

## Prevalence of Expanded Dengue Syndrome in Patients with Dengue Virus Infection at the Dr. Soetomo Hospital Surabaya in 2017 – 2018

Avina Fimas Adissadah<sup>1</sup>, Aryati<sup>2</sup>, Suhintam Pusarawati<sup>3</sup>

<sup>1</sup> Faculty of Medicine, Airlangga University, Surabaya, Indonesia.

<sup>2</sup> Department of Clinical Pathology, Faculty of Medicine, Airlangga University/Dr. Soetomo Hospital in Surabaya, Indonesia.  
E-mail: dr\_aryati@yahoo.com

<sup>3</sup> Department of Parasitology, Faculty of Medicine, Airlangga University, Surabaya, Indonesia

### ABSTRACT

Dengue Fever (DF) or Dengue Hemorrhagic Fever (DHF) is one of the infectious diseases that attracts much global attention, especially Indonesia because it impacts the mortality rate of the people in the world if adequate treatment is not given. Expanded Dengue Syndrome (EDS) is a clinical manifestation involving several organs such as lungs, liver, kidney, heart, and brain-related to dengue infections, with or without plasma leakage. This study aimed to determine the prevalence of expanded dengue syndrome in patients with dengue virus infection at the Dr. Soetomo Hospital in 2017–2018. Based on its purpose, the sampling technique used in this study was the total sampling of patients with DVI who admitted to Dr. Soetomo Hospital Surabaya. Every pediatric and adult patient who met the criteria were included in this study until a certain period in 2017–2018. After the data collection, only thirty samples of EDS from the 196 sample data were collected. Thirty patients with expanded dengue syndrome had a manifestation of different organs. Such as: neurological, cardiac, respiratory system, gastro-hepatic, and kidneys. The laboratory test results showed that most platelet counts of 51,000 – 100,000 were found in seventeen patients, while the range of hemoglobin and hematocrit was normal. From a total of thirty samples of dengue virus infection patients with EDS, there were only eighteen patients who did a serological test. The most found serological results were (+/-) anti-dengue IgM and (+) anti-dengue IgG (40%).

**Keywords:** Dengue, dengue hemorrhagic fever, tropical disease

### INTRODUCTION

Dengue Fever (DF) and its severe forms of Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) have become a primary concern for international public health. Over the past three decades, there has been a dramatic global increase in DF, DHF, and DSS frequency. Dengue is found in tropical and subtropical regions around the world, predominantly in urban and semi-urban areas. The disease is caused by a virus belonging to family *Flaviviridae* spread by *Aedes* (Stegomyia) mosquitoes. Dengue virus infection may be asymptomatic or symptomatic. Symptomatic manifestation consists of undifferentiated febrile illness (viral syndrome), DF, DHF including DSS known as grade III and grade IV DHF, and expanded dengue syndrome (Figure 1).<sup>1</sup>

Dengue virus infection is an endemic disease and can occur throughout the year, especially in tropical regions. According to WHO, during 1968 and 2009, Indonesia was one of the highest endemic areas for DHF in Southeast Asia. In 2016 from 34 provinces in Indonesia, the number of dengue cases was 202,314

