ANNEX I

PRACTICAL GUIDELINE FOR MANAGEMENT OF DENGUE IN ADULTS: 2014

Royal College Physician of Thailand

Dengue fever (DF) and dengue hemorrhagic fever (DHF) are mosquito-borne infections from dengue viruses of the flavivirus group. The four dengue virus serotypes are called DEN-1, DEN-2, DEN-3, and DEN-4. The insect vectors*, Aedes aegypti, Ae. albopictus, Ae. polynesiensis*, can transmit dengue viruses to humans and increases the risk of global pandemic dengue transmission, especially in Southeast Asia, the Western Pacific and the Americas. In Thailand, epidemic DF and DHF have expanded geographically and increased in incidence. These changes have been caused by the modern dynamics of climate change, globalization and the geographic spread of the virus and its vectors due to travel. Epidemics of DF and DHF occur throughout the year and usually peak during the rainy season, which may be between June and September. DF and DHF in Thailand usually outbreak every 3 years; however, at present, the timing of epidemics of DF and DHF in Thailand is unpredictable.

DF and DHF cases have increased over time whereas the fatality rate has decreased significantly to 0.15%. This decrease in fatality rate may have been caused by good treatment practices. DF and DHF morbidity and mortality rates have been highest in children, especially in the 5-9 year age group. While dengue infection has traditionally been considered a pediatric disease, the distribution of dengue has been rising and more cases have been observed in adolescents and adults.

In Thailand, 20%-40% of DF/DHF cases have been reported in adults, and the rate of DF/DHF reported has increased over time in adults. The clinical features of DF/DHF in adults are similar to that of children, but some adults with dengue may present with a high grade fever, myalgia, arthralgia, bone pain, bleeding, and signs of circulatory failure or development of dengue shock syndrome (DSS). The range of clinical manifestations of dengue infection includes asymptomatic disease, undifferentiated febrile disease, self-limiting febrile illness associated with myalgia, classic dengue fever, dengue hemorrhagic fever or DDS.

The incidence of dengue among Thai adults is underestimated due to under-detection of the acute febrile phase of DF, especially in older ages. Older adults usually have clinical manifestation as DF; whereas, DHF is a common manifestation of adolescents and younger adults that is similar with children. Being an adult is also a risk factor for mortality in DF/DHF because of delayed diagnosis and treatment, comorbidity associated with older age and the increasing frequency of internal hemorrhage with age.

Dengue fever: DF (WHO, 1997)

Clinical manifestations of dengue fever range from asymptomatic to dengue fever with

unusual hemorrhage, which makes dengue fever difficult to detect. A definitive diagnosis can only be made in the laboratory by detecting viral antigen, NS1, PCR (polymerase chain reaction) and/or antibodies in serum.

Criteria for diagnosis of dengue fever

Probable case: an acute febrile illness has two or more of the following manifestations;

- Headache
- Retro-orbital pain
- Myalgia
- Arthralgia
- Rash
- Hemorrhagic manifestations: petechiae, epistaxis, a positive tourniquet test
- Leukopenia, neutropenia, and atypical lymphocyte findings;

and

- Supportive serology: positive IgM/IgG antibody test by immunochromatographic test or rapid ELISA test on a late acute phase of the disease; or patients who live in an endemic area at the same time as other confirmed cases of dengue fever with negative laboratory findings of other causes of febrile illness.

Confirmed case: a case is confirmed by the following laboratory criteria:

- Detection of dengue virus genomic sequences by PCR, demonstration of dengue virus antigen by non-specific protein of dengue virus (dengue NS1) and/or a seropositive of IgM by MAC-ELISA test (anti DEN IgM ≥40 units and more than anti JE IgM, or a rise of anti DEN IgG titer of ≥2 times and convalescent IgG ≥100 unit)

Dengue hemorrhagic fever: DHF (WHO, 1997)

The following must be present:

1. Fever, or history of acute fever, lasting 2-7 days.
2. Hemorrhagic tendencies: a positive tourniquet test with bleeding.
3. Thrombocytopenia [≤100,000 cells per mm^3 (≤$100x10^9$/l) or platelet in blood smear ≤6 cells/ oil field].
4. Evidence of plasma leakage, for example, a rise in the hematocrit (Hct) ≥20% of baseline hematocrit, signs of plasma leakage such as pleural effusion, ascites or hypoalbuminemia.

