

DENGUE HEMORRHAGIC FEVER: PAST, PRESENT, AND FUTURE

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Abstract: Dengue viral infection is a global disease with a spectrum of clinical manifestations mild fever to severe disease both dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). DHF is severe form of dengue fever (DF), which can be life-threatening. Climate changes is not the only factor that affects dengue transmission, but also globalization changes includes travel and trade. The pathogenesis of dengue infection is complex. The mechanism involved antibody-dependent enhancement, NS1 and its antibodies, T cells, and DENV genomics. There are several novel methods to detect the presence of dengue virus in the body of infected patients. These include ELISA-specific IgM and IgG detection, detection of monoclonal antibodies and mosquito cell strains, and PCR reverse transcriptase detection. Several trials found novel methods to predict the severity of dengue hemorrhagic fever earlier. These include platelet count, Aspartate aminotransferase / platelet count index (APRI) Index, serum chymase level, serum cytokine/chemokine profile, Tropomyosin-alpha 1 (TPM 1), Reticulocyte Production Index (RPI), and Immature Platelet Fraction (IPF). Several pharmacological therapies are known to have potential antidengue effect. Some of these are corticosteroids, antimalarial drugs, doxycycline and tetracycline, anticholesterol drugs, IVIG, celgosivir, balapiravir, pentoxifylline and calcium supplementation. Some natural products are known to have activity against *Aedes aegypti* through antiviral mechanisms, larvacidal activity, mosquitocidal, and mosquito repellants. It can be developed as the latest therapy of dengue hemorrhagic fever on the future. The objective of this paper is to provide new insight about the development of dengue hemorrhagic fever related to the history of its distribution, pathogenesis, and the latest developments related to detection methods, severity prediction methods, and the management of dengue hemorrhagic fever on the future.

Keywords: globalization changes, novel detection methods, severity prediction methods, latest development in DHF therapy

INTRODUCTION

Dengue viral infection is a global disease with a spectrum of clinical manifestations mild fever to severe disease both dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). DHF is severe form of dengue fever (DF), which can be life-threatening.¹ In 2007, the incidence of dengue in Indonesia was 136,695 cases with incidence rate (IR) 64 cases in 100,000 population with the number of patients who died was 1,395 cases (case fatality rate/CFR 1%).² Surveillance data on 2016 identified a dengue viral infection incidence in West Java, Indonesia of 17.3 cases/1000 per-years.³ According to surveillance data on 2017 in Indonesia, annual average (2006-2015) of dengue viral infection was 612,005 cases, and 183,297 hospitalizations.⁴

The epidemic of dengue viral infection occurred at the end of the 18th century in Asia, Africa and North America. Female mosquitoes, especially *Aedes aegypti* species and rare *Aedes albopictus*, involved in the transmission of dengue virus. Currently, dengue virus has reached more than 100 countries in the world with the incidence increasing 30 times in the last 50 years. It certainly has social and economic impacts for each country.⁵

Based on the study Bhatt et al. (2013) and the data obtained from World Health Organization (WHO) about dengue related cost and the data from International Monetary Fund (IMF) about the expenditure related to loss of productivity due to dengue infection, the global economic finance related dengue estimated at 39.3 billion US Dollar (about 414 US Dollar per symptomatic case) on 2011.^{6,7}

The burden related to dengue infection is increasing. More than half the global population lives in areas with high dengue transmission risk. It is certainly a challenge for policymakers to set priorities, allocate

resources, and plan interventions.⁸ This paper provides new insight about the development of dengue hemorrhagic fever related to the history of its distribution, pathogenesis, and the latest developments related to the detection methods, severity prediction methods, and the management of dengue hemorrhagic fever on the future.

