

Dengue



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1 Introduction

Dengue is one of the most important mosquito-borne viral infections caused by single-stranded RNA virus that are transmitted by the *Aedes aegypti* and *Aedes albopictus* mosquito species. Dengue is endemic in over 140 countries in Asia, the USA, the Eastern Mediterranean, and Africa. The World Health Organization (WHO) estimated that there are more than 2.5 billion people—mainly occurs in children living in tropical and subtropical countries—at risk of dengue infection with one or more dengue viruses. There are estimated nearly 100 million symptomatic dengue infections occurring worldwide annually, nearly 75% in Asia and the Western Pacific region [1]. During the past decades, the outbreaks of dengue

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infection have been reported throughout the world with increased severity. Ecologic and demographic changes are considered to be the contributing factors to the emergence of dengue infection in the past decades. Dengue has expanded into new countries and into urban settings associated with increased distribution of *A. aegypti*, population growth, urbanization, development of slums, migration of population, movement of dengue virus by infected travelers, trade development, and improved diagnostic capabilities in medical practice [2, 3]. Increased transmission of dengue virus in tropical urban areas has been created by substandard housing and crowding as well as deterioration in water, sewer, and waste management systems, all of which are intimately associated with unplanned urbanization [4–7]. So it is likely that dengue will expand its geographic reach and become an increasing burden on health resources in affected areas during the next decade. An effective vector-control management is the only means to reduce dengue infection in endemic areas. Because vector control has achieved only limited success so far in reducing the transmission of dengue, the usage of effective dengue vaccine in target population along with the preventive measures already used such as raising public awareness may be the means to effectively control of this disease in endemic area [8].

Hyperendemic dengue with a general increase in the number of dengue cases over time is a major public health problem in many countries in South and Southeast Asia where *A. aegypti* and *A. albopictus* are widespread in both urban and rural areas, where multiple virus serotypes are circulating, and where dengue is a leading cause of hospitalization and death in children. The extent of hyperendemicity and time between serotype introductions are key determinants in a population's serotype-specific immunity and, consequently, in the age distribution of clinically apparent dengue infection. In the past, the age distribution of indigenous dengue cases in South and Southeast Asia is different from that of the Americas, where these syndromes occur in all age groups included elderly. Recently several countries in Asia have reported an epidemic shift of dengue from mainly affecting children to affecting adolescents and young adults with increased severity [9–12]. In Thailand, the affected adults aged over 15 years old are reported to comprise 30–40% of dengue virus infected cases [13]. There are some differences in clinical presentations, laboratory findings, and severe complications between children and adult with dengue [14–16]. Increasing incidence of dengue among travelers (1.0–6.7%) has been recognized as a potential hazard to tourists as various reports in international travelers returning from endemic areas [17–20]. Recent reports revealed that adult dengue appears to occur more frequently than malaria among travelers returning from Asia, so the healthcare providers in Western countries are more likely to be confronted with travel-acquired dengue infections [21–24]. In returning travelers with fever, clinical manifestations of dengue infection are comparable with observations in endemic area where dengue may go unnoticed. We emphasize the need for continued dengue surveillance in non-endemic countries with careful evaluation and follow-up of febrile travelers after visiting countries where are dengue-endemic areas [25, 26]. Travelers should be encouraged to protect themselves from mosquito

bites, in order to avoid infections and onward transmission of dengue in new areas where *A. aegypti* is established.