Note: The positive predictive value of tourniquet test with clinical of pleural effusion/ascites is 96%.

Criteria for diagnosis of dengue hemorrhagic fever: DHF (WHO, 1997)

Diagnosis of DHF is made by recognizing the clinical manifestations and hemodynamic change. Platelet count and sign of plasma leakage may help clinicians to establish an early diagnosis before the onset of shock.

Clinical manifestation as the following lists indicators of DHF/DSS

1. Fever, or history of acute fever, lasting 2-7 days.
2. Hemorrhagic tendencies: a positive tourniquet test with bleeding.

3. Hepatomegaly with tenderness.
4. Hemodynamic change or shock.

Laboratory findings

1. Platelet count ≤100,000 cells per mm^3 (≤$100x10^9$/l).
2. A rising of hematocrit ≥20% of baseline hematocrit (hemoconcentration) or signs of plasma leakage such as pleural effusion, ascites or hypoalbuminemia.
3. Leukopenia, neutropenia, and atypical lymphocyte findings.

Note: Platelet count can be calculated by slide smear. If platelets are less than 6 cells/oil field; it can be predicted that the platelet count is less than 100,000 cell per mm^3 (≤$100x10^9$/l).

The stages of DF/DHF disease can be divided into 3 stages:

Stage I (acute febrile stage): All patients have acute high grade of fever. This phase usually lasts 2-7 days. Some patients may have myalgia, facial flushing, hemorrhagic spots, or an erythematous maculopapular rash over the body and limbs. Other non-specific constitutional symptoms such as nausea, vomiting, abdominal pain or hepatomegaly may be present, especially at the end of this phase.

Stage II (critical stage): The patients go on to develop plasma leakage usually 24-48 hours after the fever begins to subside. Some patients also may have early signs of shock/circulatory failure including restlessness, hemorrhagic manifestations or severe abdominal pain.

Stage III (convalescence stage): Sudden arrest of plasma leak with clinical improvement occurs within 2-3 days. The patients usually have good appetite, normal blood pressure, a full and slow pulse, and a hematocrit that returns to baseline. Some cases also have a convalescence rash as a macular confluent rash over the face, thorax, and flexor surfaces.

Grading severity of dengue hemorrhagic fever (DHF)

DHF is classified into 4 grades of severity:

Grade I Unspecified fever, the only hemorrhagic manifestation is a positive tourniquet test and/or easy bruising without hypotension.

Grade I Spontaneous bleeding usually in the forms of skin or other hemorrhages without hypotension.

Grade III Circulatory failure manifested by a rapid, weak pulse and narrowing of pulse pressure; or hypotension with the presence of cold, clammy skin and restlessness.

Grade IV Profound shock with undetectable blood pressure or pulse.

Note: The presence of hemoconcentration and platelet count is less than 100,000 cell per mm^3 (≤$100x10^9$/l) differentiates DHF grade I and II from DF. Dengue hemorrhage fever (DHF) grade III and IV are considered to be dengue shock syndrome (DSS).

Severe dengue and warning signs in dengue infection (WHO, 2009)

Severe dengue is classified as patients with dengue infection with one or more of the

following manifestations:

1. Severe plasma leakage *eg* hypotension or poor capillary perfusion.
2. Severe bleeding.
3. Severe organ impairment: liver failure, AST/ALT >1,000 unit/ml, kidney injury, respiratory failure, alteration of consciousness.

Clinicians should evaluate signs, symptoms and laboratory tests as the warning signs of severe dengue infection, for example frequent vomiting, abdominal pain, liver tenderness, respiratory distress, irritability, spontaneous bleeding (epistaxis, bleeding per gum), retinal hemorrhage, plasma leakage, oliguria or hemoconcentration with decreased platelet count.

Descriptions

1. Dengue infection should be suspected if the patients have the following clinical presentations:

1.1. Fever of 10 days or less with myalgia, arthralgia, bone pain, headache, peri-orbital pain, flushing, nausea or vomiting.
1.2 No obvious respiratory tract symptoms or signs.
1.3 No organ specific symptoms of other infectious diseases.

Despite dengue infection, other infectious diseases (*eg*, malaria, gram-negative bacteremia) should be suspected.

