

# DENGUE FEVER AND DENGUE HEMORRHAGIC FEVER IN ADULTS

Terapong Tantawichien

Division of Infectious Diseases, Department of Medicine, Faculty of Medicine,  
Chulalongkorn University and Queen Saovabha Memorial Institute, Thai Red Cross  
Society, Bangkok, Thailand

**Abstract.** Dengue fever and dengue hemorrhagic fever are re-emerging diseases that are endemic in the Tropics. The global prevalence of dengue cases has increased in South-East Asia, Africa, the Western Pacific, and the Americas. The increasingly widespread distribution and the rising incidence of dengue virus infections are related to increased distribution of *Aedes aegypti*, an increasingly urban population, and increasing air travel. Several Southeast Asian countries show that the age of the reported dengue cases has increased from 5-9 years, to older children and young adults. Dengue infection in adolescents and adults has also been recognized as a potential hazard to international travelers returning from endemic areas, especially Southeast Asia. Dengue is one disease entity with different clinical presentations; often with unpredictable clinical evolutions and outcomes. Bleeding manifestations in adult patients, including petechiae and menorrhagia were also frequently found; however, massive hematemesis may occur in adult patients because of peptic ulcer disease and may not be associated with profound shock as previously reported in children. Although shock and plasma leakage seem to be more prevalent as age decreases, the frequency of internal hemorrhage rises as age increases. Increase in liver enzymes found in both children and adults indicated liver involvement during dengue infections. Pre-existing liver diseases in adults such as chronic hepatitis, alcoholic cirrhosis, and hemoglobinopathies may aggravate the liver impairment in dengue infection. Fulminant hepatitis is a rare but well described problem in adult patients with dengue infection. Currently, no specific therapeutic agent exists for dengue. The early recognition of dengue infection, bleeding tendency, and signs of circulatory collapse would reduce mortality rates in adult patients with dengue infection.

**Keywords:** dengue fever, dengue hemorrhagic fever, dengue infection, adult

---

Correspondence: Terapong Tantawichien, MD,  
Division of Infectious Diseases, Department of  
Medicine, Faculty of Medicine, Chulalongkorn  
University and Queen Saovabha Memorial  
Institute, Thai Red Cross Society, Bangkok  
10330, Thailand.

Tel: +66 (0) 2252 0161-4; Fax: +66 (0) 2254  
0212

E-mail: terapong\_tantawichien@hotmail.com

## INTRODUCTION

Dengue fever (DF) and dengue hemorrhagic fever (DHF) are re-emerging mosquito-borne viral infections caused by four closely related dengue viruses (serotypes 1-4) of the genus *Flavivirus*. These dengue viruses are transmitted

principally by the *Aedes aegypti* and *Ae. albopictus* mosquito species. The dengue virus has 4 antigenically similar but immunologically distinct serotypes. Infection confers lifelong immunity to the infecting serotype; therefore, a person can be infected with dengue virus up to four times during his or her lifetime. The World Health Organization (WHO) predicted that there are more than 2.5 billion people living in tropical and subtropical countries, mostly in large and small cities, at risk of dengue infection with one or more dengue viruses. The global prevalence of dengue cases has increased in South-East Asia, Africa, the Western Pacific, and the Americas. The increasingly widespread distribution and the rising incidence of dengue virus infections is related to increased distribution of *Ae. aegypti*, and to the increase in urban population in the cities of Southeast Asia and air travel. Ideal conditions for increased transmission of dengue virus in tropical urban centers have 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 (Barbazan *et al*, 2002; Guzman and Kouri, 2003; Nakhapakorn and Tripathi, 2005; Anyamba *et al*, 2006). Without an effective vaccine or antiviral agent, an effective vector control program is the only means to reduce dengue infection in endemic areas.

Dengue virus infection is an important public health problem in Asia, and mainly occurs in children less than 15 years of age. The age distribution is different in the Americas, where these syndromes occur in all age groups. However, the majority of fatalities during epidemics in the Ameri-

cas occur in children. Several Southeast Asian countries have shown that age of the reported dengue cases has increased from 5-9 years to older children and young adults (Charoensook *et al*, 1999; Pancharoen *et al*, 2002; Pongsumpun *et al*, 2002; Kulanatne *et al*, 2005). In Thailand, affected adults aged over 15 years old are reported to comprise 20%-40% of dengue virus infected cases according to the Epidemiological Surveillance System (Patumanond *et al*, 2003; Department of Epidemiology, 2012). Morbidity and mortality rates of dengue have been highest in children, especially in the 5-9 year age group. At present, the morbidity rate of DHF in Thailand has declined to 0.15% while the average age of dengue patients is increasing.

The evidence of rising age of DF/DHF cases has been explained by association with demographic transition, modern housing, and commercial development (Kyle and Harris, 2008; Cummings *et al*, 2009). Dengue infection in adolescents and adults has been recognized as a potential hazard to tourists as various reports have been published on dengue virus infection in international travelers returning from endemic areas, especially Southeast Asia (Jelinex, 2000; Brien *et al*, 2001; Stefen *et al*, 2002; Pongsumpun *et al*, 2004). The increase in international air travel and the increasing transmission of dengue in the tropics mean that healthcare providers in Western countries are more likely to be confronted with travel-acquired dengue infections. Dengue now appears to occur more frequently than malaria among travelers returning from any region except Africa and Central America (Schwartz *et al*, 2008; Burdino *et al*, 2011; Wilder-Smith, 2012; Leder *et al*, 2013).

In returning travelers, the discrepancy between the incidences of infection and clinical expression is comparable with observations in areas of endemicity, where infections may go unnoticed. The proportionate morbidity associated with dengue is especially high among travelers returning from Southeast Asia and the Caribbean. Thus, we emphasize the need for continued dengue surveillance in non-endemic countries with careful evaluation and follow-up of febrile patients who have returned home after visiting a country in which dengue is endemic (Freedman *et al*, 2006; Massad and Wilder-Smith, 2009).

Although rarely documented, dengue virus transmission without a mosquito vector has been reported. Documented dengue transmissions through needle-stick, receipt of infected blood component, tissues or organs transplantation, and transplacental infection are quite rare; however, they may be more widespread than previously recognized (Chen and Wilson, 2004; Wagner *et al*, 2004; Tan *et al*, 2005; Mohammed *et al*, 2008; Tambyah *et al*, 2008; Wilder-Smith *et al*, 2009; Tangnaratrakit *et al*, 2012).

Dengue is one disease entity with different clinical presentations and often with unpredictable clinical outcomes. Dengue virus infection produces a spectrum of clinical illness ranging from undifferentiated fever, dengue fever (DF), which is a self-limiting febrile illness associated with fever, headache, myalgia, and thrombocytopenia, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), which may be fatal. DHF/DSS is characterized by rapid onset of capillary leakage accompanied by thrombocytopenia, altered hemostasis, which is characterized by hemoconcentra-

tion (hematocrit increased > 20%), thrombocytopenia (platelet count, <100 x10<sup>9</sup>/l), vascular collapse, abdominal pain, and hemorrhagic manifestations (WHO, 1997). The 1997 WHO definition further subdivides DHF into four grades (grade I-IV) on the basis of the presence of spontaneous bleeding and the presence and severity of shock (grade IV; DSS). 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 regards to the perturbation of vascular integrity.

The low accuracy of the WHO case definition and the difficulty to identify early clinical predictors of dengue infection in adults has been described (Srikiatkachorn *et al*, 2010; Hadinegoro, 2012). Due to many reports about difficulty of using the 1997 WHO classification in clinical management, the WHO released new guidelines with a new classification in 2009, which is dengue without warning signs, dengue with a warning signs and severe dengue (WHO, 2009; 2012). The warning signs mark the beginning of the critical phase in dengue infection. These patients become worse around the time of defervescence, when the temperature drops to 37.5-38°C or less and remains below this level, usually on days 3 to 8 of illness. Being an adult is also a risk factor for mortality in DF/DHF because of delayed diagnosis and treatment, comorbidity, and the increasing frequency of internal hemorrhage with age.

