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Pathogenesis, Symptoms and Diagnosis, and Prevention of Dengue Hemorrhagic Fever in Adults

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ABSTRACT

Dengue Hemorrhagic Fever (DHF) is an infectious disease caused by the dengue virus, characterized by symptoms such as fever, muscle or joint pain, leukopenia, rash, lymphadenopathy, thrombocytopenia, and hemorrhagic tendencies. In DHF, there is plasma leakage leading to fluid accumulation in body cavities, and in severe cases, it can progress to Dengue Shock Syndrome, characterized by shock. The illness is mainly spread by Aedes aegypti and Aedes albopictus mosquitoes, presenting a substantial worldwide health issue. The diagnosis of DHF requires the presence of several criteria: fever or recent history of acute fever lasting 2-7 days, often biphasic; at least one hemorrhagic manifestation such as positive tourniquet test, ecchymosis, mucosal bleeding, hematemesis, or thrombocytopenia; and evidence of plasma leakage. Young adults are particularly susceptible to dengue fever due to their frequent outdoor activities. In Padang City, West Sumatra Province, in 2020, the age group most affected by the disease was adults aged 15 to 44 years.

Keywords: *dengue haemorrhagic fever, pathogenesis of DHF, symtoms and diagnosis of DHF.*

INTRODUCTION

Dengue Hemorrhagic Fever (DHF) is an infectious illness caused by the dengue virus, manifesting with symptoms like fever, muscle pain, and/or joint pain, accompanied by leukopenia, rash, lymphadenopathy, thrombocytopenia, and hemorrhagic tendencies. Severe cases involve plasma leakage, characterized by either hemoconcentration (increased hematocrit) or fluid accumulation in body cavities. Dengue Shock Syndrome (DSS) is a severe form of dengue fever that includes shock as a prominent feature (Suhendro et al., 2014).The vector that causes disease is found in the rainy season, where many puddles of water where mosquitoes breed. Several studies indicate that the prevalence of Dengue Hemorrhagic Fever (DHF) is associated with factors such as mobility, population density, and community behavior (Ministry of Health of the Republic of Indonesia, 2020b). These factors play a significant role in the transmission and spread of the disease within communities. Most cases are asymptomatic or mild and can be managed on their own, many are unreported and misdiagnosed like other febrile illnesses (WHO, 2023). Dengue that is not treated can trigger extraordinary events (KLB), severe dengue, and even death. This situation represents a substantial burden on societies, healthcare systems, and economies in many tropical countries worldwide (WHO, 2012). Dengue incidence has significantly

increased worldwide over the past few decades. For over five decades, dengue has emerged as a growing global public health concern. In early 2020, WHO then included dengue as one of the global health threats among 10 other diseases (WHO, 2023). The increase dengue incidence from year to year has not been accompanied by a corresponding increase in mortality rates. The death rate due to dengue, which was originally as high as 41.3% at the beginning of the discovery of this disease (1968), has decreased drastically to less than 1% since 2008 until now (Ministry of Health of the Republic of Indonesia, 2023).

METHOD

The method in this study uses literature review. The references taken are scientific-based journals with a thorough search from verified journals such as Pubmed, Scholar, Google Scholar, as many as 36 articles that have met the criteria. The search in this article is divided into two ways, namely with Publish or Perish software version 8 and manual.

RESULT AND DISCUSSION

Dengue Hemorrhagic Fever (DHF) is caused by the dengue virus, leading to clinical symptoms like fever, muscle or joint pain, along with leukopenia, rash, lymphadenopathy, thrombocytopenia, and hemorrhagic tendencies. In severe cases, plasma leakage occurs as hemoconcentration or fluid accumulation in body cavities. Dengue Shock Syndrome (DSS), a severe form, presents with shock and can be fatal (Suhendro et al., 2014; Sukohar A, 2014). These diseases are transmitted by mosquito vectors primarily Aedes aegypti and Aedes albopictus, posing significant global health challenges (World Health Organization, 2020; Ministry of Health of the Republic of Indonesia, 2021b).

