# Clinical Practice Guidelines of Dengue/Dengue Hemorrhagic Fever Management for Asian Economic Community

## *Introduction:*

### Global burden of dengue

Dengue is one of the fastest growing emerging infectious diseases in the world, and the Asia Pacific Region bears 75% of the global burden. In the Southeast Asian Region (SEAR) 10 of 11 countries have reported dengue cases while in Western Pacific Region (WEPR), 31 out of 37 countries have reported in the past two decades. The incidence of dengue has increased dramatically in recent decades. World Health Organization (WHO) currently estimates that 50-100 million dengue infections occur worldwide every year. Before 1970, only nine countries had experienced severe dengue epidemics. Today, the disease is endemic in more than 100 countries in WHO's African, Americas, Eastern Mediterranean (EMR), South-East Asia (SEA) and the Western Pacific (WP) regions. The Americas, SEA and WP are the most seriously affected where more than 1.2 million cases were reported in 2008 and over 2.3 million in 2010 (based on official data submitted by Member States to WHO). Recently, the number of reported cases has continued to increase and cases are being reported in several countries of WHO's Africa and Europe Regions. In 2010, 1.6 million cases of dengue were reported in WHO's Region of the Americas alone, of which 49,000 cases were severe dengue. The actual dengue burden of dengue infection is likely more than 3 times the burden estimate

of the WHO, according to the results of a study published in the Journal Nature. Researchers estimate 390 million infections yearly, of which 96 million have some level of severity. The increase in cases and geographical expansion of affected countries can be attributed to a number of factors. These include higher temperatures and the onset of early rainfall in many parts of the Region this year, growing population densities, and greater international and local travel. There is no specific treatment for dengue and innovative approaches are needed in preventing the disease at the community level.

## Dengue economic burden

The estimated number of disability-adjusted life years (DALYs) (in thousands) by dengue in different WHO region in the year 2004 are 391 for SEAR, 169 for WPR, 73 for the Americas, 28 for EM, 9 for the African and 670 for the world.

## Dengue and economic burden in ASEAN Economic Community (AEC) countries

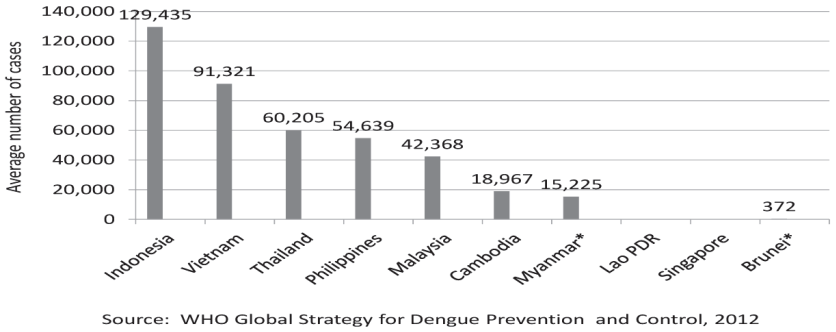
The ASEAN Member States are comprised of Brunei Darussalam, Cambodia, Indonesia, the Lao People's Democratic Republic (PDR), Malaysia, Myanmar, the Philippines, Singapore, Thailand and Viet Nam. All these 10 countries, 3 in SEAR and 7 in WEPR are endemic areas of dengue, except Brunei Darussalam and Singapore where dengue is reported in increasing number. Since dengue has a significant impact on health, economy and the entire society, making all members of the ASEAN Economic Community (AEC) to share responsibility. The estimated economic burden shows a particular high cost impact in Indonesia (323 million USD), Thailand (290 million USD) and Malaysia (128 million USD) while disease burden is highest in Indonesia (95,168 DALYs) and Philippines (37,685 DALYs).

## ASEAN Dengue Day (15th June)

Indonesia had proposed ASEAN Dengue Day, 15th June and it is an advocacy event that was agreed upon during the 10th ASEAN Health Ministers Meeting in 2010. The first regional event was held in 2011 in Jakarta, Indonesia. Then Myanmar, Vietnam and Philippines hosted the regional celebration ASEAN Dengue Day in 2012, 2013 and 2014. This ASEAN dengue day is to increase public awareness of dengue, acknowledge that ASEAN member states shoulder a large part of global burden of dengue, enhance regional collaboration on dengue and shared responsibility of dengue control, continue the shift from response-driven activities to forward planning and long-term prevention strategies and WHO has provided technical and financial support to the ASEAN Secretariat and the ASEAN Member States for the Dengue Day activities since its inception.