2 Pathogen and Pathogenesis

Dengue virus, single-stranded RNA virus member of genus *Flavivirus* in the family *Flaviviridae*, is the etiologic agent of dengue infection. There are four serotypes of dengue virus (DEN-1, DEN-2, DEN-3, and DEN-4) that are transmitted by the *Aedes aegypti* and *A. albopictus* mosquito species. Peak transmission occurs in rainfall season and high temperature in hyperendemic and endemic areas. Although dengue virus is transmitted by mosquitoes, unusual dengue transmissions through needlestick, receipt of infected blood component, tissue or organ transplantation, and transplacental infection have been reported [27–34]. After an incubation period of 4–8 days, infection by any dengue virus can produce a wide spectrum of illnesses ranging from asymptomatic or subclinical infection to undifferentiated fever, dengue fever (DF), and severe forms of the disease associated with plasma leakage (dengue hemorrhage fever: DHF), dengue shock syndrome (DSS), severe bleeding, encephalopathy, and multi-organ failure [35]. DHF is characterized by rapid onset of capillary leakage accompanied by thrombocytopenia, hemoconcentration, vascular collapse, abdominal pain, and hemorrhagic manifestations [36]. Despite the clinical classification of DF and DHF as distinct entities, they are likely to be a continuum of the same disease process with divergent outcomes with regard to the perturbation of vascular integrity. In case of dengue infection, asymptomatic cases are more frequent than the symptomatic cases with the variable ratio of asymptomatic to symptomatic dengue infections of 0.9:1 to 18:1, dependent on the geographical areas, the epidemiological contexts, and individual immunological attributes [37, 38]. However, patients with asymptomatic infection may act as reservoir for dengue virus to transmit to mosquitoes and subsequently to humans and should be considered in estimation of disease burden. Recovery from dengue infection with one serotype confers lifelong homologous immunity to that particular serotype but short-term protection against other serotypes, so secondary infection can occur with other dengue serotypes. Previous epidemiologic data reveals that secondary heterotypic dengue virus infection is a risk factor to develop severe DHF/DSS, mediated most likely by antibody-dependent enhancement (ADE) of infection. Pre-existing homotypic antibodies bind to heterotypic dengue virions (virus-antibody complexes) and enable Fc γ receptor-mediated uptake by target Fc γ receptor-bearing cells (e.g., monocyte/macrophage) resulting in increased viral replication and viremia [38]. Changing of inflammatory cytokine production (such as TNF ∞ , interleukin-1, interleukin-2, interleukin-6, interleukin-12, macrophage migration inhibitory factor, HMGB1, MCP-1) produced by T-lymphocytes, monocytes/macrophages, and endothelial cell is observed in dengue patients who have increased vascular permeability, thrombocytopenia, and activation of coagulation and fibrinolysis [39, 40]. In addition, secreted NS1 protein, anti-NS1

antibodies, and increased complement activation (C3a, C5a) might be involved in increased production of inflammatory cytokines, triggering local and systemic effects implicated in intravascular coagulopathy and virus-induced vascular leakage. Thrombocytopenia caused by bone marrow suppression, shortened platelet survival, and increased platelet consumption due to platelet adhesion occurs during the dengue infection and reaches nadir during the day of defervescence (toxic stage) [40, 41]. Although secondary dengue infection remains the strongest known risk factor for DHF/DSS, viral genetics, serotype sequence, host factors, and time interval between primary and secondary infections can modulate severity of illness [40, 42–45].

3 Clinical Manifestation

Dengue infection should be suspected if patients in dengue-epidemic or dengue-endemic area have a fever of 10 days or less with myalgia, headache, flushing, anorexia, nausea or vomiting, arthralgia, bone pain, periorbital pain with no obvious respiratory tract symptoms or signs, and no organ-specific symptoms of other infectious diseases. The clinical spectrum of dengue infection ranges from mild illness (undifferentiated fever, non-severe DF) to the life-threatening severe forms of the disease with plasma leakage (DHF/DSS), severe bleeding, or multi-organ failure, which may be fatal. Dengue fever in its classical form is nonfatal febrile illness with about 5–7 days associated with sudden onset, anorexia, myalgia, headache, and occasional rash. DHF is characterized by high continuous fever of 2–7 days and rapid onset of capillary leakage accompanied by thrombocytopenia, hemoconcentration, vascular collapse, abdominal pain, and hemorrhagic manifestations. Shock (DSS) occurs as a consequence of severe plasma volume loss into serous spaces (e.g., pleural space or peritoneum cavity) or severe internal hemorrhage. During the acute febrile phase, usually lasting 3–8 days, the clinical symptoms resemble those of DF and severe dengue (DHF), including fever, nausea or vomiting, headache, rash, and myalgia; nonetheless, abdominal pain and severe or widespread bleeding are less frequent in DF. Minor hemorrhagic manifestations such as petechiae, epistaxis, gingival bleeding, and menorrhagia do sometimes occur in patient with dengue, although DF is rarely associated with severe hemorrhage leading to shock. Age-related differences in dengue severity are poorly understood; however, there are some differences in clinical courses between children and adults. Plasma leakage (DHF) and DSS appear to be more frequent in children than adults, possibly reflecting age-dependent differences in intrinsic vascular permeability, but some reports suggest that bleeding manifestations, especially severe internal hemorrhage and hepatic dysfunction, are both more common in adults and older age groups [14, 16, 41, 43, 44, 46–50]. The symptoms generally last for 3–7 days before the fever subsides and symptoms remit. During convalescent stage, the patients with dengue infection, even in DSS, may have rapidly increasing appetite, convalescent rash on lower extremities (a confluent rash