Physicians should be aware of warning signs (persistent or severe vomiting, abdominal pain or tenderness, liver enlargement, drowsy or alteration of consciousness, fluid accumulation with re-

spiratory distress, epistaxis, gum bleeding, gastrointestinal bleeding, retinal hemorrhage, oliguria, and hemoconcentration with severe thrombocytopenia) in patients with dengue infections before the patients develop severe dengue infections (shock from plasma leakage, severe bleeding, hepatic failure, acute renal failure, and encephalopathy) (Leo *et al*, 2011; Horstick *et al*, 2012; Prasad *et al*, 2013). The outcome of dengue depends largely on early diagnosis, the immediate replacement of fluid, and intensive supportive care.

There are several factors that may influence disease severity in dengue virus infection, including host factors, virus serotype or genotype, sequence of virus infection and differences in dengue cross-reactive antibody and T-cell responses (Green and Rothman, 2006). Age-related differences in dengue severity are poorly understood, and the data on clinical features in dengue adults are limited (Guzman *et al*, 2002; Hammond *et al*, 2005; Kittigul *et al*, 2007; Tantawichien, 2012; Namvongsa *et al*, 2013; Souza *et al*, 2013). Plasma leakage, as well as DSS and leakage appear to be less frequent in adults than children, possibly reflecting age-dependent differences in intrinsic vascular permeability, but anecdotal evidence suggests that bleeding manifestations, especially internal hemorrhage and hepatic dysfunction, are both more common in older age groups (Gamble *et al*, 2000; Wichmann *et al*, 2005; Guilarde *et al*, 2008; Tantawichien, 2012).

Previous studies have described the severity of clinical bleeding found in adult dengue patients. The emergence of DF with unusual bleeding and DHF in the adolescent, adult and elderly populations has been a cause of an apparent increase

in the complications of dengue infection (Tsai *et al*, 1991; Anuradha *et al*, 1998; Agarwal *et al*, 1999; Tantawichien *et al*, 2000; Rongrungruang and Leelarasamee, 2001; Wichmann *et al*, 2005; Pungjitprapai and Tantaurchen, 2008). Older age has previously been reported to be a risk factor for mortality in patients with DF or DHF because ageing, co-morbidity, and waning immunity pose a substantial risk for fatality in elderly patients with active infection (Rigau-Perez and Laufer, 2006; Kuo *et al*, 2007; Lee *et al*, 2008; Gautret *et al*, 2012; Pang *et al*, 2012).

#### CLINICAL MANIFESTATION

Dengue is a common cause of fever in the Tropics, but its contribution to the total burden of febrile illnesses that presents to primary health facilities in endemic regions such as Thailand is largely unknown. In the early stage of dengue infection, diagnosis from clinical manifestation alone is difficult, especially in adults. Dengue has numerous differential diagnoses, including malaria, leptospirosis, rickettsial diseases, typhoid, chikungunya, other viral hemorrhagic disease, and so forth (Leelarasamee *et al*, 2004; Phuong *et al*, 2006). Dengue infection should be suspected if the patients have a fever of 10 days or less with myalgia, arthralgia, bone pain, headache, peri-orbital pain, flushing, nausea or vomiting with no obvious respiratory tract symptoms or signs and no organ specific symptoms of other infectious diseases.

After an incubation period of 4 to 7 days, the febrile period is accompanied by severe headache, retro-orbital pain, myalgia, arthralgia, nausea, and vomiting. Tantawichien *et al* (2000) described the clinical manifestations of 140 adult patients

infected with dengue virus during the epidemic of dengue infection in Bangkok from 1997 to 1998, and he reported that there was fever (3 to 8 days), nausea/vomiting, headache, and myalgia in both DF and DHF; however abdominal pain, and severe or widespread bleeding manifestations were less frequent in DF.

Over one-quarter of infected people reported a rash during the febrile phase that was initially macular or maculopapular, and some became diffusely erythematous, sparing small areas of normal skin ("islands of white in a sea of red"). Minor hemorrhagic manifestations such as petechiae, epistaxis, and gingival bleeding do occur, but severe hemorrhage leading to shock through blood loss rarely occurs. Attempts to differentiate DF clinically from other acute febrile illnesses are unlikely to be successful although the diagnosis is aided if laboratory examination indicates leukopenia, neutropenia, thrombocytopenia, or mildly elevated AST levels, as well as a positive tourniquet test.

The tourniquet test has been used as a clue for dengue infection for a long time and has been considered by the WHO in 2009 as one of the criteria for probable dengue infection. Unfortunately, the sensitivity and specificity of tourniquet test from previous report, especially in children, were not excellent, ranging between 34%-56% and 68%-94%, respectively. However, this test was regarded to be a cheap and simple clinical method that is suggestive of dengue when positive, but a negative test does not exclude the disease (Phuong *et al*, 2002; Gregory *et al*, 2011; Mayxay *et al*, 2011; Halsey *et al*, 2013).

Laboratory tests, such as reverse transcription polymerase chain reaction

(RT-PCR) or dengue nonstructural protein 1 antigen, capture assay (NS1 Ag assay) are usually used to diagnose the dengue infection antigen during the early phase of acute infection, and serological ELISA is used to detect specific IgM or IgG antibodies. However, those tests are not always available in all parts of dengue endemic countries. DF is usually a self-limiting condition, and death as a result is uncommon. Nevertheless, patients who have severe nausea/vomiting, severe hemorrhage (for example, hematemesis, hematochezia, or abnormal vaginal bleeding), hypotension, a platelet count of  $\leq 20,000/\text{mm}^3$  ( $\leq 20 \times 10^9/\text{l}$ ), AST or ALT  $> 500$  U/ml, renal failure, liver failure, heart failure, drowsiness, severe hypoxemia, pregnancy, and no opportunity to be followed up in an out-patient setting should be hospitalized in Thailand (Figs 1 and 2).

DHF is the most serious manifestation of dengue. Adults may be at lower risk of developing DHF compared to children and adolescent due to differences in capillary permeability (Gamble *et al*, 2000). During the transition from the febrile to afebrile phase, DHF patients with increased capillary permeability may manifest with the warning signs, mostly as a result of plasma leakage. The cardinal features that distinguish DHF from DF are increased vascular permeability (plasma leakage syndrome), and marked thrombocytopenia ( $< 100 \times 10^9/\text{l}$ ) associated with bleeding and hepatomegaly and/or abnormal liver function (WHO, 1997).

During the transition from the febrile to afebrile phase, DHF patients with increased capillary permeability may manifest with the warning signs, mostly as a result of plasma leakage. A 20% increase in hematocrit