## WHO Global strategy for dengue

WHO has set the objectives of the a global strategy by the year 2020 which include *reducing morbidity of dengue by 25% and mortality by 50%*, using 2010 estimates as baseline (Figure 1). Among 10 ASEAN




Source: WHO Global Strategy for Dengue Prevention and Control, 2012

**Figure 1** Highly dengue endemic ASEAN Countries as reported to WHO 2004 - 2010

countries, the average yearly incidence of dengue between 2004 – 2010 is highest in Indonesia (129,435 cases), follow by Vietnam (91,321 cases), Thailand (60,205 cases), Philippines (54,639), Malaysia (42,368 cases), Cambodia (18,967 cases) and Myanmar (15,225 cases). The recent trend continues to increase dengue cases in Brunei Darussalam, the Lao PDR and Singapore.

## Case fatality rate in AEC countries

The average case fatality rate (CFR) between 2004 – 2009 for SEARO countries; Indonesia, Myanmar and Thailand and 2004–2010 for WPRO countries (Figure 2) is highest in Indonesia (0.95%), follow by Myanmar (0.93), Brunei Darussalam (0.67%), Philippines (0.59%), Cambodia (0.3%), Lao PDR (0.2%), Thailand (0.12%), Singapore (0.11%) and Vietnam (0.04%). The average CFR in SEARO countries is 0.75 in 2009 while in WPRO countries; Asian sub-region is 0.31 in 2010. In Thailand where dengue has been the public health problem since 1958, the current CFR in 2013–2014 is 0.09%.

## Dengue burden and case fatality rate in Thailand

In Thailand, the first outbreak of dengue was in 1958 when the

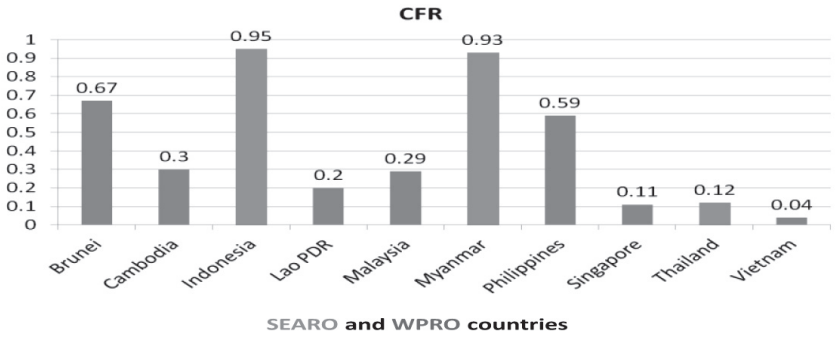
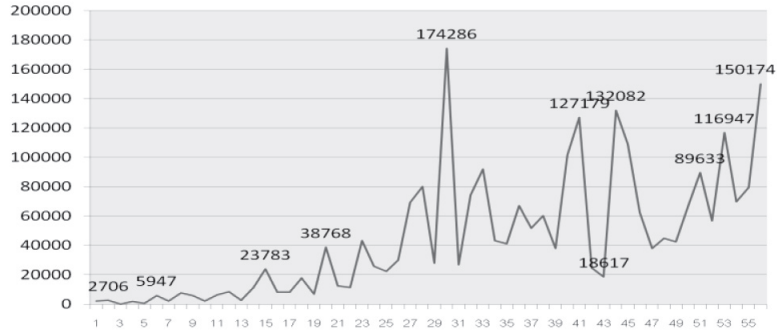