HISTORY OF DENGUE VIRAL INFECTION

Dengue viral infection has been known for centuries. Dengue symptoms were first recognized in the Chinese medical encyclopedia in 992 BC, but were actually recorded at the beginning of the Chin Dynasty (265-420 BC). The disease is considered a "liquid poison" carried by flying insects.⁹

Epidemics of cases with dengue-like symptoms occurred in the early 1635 and 1699 respectively in West India and Central America. The great epidemic occurred in 1780 in Philadelphia and often occurred in the United States in the early 20th century. The last outbreak occurred in 1945 in New Orleans. The determination of the virus as the cause of the disease and transmitted by mosquitoes was established in the 20th century.¹⁰

Epidemiology and transmission of dengue virus developed in Southeast Asia during World War II. Destruction and ecological changes occurred due to war, causing the spread of geographical distribution of viruses and vectors. The first DHF epidemic in Southeast Asia was recorded in Manila, Philippines from 1953 to 1954, followed in Bangkok, Thailand in 1958, then in Malaysia, Singapore and Vietnam in the 1960s. As the spread of economic and urbanization activities in Southeast Asia after World War II, the DF/DHF epidemic spread throughout Southeast Asia in the 1970s.¹¹

THE CURRENT GLOBAL CONDITION OF DENGUE VIRAL INFECTION

More than 3.6 billion people currently live in the tropical and subtropical regions that have high potential dengue virus transmission.^{12, 13} Global estimation vary from 50 to 200 million dengue infections, 500,000 severe dengue episodes (DHF/DSS), and more than 200,000 dengue related deaths occur annually.¹¹

In 2012, the World Health Organization (WHO) categorizes dengue as "*the most important mosquito-borne viral disease in the world*", due to its significant geographical spread of viruses/vectors and the high expenditures. Disability adjusted life year (DALY) is estimated to vary, in 2009 there is estimated to be DALY loss due to global dengue of 700,000 per year.¹¹

THE EVOLUTION OF DENGUE VIRUS

Dengue viruses have been classified according to their epidemiological effects including low, moderate, and high effects based on their transmission trends to humans and their degree of severity. Some viruses tend to be rarely transmitted to humans, while others lead to mild dengue fever manifestations. While some other genotypes have high virulence, causing symptoms with severe manifestations. Dengue virus genotypes DENV-2 and DENV-3 are commonly found in the United States and their virulence properties are lower than those in Asia.^{14, 15}

DENGUE VIRUS LIFE CYCLE AND TRANSMISION

Aedes aegypti (*Ae. aegypti*) and *Aedes albopictus* (*Ae. albopictus*) are the two most important vectors of dengue. The female *Aedes* mosquito deposits eggs on damp surfaces just above the waterline. Under optimal conditions, the adult emerges in seven days (after the aquatic stages in the life

cycle of *Aedes*). At low temperatures, it may take several weeks to emerge. The eggs can withstand desiccation (can remain in a viable dry condition) for more than a year and emerge within 24 hours once it comes in contact with water. This is also a major hurdle in prevention and control of dengue.¹⁶

Climatic conditions, particularly temperature and rainfall, have a major impact on the life cycle, breeding and longevity of vectors and thus transmission of the disease. The average survival of *Ae. Aegypti* is 30 days and *Ae. albopictus* is about eight weeks. During the rainy season, when survival is longer, the risk of virus transmission is greater. *Aedes* is a daytime feeder and can fly up to a limited distance of 400 metres.¹⁶

The female *Ae. aegypti* usually becomes infected with the dengue virus when it takes a blood meal from a person during the acute febrile (viremia) phase of dengue illness. After an extrinsic incubation period of 8 to 10 days, the mosquito becomes infected. The virus is transmitted when the infected female mosquito bites and injects its saliva into the wound of the person bitten. The cycle of dengue continues by this process. Dengue begins abruptly after an intrinsic incubation period of 4 to 7 days (range 3–14 days). There is also evidence of vertical transmission of dengue virus from infected female mosquitoes to the next generation. Though transmission primarily occurs through the bite of a vector, there are reports of dengue transmission through blood transfusion and organ transplantation. There are also reports of congenital dengue infections occurring in neonates born to mothers infected very late in pregnancy.¹⁶

THE FACTOR OF CLIMATE CHANGES

Temperature has an important role in the survival of adult vectors, viral replication, and periods of infection.¹⁰ Increased temperatures result in increased survival

and/or vector displacement to non-endemic areas outside the tropics area.¹⁷

According to the Intergovernmental Panel on Climate Change, temperatures are predicted to increase worldwide. It creates favorable climatic and environmental conditions for the development of *Aedes* species in previously non-endemic areas. Climatic suitability in many of the current non-endemic areas and future climate similarities indicate in the future that *Aedes aegypti* and *Aedes albopictus* will be more enduring.¹⁸