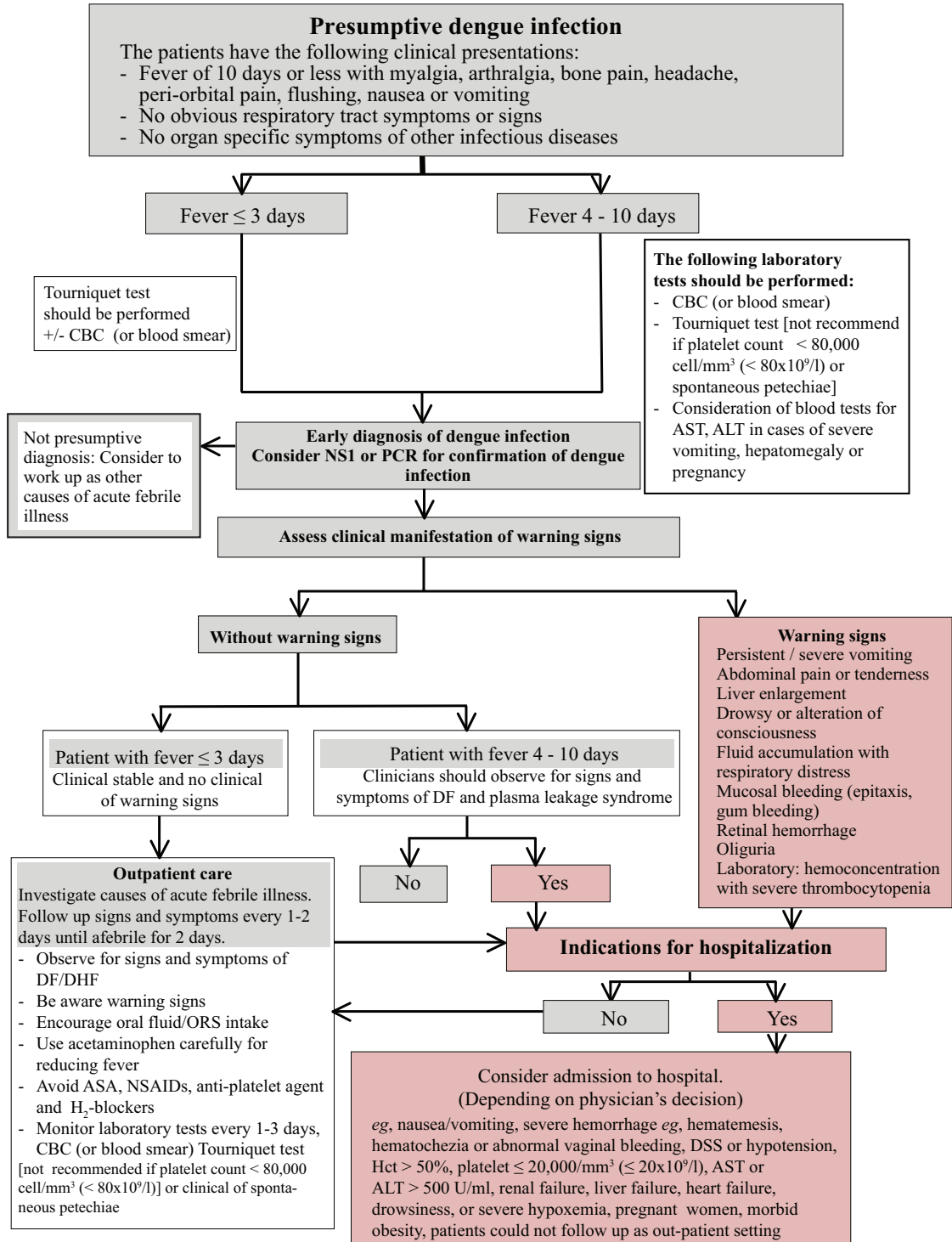


Fig 1–Guideline for outpatient management of dengue infections in adult (adapted from guidelines of Royal College Physician of Thailand, 2012).

## DENGUE IN ADULTS

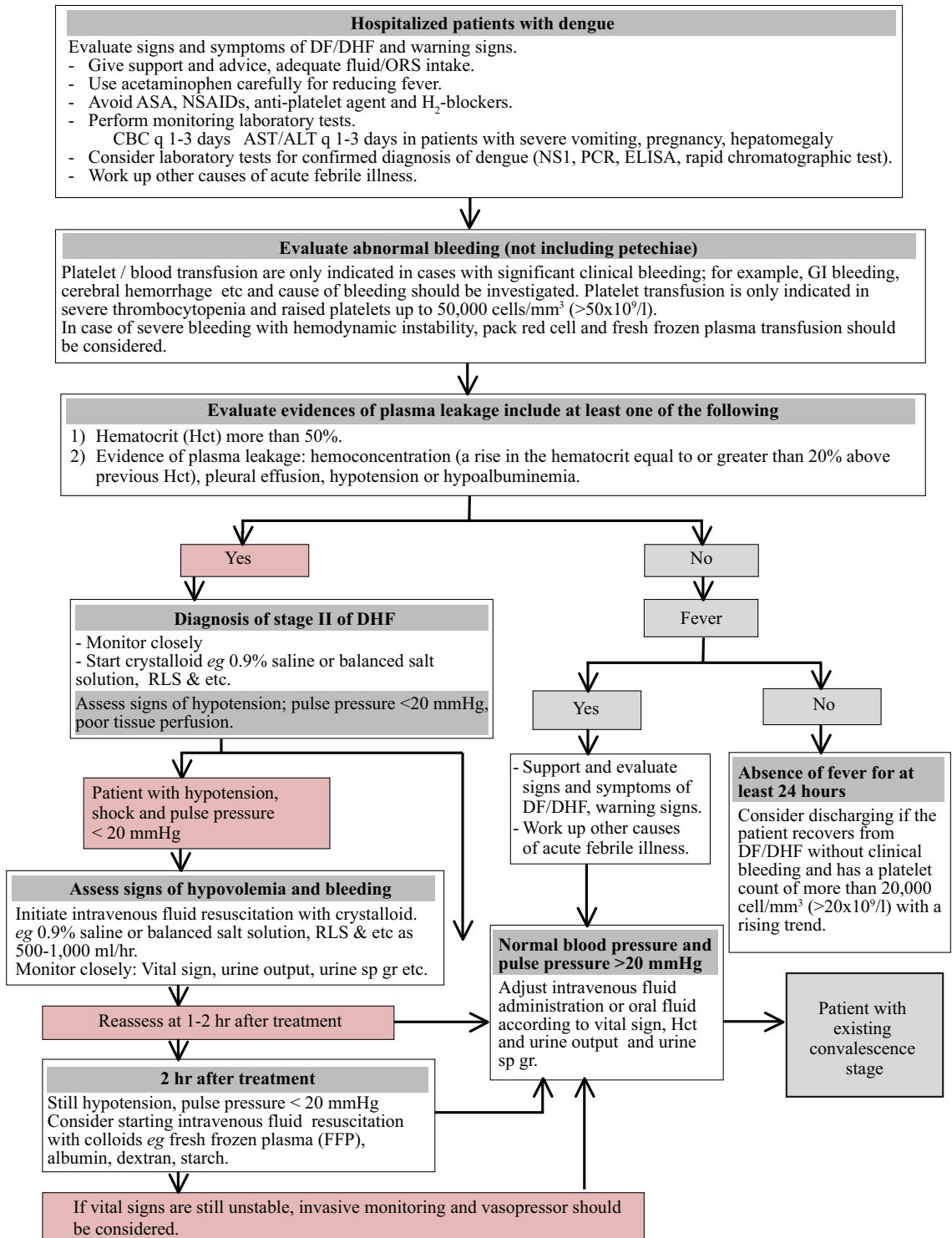


Fig 2–Guideline for inpatient management of dengue infections in adult (adapted from guideline of Royal College Physician of Thailand 2012).

over baseline is generally accepted as indicative of plasma leakage. The degree of hemoconcentration above the baseline hematocrit reflects the severity of plasma leakage; however, this may be reduced by early intravenous fluid therapy. Hematocrit readings can be affected by factors other than plasma leakage such as fever, dehydration, and bleeding. Furthermore, failure to obtain repeated measurements needed to calculate the degree of hemoconcentration often leads to difficulties in classifying dengue adult cases. Pleural fluid detected by right lateral decubitus chest roentgenogram, ultrasound detection of free fluid in the chest or abdomen, or gall bladder wall edema has been interpreted as evidence of plasma leakage, and ascites are usually only clinically detectable after intravenous fluid therapy unless plasma leakage is significant (Setcawan *et al*, 1995; Srikiatkhachorn *et al*, 2007; Wang *et al*, 2007a).

Plasma leakage syndrome and extreme decreases in platelet counts associated with bleeding frequently occur 3 to 7 days after the onset of illness. The period of clinically significant plasma leakage usually lasts 24-48 hours. In cases with a benign course of illness, blood pressure and pulse may be maintained, but a rapid and weak pulse, narrowing of the pulse pressure to less than 20 mmHg, or an unobtainable blood pressure in the most extreme cases establish DSS. If plasma loss continues and becomes excessive, the patient's situation can progress into profound shock. Clinical indicators of impending DSS include severe abdominal pain, change from fever to hypothermia, restlessness, sweating, prostration and tender hepatomegaly. DSS was an independent risk factor (odds ratio 220) for development

of acute renal failure in adult patients with DHF (Lee *et al*, 2009). Cardiac involvement was observed in few patients requiring hospitalization with clinical manifestation ranging from mild elevation of cardiac biomarkers to myocarditis and/or pericarditis and death (Miranda *et al*, 2013).

Acute respiratory failure is a rare complication in adult dengue patients but has a high mortality rate (Wang *et al*, 2007b). In agreement with previous reports, Tantawichien *et al* (2000) reported that adults with DHF had a very low frequency of DSS compared with children with DHF. 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 virus infection.