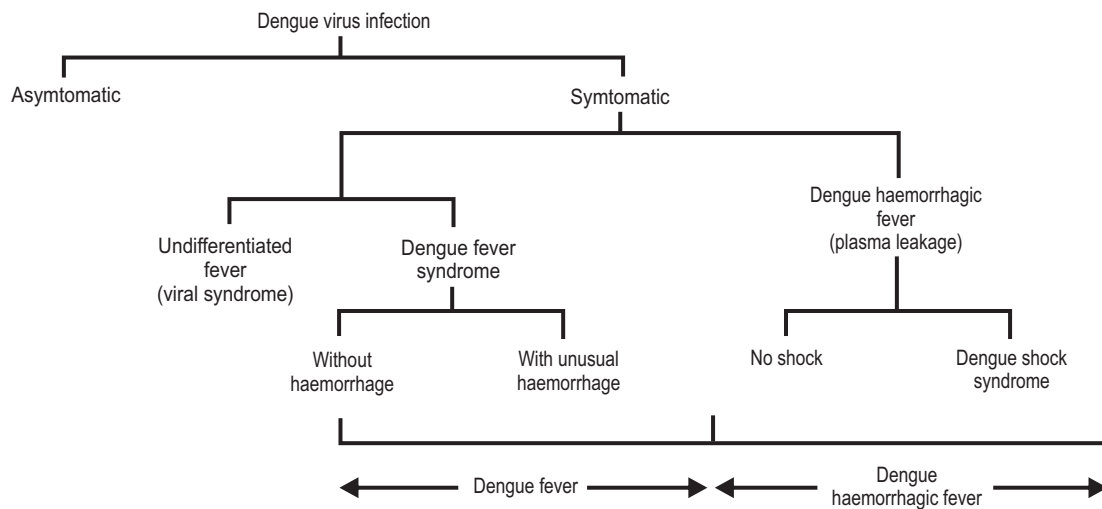
patients and 1,593 deaths. From January to May 2017, there were 17,877 cases, with 115 deaths. Until September 2017, there were 302 dengue cases in Surabaya. However, awareness of the surge in cases for the next year needs to be increased.<sup>2</sup>

Expanded Dengue Syndrome (EDS) is an unusual manifestation of patients with severe organ involvement. In recent years with the geographical spread of dengue illness and with more involvement of adults, there have been increasing reports of DF and DHF with unusual manifestations. These include: neurological, hepatic, renal, and other isolated organ involvement. These particular manifestations may be associated with coinfections, comorbidities or complications of prolonged shock.<sup>1</sup>

The mortality rate of DHF is quite high in 2016 in Indonesia. Death can be due to inadequate treatment of DSS or the late admission of patients to the hospital. In addition to DSS, there have been reported cause of death due to EDS, such as encephalopathy and Disseminated Intravascular Coagulation (DIC), and several cases accompanied by comorbidities such as HIV infection and sepsis.<sup>3</sup>

Based on the description, this study was

### Manifestations of dengue virus infection



**Figure 1.** Manifestations of dengue bvirus infection<sup>1</sup>

performed to determine the prevalence of EDS in patients with dengue virus infection at the Dr. Soetomo hospital from 2017 to 2018. An accurate assessment is an important key to adequate management so that that mortality can be reduced.

#### METHODS

The design of this study was an observational descriptive with retrospective data analysis from the medical record. The population in this study were pediatric and adult patients. They were diagnosed as a dengue virus infection with unusual manifestation (expanded dengue fever) in the medical record and treated at Dr. Soetomo Hospital in 2017-2018. The operational definition of EDS was a unique manifestation of patients with severe organ involvement such as neurological, hepatic, renal, and other isolated organ involvement. The clinical sign for dengue virus infection was the acute onset of fever lasting for two to seven days.

In most cases, any of the following hemorrhagic manifestations, hepatomegaly, and shock. The laboratory finding on dengue was thrombocytopenia  $\leq 100.000/mm^3$  and hematocrit increase of  $\geq 20\%$ . The first two clinical criteria, plus thrombocytopenia and hemoconcentration or an increased hematocrit, are sufficient to establish a clinical diagnosis of DHF.<sup>1</sup> Also, HGB and IgM/IgG Antidengue were included in this study as a variable. The liver enlargement in addition to the first two clinical criteria DHF are present before the onset of plasma leakage.<sup>1</sup>

This study also monitored patients' condition when they were discharged from Dr. Soetomo Hospital due to the high mortality rate of DHF in 2016 in Indonesia. The sampling technique used in this study was total sampling. Every patient who meets the criteria was included in this study until a certain period in 2017–2018. As a referral hospital and due to many cases available, medical record at Dr. Soetomo Hospital was used. The inclusion criteria of this study were all medical records of pediatric and adult patients. They were diagnosed as a dengue virus infection with unusual manifestation (expanded dengue syndrome) that had been treated at Dr. Soetomo Hospital. The medical record that could not be found was excluded.

Research permission was obtained from the Health Research Ethics Committee of the Dr. Soetomo Hospital, Surabaya, with number 1054/KEPK/III/2019.