Several studies that examine the relevance of climate change and temperature indicate an increased chance of dengue transmission due to high temperatures, humidity, and rainfall. Hales et al. (2002) predicts about 50-60% of the global population will live in the high dengue transmission areas by 2085.¹⁷

THE FACTORS OF GLOBALIZATION, TRAVELLING, AND TRADES

Climate change is not the only factor that affects dengue transmission, but also "*global change*". The "*global change*" means the various factors in the modern world that contribute to the development of vector-mediated diseases.¹⁹

Modern factors that contribute on the spread of vector-mediated diseases are the factors of globalization, which include travel and trade, which facilitate the transfer of

vectors to new places and suitable climatic conditions. The increasing mobility of both vector and human populations is the most important factor that can explain the recent increase in dengue transmission.¹²

The increase in dengue cases in Indonesia influenced by *Aedes aegypti* as the vector. *Aedes aegypti* occupy domestic habitats, especially man-made water reservoirs. The container index is an indicator to measure larvae density in water reservoirs, both in controllable sites and disposable sites. It shows that houses with high container index have a greater risk of dengue transmission than houses with lower index.²⁰

PATHOGENESIS DENGUE VIRAL INFECTION

NS1 and its antibodies contribute to the pathogenesis of DHF by triggering complement activation through the production of proinflammatory cytokines, autophagy induction of endothelial cells, increasing DENV replication, and autoimmune triggers. Genomic variation increases virulence, and sRNA induces viral replication; ADE mediated by FcγR increase viral replication and induces releasing cytokines and chemokines. Reactive T cells activated by specific DENV trigger the release of cytokines and chemokines, and T cell apoptosis which plays a role in the pathogenesis of DHF (fig.1).²¹

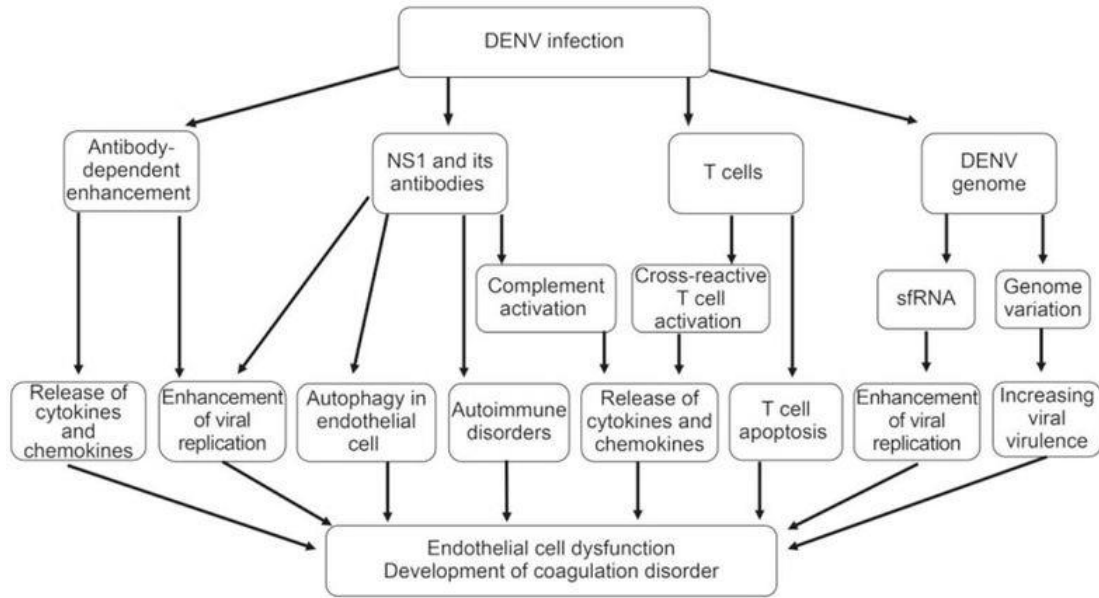


Figure 1. Mechanisms involved in the pathogenesis of DHF involving non-structural protein-1 viral antigens (NS1) and their antibodies, viral genomic variation, sfRNA, antibody-dependent enhancement (ADE), and memory T cells.²¹