Hemorrhage contributes to dengue morbidity and mortality, especially during the severe thrombocytopenia and the toxic hemorrhagic stage (3 to 5 days after the onset of illness) (Chuansumrit and Chaiyaratana, 2014). The pathogenesis of hemorrhage may be multifactorial and encompasses vasculopathy, platelet deficiency and dysfunction, as well as blood coagulation defects. Platelet counts begin to fall during the febrile stage and reach their lowest levels during the toxic stage. Bleeding complications usually occur in 5 to 8 days after onset in dengue infection. The abnormal bleeding is associated with low numbers of platelets and abnormalities of walls of vessels. Risk factors of bleeding are platelets  $\leq 20,000/\text{mm}^3$  ( $\leq 20 \times 10^9/\text{l}$ ), increased AST or ALT, prolonged PT, severe dengue hemorrhagic fever, patients with DIC, or liver failure (Chamnanchanunt *et al*, 2012).

Age had a non-linear relation to the



risk of bleeding. In almost all DHF patients, defects of coagulation activation such as a prolonged activated partial thromboplastin time (APTT) or thrombin time can be found. In addition, a decreased fibrinogen level and increased levels of fibrinogen degradation products indicating hyperfibrinolysis may also occur in DHF/DSS patients. 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. Massive bleeding such as hematemesis may occur in adults with DF or DHF. Minor hemorrhagic manifestations such as petechiae, epistaxis and gingival bleeding do sometimes occur in DF although they are rarely associated with severe hemorrhage leading to shock. Of the dengue patients with DHF, severity of hemorrhagic manifestations varied markedly with spontaneous petechiae, hematemesis, metrorrhagia, melana, and epistaxis.

Bleeding manifestations including petechiae and menorrhagia were also frequently found in adults. Bleeding from the nose, gums and upper gastrointestinal tract are not uncommon. However, massive hematemesis may occur in DF or DHF patients because of peptic ulcer disease in adults, and it is not associated with profound shock in adults as previously reported in children. Upper gastrointestinal bleeding is the most common type of severe hemorrhage in DF. In the few reports of endoscopic findings for dengue patients with upper gastrointestinal bleeding, hemorrhagic gastritis was the most common finding (40.9%-58.5%), followed by gastric ulcer, and duodenal ulcer (Tsai *et al*, 1991). In patients with preexisting

peptic ulcer disease, severe and even fatal gastric bleeding can be precipitated. The role of endoscopic therapy in upper gastrointestinal bleeding of dengue patients is still unknown (Wung *et al*, 1990). Therefore, blood transfusion therapy with concentrated platelets, packed red cell, and fresh frozen plasma to correct the bleeding tendency, anemia, coagulopathy, and hypovolemia is still the mainstay of treatment of upper gastrointestinal bleeding in dengue patients.

Females had a greater tendency to develop abnormal bleeding such as menorrhagia during hospitalization. Tantawichien *et al* (2000) reported that vaginal bleeding (menorrhagia) was the most common site of bleeding (24.6%) in female adults with dengue virus infection. Hormonal therapy, such as premarin, primolute N, or oral contraceptive pills is suggested for females exhibiting excessive menstrual bleeding. Uterine hemorrhage resulting in spontaneous abortion and severe postpartum bleeding has also been reported in pregnant women (Thaithumyanon *et al*, 1994).

Life-threatening subcapsular splenic bleeding and ruptures are rare but can happen spontaneously or as a result of trauma, which may be minor or unnoticed. Splenectomy is still the treatment of choice for splenic rupture, but numerous recent reports have documented favorable outcomes with conservative treatment (Imbert *et al*, 1993; Pungjitprapai and Tantawichian, 2008). Early diagnosis and treatment are needed to avoid a fatal outcome. Surgical procedures performed on patients with dengue infection may unmask dengue-induced hemostatic defects, resulting in unexpected hemorrhage in post-operative period that is difficult to control. Therefore,

in the case of onset of labor, the route of delivery should be considered under obstetric indications. During hemorrhaging, patients should receive blood transfusions with concentrated platelets, packed red blood cells, and fresh-frozen plasma to correct bleeding, anemia, and hypovolemic shock. Close monitoring of vital signs and hematocrit levels to assess the severity of hemorrhage are required to reduce morbidity and mortality. Most patients with dengue infection recover spontaneously, and all abnormal hemostasis normalizes during the convalescent stage or within 1-2 weeks after defervescence.

Liver involvement during dengue virus infection in adults has been described (Kuo *et al*, 1992; Kalayannarooj *et al*, 1997; Souza *et al*, 2004; Trung *et al*, 2010). Increase in liver enzymes (AST and ALT) found in both children and adults indicated liver involvement during dengue virus infections. The pathogenesis of liver involvement during dengue infections is still poorly understood. Potential mechanisms of hepatic injury involve a variety of potential insults including direct effects of the virus or host immune response 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; and tissue tropism of particular viral serotypes or genotypes (Parkash *et al*, 2010). Dengue antigens and viral RNA have been demonstrated in some of these fatal cases, and dengue viruses have been isolated occasionally from hepatic tissue. However, biopsy specimens are rarely obtained from less severe cases, and the relevance of these findings to the broad spectrum of dengue

infections remains uncertain. In endemic or epidemic areas, dengue infection should be included in the differential diagnosis of acute viral hepatitis.

Unlike conventional viral hepatitis, dengue infections have a higher level of AST than that of ALT. It has been suggested that this may be due to excessive release of AST from damaged myocytes during dengue infections. Attention must therefore be given to the use of hepatotoxic agents such as acetaminophen, antibiotics, and antiemetic drugs, all of which have the potential to aggravate liver damage in some cases of dengue. Liver transaminase should be measured in adult patients with dengue infection, especially when hepatitis is suspected, or a history of acetaminophen use of more than 2 grams per day has been noted. The levels of liver enzymes increase to a maximum 7-to-9 days after the onset of symptoms, and then often decrease to normal levels within 2 weeks. 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. It is likely that relatively more adult dengue patients have more liver impairment than children, especially during periods of epidemic.

Transaminase levels increase in virtually all dengue patients and have correlated with other markers of disease severity. Abnormal liver enzyme levels have been associated with a poor outcome in adults with vascular leakage and abnormal bleeding. Severe liver involvement may complicate the clinical picture of DF and DHF by causing liver failure and contributing directly to severe bleeding, as well as indirectly potentiating the severity of disseminated intravascular coagulopathy (DIC). Jaundice

and fulminant liver failure occur relatively late in the course of the disease usually without evidence of severe vascular leakage with shock (Innis *et al*, 1990, Ling *et al*, 2007). The association of severe liver disease and encephalopathy has been well described in both pediatric and adult patients with DF and DHF. Hence, dengue should be considered as a possible cause of acute liver failure in endemic areas if other viral markers are negative. The management of fulminant liver failure in dengue is primarily supportive. Splenomegaly is uncommonly observed in adult with dengue infection. Thickening of the gallbladder wall has been reported in conditions with hypoalbuminemia and ascites, as well as in several viral infections including DHF.

An increasing number of dengue infections have been related to other unusual manifestations. The unusual manifestations of dengue infection in adult include DF/DHF with severe internal hemorrhage, fulminant hepatic failure, encephalopathy, cardiomyopathy, cardiac arrhythmia, adult respiratory distress syndrome (ARDS), rhabdomyolysis, pancreatitis, appendicitis, co-infection with other tropical infectious diseases and neurological phenomena such as altered consciousness, convulsions, and coma resulting from encephalitis and encephalopathy (Thakane *et al*, 1996; Jusuf *et al*, 1998; Solomon *et al*, 2000; Garcia-Rivera and Rigue-Perez, 2002; Davis and Bouke, 2004; Promphan *et al*, 2004; Misra *et al*, 2006; Premaratna *et al*, 2007).

Neurological manifestations of dengue can include a wide range of neurological features in 0.5%-21% of hospitalized patients with dengue. These neurological manifestations were ascribed to non-

specific complications such as myelitis, neuro-ophthalmic complications, polyradiculopathy, neuropathy, and neuromuscular complications secondary to dengue infection (Carod-Artal *et al*, 2013). Possible causes of dengue encephalopathy include hypotension, cerebral edema, focal hemorrhage, hyponatremia, and fulminant hepatic failure. However, a documented possibility is the invasion of the central nervous system (Lum *et al*, 1996; Choikephaibulkit *et al*, 2001).

