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Literature Review

## PATHOGENESIS OF HEMORRHAGIC DUE TO DENGUE VIRUS

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### ABSTRACT

Dengue is a viral disease that is mediated by a mosquito, which causes morbidity and mortality. Viruses can increase vascular permeability which can lead to hemorrhagic diathesis or disseminated intravascular coagulation (DIC) known as dengue hemorrhagic fever (DHF). In Indonesia, dengue hemorrhagic fever (DHF) are caused by dengue virus infection which was found to be endemic accompanied by an explosion of extraordinary events that appear at various specified period. The diagnosis of dengue is determined based on the criteria of the World Health Organization (WHO, 1999), which are sudden high fever accompanied by a marked tendency to hemorrhage positive tourniquet test, petechiae, ecchymosis, purpura, mucosal hemorrhagic, hematemesis or melena and thrombocytopenia. The problem that still exists today is the mechanism of thrombocytopenia in patients with varying degrees of dengue involving levels of vWF (von Willebrand factor) and prostaglandin I<sub>2</sub> (PGI<sub>2</sub>) can not be explained. The mechanism of hemorrhagic in dengue virus infections acquired as a result of thrombocytopenia, platelet dysfunction decreased coagulation factors, vasculopathy with endothelial injury and disseminated intravascular coagulation (DIC).

**Key words:** Hemorrhagic, dengue virus, DHF, criteria, WHO

### ABSTRAK

Dengue adalah penyakit viral yang diperantarai oleh nyamuk, yang menyebabkan morbiditas dan mortalitas. Virus dapat meningkatkan permeabilitas vaskular yang dapat memicu hemorrhagic diathesis atau disseminated intravascular coagulation (DIC) yang lebih dikenal dengan demam berdarah dengue (DBD). Di Indonesia, DBD disebabkan karena infeksi virus dengue yang ditemukan untuk menjadi endemik disertai dengan suatu ledakan luar biasa dari peristiwa yang muncul di berbagai periode tertentu. Diagnosis dengue ditunjukkan berdasarkan kriteria World Health Organization (WHO, 1999), yaitu demam tinggi secara tiba-tiba yang ditandai dengan tes hemorrhage positive tourniquet, petechiae, ecchymosis, purpura, mucosal, berdarah hematemesis atau melena dan trombositopenia. Masalah yang masih ada ialah mekanisme trombositopenia di pasien dengan variasi derajat level dengue vWF (von Willebrand factor) dan prostaglandin I<sub>2</sub> (PGI<sub>2</sub>) tidak bisa dijelaskan. Mekanisme demam berdarah dengue (DBD) pada infeksi virus dengue yang diperoleh sebagai hasil trombositopenia, platelet disfungsi, faktor koagulasi menurun, endotel vasculopathy dengan cedera serta disseminated intravascular coagulation (DIC).

**Kata kunci:** Hemorrhagic, virus dengue, DBD, kriteria, WHO

### INTRODUCTION

Dengue is a viral disease transmitted by mosquitoes that cause morbidity and mortality. In some cases, the virus that causes can lead to an increase in vascular permeability and can cause hemorrhagic diathesis or disseminated intravascular coagulation (DIC) known as dengue hemorrhagic fever (DHF). Of the 20–30% of

patients will experience a shock dengue, called dengue shock syndrome/dengue shock syndrome.<sup>1</sup>

Dengue hemorrhagic fever (DHF) in Indonesia is still found to be endemic accompanied by an explosion of outbreaks that appear at various specified period. The results of epidemiological observations also show that the number of dengue fever is increasing from year to year with widespread deployment.<sup>2</sup>

The diagnosis of dengue is determined based on the criteria of the World Health Organization (WHO, 1999)<sup>3</sup> which in essence is found sudden high fever accompanied by a marked tendency to hemorrhage positive tourniquet test, petechiae, echymosis, purpura, mucosal hemorrhagic, hematemesis/melena and thrombocytopenia (platelet count of blood edge of less than 100,000/mm<sup>3</sup>) beginning on day 5–8. Determination of the diagnosis requires further confirmation by serology, antigen detection or isolation of dengue virus.<sup>2,4,5,6</sup>