CLINICAL SYMPTOMS OF DENGUE HEMORRHAGIC FEVER

Clinical manifestations of dengue infection may be asymptomatic or fever with no specific symptoms (viral syndrome), dengue fever, dengue hemorrhagic fever (DHF), or dengue shock syndrome (DSS). The emerging clinical manifestations depend on viral strains, primary/secondary infections, and host factors (age, immune status, etc.).^{16, 22}

DHF CLASSIFICATION ACCORDING TO WHO (FIG.2)²²:

1. Undifferentiated Fever

Infants, children and adults who have been infected with dengue virus, especially for the first time (i.e. primary dengue infection), may develop a simple fever indistinguishable from other viral infections. Maculopapular rashes may accompany the fever or may appear during defervescence.²²

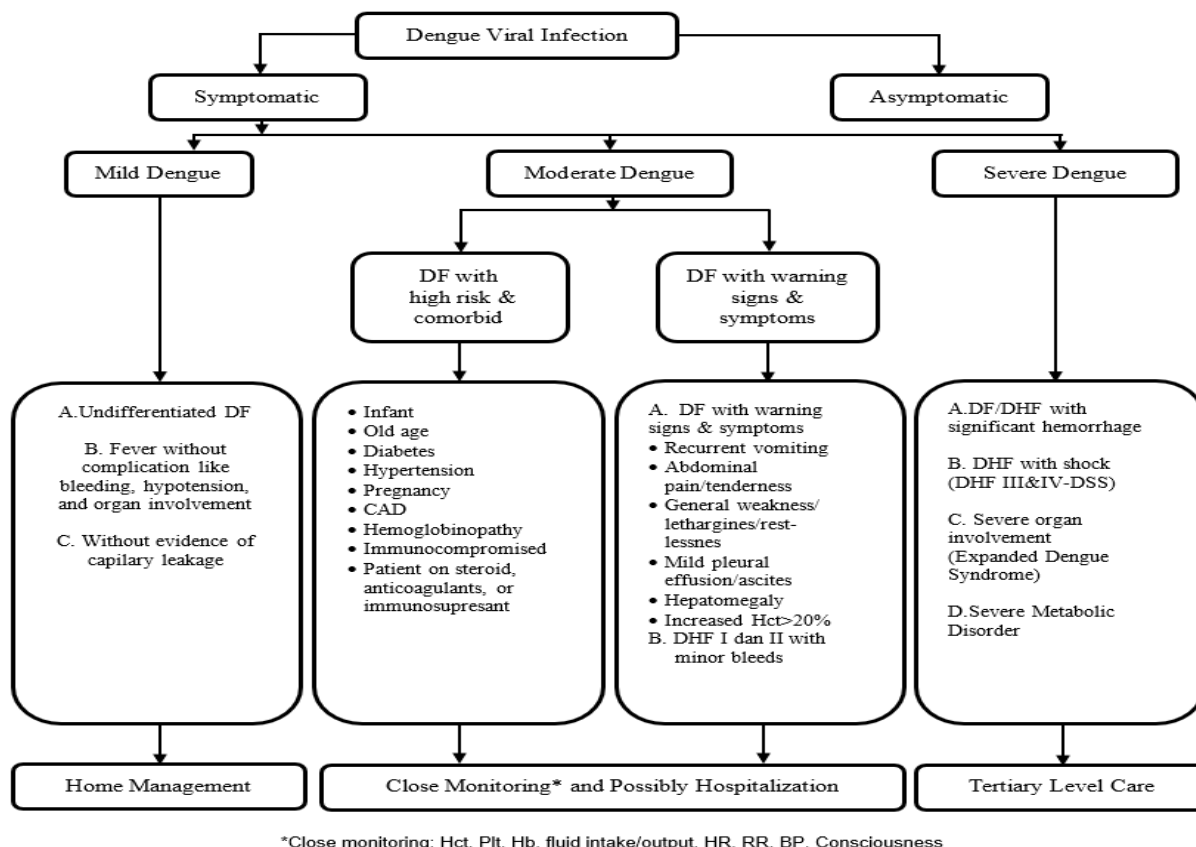


Figure 2. WHO recent classification of dengue fever.²²

2. Dengue Fever

Dengue fever (DF) is most common in older children, adolescents and adults. It is generally an acute febrile illness, and sometimes biphasic fever with severe headache, myalgias, arthralgias, rashes, leucopenia and thrombocytopenia may also be observed. Although DF may be benign, it could be an incapacitating disease with severe headache, muscle and joint and bone pains (break-bone fever), particularly in adults.²²