with characteristic, scattered, round areas on pale skin), and sinus bradycardia. Most patients with dengue infection recover spontaneously, and abnormal hemostasis normalizes during the convalescent stage or within 1–2 weeks after defervescence. The emergence of severe bleeding, fulminant hepatic failure, and encephalopathy in DF and DHF have been the causes of an apparent increase in the complications of dengue in the adolescent, adult, and elderly [47–49, 51–54]. High mortality rate has previously been reported in elderly patients with dengue infection because of medical comorbidity and waning of host immunity [55–59].

The prognosis of dengue infection depends on early diagnosis, recognition of plasma leakage, and treatment with immediate replacement of fluid and intensive supportive care. The classification of severity has a high potential for being of physician's practice as to where and how intensively the patient should be observed and treated with intravenous fluids, blood, or plasma transfusion and medicines. WHO released a new classification in 2009, which is dengue with or without warning signs and severe dengue because WHO 1997 classification (DF, DHF, DSS) was poorly related to disease severity, difficult to use in clinical setting, and unhelpful in triage in outbreaks [35, 36, 60, 61]. These warning signs (persistent or severe vomiting, abdominal pain or tenderness, liver enlargement, drowsy or alteration of consciousness, fluid accumulation with respiratory distress, epitaxis, gum bleeding, gastrointestinal bleeding, retinal hemorrhage, oliguria, and hemoconcentration with severe thrombocytopenia) are used to alert the clinicians to monitor dengue infection progress. Physicians should be aware of these warning signs in patients with dengue infections before they develop severe dengue [62–64]. Severe dengue is defined by one or more of the following: plasma leakage (DHF) that may lead to shock (DSS), severe bleeding, and severe organ impairment such as hepatic failure, acute renal failure, and encephalopathy) as Fig. 1 [14, 35, 39–47]. If untreated, mortality can be as high as 20%, whereas appropriate case management and intravenous rehydration can reduce mortality to less than 1%. Virus factors (serotypes, structural and nonstructural proteins of dengue virus, and viral load) and host factors (age, gender differences, genetic, nutritional status, immune reaction, and coexisting medical conditions) might be involved in the severity of dengue infection.

3.1 Dengue Hemorrhagic Fever and Dengue Shock Syndrome

Typically DHF resembles DF in many clinical respects, but it is characterized by high continuous fever of 2–7 days, hemorrhagic diathesis, hepatomegaly, and circulatory disturbance (DSS). The critical stage associated with plasma leakage (20% increase in hematocrit over baseline) and marked thrombocytopenia ($<100 \times 10^9/L$) associated with bleeding frequently occur at the end of febrile phase of

Dengue with or without warning signs

Probable Dengue

Patient with acute febrile illness and two of the following criteria:
 Nausea, vomiting
 Rash
 Aches, pains
 Positive Tourniquet test
 Leukopenia
 Any warning signs
 +/- Laboratory confirmation of dengue infection

Patient without warning sign:

Patient with warning signs:
 (Requiring stick observation and medical intervention)

Persistent / severe vomiting
 Abdominal pain or tenderness
 Liver enlargement
 Lethargy, restlessness
 Clinical fluid accumulation
 Mucosal bleeding (epitaxis, gum bleeding)
 Increased Hct concurrent with rapid decreased platelet count

Severe dengue

-Severe plasma leakage
 -Severe hemorrhage
 -Severe organ impairment

Criteria for severe dengue:
 Severe plasma leakage leading to Dengue shock syndrome (DSS)
 Fluid accumulation with respiratory distress
 Severe bleeding: as evaluation
 Severe organ impairment

- Liver enzymes:
 AST/ALT \geq 1,000 Unit/ml
- CNS: Impaired conciousness
- Organ failure:
 Acute renal failure
 Respiratory failure
 Severe myocarditis , etc.