#### RESULTS AND DISCUSSION

**Table 1.** Distribution of age group and gender of patients with DVI who have admitted to Dr. Soetomo Hospital Surabaya in 2017-2018

Age Group (years)	Male	Female	Total (percentage)
00 – 17	37	31	68 (43.59%)
18 – 65	39	45	84 (53.85%)
66 – 79	3	0	3 (1.92%)
80 – 99	0	1	1 (0.64%)
Total	79 (50.64%)	77(49.36%)	156 (100%)

Total patients based on gender and age group can be seen in Table 1. The patients were predominantly 18–65 years old (53.85%). This result was in line with research by Karyanti *et al.*, which found a rapid increase in the incidence of DHF during the last 45 years in Indonesia, with the peak incidence shifting from children to older age groups.<sup>4</sup> The gender ratio of IVD patients was 50.64%:49.36%. The number of males patients was more significant than females patients. The high incidence of dengue virus infection in males was probably caused by extensive exposure to *Aedes aegypti*. This finding is also supported by the existence of an Asian culture in which males spend more time outside the home than females.

Out of 156 patients with DVI, there were only 30 patients included in DVI with unusual manifestation (EDS) (Table 2).

**Table 2.** Diagnosis distribution of patients with DVI who admitted to Dr. Soetomo Hospital Surabaya in 2017–2018

Diagnosis	Total (percentage)
DF	38 (24.36%)
DHF I	41 (26.28%)
DHF II	37 (23.71%)
DHF III	5 (3.21%)
DHF IV	5 (3.21%)
EDS	30 (19.23%)
	156 (100%)

Table 3 outlines 30 subjects who were included based on inclusion criteria. The neurological system was the most found manifestation (36.67%) of EDS, from all the obtained manifestations.

Neurological manifestations like seizures, encephalopathy, encephalitis/aseptic meningitis, intracranial hemorrhages, and neuropathies have been reported in the past.<sup>6</sup> There were only encephalopathy (20%), encephalitis (10%), and seizure fever (6.67%), which were reported in these studies. These manifestations are secondary to direct tissue invasion of virus (neurotoxicity), cytokine-mediated damage to the blood-brain barrier, capillary hemorrhage, DIC, cerebral edema and metabolic disorders like hyponatremia, hypoxia, hepatic encephalopathy, and uremic encephalopathy.<sup>5</sup>

Cardiac manifestations of dengue are uncommon, but cardiac rhythm disorders such as atrioventricular blocks, atrial fibrillation, sinus node dysfunction, and ectopic ventricular beats have been reported to attribute to viral myocarditis.<sup>5,6</sup> Myocarditis (10%) and cardiomyopathy (6.67%) patients were found in this study.

Manifestation for respiratory systems such as ARDS (10%) and pulmonary hemorrhage (3.3%) was found in this study. Acute respiratory distress syndrome is one of the dreaded complications of dengue hemorrhagic fever, secondary to increased alveolar-capillary membrane permeability leading to interstitial and alveolar edema. Early restoration of

**Table 3.** Distribution of EDS on patients with DVI who admitted to Dr. Soetomo Hospital in 2017–2018

	Total	
	N=30	Percentage %
<b>Neurological system</b>	11	36.67%
Encephalopathy	6	20%
Encephalitis	3	10%
Febrile Seizure	2	6.67%
<b>Cardiac</b>	5	16.67%
Cardiomyopathy	2	6.67%
Myocarditis	3	10%
<b>Respiratory system</b>	4	13.33%
Acute Respiratory Distress Syndrome (ARDS)	3	10%
Pulmonary hemorrhage	1	3.3%
Gastro-hepatic	4	13.33%
Cholecystitis	2	6.65%
Hepatitis	2	6.65%
<b>Renal</b>	6	20%
Acute renal failure	4	13.33%
Hemolytic Uremic Syndrome (HUS)	2	6.66%
Musculoskeletal	0	0%

adequate tissue perfusion is critical to prevent the progression of dengue shock syndrome to ARDS.<sup>5</sup>

Hepatitis, fulminant hepatic failure, acalculous cholecystitis, acute pancreatitis, acute parotitis, and febrile diarrhea are among the gastrointestinal manifestations reported.<sup>5</sup> In this study, cholecystitis (6.65%) and hepatitis (6.65%) were found.