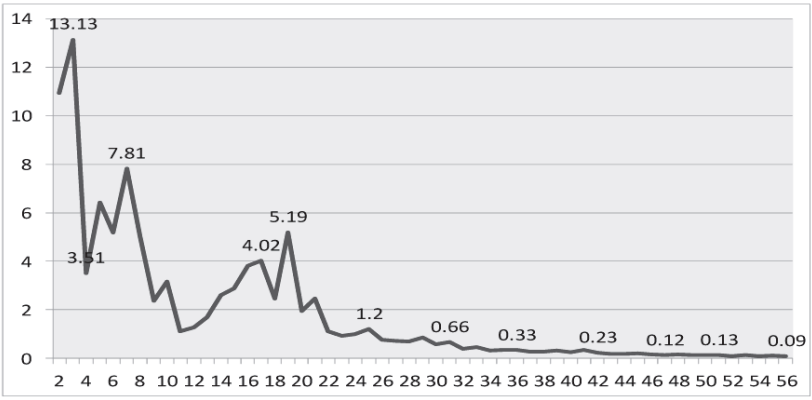

**Figure 2** CFR of Dengue in ASEAN Countries: 2009/ 2010

total case was about 3,000 cases and the CFR was 14%. The much improvement in diagnosis and management of dengue is due to the dengue management guidelines established from Queen Sirikit National Institute of Child Health (previously known as the Children's Hospital, Bangkok). This dengue management guidelines including the dengue classification has been adopted by WHO in 1975 and distributed worldwide to be used and resulted in the markedly reduction in the dengue CFR. These original guidelines had been updated in 1986, 1997 and 2011 (WHO SEARO). The incidence of dengue in Thailand has been increased and reached the peak of 174,286 in 1987 (Figure 3), but the CFR is continuously decreased. In 1999, the Ministry of Public Health has launched the National Plan for the Prevention and Control of Dengue to celebrate the 72nd Birthday Anniversary of King Bhumipol. Since then the dengue national guidelines have been more widely distributed all over the country together with the capacity building by intensive short course for all doctors, nurses and healthcare personnel in dengue case management, which results in continuous and sustainable very low dengue CFR as shown in Figure 4. The CFR of dengue in 2013 is 0.09% (Figure 4).




Source: Epidemiology Bureau, MOPH, Thailand

**Figure 3** Dengue case report in Thailand: 1958 – 2013




Source: Epidemiology Bureau, MOPH, Thailand

**Figure 4** Dengue CFR in Thailand: 1958 - 2013

With Thailand successful story of continuously decreasing dengue CFR, so DHF Center of Excellence (COE), Queen Sirikit National Institute of Child Health which has been designated as WHO Collaborating Centre for Case Management of Dengue/DHF/DSS since 1997 has plan to share our experiences in establishing this Dengue/DHF case management guidelines for 10 ASEAN Economic Community by follow the recommendation of report of an informal expert consultation on dengue case management in Colombo, Sri Lanka, 12-14 August, 2013 as below because we have experience in dengue case management and have been played a leading role in establishing, updating our dengue national dengue/ DHF guidelines including capacity building in strengthening dengue case management for healthcare personnel at all levels.

## *WHO SEARO recommendation regarding dengue case management*

- DHF/DSS should continue to remain as the most important category in the disease classification of dengue illness.

● A uniform reporting system based on DF and DHF classification should be proposed to all Member States on arrival of the final diagnosis. The final diagnosis should be clearly stated. For surveillance purpose, any "unusual dengue" category must be reported.

● A formal Regional Expert Group on Clinical Management, representing all Member States, should be established which would be coordinated by WHO.

● Networking among the expert groups on clinical management within the countries should be fostered.

● Inter-country cooperation networking pertaining to any development in disease and management as well as promotion of collaborative research should be extended to experts.

● TDR (2009) guidelines should be harmonized with the WHO (1997) guidelines and revised WHO (2011) guidelines on the following basis:

o recognize plasma leakage first, using WHO (1997) or (2011) dengue guidelines;

o then apply warning signs TDR (2009) in order to prevent shock, complications of fluid overload or organ(s) failure.

● Dengue case classification should be harmonized as follows:

o DF and DHF are two different clinical entities of dengue infections: DF is without plasma leakage, DHF is with on-going plasma leakage

o DF dose not progress to DHF

o DHF or DSS is the same disease with different degree of plasma leakage

● Standard criteria for diagnosis and management should be standardized.

● A standardized recording and reporting system should be established in countries:

o uniformity of reporting system is a must - based on final diag-

nosis

o reporting system should follow international Classification of Diseases ($10^{th}$ revision) (ICD10) : A 90 - DF; A 91 - DHF; A91a - DSS; A99 - unconfirmed dengue

- Inter-country cooperation, new genotype sharing of information should be extended.
- One or two focal points from each country should be identified, and country representatives must be consulted on issues related to clinical management and guideline formation.