2. Presumptive diagnosis of dengue infection should be considered in patients with the following signs or symptoms.

2.1 Fever of 3 days or less with positive tourniquet test or white blood cell count (WBC) less than 10,000/mm^3 (<$10x10^9$/l).
2.2 Fever of 4-10 days with WBC less than 5,000/mm^3 (<$5x10^9$/l), platelet count less than 140,000/mm^3 (<$140x10^9$/l), or hematocrit (Hct) of 45% or more.

In these patients, the laboratory diagnosis of acute dengue infection can be performed for the confirmation.

The tourniquet test is performed by using the optimal size of the blood pressure cuff. The cuff is inflated at the mid-point between systolic and diastolic for 5 minutes. The interpretation is done at 1 minute after cuff deflation. The petechiae count per 1 square inch should be recorded. A count of 10 or more petechiae per square inch is considered as a positive test.

3. The laboratory test for definite diagnosis of acute dengue infection.

3.1 Fever of 1-3 days, NS1 or PCR from serum or plasma (diagnostic yield of 80-90%, but the yield decreases after 3 days of fever) and/or collection of the first serum for antibody should be considered.
3.2 Fever of 4 days or more, antibody tests, for example, ELISA or rapid immunochromatography test (rapid test IgM has a 10-20% rate of false positive and false negatives) should be considered.

Investigation for acute dengue infection:

- Viral isolation and identification, NS-1, or PCR;
- Antibody capture EIA.

For single serum: anti DEN IgM of ≥ 40 units and greater than anti-JE IgM is considered as positive of dengue infection.

For paired sera: anti-DEN IgM of the first serum of <15 units and ≥30 units from the second serum is considered as positive of dengue infection.

a. Primary infection: Anti-DEN IgM/IgG ratio ≥1.8:1 is considered as primary infection.

b. Secondary infection:

i. Anti-DEN IgM/IgG ratio <1.8:1 is considered as secondary infection.

ii. Anti-DEN IgG (convalescence serum):IgG (acute serum) rise of ≥2 times and Anti-DEN IgG (convalescent serum) ≥100 units.

There are several commercial kits of rapid tests for dengue infection. However, the sensitivity, specificity, and accuracy vary among these tests. Therefore, these tests are suitable for screening, and should be confirmed by the above tests.

4. Physicians should be aware of warning signs (signs, symptoms, and hematocrit) in patients with dengue infections before the patients develop severe infections (shock from plasma leakage, abnormal hemorrhage or organ failure) (Fig 1).