Dengue fever can occur throughout the year and affects individuals of all age groups (Agustini II & Bangkele EY, 2018). Dengue Hemorrhagic Fever (DHF) is endemic in more than 100 countries spanning Africa, the Americas, the Eastern Mediterranean, Southeast Asia, and the Western Pacific regions. The Americas, Southeast Asia, and the Western Pacific are particularly affected, with Asia bearing 70% of the global burden. Dengue thrives in tropical and subtropical climates worldwide, predominantly in urban and semi-urban areas (WHO, 2023).

In Indonesia, the Incidence Rate of Dengue in 2019 was 51.48 per 100,000 population. There is an increase from the previous two years, namely 2017 and 2018 with a Dengue Incidence Rate of 26.1 and 24.73 per 100,000 population, respectively. In West Sumatra province, the incidence rate of Dengue cases is 41.59 per 100,000 population. Nationally, the Case Fatality Rate (CFR) for Dengue showed a slight decrease from 0.71% in 2018 to 0.67% in 2019. Specifically, in West Sumatra Province, the CFR is 0.40% (Ministry of Health of the Republic of Indonesia, 2020b & Ministry of Health of the Republic of Indonesia, 2020a). From 2020 to 2022, there was a notably volatile pattern in Dengue cases, possibly influenced by the Covid-19 pandemic situation in Indonesia. Additionally, the initial symptoms of Dengue and Covid-19 are similar, which can complicate early diagnosis and management (Ministry of Health of the Republic of Indonesia, 2023).

The total number of dengue cases in Indonesia rose from 73,518 individuals in 2021 to 131,265 cases in 2022. Concurrently, the number of deaths increased from 705 individuals in 2021 to 1,183 individuals in 2022. (Nababan, 2023). The Padang City Health Office indicates that Dengue Hemorrhagic Fever (DHF) cases are experiencing an increasing trend. There were 441 cases in 2022, compared to only 366 cases in 2021. The Head of the Padang City Health Office, Dr. Sri Kurnia Yati, along with the Head of Disease Prevention and Control (P2P), mentioned that the age group most affected by the disease in Padang City is adults aged 15 to 44 years (Padang Health Office, 2022).

The dengue virus, part of the Flaviviridae family, is primarily transmitted by mosquitoes of the Aedes genus, particularly Aedes aegypti. There are four serotypes of the dengue virus (DENV) – DENV-1, DENV-2, DENV-3, and DENV-4 – which are distinct yet antigenically related. These serotypes are responsible for causing disease in tropical and subtropical regions globally (Halstead SB, 2019). These viruses are classified as group B Arthropod-borne viruses (arboviruses). In Indonesia, all four types of dengue virus have been identified, with types 2 and 3 being the most prevalent. Research conducted in Indonesia indicates that Dengue type 3 is the dominant serotype responsible for severe cases (Suhendro et al., 2014).

1. Risk Factors

The high prevalence of dengue disease is inseparable from the imbalance between causative factors originating from infectious vectors (mosquitoes), hosts (humans), and the environment (Suwandono A, 2019). One of the host factors that affect the incidence of dengue is immune status, which is a defense in a person's body that is influenced by age, gender, type of infection, and nutritional status. According to research by Indah Jayani and Fadilah in 2019, dengue cases are more common in children under 15 years old and children with more nutritional status will suffer more severe symptoms if infected with dengue disease (Jayani I, 2019). In addition, there are also environmental factors that affect the existence of infectious vectors. These factors consist of high temperature, climate, population density and mobility, unqualified clean water facilities, and disadvantaged community behavior (Sandra et al., 2019).

2. Pathogenesis Of Dengue Hemorrhagic Fever

Until now, there is no single theory that can fully explain the pathogenesis of dengue infection. This happens because there is no animal model that can fully show reactions and symptoms like in humans when infected with the dengue virus (Ministry of Health of the Republic of Indonesia, 2021b; Begum et al, 2019) Pathogenesis occurs due to the complex interaction between viruses, genes, hosts and host immune responses (Bhatt et al., 2021).