Research in the 20s on the new man can prove that dengue viruses can create pain. Pathogenesis is unclear. It was still considered a theory malignancy virus and the number of viruses that infect the body. This theory developed viral virulence theory, to study genotype, phenotype and molecular epidemiology of dengue. Since the '50s developing immunological theories have much effect on the current. From epidemiological observations, clinical and laboratory appears theories of secondary infection by other viruses sequenced, and activation of antigen-antibody theory complement.<sup>5</sup>

From this developed into the theory of infection enhancing antibodies, which then appears endotoxemia role and the role of T lymphocytes Then came the theory and theoretical mediators of apoptosis. So far no one theory can completely explain the pathogenesis of DHF.<sup>5</sup>

Hemorrhagic and fever are characteristic of dengue disease. Over 30 years the researchers concluded that the occurrence of hemorrhagic may occur due to vascular disruption/vasculopathy, thrombocytopenia and impaired platelet function and clotting disorders/coagulopathies.<sup>2,7,8</sup> The problem that still exists today is the mechanism of thrombocytopenia in patients with varying degrees of dengue involving levels of vWF (von Willbrand factor) and prostaglandin I<sub>2</sub> (PGI<sub>2</sub>) can not be explained.<sup>2,6</sup>

## EPIDEMIOLOGY

According to history, the beginning of dengue fever from Egypt and then spread throughout the world. Mosquitoes live in the fertile parts of the world that has a tropical climate and subtropics like Asia, Africa, Australia and America.<sup>8,9</sup> In Indonesia, the first case of dengue fever reported in the Jakarta and Surabaya in 1968. The following years the number of cases of dengue fever each year fluctuated and tended to increase.<sup>6,10</sup>

Data from the Ministry of Health were recorded in 1998 dengue cases from January 2004 to April 2004, there were a total of 58 301 cases of dengue fever in which 658 cases of dengue fever were fatal, especially in the provinces on the island of Java with more than 35% of cases are in the provinces of Jakarta. It seems that the highest outbreak in the province of Jakarta, Central Java, East Nusa Tenggara. However, in the province of West Java, Bali, South Sumatra, Lampung, East Kalimantan, South Sulawesi and West Nusa Tenggara are the trend of increased cases. The

most frequent serotypes are circulating dengue-3 (Den-3) that is 37% even though the three other serotypes (Den-4 (19%), Den-2, Den-1) also exist.<sup>11</sup>

In the 1998 pandemic, WHO reported more than 1.2 million cases of dengue fever and DHF from 56 countries in Indonesia where there are 72 133 cases and cases of death by 1414 with a Case Fatality Rate (CFR) 2.0%.<sup>9,11</sup>

Since 1993–1997 the majority of DHF patients 5–14 years age group by 60%, the highest in the 4–12 years of age and at tahun 1996–1997 has shifted at the age of 15 years.<sup>10,12</sup>

## PATHOGENESIS HEMORRHAGIC

Hemorrhagic manifestations in DHF is most often found in the form of petechiae on the skin and sometimes in the submucosa. Positive tourniquet test an increase in capillary fragility encountered earlier. Symptoms of severe hemorrhagic that often occurs is in the form of gastrointestinal hemorrhagic or hematemesis and melena. In the case of prolonged shock with massive hemorrhagic can occur in the heart, lungs, liver and brain.<sup>5,6,7,13</sup>

Increased hematocrit value is a manifestation of hemoconcentration that occurs due to leakage of plasma into the extravascular space with an effusion of serous fluid through the damaged capillaries. As a result of this leakage of plasma volume is reduced which may result in hypovolemic shock and circulatory failure. Hemoglobin levels in the first days are usually normal or slightly decreased. But later levels will rise following an increase in hemoconcentration and earliest hematologic abnormalities that can be found in DHF.<sup>14,15</sup>

### A. VASCULOPATHY

Characteristics of DBD plasma leakage is the manifestation hemoconcentration, pleural effusion or ascites and. Previous allegedly plasma leakage due to increased vascular permeability in addition to the discovery of two new suspects endothelial cell destruction accompanied by the release of inflammatory mediators (IL-6, IL-8 and RANTES) were released by the dengue virus. Dengue virus also activate complement and induce the expression of adhesion molecules such as ICAM-1, in which the expression of ICAM-1 along with IL-8 and RANTES will also increase vascular permeability.<sup>16</sup>