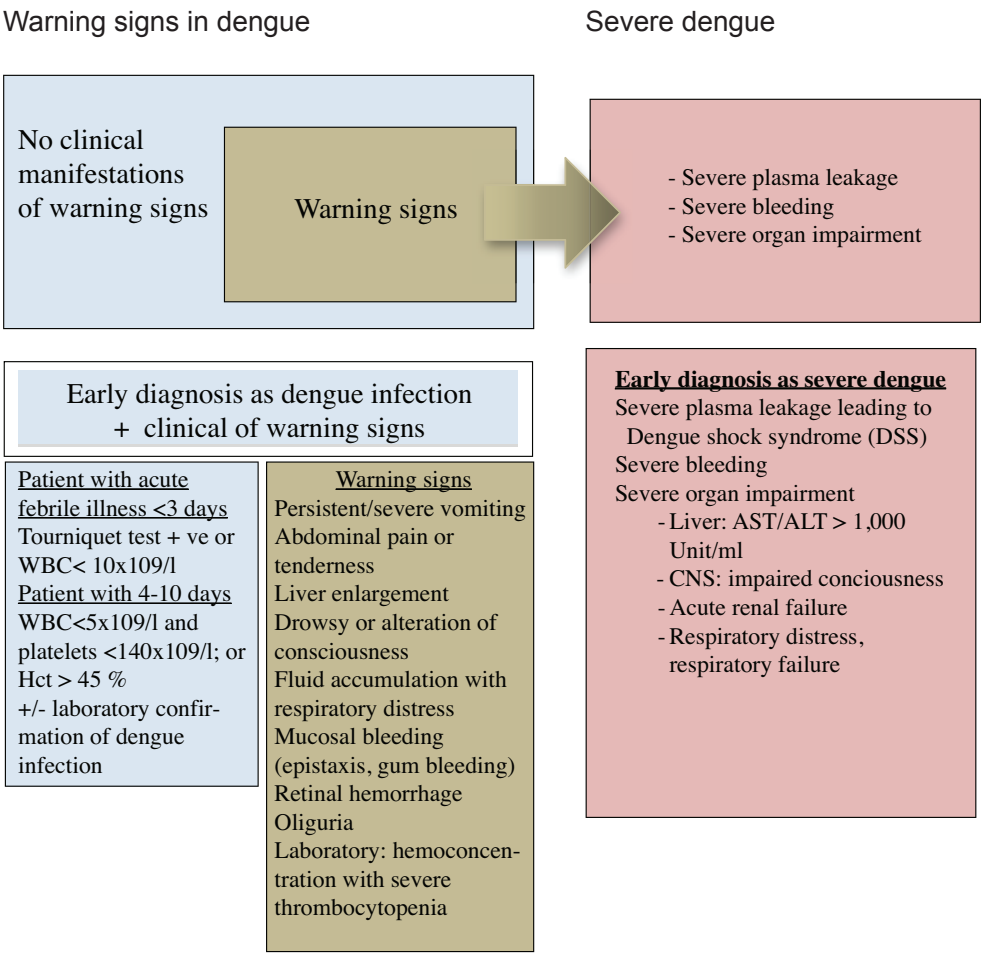

Fig 1–Clinical manifestation in severe dengue and the warning signs in dengue infection.

Guidelines for outpatient/inpatient management of dengue infections and adults (Figs 2 and 3)