Aedes spp mosquitoes that have been infected with the dengue virus, will remain infective throughout their lives and continue to transmit to vulnerable individuals when biting and sucking blood. After entering the human body, the dengue virus goes to the target organs, namely hepatic cuffer cells, endothelium of blood vessels, lymph nodes, bone marrow and lungs. Several studies have shown that monocyte cells and macrophages have a role in this infection, starting with the attachment and entry of the viral genome into the cell with the help of cell organelles and forming intermediate components and structural components of the virus. Once the structural components are assembled, the virus is released from inside the cell. This infection causes a protective immune reaction against the virus serotype but there is no cross protection against other virus serotypes (Candra, 2020). In vitro, the antibody against dengue virus has 4 biological functions, namely virus neutralization, complement cytolysis, anti-body dependent cell-mediated cytotoxity (ADCC) and antibody dependent enhancement (ADE) (Darwis D, 1999).

Based on its role, it consists of neutralizing antibodies that have specific serotypes that can prevent viral infections, and non-neutralizing serotypes that have a cross-reactive role and can increase infections that play a role in the pathogenesis of dengue and DSS (Soegijanto, 2022).

The immune responses involved in dengue pathogenesis include: a) Humoral responses: This involves antibody formation, which plays a crucial role in virus neutralization, complement-mediated cytolysis, and antibody-mediated cytotoxicity. However, antibodies can also facilitate viral replication in monocytes and macrophages

through a process known as antibody-dependent enhancement (ADE). b) Cellular immune responses: T-helper (CD4) and T-cytotoxic (CD8) cells are integral to the cellular immune response against the dengue virus. TH1 cells produce interferon gamma, IL-2, and lympholycin, whereas TH2 cells produce interleukins such as IL-4, IL-5, IL-6, and IL-10. c) Monocytes and macrophages: These cells play a role in viral phagocytosis through antibody opsonization. However, this process can lead to increased viral replication and cytokine production by macrophages. d) Complement activation: Immune complex-mediated activation of the complement system results in the production of C3a and C5a, which contribute to the inflammatory response. These immune responses collectively contribute to the pathogenesis of dengue fever and its severe forms (Suhendro et al., 2014; Soegijanto S, 2006).

In dengue, the theory of secondary heterologous infection posits that increased platelet aggregation leads to platelet destruction by the reticuloendothelial system (RES), resulting in thrombocytopenia (Ministry of Health of the Republic of Indonesia, 2011).

All of these theories state that the main battlefield of dengue infection is in the endothelium of blood vessel capillaries. The endothelium has an important function of maintaining vascular tone, preventing blood clots and migration of blood cells, producing chemoattractants, and maintaining blood vessel permeability. This function is necessary so that the blood supply to the organs of the body is well maintained, so the endothelial cells must remain stable. The stability of vascular endothelial cells is maintained by the links between cells composed of protein molecules. The links between endothelial cells that play the most role are tight junctions and adherens junctions. The links between endothelial cells form a very narrow gap between endothelials (paracellular pathways) and can only be passed by small molecules less than 2 nm in diameter such as water, urea, glucose, electrolytes, etc. When the gap between the endothelium widens, larger molecules and blood cells can pass through (plasma leakage). In dengue, plasma leakage occurs due to various factors released during infection. Interleukins such as IL-1 and IL-6, tumor necrosis factor alpha (TNF-α), histamine, bradykinin, anaphylatoxins C3a and C5a, vascular endothelial growth factor (VEGF), complement activation products, thrombin, and antibodies are released and contribute to the activation and contraction of actin filaments in capillary endothelial cells. This process compromises the integrity of capillary walls, leading to plasma leakage and fluid accumulation in body cavities, a hallmark of severe dengue disease. Contraction causes the link proteins between endothelial cells (tight junction and adherens junction) to enter the cell, so that the gap between cells widens and causes plasma leakage (Ministry of Health of the Republic of Indonesia, 2020b; Anderson et al., 2014). Leukocyte cells are indeed implicated in the process of plasma leakage in dengue fever. When endothelial cells are activated during infection, they express cell adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin, P-selectin, and platelet endothelial cell adhesion molecule-1 (PECAM-1). These molecules facilitate the attachment and migration of leukocytes across the endothelium. This interaction contributes to inflammation and further compromises the integrity of blood vessel walls, exacerbating plasma leakage seen in severe dengue cases. As the adesion molecule increases, more leukocytes attach to the endothelium, triggering local inflammation, damaging endothelial cells, and worsening plasma leakage. Leukocyte migration will cause leukopenia and also potentially cause plasma leakage. Platelets are one of the important parameters in dengue. Low platelets can occur due to viral suppression in the bone marrow, peripheral platelet destruction, and platelet consumption in blood vessels (Hukom et al., 2013). ccording to Das et al. (2022), the dengue virus (DENV) can directly or indirectly interfere with the function of bone marrow progenitor cells, leading to a reduced capacity for proliferation of hematopoietic cells. This interference can impact the production of blood cells in the bone marrow, potentially contributing to