Vascular disorders due to dengue virus infection simplest can be seen with a positive tourniquet test with ptekie that often appear at the beginning of a fever before the thrombocytopenia. Research by performing a biopsy of the skin surface which berptekie showed infiltration of lymphocytes and macrophages containing dengue antigen. Other studies obtain IgM antidengue, complement and fibrinogen in skin berptikie biopsied. Though not known for certain, the presence of vasculopathy likely the result of a direct effect of dengue virus-mediated immune response.<sup>7</sup>

Endothelium is the inner blood vessel is a single-layered cell (monolayer) influential due to injury. In viral infections, including dengue virus infection, endothelial cell death can occur through the mechanism of apoptosis triggered by TNF $\alpha$  and cytokine products of immune response due to dengue virus infection.<sup>2,8</sup>

Funahara at 1987<sup>17</sup> proved that dengue virus antigen can attack directly without platelet immune respons, the bond between dengue virus antigens and antibodies interact with platelets dengue virus, and dengue virus infection causes modulation of the endothelium. Abbas AK. 2007<sup>18</sup> suggested that individual as a result of an activated immune response of dengue virus can have a positive impact in the form of destruction of the virus or on the contrary, the negative impact that ended with endothelial injury and death through cytokine that plays an important role in the course of disease caused by dengue virus infection is TNF $\alpha$ , IL-1, IL-6 and IFN $\gamma$ . Various research findings indicate that endothelial injury led to the emergence of a variety of adhesive molecules derived from endothelial cells themselves and from the sub-endothelial triggering platelet aggregation. That is, the process of apoptosis that occurs in endothelial cells by TNF as fasligand cause endothelial cells loose the bonds with which the sub-endothelial molecules obtained vonWillebrand (vWF), which appears on the surface and leads to platelet aggregation. Nawroth at 1986<sup>19</sup> found that endothelial injury followed by an increase in procoagulant activity, while Holvoet at 1998<sup>20</sup> found that endothelial injury followed by a decrease in anticoagulant activity. The research findings if Mauro at 1992 showed that IL-6 has the ability to increase endothelial permeability. This means, IL-6 seems to also cause injury to the endothelium.<sup>21</sup> Endothelial disruption due to injury can be examined by inhibition and plasminogen activator-1 (PAI-1) are increased in the circulation.<sup>6</sup>

New development of endothelial dysfunction is the concept of microparticles. All DHF patients show decreased levels of microparticles during acute illness and increased significantly in the past rekonvalesensi. Further research is needed to address the extent to which the role of microparticles causes increased capillary permeability and in certain circumstances lead to disseminated intravascular coagulation.<sup>6</sup>

## B. THROMBOPATI AND THROMBO-CYTOPENIA

Thrombocytopenia is one simple criteria proposed by the WHO as a clinical diagnosis of dengue disease. The cause of thrombocytopenia in DHF is still controversial. Thrombocytopenia and hemoconcentration are two circumstances which almost always appear on the disease caused by dengue virus infection. In patients with DHF, tombsitopenia be due to decreased production of platelets by the bone marrow, increased destruction of platelets in the Reticulo Endothelial System (RES) and aggregation of platelets by damaged vascular endothelium.<sup>2,5</sup> And allegedly also due to intravascular coagulation and consumption of clotting factors and platelets are increased.<sup>2,5,15</sup>