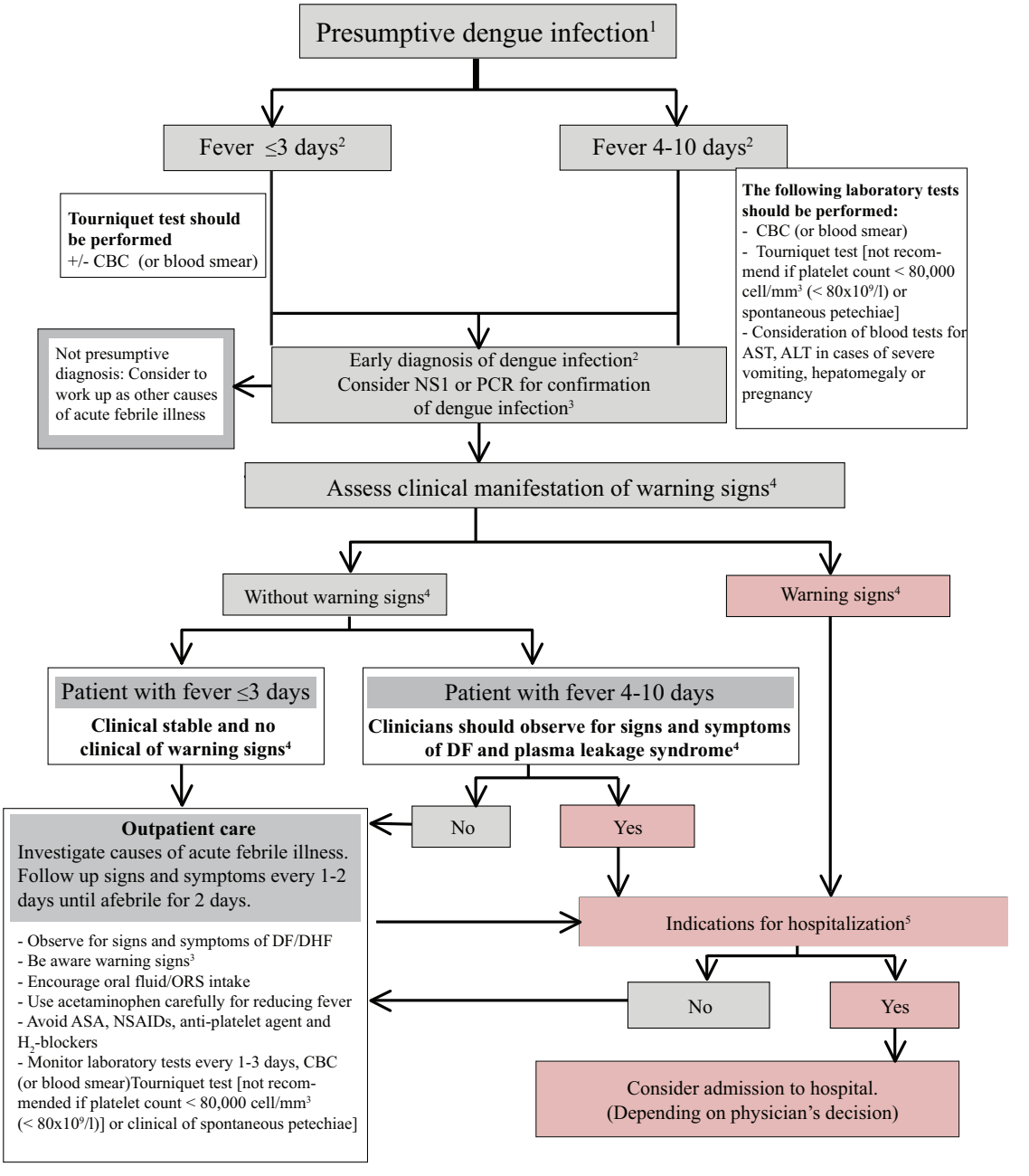

Fig 2–Guidelines for management of dengue infections in adults.