Fig. 1 Dengue case classification: dengue with or without warning signs and severe dengue (modified from WHO guideline 2009) [35]

illness [36]. Right side pleural fluid detected by chest roentgenogram or free fluid in the peritoneal cavity and thickening of gall bladder wall detected by ultrasonography has been interpreted as evidence of plasma leakage, which is usually only clinically detectable after intravenous fluid therapy unless plasma leakage is significant [65–67]. The right side or bilateral pleural effusion is generally not prominent but becomes increasingly more after excessive intravenous fluid administration. In mild DHF cases, the changes in blood pressure and pulse may be minimal and transient. Patients recover shortly after treatment. In more severe

DHF cases, a rapid, weak pulse, narrowing of the pulse pressure to less than 20 mm Hg, or an unobtainable blood pressure establishes DSS [36]. Clinical indicators of impending DSS include severe abdominal pain, change from fever to hypothermia, restlessness, sweating, prostration, and tender hepatomegaly. If plasma loss continues and becomes excessive, the patient's situation can progress rapidly into profound shock. Prolonged shock often complicates metabolic acidosis, severe gastrointestinal bleeding, and disseminated intravascular coagulopathy (DIC). DSS was an independent risk factor (odds ratio 220) for development of acute renal failure in adult patients with DHF [68]. Cardiac involvement was observed in few patients ranging from abnormality of electrocardiogram, mild elevation of cardiac biomarkers to myocarditis and/or pericarditis and death [69]. Acute respiratory failure is a rare complication but has a high mortality rate [70]. Although children are more likely to develop hypovolemic shock than adults in DHF characterized by increased microvascular permeability, a high mortality rate is seen in the adults and elderly with dengue infection [42, 49, 51, 55, 57, 62]. High fatality rate of dengue in adults was significantly associated with pre-existing comorbid medical illnesses such as cardiac diseases and renal diseases [49, 56–59, 62]. Because the altered vascular permeability is short-lived and spontaneously converts to normal level, the period of clinically significant plasma leakage usually lasts 24–48 h after defervescence. Diuresis ensues as plasma leakage terminates. Convalescent rash, transient hypertension, and sinus bradycardia were described during convalescence in patients with DHF/DSS.

3.2 Hemorrhage Associated with Dengue Infection

Hemorrhage contributes to morbidity and mortality, especially during the severe thrombocytopenia, usually occurring in 5 to 8 days after onset of illness [41]. The pathogenesis of abnormal bleeding in dengue is multifactorial and encompasses severe thrombocytopenia, platelet dysfunction, blood coagulation defects, and vasculopathy. There are typical coagulopathies of increased APTT and low fibrinogen levels in most patients, but severe thrombocytopenia and platelet dysfunction are probably the major cause of clinical bleeding. Variable degree of hemorrhage may occur at any sites, most commonly petechiae, epistaxis, gingival bleeding, or menorrhagia, and usually occurs on days 5–8 of the illness. Bleeding from the nose, gums, and upper gastrointestinal tract are not uncommon in patients with dengue infection. Vaginal bleeding (menorrhagia) is a common site of bleeding (24.6% in adults with dengue infection), and hormonal therapy such as Premarin and Primolut N is suggested for patients exhibiting excessive vaginal bleeding [48]. Of the dengue patients with plasma leakage (DHF), severity of bleeding varied markedly with spontaneous petechiae, hematemesis, melena, menorrhagia, and epistaxis. Risk factors of severe bleeding are platelets $\leq 20,000/\text{mm}^3$ ($\leq 20 \times 10^9/\text{L}$), high aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level, prolonged prothrombin time (PT), severe plasma leakage (DSS), DIC, or fulminant hepatic failure