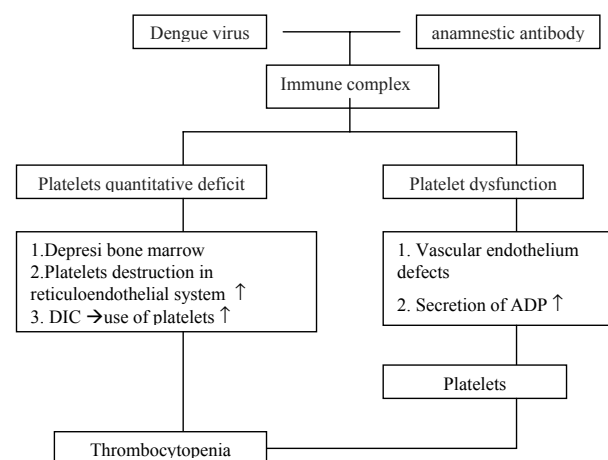
Nimmannitya at 1999<sup>7</sup> suggested that the main cause of thrombocytopenia is a decrease in consumption and platelets in peripheral desruksi. Destruction of platelets played by complement activation as the bond between platelets with fragments and dengue virus antigen, or it can occur by direct attack against platelets without dengue virus through immune responses.<sup>2</sup> Mitrakul at 1987<sup>22</sup> concluded that the occurrence of thrombocytopenia due to the shortening of the life of platelets and platelet function decline due to dengue virus infection.<sup>7</sup>

From these studies it can be concluded that in patients with DHF decreased production, increased destruction and excessive use of platelets, resulting in thrombocytopenia. In addition to the quantitative deficit, there is also a platelet function disorder. This is evidenced by the increased secretion of ADP and plasma prostaglandin metabolite (PGI 2), namely 6-keto-PGFI $\alpha$  (6KPGF1).<sup>15</sup>

Several reports from the literature indicating normal platelets do not stick to the vascular endothelium, except when there is activation of such damage or tear the vascular intima layer vascular structure.<sup>8,22</sup>

The platelet response to activation, in general there are four types: (1) changes in platelet shape from flat pieces into a round spiked, (2) adhesion, platelet attachment to the vessel wall subendotelium or on the network of collagen, (3) aggregation, platelet attachment of one each other, (4) secretion, such as ADP, tromboxane A2 (TXA), serotonin, calcium and others. ADP -induced platelet aggregation of platelets that have been attached to the walls of blood vessels are damaged while PGI2 is a platelet aggregation inhibitor. PGI2 effects besides opposed to ADP, is also opposed to tromboxane A2 which is also secreted by dense granules in platelets.<sup>7,8,22</sup>

Inactivation of platelets by PGI2 in endothelial suspected as responsible for the absence of platelet adherence. But this hypothesis is not supported by research and the mechanisms by which PGI2 to prevent platelet adherence remains unclear.<sup>2,8,22</sup>



**Figure 1.** Mechanisms of thrombocytopenia in DHF.<sup>23</sup>

### C. COAGULOPATHY

Hemostasis of blood vessels is maintained through a balance between coagulation and fibrinolysis. Coagulation system is activated via the intrinsic and extrinsic pathways to convert fibrinogen to fibrin. While the fibrinolysis system damage tissue degradation products of fibrin to fibrin (FDP).<sup>15</sup>

Many studies have identified the mechanism of occurrence of hemorrhagic in some cases the presence of coagulopathy DHF. Almost all cases of DHF with shock occurs coagulopathy. with prolongation of activated partial thromboplastin time (APTT).<sup>7</sup> In acute infection with dengue virus, which is commonly used coagulation parameters are platelets and (APTT) and the parameters of fibrinolysis is tissue plasminogen activator (tPA) and plasminogen activator inhibitor (PAI-1).<sup>15,16</sup>

Studies that have been conducted in Indonesia noted the thrombocytopenia, a decrease in plasma fibrinogen and factor VIII and increased fibrin degradation product D-dimer (FDP-D).<sup>7</sup>

Mechanisms that might explain the occurrence of coagulopathy is the presence of viral antibody complexes or mediators phagocytes infected with dengue virus. Coagulation is activated sequentially following the cascade that begins with the activation of factor XII into factor XIIa. Subsequently activates Factor XII fibrinolysis system with changes of plasminogen to plasmin. Plasmin will break down the fibrin polymer into fragments X and Y. The Y fragment is broken down into two fragments D and one fragment E, known as the D - dimer. The degradation of fibrin (FDP) has the properties as an anti-coagulant, so that considerable amounts will inhibit hemostasis.<sup>6,15</sup>

Activation of coagulation and fibrinolysis system prolonged the resulting decline in various coagulation factors such as fibrinogen, II, V, VII, VIII, IX and X and plasminogen. This situation caused and worsened the hemorrhagic in DHF patients, coupled with the presence of thrombocytopenia.<sup>15</sup>