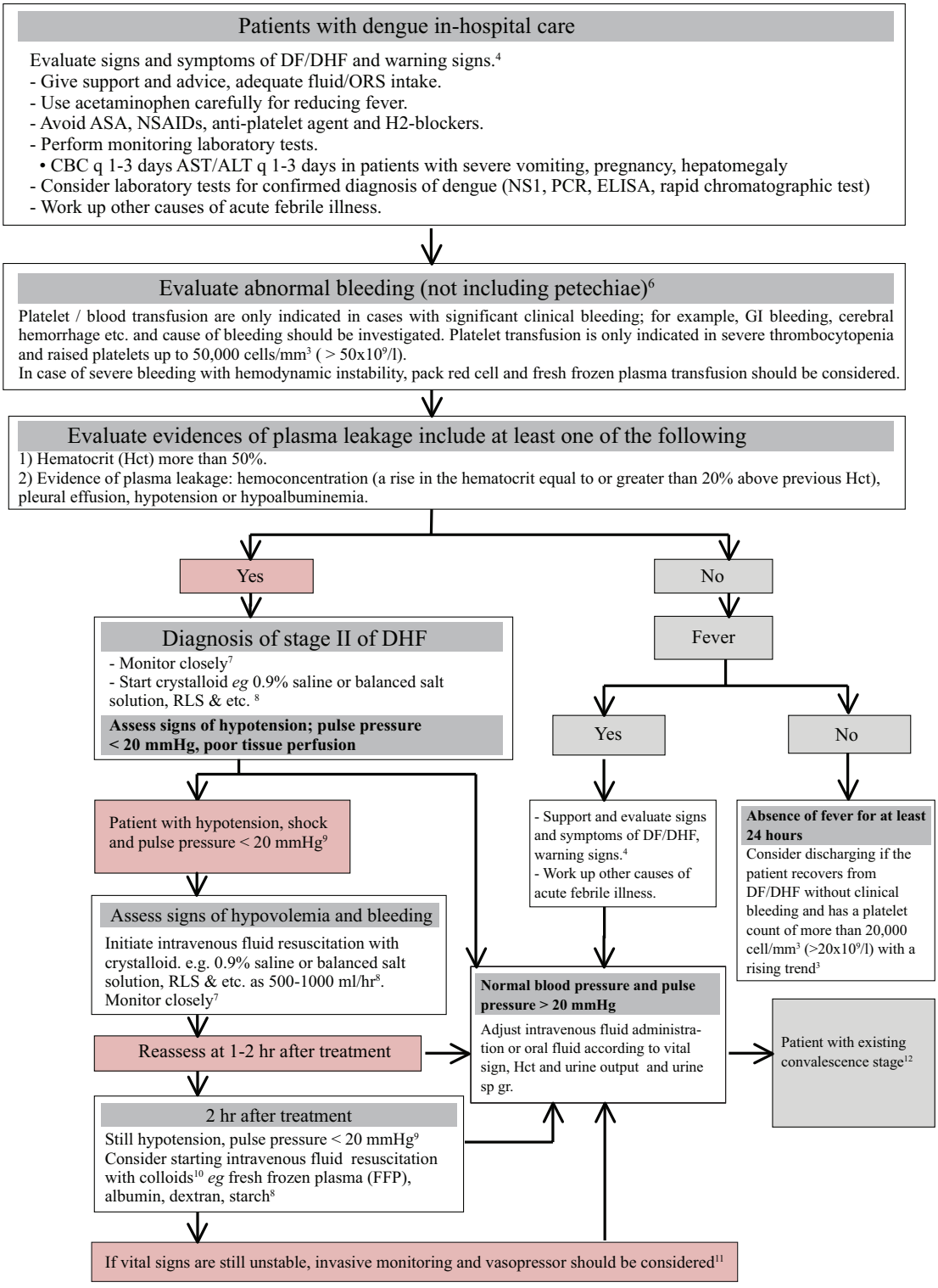

Fig 3–Guidelines for the management of dengue infections in adults.

5. Indications for admission of patients with dengue infection:

5.1 Signs/symptoms that the physician considers make the admission of the patient necessary, for example, nausea/vomiting;

5.2 Severe hemorrhage, for example, hematemesis, hematochezia or abnormal vaginal bleeding;

5.3 Dengue shock syndrome, or hypotension;

5.4 Hct > 50%;

5.5 Platelet ≤20,000/mm^3 (≤20x10^9/l);

5.6 AST or ALT >500 U/ml;

5.7 Renal failure, liver failure, heart failure, drowsiness, or severe hypoxemia;

5.8 Pregnant women;

5.9 Morbid obesity;

5.10 Patients could not follow up as out-patient setting.

6. Bleeding complications usually occur in 5-8 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 ≤20,000/mm^3 (≤20x10^9/l), increased AST or ALT, prolonged PT, severe dengue hemorrhagic fever, patients with DIC or liver failure. Patients with coagulopathy usually have GI bleeding.

6.1 Platelet transfusion is not necessary in patients with only petechiae or minor bleeding despite low platelets. The indications for platelet transfusions are bleeding associated with active peptic ulcer, trauma, liver failure, receiving antiplatelet, or platelets <10,000/mm^3 (<10x10^9/l).

6.2 In patients with severe GI bleeding, other conditions such as peptic ulcers or gastritis should be suspected. In some GI bleeding, there may be only melena without hematemesis.

6.3 In women, uterine bleeding can be found in 5-25% of dengue infections. Most uterine bleeding is not severe and does not require blood or platelet transfusion. However, hormonal therapy might be indicated in some cases.

6.4 In patients receiving anti-platelet, anti-coagulant or heparin, the bleeding complications may be more severe.

7. Close monitoring:

7.1 Vital signs, peripheral perfusion, and clinical assessment should be assessed every 15-30 minutes until resolution of shock, and every 1-4 hours thereafter.

7.2 Hematocrit should be monitored 1-4 times per day according to clinical presentations and platelet count should be achieved as indicated.

7.3 Fluid intake and output should be assessed every 1-4 hours. An adequate urine output of 0.5-1 ml/kg/hour and a urine specific gravity of 1.010-1.020 should be achieved. Massive pleural effusion or ascites may cause breathing difficulty and physicians should be wary of this.

7.4 In severe cases or cases with co-morbidity, pulse oximetry, ECG, arterial blood gas, blood sugar, serum electrolyte, lactate, BUN/Cr, liver function test, coagulogram should be measured as indicated.