hematological manifestations such as thrombocytopenia and leukopenia observed in dengue-infected individuals. Damaged platelets release VEGF and activate the endothelium and further exacerbate plasma leakage. A combination of various mechanisms that occur in dengue can manifest as petekie hemorrhage. Petekie arises due to disruption of vascular integrity due to stimulation of proinflammatory cytokines, thrombocytopenia, coagulation disorders, and viral infections in endothelial cells. Petekie at the beginning of the sick course is due to dengue virus infection in capillary endothelial cells (vasculopathy) while petekie at the next sick course is due to a very low platelet count and coagulation disorders. Petekie at the beginning of the painful journey of dengue infection causes blood vessels to leak more easily. (Ministry of Health of the Republic of Indonesia, 2020b) Dengue disease has two main pathological changes, namely increased capillary permeability and hemostasis disorders. First, there is an increase in capillary permeability which can cause a loss of plasma volume in the blood vessels resulting in hemoconcentration. An increase in hematocrit is very common in shock cases, so it is necessary to check hematocrit values in monitoring dengue cases (Hukom et al., 2013).

3. Symptoms And Diagnosis Of Dengue Hemorrhagic Fever

The clinical manifestations of dengue virus infection can vary widely, from asymptomatic cases to various forms of illness such as atypical fever, dengue fever, dengue hemorrhagic fever, dengue shock syndrome, and extended dengue syndrome. Typically, patients experience fever for 2-7 days, followed by a critical phase lasting 2-3 days. During this critical phase, the fever subsides, but there is a risk of progressing to shock if the patient does not receive appropriate treatment (Suhendro et al., 2014).

Dengue fever: During the acute phase of dengue fever, which lasts 2-7 days, patients typically present with two or three of the following clinical manifestations: headache, retroorbital pain (pain behind the eyes), myalgia (muscle pain), arthralgia (joint pain), skin rash, and hemorrhagic manifestations such as petechiae or a positive tourniquet test. Laboratory findings often include leukopenia (less than 5000 cells/mm^3), thrombocytopenia (platelets less than 150,000 cells/mm^3), and an increase in hematocrit by 5-10%. Serological testing confirms dengue positivity or identifies Dengue Fever (DF) / Dengue Hemorrhagic Fever (DHF) in patients diagnosed at the same location and time (Suhendro et al., 2014).

Dengue hemorrhagic fever (DHF): The WHO criteria for diagnosing dengue fever, as outlined in 1997, require the presence of several conditions: fever or a history of acute fever lasting 2-7 days, usually biphasic; at least one bleeding manifestation such as a positive tourniquet test, ecchymosis, mucosal hemorrhage, bleeding from other sites, hematemesis, or melena; and thrombocytopenia, defined as a platelet count of less than 100,000 cells/mm^3. At least one sign of plasma leakage, such as: An increase in hematocrit by more than 20% compared to baseline or standard values adjusted for age and sex, A decrease in platelet count by more than 20% after fluid therapy compared to previous values, Clinical signs of plasma leakage like pleural effusion, ascites, or hypoproteinemia.