[71]. Massive hematemesis may occur in adults with DF or DHF caused by pre-existing peptic ulcer or hemorrhagic gastritis, and it may be not associated with profound shock in adults as previously reported in children. In the few reports of endoscopic findings for dengue adults with upper gastrointestinal bleeding, hemorrhagic gastritis was the most common finding (40.9–58.5%), followed by gastric ulcer, and duodenal ulcer [53]. However, the role of endoscopic therapy in upper gastrointestinal bleeding of dengue patients is still unknown [72]. Life-threatening internal hemorrhage such as subcapsular splenic bleeding and ruptures is rare but can happen spontaneously or as a result of trauma, which may be unnoticed. Splenectomy is still the treatment of choice for splenic rupture, but numerous recent reports have documented favorable outcomes with conservative treatment [54, 73]. Early diagnosis, intensive supportive care, and replacement therapy are needed to avoid a fatal outcome in dengue patients who have severe hemorrhage.

There are pregnant women with DF or severe dengue reported in Asia, highlighting the concept that young women in hyperendemic and endemic area remain susceptible to dengue infection [74–76]. The obstetricians must be aware that dengue infection of pregnant women may occur and some history or laboratory results consistent with dengue infection must be identified. Dengue during pregnancy is also particularly important in pregnant travelers from non-endemic countries to countries where dengue is endemic [77]. Uterine hemorrhage resulting in spontaneous abortion and severe postpartum bleeding has also been reported in pregnant women [76]. Surgical procedures such as cesarean section performed on patients with dengue infection may unmask dengue-induced hemostatic defects, resulting in unexpected hemorrhage in postoperative period that is difficult to control [78]. It also has been reported that dengue infection was vertically transmitted to the fetus and led to a full-blown illness in the neonate similar to that seen in children and adults [74]. Although the effects of dengue infection on pregnant women and their fetuses or newborns are unclear, recent studies have demonstrated that this infection did not cause any infant abnormalities but may have been responsible for fetus deaths and morbidity in pregnant women [79–81].

3.3 Severe Organ Impairment and Unusual Manifestations

Hepatomegaly and increased levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were more commonly found in patients with dengue infection especially DHF [82–87]. So dengue infection should be included in the differential diagnosis of acute viral hepatitis in Asia. Unlike conventional viral hepatitis, patients with dengue have a level of AST that are greater than that of ALT which may be due to excessive release of AST from damaged myocytes during dengue infections, and these levels of liver enzymes increase to a maximal 7–9 days after onset of illness, then decrease to normal levels within 2 weeks [48, 49, 82–84]. Potential mechanisms of liver injury involve a variety of potential insults including direct effects of infected virus serotypes or an adverse consequence of

dysregulated host immune responses on liver cells; compromised circulation and/or hypoxia caused by hypotension or localized vascular leakage inside the liver capsule; hepatotoxic effects of drugs such as acetaminophen or traditional herbal remedies, coinfection with other viruses such as virus hepatitis A, B, and C; and pre-existing underlying diseases (e.g., hemoglobinopathies, alcoholic liver diseases) [88]. Attention must therefore be given to the use of hepatotoxic drugs such as acetaminophen, antibiotics, and antiemetic drugs, all of which have the potential to aggravate liver damage in patient with dengue. Previous reports have found evidence that acetaminophen overdose may play an important role in causing acute liver failure in dengue patients [89, 90]. It is likely that relatively more adult dengue patients have more liver impairment than children. Pre-existing liver diseases such as chronic infection with virus hepatitis B or C, alcoholic liver disease, and cirrhosis may aggravate the liver impairment of dengue. Abnormal liver enzyme levels have been associated with severity and a poor outcome in patients with vascular leakage and abnormal bleeding [86, 87]. Increased levels of bilirubin and alkaline phosphatase were observed in a few patients. Severe liver impairment occurred in late stage of disease may complicate the outcome of dengue infection by causing acute hepatic failure and contributing directly to severe bleeding, as well as potentiating the severity of DIC [89, 90]. Severe jaundice and high mortality are observed in dengue patients with fulminant hepatic failure. The management of fulminant hepatic failure in dengue is primarily intensive supportive care; however, therapy with *N*-acetylcysteine (NAC) or providing artificial liver support was previously described [87].