8. Guidelines for fluid replacement and resuscitation in dengue patients with plasma leakage syndrome.

Stage II of dengue hemorrhage fever (plasma leakage syndrome)			
Normal blood pressure and pulse pressure >20 mmHg	**Hypotension and/or pulse pressure ≤20 mmHg**	**Shock**	**Persistent shock despite adequate crystalloid replacement**
End point	**End point**	**End point**	**End point**
Target: Normal blood pressure and pulse pressure >20 mmHg. Urine sp gr 1010-1020. Keep urine output 0.5-1.0 ml/kg/hr, Hct~40%-45%. **Limitation:** Leakage syndrome, *eg*, pleural effusion, ascites, crepitation.	**Target:** Normal blood pressure and pulse pressure >20 mmHg. Urine sp gr 1010-1020. Keep urine output 0.5-1.0 ml/kg/hr, Hct~40%-45%. **Limitation:** Leakage syndrome, *eg*, pleural effusion, ascites, crepitation.	**Target:** Normal blood pressure and pulse pressure >20 mmHg. Urine sp gr 1010-1020. Keep urine output 0.5-1.0 ml/kg/hr, Hct~40%-45%. **Limitation:** Leakage syndrome, *eg*, pleural effusion, ascites, crepitation.	**Target:** Normal blood pressure and pulse pressure >20 mmHg. Urine sp gr 1010-1020. Keep urine output 0.5-1.0 ml/kg/hr, Hct~40%-45%. **Limitation:** Leakage syndrome, *eg*, pleural effusion, ascites, crepitation.
Methods	**Methods**	**Methods**	**Methods**
IV 5%D saline, NSS for patients without shock, (intravenous fluid replacement only in patients with vomiting, or cannot tolerate oral diet or ORS), with rate of 40-80 ml/hr and adjust according to vital signs, Hct, urine output, urine sp.gr. If patients turn to critical phase, the rate of fluid replacement should be adjusted as indicated by vital signs, Hct, urine output.	IV isotonic crystalloid, *eg*, 0.9% saline or RLS 5-7 ml/kg/hr for 1-2 hr. • If clinical setting and parameters are improved, decrease the rate to 3-5 ml/kg/hr for 2-4 hr, and then 2-3 ml/kg/hr until stable vital signs. • If clinical setting and parameters are worsened or not improved, increase the rate to 7-10 ml/kg/hr for 1-2 hr and re-evaluate within 2-4 hr. If not improved, patients should be treated as "shock."	IV isotonic crystalloid *eg*, 0.9% saline or RLS 10-20 ml/kg/hr (500-1000 ml) for 1-2 hr. • If clinical setting and parameters are improved, decrease the rate to 5-7 ml/kg/hr for 1-2 hr and then gradually decrease the rate. • If clinical setting and parameters are worsened or not improved, change solution to colloid, *eg*, 5% albumin, dextran, or FFP 10 ml/kg/hr for 1 hr. If not improved, patients should be treated as'persistent shock despite adequate crystalloid replacement.'	Evaluate for other co-morbidities, *eg,* severe bleeding, metabolic acidosis, severe sepsis, pneumothorax. Start vasopressors, *eg*, norepinephrine 0.1-0.2 mcg/kg/min. Adjust dosage every 10-15 min (max dose 1-2 mcg/kg/min), and decrease dosage when clinical setting and parameter are improved. **Note** Patients with shock should have their vital signs and parameters closely monitored until resolution of shock.

9. Blood pressure and pulse rate are essential for evaluation of patients with dengue. In some instances, patients with circulatory failure might be fully conscious with only fatigue. In patients with underlying hypertension who develop inadequate tissue perfusion, the blood pressure might be within normal range, so the administration of antihypertensive agents should be done careful.

10. If shock does not response to crystalloid, the colloid solutions (such as FFP, NSS plus albumin, or dextran) should be used instead. However, dextran should be used with caution because it can cause platelet dysfunction. The admiration of starch does not reduce mortality in non-dengue shock and might cause acute renal failure.

11. Administration of vasopressors should be evaluated individually because they might raise blood pressure in spite of inadequate intravascular volume. In dengue hemorrhagic fever, the plasma leaks profusely and continuously from the blood vessels, so the priority of treatment is intravascular volume replacement. However, in situations of prolonged shock despite adequate intravascular replacement, or of development of the signs/symptoms of volume overload in the patient such as pulmonary edema, vasopressors should have a role in rising of blood pressure. At the time of writing, no studies of the efficacy of vasopressors in dengue shock syndrome exist; however, the Surviving Sepsis Guidelines, 2012 should be applied in this situation. According to these guidelines, norepinephrine should be considered, as the first agent and vasopressin or adrenaline should be added if the patient does not respond to norepinephrine. Dopamine should be avoided in this situation because of the increased risk of arrhythmia.