Some studies have indicated that 5.5% of the patients with DHF/DSS also had dual infection (for example, urinary tract infection, diarrhea, or bacteremia) (Pancharoen and Thisyakorn, 1998; Tantawichien, 2012). Dual infection should be suspected in atypical presentation; for example, prolonged fever for more than 10 days, mucus diarrhea, jaundice, persistent abdominal pain, recurrent fever, WBC > 10,000/mm<sup>3</sup> (> 10x10<sup>9</sup>/l) with neutrophilia, or presence of the band form of neutrophil. The patient with dengue infection may have subsequent nosocomial infection after hospitalization. Failure in making a diagnosis of concurrent infection in patients with DHF may lead to otherwise preventable morbidity and mortality. A previous report revealed that prolonged fever and acute renal failure were independent predictive factors for dual infection (Lee *et al*, 2005).

In dengue endemic areas, obstetricians must be aware that dengue infection of pregnant women may occur and some history or laboratories consistent with dengue infection such as fever without coryza, facial flushing, petechiae hemorrhage, thrombocytopenia, and an increase of atypical lymphocytes must be identified. Many cases of DF/DHF among pregnant

women have been reported in Southeast Asia, highlighting the concept that some women in endemic area remain susceptible to dengue infection (Bunyavejchevin *et al*, 1997; Corles *et al*, 1999). Dengue during pregnancy is also particularly important in pregnant travelers from non-endemic countries to countries where dengue is endemic (Carroll *et al*, 2007).

Younger mothers would be more likely to become infected compared to older mothers, who are more likely to be seropositive and, therefore, less susceptible for dengue infections. Because surgical procedures performed on patients with dengue infection may unmask dengue-induced hemostatic defects, resulting in unexpected hemorrhage in post-operative period that is difficult to control. The route of delivery in such patients at the onset of labor should be considered under obstetric indications (Adam *et al*, 2010). It also has been reported that dengue infection was vertically transmitted to the fetus and that this led to a full-blown illness in the neonate similar to that seen in children and adults (Bunyavejchevin *et al*, 1997).

A low rate of fetal transmission is consistent with other studies that have reported no cases of congenital dengue infection in neonates born to mothers infected early in pregnancy. Accordingly, the gestation of maternal infection is an important factor related to fetal infection risk with symptomatic infection possibly unlikely with early gestational infection and increased with infection late in pregnancy (Waduge *et al*, 2006; Basurko *et al*, 2009; Pouliot *et al*, 2010; Chitra and Panicker, 2011). All reported cases of symptomatic congenital dengue infection have occurred in neonates born to mothers infected very late in pregnancy

mainly when they were symptomatic at the time of delivery. 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 (Basurko *et al*, 2009).

The outcome of DHF and DSS depends largely on early diagnosis, the immediate replacement of fluid, and comorbidities. Adults have a higher prevalence of underlying diseases; for example, coronary artery disease, peptic ulcer, hypertension, diabetes mellitus, cirrhosis, or chronic kidney disease, which should be considered in management of adult dengue (Rigau-Perez and Laufer, 2006; Sam *et al*, 2013). With support through the critical period of illness, spontaneous resolution of vasculopathy and circulatory failure usually can be expected within 2 to 3 days with complete recovery afterward. At that time, the temperature decreases, and can increase slightly the day after. This pattern is known as the biphasic temperature curve. In the defervescence period, the patients usually have more appetite, bradycardia. Also, they develop a generalized, maculopapular rash with itching, sparing the palms and soles. This rash usually disappears in 1 to 5 days. The duration of dengue illness ranges from 7 to 10 days in most cases. Adults may have profound fatigue or mood disturbance for several weeks after recovery.

## DIAGNOSIS

Early definite diagnosis of dengue infection can help clinicians in initiation of

early supportive care, adequate management, and identification of patients with severe dengue, who should be closely monitored for signs of plasma leakage, bleeding, and end 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. 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 human serum (Poerscha *et al*, 2005). The sensitivity of each approach is influenced by the duration and severity of the patient's illness. 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 patient presenting with an acute undifferentiated febrile illness.

However, monitoring all these patients for the development of warning signs of severity may impose a great burden on healthcare services. In the very early stage of illness when patients generally seek medical attention within the first 2-to-3 days of fever without specific symptoms, only RT-PCR or dengue virus NS1 Ag assay can reliably confirm the diagnosis of dengue. RT-PCR is definitely the most satisfactory test that might detect dengue viruses up to the seventh day after the onset of the symptoms, especially in severe cases (Yamada *et al*, 2002; Lanciotti, 2003). In addition, the presence of dengue virus in frozen and fixed tissues, saliva or urine can be determined by RT-PCR. As an

alternative, the detection of viral antigens has been proposed, and more recently attention has been focused on NS1 of the dengue virus (Alcon *et al*, 2002; Vazquez *et al*, 2010). A high circulating level of dengue virus NS1 was demonstrated in the early stage of dengue infection by different ELISA assays in the plasma and/or sera of dengue patients.

Hemagglutination-inhibition (HI), complement fixation (CF), neutralization test (NT), immunoglobulin M (IgM) capture enzyme linked immunosorbent assay (MAC-ELISA), and indirect immunoglobulin G ELISA have been used for the diagnosis of dengue infection. The dengue antibodies are better detected around the fifth day after the onset of the disease, making this technique unfeasible for rapid diagnosis. Until now, ELISA has been considered the most useful test for dengue diagnosis due to its high sensitivity and ease of use. ELISA has been used to detect acute phase (IgM) and convalescent phase (IgG) antibodies. The IgM antibody titers in primary infections are significantly earlier and higher than in secondary infections.

Some adult patients with primary infection such as travelers from Europe or North America have IgM detectable by the second to the fourth day after the beginning of the symptoms while patients with secondary infections mount rapid anamnestic antibody responses in which dengue virus-reactive IgG may predominate over IgM. There are several commercial kits of rapid tests of IgM and IgG detection for diagnosis of dengue infection (Kittigul and Suankeow, 2002; Blacksell *et al*, 2006). However, the sensitivity, specificity, and accuracy vary among these tests. In clinical settings where methods of RT-PCR are not avail-



able, combination tests for elevated levels of soluble NS1 or dengue virus–reactive IgM in serum is a pragmatic diagnostic approach in an adult patient in whom dengue infection is suspected.

## TREATMENT AND PREVENTION

Currently, no specific therapeutic agent to treat dengue infection is available, and treatment remains supportive with particular emphasis on careful fluid management. The early recognition of dengue infection, bleeding tendency, signs of circulatory collapse, and complications would reduce mortality rates in adult patients with dengue infection. Mild dengue infections may be treated at home with oral hydration and antipyretics with instructions to return to the hospital immediately if bleeding or warning signs suggestive of severe disease develop. Oral rehydration is indicated to replace losses from vomiting and high fever. It is necessary to avoid the use of salicylates, NSAIDs, and traditional medicines that may contain hepatotoxic agents.

Development of any warning sign (eg, severe vomiting, gastrointestinal hemorrhage, hypotension, high liver transaminase, acute renal impairment, alteration of consciousness, severe thrombocytopenia, etc) indicates the need for hospitalization and close observation with appropriate use of parenteral fluids in patients with inadequate oral intake or a rapidly increasing hematocrit. Attentive clinical monitoring of patients with severe dengue or suspected DHF-DSS and anticipatory and supportive care are life saving 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 pulse, blood pressure, skin perfusion, urine output, urine specific gravity, and hematocrit to trigger intravenous fluid or transfusion therapy (Nhan *et al*, 2001).

Patients with DHF need to be monitored closely for signs of shock until at least 24–48 hours after defervescence. The mainstay of treatment for DHF remains prompt fluid resuscitation to counteract massive plasma leakage. Timely and effective intravenous crystalloid replacement of plasma losses results in a favorable outcome in most adult cases. For patients suffering from DSS, the mainstay of therapy is early and effective replacement of plasma loss. To limit the risk of the development of fluid overload, parenteral fluid therapy should be kept to the minimum required to maintain cardiovascular stability until permeability reverts to a normal level. WHO recommends immediate volume replacement with Ringer's lactate, or physiologically normal saline solution, followed by fresh frozen plasma or colloid solutions such as albumin, or dextran in the event that shock persists. Crystalloid solutions should be used initially, and isotonic colloid solutions should be reserved for patients presenting with profound shock or those who do not have a response to initial crystalloid therapy. Recently, two randomized controlled trials evaluated therapeutic responses to colloid and crystalloid solutions (Dung *et al*, 1999; Wills *et al*, 2005; Akech *et al*, 2011).