Dengue associated acute kidney injury secondary to the hemolytic uremic syndrome is highly rare, and only limited case reports are available.<sup>7</sup> In this study, acute renal failure (13.33%) and HUS (6.67%) were found. Shock-induced acute tubular necrosis is the leading cause of renal failure in dengue patients apart from other rare causes like multi-organ dysfunction and rhabdomyolysis.<sup>8</sup>

**Table 4.** The condition of patients with EDS when they were discharged from Dr. Soetomo Hospital in 2017-2018

	Total (percentage)
Recovered	12 (40%)
Forced discharge	11 (36.67%)
Died	6 (20%)
Total	30 (100%)

The condition of the patient when they were discharged from the hospital can be seen in Table 4. From the table, it can be seen that the most found condition was recovered. However, there were still patients who died while being treated in hospital. It was caused by myocarditis, renal failure, and ARDS. Laboratory findings that were reported in this study were thrombocyte, hemoglobin, hematocrit, and IgM-IgG anti-dengue. Laboratory findings can be seen in Table 5.

In Table 5 most patients came to the hospital when total thrombocyte was 51,000-100,000 (46.67%). Most of the patients were just aware of their illness and wanted to go to the hospital when it has reached a critical phase. A decrease of a platelet

**Table 5.** Laboratory findings of patients with EDS when admitted to Dr. Soetomo Hospital in 2017-2018

Laboratory Parameter	Total (N=30)	
	N = 30	%
<b>Thrombocyte</b>		
< 10	1	3.33%
10 – 50	9	30%
51 – 100	14	46.67%
101 – 150	2	6.67%
≥ 150	1	3.33%
<b>HCT</b>		
Normal	17	56.67%
High	9	30%
Low	4	13.33%
<b>HGB</b>		
Normal	17	56.67%
High	11	36.67%
Low	2	6.66%

count below 100 000 per  $\mu$ L may be observed in dengue fever, but it is a constant feature of dengue hemorrhagic fever. Thrombocytopenia is usually observed in the period between day three and day eight following the onset of illness.<sup>1</sup> There was one data of normal thrombocyte, possibly because the patient was already on the recovery stage when referred to Dr. Soetomo Hospital due to unusual manifestation.

Most DVI patients who were in the critical phase showed normal hematocrit levels.<sup>9</sup> Hematocrit normal range for males and females is 42-52 and 37-47, respectively. In this study, most of the patients with EDS came to the hospital with normal hematocrit (56.67%) and hemoglobin. It showed that most patients with EDS went to the hospital with normal hemoglobin levels (56.67%) and low hemoglobin levels (36.67%). Hemoglobin normal range for males and females are 14-18 and 12-16, respectively.

**Table 6.** Anti-dengue IgM-IgG test on patients with EDS when admitted to Dr. Soetomo Hospital in 2017-2018

Length of Sick (days)	Anti-dengue			Total (percentage)
	IgM (+) IgG (-)	IgM (-/+) IgG (+)	IgM (-) IgG (-)	
< 4	0	1	1	2 (6.67%)
4 – < 7	3	10	2	15 (50%)
≥ 7	0	1	0	1(3.33%)
Not checked				12(40%)
Total	3(10%)	12(40%)	3(10%)	30 (100%)

IgM can appear as early as day 3–5 in primary infection, peaking several weeks after recovery and remains at detectable levels for several months. IgG does not generally appear during the acute phase of the primary disease. However, during secondary infection, there is a rapid anamnestic IgG response to shared epitopes on multiple viral proteins between the first and second infecting serotypes. IgG appears as early as three days after onset of illness.<sup>10</sup> In this study, from a total of thirty samples of dengue virus infection patients with EDS, only eighteen patients did a serological test.

### CONCLUSION AND SUGGESTION

Based on the results and discussion above, it can be concluded that there were only 30 patients (19.23%) from 156 samples with EDS at the Dr. Soetomo Hospital in 2017-2018. There were death cases of EDS caused by myocarditis, renal failure, and ARDS. Therefore, accurate assessment is an essential key to adequate management so that that mortality can be reduced.

Further studies are needed regarding deeper observation of EDS because data was screened from the hospital registry of DVI, which means that some of the physicians possibly mentioned another related diagnosis instead of the DVI at the beginning, in addition to a possibility of lost to record in the hospital registry.

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