12. Signs and symptoms of the convalescence stage should be assessed:

- Improved well-being and appetite.
- Absence of fever, normal blood pressure, bradycardia, convalescence rash at legs or arms which is associated with pruritus.
- Hct <50% and stable, increased WBC with a percentage of lymphocytes greater than the percentage of neutrophils, increased platelet count.

If patient is in the convalescence stage, the rate of intravenous fluid should be decreased to prevent volume overload from re-accumulation of fluid from the third space. If fever is absent for more than 1 day with no clinical bleeding with an increasing platelet count of more than 20,000/mm^3 (> $20x10^9$/l), the patient can be discharged.

Guidelines for the management of dengue fever and dengue hemorrhagic fever in pregnancy

The diagnosis and treatment of dengue fever and dengue hemorrhagic fever in pregnancy are the same as non-pregnant patients. In an epidemic of dengue infection, dengue infection should be considered in a pregnant woman who has fever.

Special consideration in pregnancy

Diagnosis:

- Physiologic hemodilution in pregnancy may obscure hemoconcentration in DHF.
- Dengue infection should be a differential diagnosis of pregnancy-related condi-

tions, especially HELLP (hemolysis, elevated liver enzymes, thrombocytopenia) syndrome.

- Treatments are anti-pyretic drug, hydration, rest and supportive care. Platelet transfusion is indicated in in-labor pregnancy when the platelet count is <50,000/mm^3 (< $50x10^9$/l).

Effects of dengue infection on pregnancy:

- There are increased risks of abortion, premature uterine contraction, intra-partum and post-partum hemorrhage, maternal death, fetal distress, low birth weight, or death fetus *in utero* which is associated with disease severity and gestational age.
- With a vertical transmission rate of 1.6-10.5%, dengue infection is a cause of low platelets in the new born (usually occurs in pregnant women who have had fever for 1 week before delivery).

Effect of pregnancy on dengue infection:

- Pregnant patients have higher risk of severe disease than non-pregnant patients.

Special consideration in adult patients

1. Co-morbidity/underlying diseases

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 dengue management.

2. Elevation of transaminase level

More than 90% of cases of DF/DHF in adults have elevated transaminase levels, of which ALT is usually elevated more than AST. In nearly all patients, the elevated AST and ALT are found within 48 hours before defervescence. AST and ALT will reach their peak in 7-9 days after onset and subside within 2-3 weeks after defervescence. Acute liver failure is rarely observed; however, administration of hepatotoxic medications such as antipyretics or antiemetics should be careful and avoided in patients who have elevated transaminase.

3. Jaundice

Jaundice presents infrequently in dengue infection. Therefore, if jaundice presents, other diseases should be suspected such as acute cholangitis, hepatotrophic viral hepatitis, drug allergy, malaria, acute pancreatitis, or secondary bacterial infection. In unconjugated hyperbilirubinemia, the degree of jaundice is mild and may be caused by acute hemolysis in patients with Thalassemia, hemoglobinopathy. In case of dengue infection with severe jaundice, the severe complications such as liver failure, pancreatitis, severe bacterial sepsis or dual infection should be suspected.

4. Dual infection

Dual infection should be suspected in atypical presentation, for example, fever for more than 10 days, diarrhea, jaundice, persistent abdominal pain, recurrent fever, WBC >10,000/mm^3 (>$10x10^9$/l) with neutrophilia or presence of the band form of PMN. The patient with dengue infection may have subsequent nosocomial infection after hospitalization.

5. Internal hemorrhage in dengue infection

In a rapid decrease of Hct, internal hemorrhage should be suspected. Blood components such as PRC, FFP, and platelet concentration should be replaced as soon as possible after the patient has not responded to intravenous fluid.

Conclusions of guideline for the management of dengue infection in adults

1. Dengue infection should be suspected and monitored in adult patients who present with fever, because misdiagnosis and delayed treatment will worsen the disease progression and prognosis.

2. Complications of dengue infection should be closely monitored, for example, abnormal bleeding according to thrombocytopenia, shock (grade III or IV). Clinical assessment, hematocrit level, urine output, and urine specific gravity are used to adjust the rate of intravenous fluid.

3. Liver transaminase should be measured in adult patient especially when hepatitis is suspected or a history of paracetamol use of more than 2 gram per day has been noted. When AST and ALT are elevated, hepatotoxic medications such as paracetamol should be avoided.

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