Results indicate that Ringer's lactate performed the least well and that the more severely ill patients identified by a narrow pulse pressure ( $\leq 10$  mmHg) would benefit more from initial resuscitation with colloid solution than with crystalloid solution.



Whole blood, platelet, and fresh-frozen plasma transfusions can be lifesaving for patients with severe bleeding that compromises cardiovascular function, but it should be undertaken with care because of the risk of fluid overload. The use of prophylactic blood or platelet transfusions may be harmful and should be avoided, and invasive procedures should be minimized to avoid hemorrhagic complications. Currently, there is no evidence to support the use of any adjunctive therapies such as corticosteroid, desmopressin, or carbazochrome sodium sulfonate (AC-17) for dengue infection.

Dengue prevention currently relies on public health and community-based *Aedes aegypti* control programs to remove and destroy mosquito-breeding sites. The most advanced approach is a potential vaccine consisting of a tetravalent combination of attenuated dengue strains, and other approaches are undergoing initial clinical evaluation. Dengue will continue to spread worldwide until a safe and effective vaccine is available alongside sustainable mosquito control practices. Furthermore, as the eventual implementation of a 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.

## REFERENCES

- Adam I, Jumaa AM, Elbashir HM, Karsany MS. Maternal and perinatal outcomes of dengue in Port Sudan, Eastern Sudan. *Viral J* 2010; 7: 153.
- Agarwal R, Kapoor S, Nagar R, *et al.* A clinical study of the patients with dengue hemorrhagic fever during the epidemic of 1996 at Lucknow, India. *Southeast Asian J Trop Med Public Health* 1999; 30: 735-40.
- Akech S, Ledermann H, Maitland K. Choice of fluids for resuscitation in children with severe infection and shock: systematic review. *BMJ* 2011; 341: c4416.
- Alcon S, Talarmin A, Debruyne M, Falconar A, Deubel V, Flamand M. Enzyme-linked immunosorbent assay specific to dengue virus type 1 nonstructural protein NS1 reveals circulation of the antigen in the blood during the acute phase of disease in patients experiencing primary or secondary infections. *J Clin Microbiol* 2002; 40: 376-81.
- Anuradha S, Singh NP, Rizvi SNA, *et al.* The 1996 outbreak of dengue hemorrhagic fever in Delhi, India. *Southeast Asian J Trop Med Public Health* 1998; 29: 503-6.
- Anyamba A, Chretien JP, Small J, Tucker CJ, Linthicum KJ. Developing global climate anomalies suggest potential disease risks for 2006-2007. *Int J Health Geogr* 2006; 5: 60.
- Barbazan P, Yokgan S, Gonzalez JP. Dengue hemorrhagic fever epidemiology in Thailand: description and forecasting of epidemics. *Microb Infect* 2002; 4: 699-705.
- Basurko C, Carles G, Youssef M, Guindi WE. Maternal and fetal consequences of dengue fever during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2009; 147: 29-32.
- Blacksell SD, Newton PN, Bell D, *et al.* The comparative accuracy of 8 commercial rapid immunochromatographic assays for the diagnosis of acute dengue virus infection. *Clin Infect Dis* 2006; 42: 1127-34.
- Brien D, Tobin S, Brown GV, Torresi J. Fever in returned travelers. *Clin Infect Dis* 2001; 33: 603-9.
- Bunyavejchevin S, Tanawattacharoen S, Taechakraichana N, *et al.* Dengue hemorrhagic fever during pregnancy. *J Obstet Gynaecol Res* 1997; 23: 445-8.
- Burdino E, Milia MG, Sergi G, *et al.* Diagnosis of dengue fever in North West Italy in travelers from endemic areas: A retrospective

- study. *J Clin Virol* 2011; 51: 255-9.
- Carod-Artal FJ, Wichmann O, Farrar J, Gasc J. Neurological complications of dengue virus infection. *Lancet Neurol* 2013; 16: 906-19.
- Carroll D, Toovey S, Gompel AV. Dengue fever and pregnancy—a review and comment. *Travel Med Infect Dis* 2007; 5: 183-8.
- Chamnanchanunt S, Kanagaraj D, Thanachartwet V, Desakorn V, Rojnuckarin P. Early predictors of clinically significant bleeding in adults with dengue infection. *Southeast Asian J Trop Med Public Health* 2012; 12: 890-8.
- Charoensook O, Foy HM, Teeraratkul A, Silarug N. Changing epidemiology of dengue hemorrhagic fever in Thailand. *Epidemiol Infect* 1999; 122: 161-6.
- Chen LH, Wilson ME. Transmission of dengue virus without a mosquito vector: nosocomial mucocutaneous transmission and other routes of transmission. *Clin Infect Dis* 2004; 39: e56-60.
- Chitra TV, Panicker S. Maternal and fetal outcome of dengue fever in pregnancy. *J Vector Borne Dis* 2011; 48: 210-3.
- Chokephaibulkit K, Kankirawatna P, Apintanapong S, et al. Viral etiologies of encephalitis in Thai children. *Pediatr Infect Dis J* 2001; 20: 216-8.
- Chuansumrit A, Chaiyaratana W. Hemostatic derangement in dengue hemorrhagic fever. *Thrombosis Res* 2014; 133: 10-6.
- Corles G, Peiffer H, Talarmin A. Effects of dengue fever during pregnancy in French Guiana. *Clin Infect Dis* 1999; 28: 637-40.
- Cummings DA, Iamsirithaworn S, Lessler JT, et al. The impact of the demographic transition on dengue in Thailand: insights from a statistical analysis and mathematical modeling. *PLoS Med* 2009; 6: e1000139.
- Davis JS, Bourke P. Rhabdomyolysis associated with dengue virus infection. *Clin Infect Dis* 2004; 38: e109-11.
- Department of Epidemiology, Ministry of Public Health, Thailand. Annual epidemiological surveillance report: Thailand. Bangkok: Department of Epidemiology, 2012. [Cited 2014 Feb 20]. Available from: <http://epid.moph.go.th>
- Dung NM, Day NPJ, Tam DTH, et al. Fluid replacement in dengue shock syndrome. *Clin Infect Dis* 1999; 29: 787-94.
- Freedman DO, Weld LH, Kozarsky PE, et al. Spectrum of disease and relation to place of exposure among ill returned travelers. *N Engl J Med* 2006; 354: 119-30.
- Garcia-Rivera EJ, Rigue-Perez JG. Encephalitis and dengue. *Lancet* 2002; 360: 261.
- Gamble J, Bethell D, Day NP, et al. Age-related changes in microvascular permeability: a significant factor in the susceptibility of children to shock? *Clin Sci (Lond)* 2000; 98: 211-6.
- Gautret P, Gaudart J, Leder K, et al. Travel-associated illness in older adults (>60 y). *J Travel Med* 2012; 19: 169-77.
- Green S, Rothman A. Immunopathological mechanisms in dengue and dengue hemorrhagic fever. *Curr Opin Infect Dis* 2006; 19: 429-36.
- Gregory CJ, Lorenzi OD, Colón L, et al. Utility of the tourniquet test and the white blood cell count to differentiate dengue among acute febrile illnesses in the emergency room. *PLoS Negl Trop Dis* 2011; 5: e1400.
- Guzman MG, Kouri G. Dengue and dengue hemorrhagic fever in the Americas. *J Clin Virol* 2003; 27: 1-13.
- Guzman MG, Kouri G, Bravo J, Valdes L, Vazquez S, Halstead SB. Effect of age on outcome of secondary dengue 2 infections. *Int J Infect Dis* 2002; 6: 118-24.
- Guilarte AO, Turchi MD, Siqueira JB, et al. Dengue and dengue hemorrhagic fever among adults: clinical outcomes related to viremia, serotypes, and antibody response. *J Infect Dis* 2008; 197: 817-24.
- Hadinegoro SR. The revised WHO dengue case classification: does the system need to be modified? *Paediatr Int Child Health* 2012; 32 (suppl 1): 33-8.
- Halsey ES, Vilcarrromero S, Forshey BM, et al.

