for prevention efforts in the community as well as the rational implementation of dengue vaccines and antiviral drug.[18]

The frequency of male affected in this study was more than female, similar to studies in India and Mexico,[19-21] but contrary to the studies in the following cities in Indonesia: Yogyakarta, Jakarta, and Bandung.[22-24] A study from 6 countries in Asia suggested that the males have a habit of being outdoors which provides a greater opportunity of getting dengue infection due to mosquito bites.[25] However, a previous study showed that there is no difference of immune system response to dengue infection in different gender, evidenced by the same amount of cytokines and antibody produced by female and male dengue patients.[26]

Most patients were hospitalized for five days or fewer in this study. A similar report was also found in a previous study conducted at the Central General Hospital of Dr. Sadikin, which reported that almost 60% of children with severe dengue hospitalized for shorter than six days.[24] A cohort study in adult dengue patients found no significant difference in the duration of hospitalization among patients with DF, DHF, and DSS, although there was a trend of increasing duration of hospitalization according to the severity of dengue infection.[27]

A fourth-degree DHF patient in this study was hospitalized for fourteen days with complications of sepsis and involvement of the liver, lungs, and systemic. The severity of dengue infection is thought to contribute to the duration of hospitalization. Duration of hospitalization can be considered as an outcome variable which is an indicator of patient's treatment.[28] However, researchers assumed that all patients have been treated according to WHO clinical guidelines, which regulates the management of care according to patient needs. This approach has been validated by Toledo et al. who studied the duration of hospitalization with mortality in patients with severe dengue infection and comorbid diseases using systematic literature review.[29]

The majority of the patients came to the hospital with the length of fever ≥4 days, similar to studies conducted in Denpasar and Medan.[30,31] Shock usually manifests between the fourth and sixth days of a critical phase in the course of dengue infection.8 Most patients in this study were referred from other health services, as in previous research.[17,22,30] Clinicians must prepare responsive and anticipatory measures to monitor the patient, to prevent a worsening of condition into a heavier spectrum of dengue infection. Rapid diagnosis and treatment of dengue patient depend on the availability of health service facilities and awareness of the community in seeking health service.[32]

Abnormal nutrition status was observed in most of the patients, in which 17 (35.4%) children have moderate malnutrition and 13 (27.1%) children were obese. In contrast, studies in Medan and Bandung showed that normal weight was predominant in children with severe dengue infection.[24,31] Nutritional status is often associated with an immune system response that influences the severity of dengue infection. Moderate malnutrition is associated with decreased cell-mediated immunity which is indicated by a decrease in the number of CD4+ cells, complement production, and tumor necrosis factor (TNF).[33] Hypothetically, obesity can affect the severity of dengue through an inflammatory pathway. Macrophages, which are an important source of inflammatory cytokines, are reported to be able to infiltrate fat tissue and their amount is directly correlated to fat cell size and obesity.[34] Simultaneously, an increased deposition of white fat tissue in obese individuals causes an increased production of certain cytokines, which can increase capillary permeability and thus increase the risk of shock.[35] However, a systematic review and meta-analysis of 13 studies failed to show any consistency regarding the relationship between nutritional status and dengue infection.[36]

There were no dengue patients found with malignancy and congenital disease in this study. A retrospective study in 26 Taiwanese elderly with cancers reported the pre-existing cancers had a reduced risk of severe dengue

infection with an ORR of 0.9, yet pre-existing organ failure such as acute kidney failure doubled the mortality risk.[37] Tolerance of tumor antigen can be resolved through high levels of type 1 helper (TH 1) cells induced in dengue infection.[38] Research regarding dengue patients with malignancy and congenital disease in Indonesia is limited, therefore further studies need to be done.

Of all patients, two (4.2%) children who were from referral died. The percentage of death was lower than that of previous studies in some cities in Indonesia regarding children with DSS or severe dengue infection, such as 15.4% in Denpasar; 23.8% in Bandung; 25% in Medan; and 34.4% in Yogyakarta.[30,31,22,24] Based on data of patients who died, genetic factor of patient was thought to contribute the most in affecting the severity of dengue infection, indicated by the different vulnerability of individuals against manifestations of severe dengue infection. However, other factors such as community behavior and health services also play a role,[39] as reflected through health-seeking behavior in the community and proper treatment of dengue patients by clinicians.

Deaths due to dengue infection can be reduced by carrying out early identification and proper management particularly in severe cases. Besides, training of medical personnel and an effective referral system also have to be put in place. Conducting dengue epidemiological surveillance, providing education to the community, and implementing vector control programs are efforts to prevent transmission of dengue viral in community.[40]

Conclusion

This study is not in line with the tendency of shifted dengue incidence to older age groups (>15 years old) in Indonesia. All severe dengue patients had severe plasma leakage and no found with severe hemorrhage and organ impairment. The majority of the patients were male, had moderate malnutrition, from other health services referrals, day of illness ≥4 days, and hospitalized ≤5 days.

Conflicts of Interest

The authors report no conflicts of interest.

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