The unusual manifestations of dengue infection have been recognized including severe internal hemorrhage, fulminant hepatic failure, encephalopathy, cardiomyopathy, cardiac arrhythmia, adult respiratory distress syndrome (ARDS), rhabdomyolysis, pancreatitis, appendicitis, coinfection with other viruses or tropical infectious diseases, and neurological complications (e.g., altered consciousness, seizures, paresis, and coma resulting from encephalitis and encephalopathy) [91–98]. The neurological manifestations secondary to dengue infection including encephalopathy, encephalitis, myelitis, neuro-ophthalmic complications, polyradiculopathy, neuropathy, and neuromuscular complications were ascribed in 0.5–21% of hospitalized patients [92, 94, 95, 99]. Possible causes of encephalopathy in patient with dengue include hypotension, cerebral edema, focal hemorrhage, hyponatremia, fulminant hepatic failure, and the direct invasion of dengue virus in the central nervous system [100, 101]. Acute renal failure is an accompanying presentation in DSS or dengue-associated fulminant hepatic failure. Previous studies revealed that 5.5% of the patients with DHF/DSS also had dual infection (e.g., urinary tract infection, diarrhea, or bacteremia) [48, 102]. Dual infection should be suspected in patients who have atypical manifestations, for example, fever for more than 10 days, mucus diarrhea, jaundice, persistent abdominal pain, recurrent fever, $WBC > 10,000/mm^3$ ($>10 \times 10^9/L$) with neutrophilia, or the presence of the band form of neutrophil and acute renal failure [103]. The patient with severe dengue infection may have secondary bacterial sepsis, e.g., bacteremia,

and UTI after hospitalization. Failure in making a diagnosis of concurrent infection in patients with dengue may lead to otherwise preventable mortality [104].

4 Diagnosis

Attempts to differentiate dengue infection clinically from other acute febrile illnesses are unlikely to be successful; although, the diagnosis is aided if laboratory examination indicates leukopenia, thrombocytopenia, or mildly elevated AST levels. Early definite diagnosis of dengue infection can help clinicians in initiation of early supportive care, adequate fluid administration, and identification of patients with severe dengue who should be closely monitored for signs of plasma leakage, bleeding, and organ damage. This information might promote early supportive therapies, prevent the use of potentially harmful drugs, encourage assessment of complications, ensure the adequate use of treatment guidelines, and lead to the effective control of dengue outbreaks. The tourniquet test considered by the WHO has been used as a clue for probable dengue infection for a long time [35]. Unfortunately, the sensitivity and specificity of tourniquet test were not excellent, ranging between 34 and 56% and 68 and 94%, respectively, and a negative test does not exclude the disease [105–107].

Laboratory diagnosis of dengue infection is established either directly by isolation or detection of viral components in serum or tissue or indirectly by detection of virus-specific antibodies in serum [108]. The sensitivity of each approach is influenced by the duration and severity of the patient's illness. Within the first 2–3 days of illness, only reverse transcription polymerase chain reaction (RT-PCR) or dengue virus NS1 Ag assay can reliably confirm the diagnosis of dengue. Determination of dengue virus by RT-PCR in serum, tissues, saliva, or urine is definitely the most satisfactory test that might detect dengue viruses up to the 7th day after the onset of the symptoms, especially in severe cases [109–111]. A high circulating level of dengue virus NS1 was demonstrated in the early stage of dengue infection by different ELISAs in the plasma and/or sera of dengue patients [112]. Until now, ELISA used to detect acute phase (IgM), and convalescent phase (IgG) antibodies have been considered the most useful test for dengue diagnosis due to its high sensitivity and ease of use. Because dengue antibodies are better detected around the 5th day after the onset of the illness, antibody detections are unfeasible for rapid diagnosis. There are several commercial kits of rapid tests of IgM and IgG detection, but the sensitivity, specificity, and accuracy vary among these tests [113, 114]. Various combination tests for elevated levels of NS1 and dengue IgM/IgG in serum have yielded sensitivities between 75.5 and 92.9% with specificities ranging from 75.0 to 100% and are a pragmatic diagnostic approach in a patient in whom dengue infection is suspected. It should be stressed that in dengue-endemic areas, while early accurate laboratory tests are not widely available, dengue infection should be considered in every children and adults presenting with an acute undifferentiated febrile illness.