- Performance of the tourniquet test for diagnosing dengue in Peru. *Am J Trop Med Hyg* 2013; 89: 99-104.
- Hammond SN, Balmaseda A, Perez L, *et al.* Differences in dengue severity in infants, children, and adults in a 3-year hospital-based study in Nicaragua. *Am J Trop Med Hyg* 2005; 73: 1063-70.
- Horstick O, Farrar J, Lum L, *et al.* Reviewing the development, evidence base, and application of the revised dengue case classification. *Pathog Global Health* 2012; 106: 94-101.
- Imbert P, Sordet D, Hovette P, Touze JE. Splenic rupture in a patient with dengue fever. *Trop Med Parasitol* 1993; 44: 327-8.
- Innis BL, Myint KSA, Nisalak A, *et al.* Acute liver failure is one important cause of fatal dengue infection. *Southeast Asian J Trop Med Public Health* 1990; 21: 695-6.
- Jelinek T. Dengue fever in international travelers. *Clin Infect Dis* 2000; 31: 144-7.
- Jusuf M, Sudjana P, Djumhana A, Absurachman SA. DHF with complication of acute pancreatitis related hyperglycemia. *Southeast Asian J Trop Med Public Health* 1998; 29: 367-9.
- Kalayannaroj S, Vaughn DW, Nimmannitya S, *et al.* Early clinical and laboratory indicators of acute dengue illness. *J Infect Dis* 1997; 176: 313-21.
- Kittigul L, Suankeow K. Use of a rapid immunochromatographic test for early diagnosis of dengue virus infection. *Eur J Clin Microbiol Infect Dis* 2002; 21: 224-6.
- Kittigul L, Pitakarnjanakul P, Sujirarat D, Siripanichgon K. The differences of clinical manifestations and laboratory findings in children and adults with dengue virus infection. *J Clin Virol* 2007; 39: 76-81.
- Kuo MC, Chang JM, Lu PL, Chiu YW, Chen HC, Hwang Hj. Case report: difficulty in diagnosis and treatment of dengue hemorrhagic fever in patients with chronic renal failure. *Am J Trop Med* 2007; 76: 752-6.
- Kuo CH, Tai DI, Chang-Chien CS, *et al.* Liver biochemical tests and dengue fever. *Am J Trop Med Hyg* 1992; 47: 265-70.
- Kulanatne SAR, Gawarammana IB, Kumarasiri PRV. Epidemiology, clinical features, laboratory investigations and early diagnosis of dengue fever in adults. *Southeast Asian J Trop Med Public Health* 2005; 36: 686-92.
- Kyle JI, Harris E. Global spread and persistence of dengue. *Ann Rev Microbiol* 2008; 62: 71-92.
- Lanciotti RS. Molecular amplification assays for detection of flaviviruses. *Adv Virus Res* 2003; 61: 67-99.
- Lee IK, Liu JW, Yang KD. Clinical characteristics and risk factors for concurrent bacteremia in adults with dengue hemorrhagic fever. *Am J Trop Med Hyg* 2005; 72: 221-6.
- Lee IK, Liu JW, Yang KD. Clinical and laboratory characteristics and risk factors for fatality in elderly patients with dengue hemorrhagic fever. *Am J Trop Med Hyg* 2008; 79: 149-53.
- Lee IK, Liu JW, Yang KD. Clinical characteristics, risk factors, and outcomes in adults experiencing dengue hemorrhagic fever complicated with acute renal failure. *Am J Trop Med* 2009; 80: 651-5.
- Leelarasamee A, Chupaprawan C, Chenchitkul M, Udompanthurat S. Etiologies of acute undifferentiated febrile illness in Thailand. *J Med Assoc Thai* 2004; 87: 464-72.
- Leder K, Torresi J, Brownstein JS, *et al.* Travel-associated illness trends and clusters, 2000-2010. *Emerg Infect Dis* 2013; 11: 1049-57.
- Leo YS, Thein TL, Fisher DA, *et al.* Confirmed adult dengue deaths in Singapore: 5-year multi-center retrospective study. *BMC Infect Dis* 2011; 11: 123.
- Ling LM, Wilder-Smith A, Leo YS. Fulminant hepatitis in dengue haemorrhagic fever. *J Clin Virol* 2007; 38: 265-8.
- Lum LCS, Lam SK, Choy YS, *et al.* Dengue encephalitis: a true entity? *Am J Trop Med Hyg* 1996; 54: 256-9.

- Mayxay M, Phetsouvanh R, Moore CE, *et al.* Predictive diagnostic value of the tourniquet test for the diagnosis of dengue infection in adults. *Trop Med Int Health* 2011; 16: 127-33.
- Massed E, Wilder-Smith A. Risk estimates of dengue in travelers to dengue endemic areas using mathematical models. *J Travel Med* 2009; 16: 191-3.
- Misra UK, Kalita J, Syam UK, Dhole TN. Neurological manifestations of dengue virus infection. *J Neurol Sci* 2006; 244: 117-22.
- Mohammed H, Linnen JM, Muñoz-Jordán JL, *et al.* Dengue virus in blood donations, Puerto Rico, 2005. *Transfusion* 2008; 48: 1348-54.
- Miranda CH, Borges MC, Matsuno AK, *et al.* Evaluation of cardiac involvement during dengue viral infection. *Clin Infect Dis* 2013; 57: 812-9.
- Nakhapakorn K, Tripathi NK. An information value based analysis of physical and climatic factors affecting dengue fever and dengue haemorrhagic fever incidence. *Int J Health Geogr* 2005; 4: 13.
- Namvongsa V, Sirivichayakul C, Songsithichok S, Chanthavanich P, Chokejindachai W, Sitcharungsi R. Difference in clinical features between children and adult with dengue hemorrhagic shock syndrome. *Southeast Asian J Trop Med Public Health* 2013; 44: 72-9.
- Nhan NT, Phuon CXT, Kneen R, *et al.* Acute management of dengue shock syndrome. *Clin Infect Dis* 2001; 32: 204-12.
- Pancharoen C, Kulwichit W, Tantawichien T, Thisyakorn U, Thisyakorn C. Dengue infection: a global concern. *J Med Assoc Thai* 2002; 85 (suppl): 25-33.
- Pancharoen C, Thisyalorn U. Coinfection in dengue patients. *Pediatr Infect Dis J* 1998; 17: 81-2.
- Pang J, Salim A, Lee VJ, *et al.* Diabetes with hypertension as risk factors for adult dengue hemorrhagic fever in a predominantly dengue serotype 2 epidemic: a case control study. *PLoS Negl Trop Dis* 2012; 6: e1641.
- Parkash O, Almas A, Jafri SM, Hamid S, Akhtar J, Alishah H. Severity of acute hepatitis and its outcome in patients with dengue fever in a tertiary care hospital, Karachi, Pakistan (South Asia). *BMC Gastroenterol* 2010; 10: 43.
- Patumanond J, Tawichasri C, Nopparat S. Dengue hemorrhagic fever, Uttaradit, Thailand. *Emerg Infect Dis* 2003; 9: 1348-50.
- Phuon CXT, Nhan NT, Wills B, *et al.* Evaluation of the World Health Organization standard tourniquet test and a modified tourniquet test in the diagnosis of dengue infection in Vietnam. *Trop Med Int Health* 2002; 7: 125-32.
- Phuong HP, Vries PJ, Nga T. Dengue as a cause of acute undifferentiated fever in Vietnam. *BMC Infect Dis* 2006; 6:123.
- Poerscha CO, Pavonia DP, Queiroza MH, *et al.* Dengue virus infections: comparison of methods for diagnosing the acute disease. *J Clin Virol* 2005; 32: 272-7.
- Pongsumpun P, Patanarapelert K, Sriprom M, Varamit S, Tang IM. Infection risk to travelers going to dengue fever endemic regions. *Southeast Asian J Trop Med Public Health* 2004; 35: 155-9.
- Pongsumpun P, Yokson S, Tang IM. A comparison of the age distributions in the dengue hemorrhagic fever epidemic in Santiago de Cuba (1997) and Thailand (1998). *Southeast Asian J Trop Med Public Health* 2002; 33: 255-8.
- Pouliot SH, Xiong X, Harville E, *et al.* Maternal dengue and pregnancy outcomes: a systematic review. *Obstet Gynecol Sur* 2010; 65: 107-18.
- Prasad D, Kumar C, Jain A, Kumar R. Accuracy and applicability of the revised WHO classification (2009) of dengue in children seen at a tertiary healthcare facility in northern India. *Infection* 2013; 41: 775-82.
- Premaratna R, Bailey S, Ratnasena GN, Silva HJ. Dengue fever mimicking acute appendicitis. *Trans R Soc Trop Med Hyg* 2007; 101: 683-5.
- Promphan W, Sopontamanarak S, Prvekprasert