Dengue Shock Syndrome: all dengue criteria plus failure of circulation with a fast and weak pulse, blood pressure drops (<20 mmHg), hypotension compared to the standard of age, cold, moist and restless skin. (Suhendro et al., 2014) An increase in hematocrit value describes the condition of hemoconcentration that is always found in dengue patients, and is a sensitive indicator of plasma leakage, so it is necessary to carry out regular hematocrit examinations. An increase in hematocrit levels of more than 20% (hemoconcentration) occurs due to plasma leakage from the in vascular space to the extravascular space accompanied by reduced fluid effusion, causing an increase in hematocrit levels which increases the incidence of hypovolemic shock and circulatory disorders. It generally occurs on the third day of fever (Suhendro et al.,

2014). Hematocrit values will decrease when hemodilution occurs, which can result from a decrease in blood cellular levels or an increase in blood plasma levels, as seen in conditions like anemia (Hidayat et al., 2017).

4. Classification Of Dengue Virus Infection Degrees

The management of dengue fever needs to know the classification of the degree of the disease as follows:

Grade I (DD): fever with two or more signs of headache, retro orbital pain, antralgia, myalgia, leukopenia, no plasma leakage found. Grade II (DHF): symptoms above with spontaneous bleeding, thrombocytopenia (<100,000 cells/mm^3), evidence of plasma leakage. Grade III (DHF): The above symptoms include symptoms of circulatory failure (cold, damp and restless skin), thrombocytopenia (<100,000 cells/mm^3), evidence of plasma leakage. Grade IV (DHF): Severe shock accompanied by immeasurable blood pressure and pulse. thrombocytopenia (<100,000/mm^3), evidence of plasma leakage. Degrees III and IV are also called Dengue shock Syndrome (DSS) (Suhendro et al., 2014 &. World Health Organization, 1997).

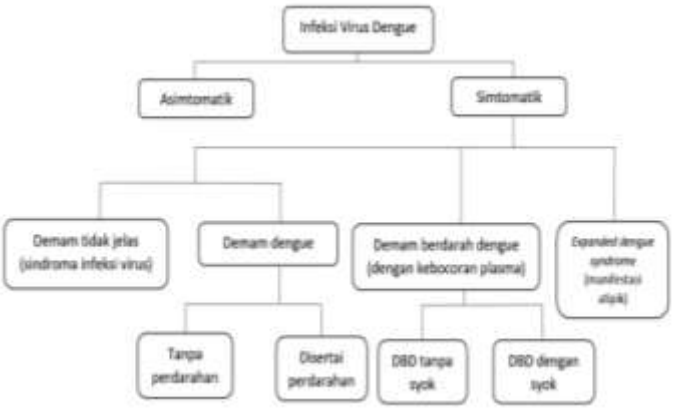

Figure 1. Clinical manifestations of dengue virus infection. (Ministry of Health of the Republic of Indonesia, 2020a).
Source: Data Processing

Laboratory Examination: Routine blood tests for Hb, Ht, Leukocytes and Platelets and must be peripheral blood of relative lympositosis accompanied by blue plasma lymphocytes. Definitive diagnosis with Reverse Transcriptase Polymerase Chain Reaction (RT-PCR), serological tests in the form of total IgM antibodies or more IgG. Examination of PT, APTT, Fibrinogen. D-Dimer. PDP. Protein and albumin in plasma leakage, SGOT/SGPT daopat increased. Urea, crestinin bils sds interfere with kidney function. Electrolyte examination. Radiological examination: Chest photo of pleural effusion in case of plasma secretion, ultrasound in case of ascisicle. (Suhendro et al., 2014).

Dengue disease that does not receive immediate treatment can cause death, up to 50%, but the mortality rate can be minimized to 5% and can even reach 3% or lower with quick action or treatment (Ministry of Health of the Republic of Indonesia, 2017).