3. Dengue Haemorrhagic Fever

Dengue haemorrhagic fever (DHF) is more common in children less than 15 years of age in hyperendemic areas, in association with repeated dengue infections. However, the incidence of DHF in adults is increasing.

DHF is characterized by the acute onset of high fever and is associated with signs and

symptoms similar to DF in the early febrile phase. There are common haemorrhagic diatheses such as positive tourniquet test (TT), petechiae, easy bruising and/or GI haemorrhage in severe cases. By the end of the febrile phase, there is a tendency to develop hypovolemic shock (dengue shock syndrome) due to plasma leakage.²²

The presence of preceding warning signs such as persistent vomiting, abdominal pain, lethargy or restlessness, or irritability and oliguria are important for intervention to prevent shock. Abnormal haemostasis and plasma leakage are the main pathophysiological hallmarks of DHF. Thrombocytopenia and rising haematocrit/haemoconcentration are constant findings before the subsidence of fever/ onset of shock. DHF occurs most commonly in children with secondary dengue infection. It

has also been documented in primary infections with DENV-1 and DENV-3 as well as in infants.²²

EXPANDED DENGUE SYNDROME

Unusual manifestations of patients with severe organ involvement such as liver, kidneys, brain or heart associated with dengue infection have been increasingly reported in DHF and also in dengue patients who do not have evidence of plasma leakage. These unusual manifestations may be associated with coinfections, comorbidities or complications of prolonged shock. Most DHF patients who have unusual manifestations are the result of prolonged shock with organ failure or patients with comorbidities or coinfections.²²

HIGH RISK GROUP

The following high risk groups may have severe manifestations or complications with DF/DHF, therefore this group of patients should be closely monitored for the development of severity¹⁶ :

- Pregnancy
- Infant
- Elderly
- Obesity
- Peptic ulcer diseases
- G6PD deficiency
- Thalassemia
- Coronary Artery Disease
- Chronic diseases: diabetes, COPD, bronchial asthma, hypertension
- Patients on steroid, antiplatelet, anticoagulant drugs
- HIV infected persons/ Immuno-compromised persons

EXPANDED DENGUE SYNDROME (EDS)

Mild or severe organ involvement may be found in DF/DHF. Unusual manifestations of DF/DHF are commonly associated with

co-morbidities and with various other co-infections.

Table 1. Clinical manifestation of expanded dengue syndrome¹⁶

System	Unusual or atypical manifestation
CNS	Encephalopathy, encephalitis, febrile seizures, intracranial bleeding
GI tract	Acute hepatitis / fulminant hepatic failure, cholecystitis, cholangitis acute pancreatitis
Renal	Acute renal failure, haemolytic uremic syndrome, acute tubular necrosis
Cardiovascular	Cardiac arrhythmia, cardiomyopathy, myocarditis, pericardial effusion
Respiratory	Pulmonary oedema, ARDS, pulmonary haemorrhage, pleural effusion
Eye	Conjunctival bleeding, macular haemorrhage, visual impairment, optic neuritis

EARLY DETECTION OF DENGUE INFECTION

IgM dan IgG specific-ELISA

Primary infection is characterized by an increase in dengue-specific IgM antibodies at four to five days after the onset of. IgM antibodies can be detected for three to six months, while IgG can be detected throughout life. In secondary dengue infections, IgM antibody levels are lower than primary infection and sometimes undetectable, whereas IgG antibody levels rise rapidly in secondary infections, even in the acute phase. Thus, the high titer of IgG in the early stages of the disease is a criterion of

secondary infection. The sensitivity of IgM ELISA ranges from 90-97% when compared to standard gold haemagglutination inhibition test. A number of commercial kits are available on the market to detect antidengue antibodies.²³