5 Management

No specific therapeutic agent to treat dengue infection is available, so treatment remains supportive care with particular emphasis on careful fluid administration. The early recognition of warning signs, plasma leakage, abnormal bleeding, signs of circulatory collapse, and other serious complications would reduce morbidity/mortality rates in patients with dengue infection. Dengue patient without warning signs may be treated at home with oral hydration and antipyretics with instructions to follow up at out-patient care and return to the hospital immediately if bleeding or warning signs suggestive of severe dengue develop. Oral rehydration is indicated to replace losses from vomiting and high fever. Acetaminophen, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), and traditional medicines are commonly prescribed to febrile patients that these medications may cause severe bleeding or hepatic injury in dengue patients. Development of any warning signs indicates the need for close observation and hospitalization with appropriate use of intravenous fluids in patients with inadequate oral intake or a rapidly increasing hematocrit [35]. Monitoring all these patients for the development of warning signs of severity as recommended by WHO may impose a great burden on healthcare services in limited-resource countries. However, the patients with dengue infection should be hospitalized immediately if any of the followings are observed: severe nausea/vomiting, restlessness or lethargy, severe hemorrhage (e.g., hematemesis or hemochezia), narrowing of pulse pressure (≤ 20 mmHg) or hypotension, sudden rise in hematocrit or continuous elevated hematocrit despite the administration of fluid, a platelet count of $\leq 20,000/\text{mm}^3$ ($\leq 20 \times 10^9/\text{L}$), AST or ALT > 500 U/mL, oliguria or acute renal failure, liver failure, heart failure, severe hypoxemia, pregnancy, and no opportunity to be followed up in an out-patient setting [115, 136].

Attentive clinical monitoring of patients with severe dengue or suspected DHF/DSS and intensively supportive treatment are lifesaving and have reduced fatality rates. The critical activities for hospitalized dengue patients are monitoring of abnormal bleeding, circulation, and vascular leakage by serial clinical assessments of hypovolemia/shock and rising of hematocrit to trigger intravenous fluid or blood component transfusion. Close monitoring measurements (e.g., vital signs, urine output, and serial hematocrit levels) to assess the severity of plasma leakage and promptly effective intravenous fluid resuscitation with crystalloid to counteract massive plasma leakage are required in critical stage of DHF to reduce morbidity and mortality. Patients with DHF need to be monitored closely for signs of shock until at least 24–48 h after defervescence. For patients suffering from plasma leakage with shock (DSS), the mainstay of therapy is early and effective replacement of plasma loss. The WHO recommends immediate volume replacement with Ringer's lactate, or physiologically normal saline solution, followed by plasma expander such as fresh frozen plasma or colloid solutions (albumin and dextran) in the event that shock persists [116]. Therapeutic responses to colloid and crystalloid solutions from two randomized controlled studies revealed that Ringer's lactate performed the least well and that the more severely ill patients identified by a narrow pulse pressure would benefit more from initial resuscitation with colloid solution than with