- P, Kajornwattanakul W, Kongpattanayothin A. Dengue myocarditis. *Southeast Asian J Trop Med Public Health* 2004; 35: 611-9.
- Pungjitprapai A, Tantawichien T. A fatal case of spontaneous rupture of the spleen due to dengue virus infection: case report and review. *Southeast Asian J Trop Med Public Health* 2008; 39: 383-6.
- Rigau-Perez JG, Laufer MK. Dengue-related deaths in Puerto Rico, 1992-1996: diagnosis and clinical alarm signals. *Clin Infect Dis* 2006; 42: 1241-6.
- Rongrungruang Y, Leelarasamee A. Characteristics and outcomes of adult patients with symptomatic dengue virus infections. *J Infect Dis Antimicrob Agents* 2001; 18: 19-23.
- Royal College Physician of Thailand (RCPT). Practical guideline for management of dengue in adults. Bangkok: RCPT, 2014. [Cited 2014 Sep 27]. Available from: <http://www.rcpt.org/index.php/news/2012-09-24-09-26-20.html>
- Sam SS, Omar SFS, Teoh BT, Abd-Jamil J, AbuBakar S. Review of dengue hemorrhagic fever fatal cases seen among adults. *PLoS Negl Trop Dis* 2013; 7: e2194.
- Schwartz E, Weld LH, Wilder-Smith A, et al. Seasonality, annual trends, and characteristics of dengue among ill returned travelers, 1997-2006. *Emerg Infect Dis* 2008; 14: 1081-8.
- Setiawan MW, Samsi TK, Pool TN, Sugianto D, Wulur H. Gallbladder wall thickening in dengue hemorrhagic fever: an ultrasonographic study. *J Clin Ultrasound* 1995; 23: 357-62.
- Solomon T, Dung NM, Vavghn DW, et al. Neurological manifestations of dengue infection. *Lancet* 2000; 335: 1053-9.
- Souza LJ, Alves JG, Nogueira RMR, et al. Aminotransferase changes and acute hepatitis in patients with dengue fever. *Braz J Infect Dis* 2004; 8: 156-63.
- Souza LJ, Pessanha LB, Mansur LC. Comparison of clinical and laboratory characteristics between children and adults with dengue. *Braz J Infect Dis* 2013; 17: 27-31.
- Srikiatkhachorn A, Gibbons RV, Green S, et al. Dengue hemorrhagic fever: the sensitivity and specificity of the World Health Organization definition for identification of severe cases of dengue in Thailand, 1994-2005. *Clin Infect Dis* 2010; 50: 1135-43.
- Srikiatkhachorn A, Krautrachue A, Ratanaprakarn W, et al. Natural history of plasma leakage in dengue hemorrhagic fever: a serial ultrasonographic study. *Pediatr Infect Dis J* 2007; 26: 283-90.
- Stephen C, Allwinn R, Brodt HR, et al. Travel-acquired dengue infection: clinical spectrum and diagnostic aspects. *Infection* 2002; 30: 225-8.
- Tambyah PA, Koay ESC, Poon MLM, Lin R, Ong BKC. Dengue hemorrhage fever transmitted by blood transfusion. *N Engl J Med* 2008; 359: 1526-7.
- Tan F, Loh D, Prabhakaran K. Dengue haemorrhagic fever after living donor renal transplantation. *Nephrol Dial Transplant* 2005; 20: 447-8.
- Tangnaratchakit K, Tirapanich W, Tapaneya-Olarn W, et al. Severe nonfebrile dengue infection in an adolescent after postoperative kidney transplantation: a case report. *Transplant Proc* 2012; 44: 303-6.
- Tantawichien T. Dengue fever and dengue haemorrhagic fever in adolescents and adults. *Paediatr Int Child Health* 2012; 32 (suppl): 22-7.
- Tantawichien T, Thisyakorn U, Pisarnpong A, Israsena S, Suwangool P. Dengue fever and dengue hemorrhagic fever in adults [Abstract]. Chiang Mai: The First International Conference on Dengue and Dengue Hemorrhagic fever, 20-24 November 2000: 16-17.
- Thaithumyanon P, Thisyakorn U, Deerojnawong J, Innis BL. Dengue infection complicated by severe hemorrhage and vertical transmission in parturient woman. *Clin Infect Dis* 1994; 18: 248-9.
- Thakane J, Walhelzar B, Banerjee K. Hemor-



- rhagic manifestations and encephalopathy in case of dengue in India. *Southeast Asian J Trop Med Public Health* 1996; 27: 471-5.
- Trung DT, Thao le TT, Hien TT, *et al.* Liver involvement associated with dengue infection in adults in Vietnam. *Am J Trop Med Hyg* 2010; 83: 774-80.
- Tsai CJ, Kuo CH, Chen PC, *et al.* Upper gastrointestinal bleeding in dengue fever. *Am J Gastroenterol* 1991; 86: 33-5.
- Waduge R, Malavige GN, Pradeepan M, Wijeyaratne CN, Fernando S, Seneviratne SL. Dengue infections during pregnancy: a case series from Sri Lanka and review of the literature. *J Clin Virol* 2006; 37: 27-33.
- Wagner D, With K, Huzly D, *et al.* Nosocomial acquisition of dengue. *Emerg Infect Dis* 2004; 10: 1872-3.
- Wang CC, Wu CC, Liu JW, *et al.* Chest radiographic presentation in patients with dengue hemorrhagic fever. *Am J Trop Med Hyg* 2007a; 77: 291-6.
- Wang CC, Liu SF, Liao SC, *et al.* Acute respiratory failure in adult patients with dengue virus infection. *Am J Trop Med Hyg* 2007b; 77: 151-8.
- Wichmann O, Hongsiriwan S, Bowonwatanuwang C, *et al.* Risk factors and clinical features associated with severe dengue infection in adults and children during the 2001 epidemic in Chonburi, Thailand. *Trop Med Int Health* 2005; 72: 221-6.
- Wilder-Smith A. Dengue infections in travelers. *Pediatr Int Child Health* 2012; 32: 28-32.
- Wilder-Smith A, Chen LH, Massad E, Wilson ME. Threat of dengue to blood safety in dengue-endemic countries. *Emerg Infect Dis* 2009; 15: 8-11.
- Wills BA, Dung NM, Loan HT, *et al.* Comparison of three fluid solutions for resuscitation in dengue shock syndrome. *N Engl J Med* 2005; 353: 877-89.
- World Health Organization (WHO). Dengue hemorrhagic fever: diagnosis, treatment, prevention and control. Geneva: WHO; 1997.
- World Health Organization (WHO). Dengue, guidelines for diagnosis, treatment, prevention and control. Geneva: WHO, 2009.
- World Health Organization (WHO). Handbook for clinical management of dengue. Geneva: WHO, 2012.
- Wung JY, Tseng CC, Lee CS, Cheng KP. Clinical and upper gastroendoscopic features of patients with dengue virus infection. *J Gastroenterol Hepatol* 1990; 5: 664-8.
- Yamada KI, Takasaki T, Nawa M, Kurane I. Virus isolation as one of the diagnostic methods for dengue virus infection. *J Clin Virol* 2002; 24: 203-9.
- Vazquez S, Ruiza D, Barreroa R. Kinetics of dengue virus NS1 protein in dengue 4-confirmed adult patients. *Diagn Microbiol Infect Dis* 2010; 68: 46-9.