Mosquito Cell Lines and Monoclonal Antibody

This method relies on host cell culture that acts as an indicator of viral infection, among others by assessing the cytopathic effect on cell culture that provides symptoms of illness and death to the host. This method is most often used to perform virus isolation.²³

Reverse Transcriptase PCR

In recent years, reverse transcriptase-polymerase chain reaction (RT-PCR) has been developed for a number of RNA viruses, including dengue virus. This technique allows multiplying biological amplification of nucleic acids and widely used to rapidly diagnose emerging viral infections. The main advantage of this molecular method is its speed in screening dengue virus with high sensitivity and specificity. It can monitor infection rates found in mosquitoes, both in adult and larval mosquitoes with a high degree of accuracy.²³

THE MANAGEMENT OF DENGUE HEMORRHAGIC FEVER

The Management of Dengue Fever (DF)

Management of dengue fever is symptomatic and supportive include ¹⁶ :

Bed rest is advisable during the acute phase. Use cold/tepid sponging to keep temperature below 38.5 C.

- a. Antipyretics may be used to lower the body temperature. Aspirin/NSAIDs like Ibuprofen, etc should be avoided since it may cause gastritis, vomiting, acidosis, platelet dysfunction and severe bleeding. Paracetamol dose can be repeated at the

intervals of 6 hrs depending upon fever and body ache.

- b. Oral fluid and electrolyte therapy is recommended for patients with excessive sweating or vomiting.
- c. Patients should be monitored for 24 to 48 hours after they become afebrile for development of complications.

Management of DHF Grade I and Grade II

Any person who has dengue fever with thrombocytopenia, high haemoconcentration and presents with abdominal pain, black tarry stools, epistaxis, bleeding from the gums etc. needs to be hospitalized. All these patients should be observed for signs of shock. The critical period for development of shock is during transition from febrile to afebrile phase of illness, which usually occurs after third day of illness. Rise of haemoconcentration indicates plasma leakage and loss of volume for which proper fluid management plays an important role.¹⁶

Management Of DHF Grade III/IV

Immediately after hospitalization, the haematocrit, platelet count and vital signs should be examined to assess the patient's condition and intravenous fluid therapy should be started. The patient requires regular and continuous monitoring. If the patient has already received about 1000 ml of intravenous fluid, it should be changed to colloidal solution preferably Dextran40 or if haematocrit further decreases fresh whole blood transfusion 10-20ml/kg/dose should be given. However, in case of persistent shock even after initial fluid replacement and resuscitation with plasma or plasma expanders, the haematocrit continues to decline, internal bleeding should be suspected. It may be difficult to recognize and estimate the degree of internal blood loss in the presence of haemoconcentration. It is thus recommended to give whole blood in

small volumes of 10ml/kg/hour for all patients in shock as a routine precaution. Oxygen should be given to all patients in shock.¹⁶

PHARMACOLOGICAL THERAPY

Corticosteroids

Corticosteroids are potent immunosuppressants and effective against dengue infection. Despite unsatisfactory results after the administration of corticosteroid therapy in the acute phase of dengue infection, there were some research data showed good response after corticosteroid administration in severe dengue manifestations. A clinical trial examined the effectiveness of corticosteroid administration in 149 adult patients with DHF grade II. Patients were divided into three groups, among others, the first group received full-dose short-term corticosteroid therapy (intravenous dexamethasone 4 mg every 6 hours for 2-3 days), the second group was given intermittent intravenous dexamethasone (4 mg was given only when episodes of fever occurred), and the group third did not get corticosteroid therapy. There was no effect of corticosteroid on the severity of thrombocytopenia and liver damage. However, symptomatic symptoms and duration of hospitalization were significantly shorter in the group receiving short course of intravenous dexamethasone at full dose.²⁴