The complement system and the kinin system plays a role in the inflammatory process is activated by factor XIIa also resulted an by increase in blood vessels which play a role in the occurrence of shock.<sup>15,24</sup>

### D. DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

DIC is a clinical syndrome characterized by widespread activation of coagulation system resulting in the formation of intravascular fibrin and eventually thrombosis of blood vessels resulting in decreased blood to organs and cause organ failure. Due to excessive coagulation deficiency of platelets and coagulation factors that can cause heavy hemorrhagic.<sup>25</sup>

The role of DIC in patients with DHF have been widely studied. The occurrence of DIC in patients with DHF is still a question mark.<sup>15,25</sup> The mechanism is based on the possibility of activating factor XII antigen antibody, platelet release reaction or peeling endothelium and exposed subendothelial collagen and basement membrane.<sup>25</sup>

One study shows that in patients with DHF were found to increase the minimum levels of FDP, and not associated with disease severity. In patients with increased FDP, found partial thromboplastin time and prothrombin time were slightly elongated. FDP were increased with thrombocytopenia showed intravascular coagulation process is resulting in hemorrhagic but not prove DIC. However DHF with shock and prolonged acidosis can trigger DIC.<sup>15</sup>

While other researchers say that in all cases of dengue are found manifestations of acute type DIC. So it is clear that the natural course of the disease dengue fever which would cause the complex pathophysiology of the various systems in the body of the patient (Figure 2).<sup>15</sup>

The results of the latest research on the mechanism of hemorrhagic in DHF, states that hemorrhagic due to consumptive coagulopathy that occurs in most cases. Almost all the cases with coagulopathy shock occurs, manifested as prolonged partial thromboplastin time. Changes in liver function and normal prothrombin time/ slightly elongated, support the occurrence of consumptive coagulopathy.<sup>7,22</sup>

It can be concluded that the disturbance of hemostasis in dengue fever can be caused by multifactorial including vasculopathy (capillaries and venules), thrombocytopenia, platelet dysfunction and coagulopathy.<sup>2,5,6,7</sup>

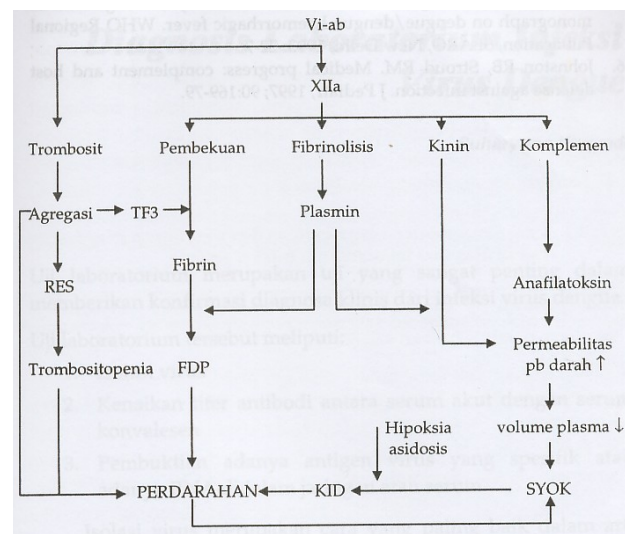


Figure 2. Pathophysiology of Hemorrhagic in DHF.<sup>15</sup>

## SUMMARY

The diagnosis of dengue is determined based on the criteria of the World Health Organization (WHO, 1999),<sup>3</sup> the contents of which are found sudden high fever accompanied by a marked tendency to hemorrhage positive tourniquet test, petechiae, ecchymosis, purpura, mucosal hemorrhagic, hematemeses or melena and thrombocytopenia.

The problem that still exists today is the mechanism of thrombocytopenia in patients with varying degrees of dengue involving levels of vWF (von Willebrand factor) and prostaglandin I<sub>2</sub> (PGI<sub>2</sub>) can not be explained.

The mechanism of hemorrhagic in dengue virus infections acquired as a result of thrombocytopenia, platelet dysfunction, decreased coagulation factors, vasculopathy with endothelial injury and disseminated intravascular coagulation (DIC).

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