crystalloid solution [117–119]. In order to assess adequate volume replacement, the rate of intravenous fluid should be adjusted throughout the period of plasma leakage by frequent assessments of vital signs, hematocrit, and urine output and be kept to the minimum required to maintain cardiovascular stability until permeability reverts to a normal level. In cases with persistent shock despite a declining hematocrit after fluid resuscitation with crystalloid or colloid solutions, internal or concealed bleeding should be suspected. Transfusion therapy with packed red cell, concentrated platelets, and fresh frozen plasma to correct the bleeding tendency, anemia, coagulopathy, and hypovolemia is still the mainstay of treatment of severe bleeding in dengue patients. The prophylactic blood or platelet transfusions for severe thrombocytopenia may be harmful and should be avoided in uncomplicated cases [120]. The invasive procedures should be minimized to avoid hemorrhagic complications. Metabolic acidosis and hyponatremia occur more commonly in DSS, so sodium bicarbonate infusion should be considered along with early adequate fluid replacement. Medical comorbidities in adult and elderly patients, for example, coronary artery disease, peptic ulcer, hypertension, diabetes mellitus, cirrhosis, or chronic kidney disease, which should be considered for proper management, may contribute to the severity of dengue infection [55, 97, 121–123]. There is no evidence to support the use of chloroquine, corticosteroid, interferon, immune globulin, desmopressin, or carbazochrome sodium sulfonate (AC-17) for severe dengue infection [124–127]. With intensive support through the critical period of illness, spontaneous resolution of vasculopathy and circulatory failure usually can be expected within 2–3 days with complete recovery afterward. In the recovery period, the patients usually have more appetite, bradycardia, and convalescent rash and may have fatigue or mood disturbance for several weeks.

6 Prevention

To reduce burden of dengue, the WHO has set out specific objectives in global dengue control strategy: estimation of the true burden of dengue by 2015 and a reduction of dengue morbidity and mortality by 2020 by at least 25 and 50%, respectively (using 2010 as the baseline) [128]. It seems clear that implementations of effectively sustainable vector control and effective dengue vaccines are keys to success for this disease control. The WHO has recommended integrated vector management (IVM), an evidence-based approach which encourages optimal use of resources by examining local in-country evidence. Challenges of vector management remain in the development and deployment of vector-control strategies that effectively minimize dengue replication and transmission. Dengue prevention currently relies on public health and community-based *A. aegypti* control programs with chemical or biological methods to remove and destroy mosquito-breeding sites [129]. Because this IVM approach has not succeeded in most of the Asian countries especially dengue-endemic regions, the new tools are needed to prevent and control dengue, including the development of a safe and efficacious dengue vaccine. The potential dengue vaccine is a vaccine consisting of a tetravalent combination of attenuated dengue strains, which

simultaneously induce protective and durable immune responses against all four dengue serotypes. Recent studies in Asia and Latin America show that recombinant live-attenuated tetravalent dengue vaccine (CYD-TDV) was safe and moderately efficacious when given three injections at months 0, 6, and 12 to children and adolescents [130, 131]. Overall vaccine efficacy of CYD-TDV was estimated to be 60% against virologically confirmed dengue (VCD) infection, with high levels of protection offered against hospitalization (80%) in subjects aged 2–16 years. However, variations of vaccine efficacy against VCD were observed in endemic settings, dengue serotype, and individual's pre-existing dengue antibody [130, 131]. Recent pooled analyses of the first 2–3 years of long-term follow-up provided further supportive evidence of efficacy against hospitalized dengue in children 9 years of age or older [132]. This vaccine has recently obtained licensure for use in children 9 years of age or older (9–45 years old) in Mexico, the Philippines, Brazil, Thailand, Singapore, and several other endemic countries. In view of the high disease burden in endemic countries, this vaccine, despite moderate overall efficacy, could have a substantial effect on public health [133–135]. The implementation of an efficacious dengue vaccine will shift the burden of disease; the age-related differences in clinical manifestations and prognoses described here indicate the importance of comparing a wide range of ages in future clinical studies of dengue.

7 Conclusion

Increase in the number of dengue cases is a major public health problem in many countries in South and Southeast Asia where *A. aegypti* and *A. albopictus* are widespread in both urban and rural areas. Several countries in Asia have reported an epidemic shift of dengue from mainly affecting children to affecting adolescents and young adults with increased severity. The clinical spectrum of dengue ranges from mild illness (undifferentiated fever and DF) to the life-threatening infection (DHF/DSS, severe bleeding, and multi-organ failure), which may be fatal. The early recognition of warning signs, plasma leakage, abnormal bleeding, circulatory collapse, and other serious complications would reduce mortality rates in patients with dengue infection. The implementations of effectively integrated vector management and efficacious dengue vaccines are keys to success for disease control in hyperendemic/endemic areas.

Conflicts of Interest Both authors have no conflicts of interest to declare.

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