Antimalaria

A randomized design study involving 129 patients with dengue infection in Brazil, 37 patients were confirmed to have dengue infection, 19 patients received chloroquine therapy and 18 patients received placebo treatment. The therapy 500 mg chloroquine (300 mg base) twice a day did not affect the duration and severity of the disease. However, the intensity of pain and daily activity of the patients was significantly

better in the group receiving chloroquine therapy.²⁵

Doxycycline and Tetracycline

In a study conducted by Castro et al. (2011), patients suffering from dengue fever and dengue hemorrhagic fever after 72 hours diagnosed were given placebo (n = 34), tetracycline (n = 35), and doxycycline (n = 45). Parameters assessed were levels of IL-6, IL-1, TNF, TNF receptor 1, and IL-1 receptor antagonist (IL-1 Ra) measured at initial therapy, day-3, and day-7 therapy. Tetracycline or doxycycline can lower cytokine levels and increase IL-1Ra. When compared with tetracyclines, doxycycline has a better immunomodulatory effect.²⁶

Anticholesterol

Disorders that occur in cholesterol biosynthesis may affect dengue virus replication. This is apparent when screening siRNA studies to identify the molecules that regulate dengue virus replication. The results showed that mevalonate (diphospho) decarboxylase inhibited DENV-2 replication.²⁷

Intravenous Immunoglobulin (IVIG)

A randomized controlled trial, 10 dengue fever patients were given IVIG treatment and 5 dengue fever patients were given IVIG therapy, while in the control group (not IVIG therapy) were 9 dengue fever patients and 7 dengue hemorrhagic patients. Under the standard protocol IVIG therapy was given 0.4 g / kg / day on the second, third and fourth days of hospitalization. The conclusion obtained there was no significant effect of platelet count increase between the second day until the seventh.²⁸

Celgosivir

In phase 1b studies, with double blind randomized designs, 50 patients were included to prove the therapeutic effect of

celgosivir. Twenty-four patients receiving initial therapy 400 mg celgosivir, followed by 200 mg every 12 hours for 9 doses, their effects and therapeutic safety compared to the group receiving placebo treatment (n = 26). Celgosivir significantly lower viral load and febrile incidence than the placebo group.²⁹

Balapiravir

In the early phase of the study, multiple randomized controlled trial, involving dengue patients within the first 48 hours. Patients were given placebo (n = 30), balapiravir 1500 mg (n = 10), and balapiravir 3000 mg (n = 22) orally for 5 days. Balapiravir decrease viremia and NS1 antigen and decrease fever time significantly compared to the group given placebo.³⁰

BLEEDING CONTROL IN DENGUE HEMORRHAGIC FEVER

Local procedure may be performed at the site of bleeding, i.e pressure on the anterior nasal to control epistaxis, firm pressure on the veinpuncture site, and fibrin sealant application at the tooth extraction site. Gastric lavage with cold saline solution is contraindicated in patients with hematemesis. However, nasogastric tube insertion to control gastric bleeding should be done carefully by trained personnel. In addition, other supportive therapies such as tranexamic acid may be used to prevent fibrinolysis, especially in mucous membranes from the oral cavity, intravenous estrogens by 25 mg every 6 hours with 24-hour intervals for menorrhagia, and H2 blockers for gastritis.³¹

FOGGING: A CONTROVERSY

Fogging is an effort to reduce the incidence of dengue hemorrhagic fever. It is performed by spraying insecticides into the air with a range from 1 to 30 μ m in diameter median volume in order to kill adult mosquitoes. This method has been used in

almost all Southeast Asian countries for 25 years. Several recent studies have concluded that fogging has little effect on mosquito population decline and dengue virus transmission.²²

Fogging has less effectiveness because it kills only adult mosquitoes and only temporary without the residual effect. Its effects depend on weather factors such as wind speed, wind direction, humidity, and ambient temperature. There are several reasons for limiting fogging. Besides, because the fogging program requires high expenditure, the widespread use of insecticides also causes problems in the community. The advantages of suppressing insect species and the risk of insecticide resistance in mosquito species should be taken into consideration.³²

ALTERNATIVE NATURAL THERAPY

Some natural medicines are known to have activity against *Aedes aegypti* through antiviral mechanisms, larvicidal activity, mosquitocidal, and mosquito repellants²³ :

- a. *Eupatorium perfoliatum* (Boneset)
- b. *Boesenbergia rotunda* (Temu kunci)
- c. *Kaempferia parviflora*
- d. *Carica papaya*
- e. *Solanum villosum* (tanaman berry)
- f. *Combretum collinum*
- g. *Azadirachta indica* dan *Pongamia glabra*
- h. *Nyctanthes arboristis*, *Catharanthus roseus*, *Eupatorium odoratum*
- i. *Citrus limetta*
- j. *Acalypha alnifolia*
- k. *Delonix elata*
- l. *Psidium guava* (jambu biji)
- m. *Phoenix dactylifera* L. (kurma)
- n. *Monascus purpureus* (angkak)