Young adults have high mobility and smooth transportation development, making it easier to contract the dengue virus that has never existed before in an area. (Steven et al., 2013). Sumarno said that the disease can spread starting from a source of transmission or a big city, then following traffic or population mobility. The higher the mobility, the greater the possibility of spreading dengue disease. Therefore, the young

adult age group is often the main target of dengue fever because many have a lot of activities during the day outside the home. (Misnardiarly, 2009).

5. Prevention

Mosquito larvae control programs are widely encouraged at home and have been proven to reduce the number of mosquitoes at home so that infected inside the house become small but outside the house becomes large (Vebriani et al., 2016). Many adults infected with dengue can be caused by a lot of activities outside the home and lack of vigilance with self-protection from mosquito bites, mosquitoes are very easy to fly from one house to another, from one office to another or to public places such as houses of worship, restaurants, and others (Misnardiarly, 2009).

Implementing the 3M Plus Mosquito Nest Eradication (PSN) strategy involves several key actions to combat the breeding of dengue fever mosquitoes: 1). Draining: Regularly cleaning and draining water reservoirs such as bathtubs, jugs, water tanks, and drums. It is essential to scrub the walls of these containers to remove mosquito eggs that may be attached. This should be done daily during the rainy season and pancaroba (transition period between seasons) to disrupt the mosquito life cycle, as mosquitoes can survive in dry places for up to 6 months. 2). Closing: Securely closing water reservoirs such as bathtubs and drums, or burying used containers in the ground to prevent them from accumulating water and becoming mosquito breeding sites. 3). Recycling: Reusing or recycling used goods that could potentially become breeding grounds for dengue fever mosquitoes. This includes ensuring items are disposed of properly or repurposed to minimize standing water. Additionally, the Plus component includes supplementary preventive measures: Raising fish that consume mosquito larvae, using mosquito repellents, Installing wire mesh on windows and ventilation openings, Collaborating with the community to maintain cleanliness and eliminate potential mosquito breeding sites. These efforts must be continuous, consistent, and targeted to effectively reduce the mosquito population and prevent the spread of dengue fever (Ministry of Health of the Republic of Indonesia, 2021a).

We must be aware of the signs and symptoms of dengue. Immediately report to the nearest health service facility if you suspect dengue (Ministry of Health of the Republic of Indonesia, 2021a). If people experience symptoms of dengue fever, it is very important to come to the hospital to check it so that it can be quickly treated according to the severity they are experiencing (Agustini & Bangkele, 2018). The number of patients at grade 1 is due to fast treatment so that dengue can be prevented to the next degree (Syumarta et al., 2014). If people experience symptoms of dengue disease itself, it is very important to come to the hospital to check it so that it can be quickly treated according to the severity of the disease they are experiencing (Agustini et al., 2018).

CONCLUSION

Dengue Hemorrhagic Fever (DHF) is an illness triggered by the dengue virus, characterized by symptoms including fever, muscle and joint pain, leukopenia, rash, lymphadenopathy, thrombocytopenia, and a tendency to hemorrhage. In dengue fever, there is plasma permeation characterized by hemoconcentration or accumulation of fluid in the body cavity. Dengue shock syndrome is characterized by shock. DHF is endemic in over 100 countries across Africa, the Americas, the Eastern Mediterranean, Southeast Asia, and the Western Pacific. The Americas, Southeast Asia, and the Western Pacific are the most affected regions, with Asia bearing 70% of the global burden. Dengue is transmitted by Aedes aegypti and Aedes albopictus mosquitoes, predominantly affecting young adults due to their outdoor activities. Diagnosis requires meeting specific criteria: fever or history of acute fever for 2-7 days, often biphasic, accompanied by at least one bleeding manifestation (e.g., positive tourniquet test,

ecchymosis, mucosal bleeding), thrombocytopenia, and signs of plasma leakage. Prevention includes controlling mosquito larvae through continuous, targeted implementation of 3M Plus Mosquito Nest Eradication (PSN).

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