RECENT PREDICTORS OF DENGUE HEMORRHAGIC FEVER SEVERITY Platelet Count

Thrombocytopenia in patients clinically suspected to have dengue infection may be a

predictor of DHF or DSS. Thus, it guiding clinicians to provide supportive therapy earlier and provide appropriate maintenance therapy. There was a strong correlation between low platelet count and positive dengue parameters ($P < 0.001$). In patients clinically suspected of having dengue infection, when accompanied by thrombocytopenia, prompt earlier therapy should be provided to suppress morbidity and mortality rates due to dengue infection complications..³³

Aspartate Aminotransferase/ Platelet Count Index (APRI) Index

The formula of APRI Index³⁴:

$$\text{APRI} = [\text{AST (U/L)}/\text{upper limit normal}/\text{PLT (x10}^9\text{/L)}] \times 100$$

Based on the study Hao et al. (2018), it was concluded that white blood count, prothrombine time, and APRI may help identify patients at risk of severe dengue conditions. APRI is a valuable predictor of a patient suffering from severe dengue.³⁴

Chymase Serum Level

Based on the study Tissera et al. (2017), chymase level was a strong predictor of DHF in patients with acute phase dengue. Increased chymase concentrations predict the risk of complications more precisely before the apparent of warning signs.³⁵

Serum Cytokine/Chemokine Profile

Several studies have examined the levels of serum cytokines in dengue patients primarily associated with an increase in early markers of severe dengue. Based on the result of this research, there is difference of inflammatory marker between DF and DHF. IL-1, IFN- γ , IL-10, and IP-10 are reported to increase in DHF and MIF as well as MIP1- β increase in DF..¹³

Tropomyosin-Alpha 1 (TPM 1)

Soe et al. (2018) identified several plasma proteins including PFKFB4, TPM1, PDCL3, PTPN20A were increased in severe dengue patients. TPM1 levels were significantly increased in the majority of dengue patients.³⁶

Reticulocyte Production Index (RPI)

RPI is a potential marker to determine the regeneration capacity of the bone marrow. Clinicians will be easier to ensure that the platelet count will return to normal. Thus it can ensure that the patient does not fall into the state of bone marrow failure.³⁷

Immature Platelet Fraction (IPF)

IPF cutoff value ≥ 6.25 indicates 67% chance of platelet count increase of 20,000/mm³ within 48 hours. A cut-off value of 10.6 or more indicates 100% chance of platelet count increase of 20,000/mm³ within 48 hours.³⁸

CONCLUSION

Modern factors have an influence on the spread of vector-mediated diseases are globalization, include travel and trade, which facilitate the transfer of vectors to new places and suitable climatic conditions. The increasing mobility of both vector and human populations is the most important factor that can explain the recent increase in dengue transmission.

The pathogenesis of dengue infection is complex. Some of the mechanisms that can explain the occurrence of such infections include the involvement of antibody-dependent enhancement, NS1 and its antibodies, T cells, and DENV genomics.

Several methods can be performed to detect the presence of dengue virus in the body of infected patients. These include ELISA-specific IgM and IgG detection, detection of monoclonal antibodies and

mosquito cell strains, and PCR reverse transcriptase detection.

There are several pharmacological therapies have potential antidengue activity. These drugs include corticosteroids, antimalarial, doxycycline and tetracycline, anticholesterol, IVIG, celgosivir, balapiravir, and pentoxifylline and calcium supplementation. Some natural medicines were also known to have activity against *Aedes aegypti* through antiviral mechanisms, larvicidal activity, mosquitocidal, and mosquito repellants.

Several tests used to predict the severity of dengue hemorrhagic fever at the early stage of the disease. These include platelet count, aspartate aminotransferase/ platelet count index (APRI), serum chymase level, serum cytokine/chemokine profile, tropomyosin-alpha 1 (TPM 1), Reticulocyte Production Index (RPI), and immature platelet fraction (IPF).

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