## ICD10 for dengue infection

The new ICD10, dengue infections are classified as follow:

- A90 - Dengue fever
- A91 - Dengue hemorrhagic fever
- A91 a - Dengue shock syndrome
- A99 - Unconfirmed dengue

### *Clinical presentation of dengue infections*

Dengue viruses which have 4 serotypes: DEN1, DEN2, DEN3 and DEN 4, cause different clinical presentations range from mild to the most severe disease, that can lead to death if no proper intervention. Dengue viruses are transmitted to human by the day-time biting mosquitoes, Aedes Egypti and Aedes albopictus. The CFR of dengue in newly outbreak countries may be as high as 10-30%. ***Clinical presentations of dengue infections***

The majority of dengue infected patients are asymptomatic. Only about 10% are symptomatic. The symptomatic cases have different clinical presentations: undifferentiated fever - UF or viral-like syndrome (50%), dengue fever - DF (40%) and more severe manifestation dengue hemorrhagic fever - DHF (10%) and dengue shock syndrome - DSS (1-2%).

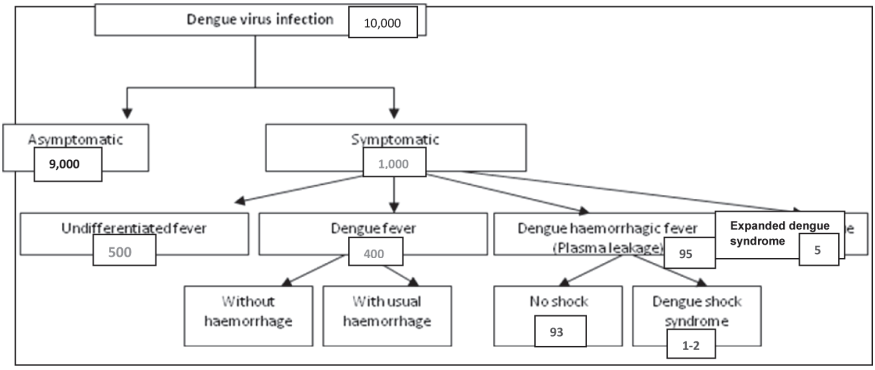



**Figure 5** Clinical presentations of dengue infections

Reports of the expanded syndrome – EDS has been increasing in the past decade especially from newly outbreak countries or endemic countries, where healthcare facilities are limited and the incidence is rather low compare to other clinical presentation (< 5%).

***UF*** manifestations like other acute febrile illness or viral illnesses, is very mild and undiagnosed without dengue confirmed laboratories. ***DF*** may be diagnosed clinically in older children and adults, if they have classic signs and symptoms of severe headache, retro-orbital pain, myalgia, arthralgia / bone pain together with rashes. Sometimes it is called 'Break bone fever'. ***DHF*** is different from UF and DF in that the patient has typical 2 pathophysiologic hallmarks of selective plasma leakage into pleural and peritoneal cavities (detected as pleural effusion and ascites) and a tendency to bleed. Shock may develop in DHF cases with massive plasma leakage without proper intervention and result in ***DSS.*** More than half of ***EDS*** is commonly the result of undetected DSS, which result in prolonged shock and organ(s) failure. Neurological manifestations are common presentation of EDS, and usually it is the results of liver failure and encephalopathy. Confusion and speak fowl language are early manifestations of dengue/ DHF/ DSS/ EDS encephalopathy. Convulsion and coma are late presen-

tations. Other causes of EDS are dengue infections in hosts with co-morbidities or co-infections with other microbial agents. So far, we don't have predictors of more severe dengue infections and during febrile phase, the presentations are almost the same for DF, DHF, DSS or EDS, i.e. high fever without localizing signs and symptoms. Bleeding manifestations: petechiae, epistaxis, gum bleeding, hematemesis, melena,... may be the clues to differentiate dengue from other acute febrile illnesses in the majority of patients. We have to follow probably all suspected dengue cases until the time that the fever is coming down, that is co-incident with critical period of plasma leakage.

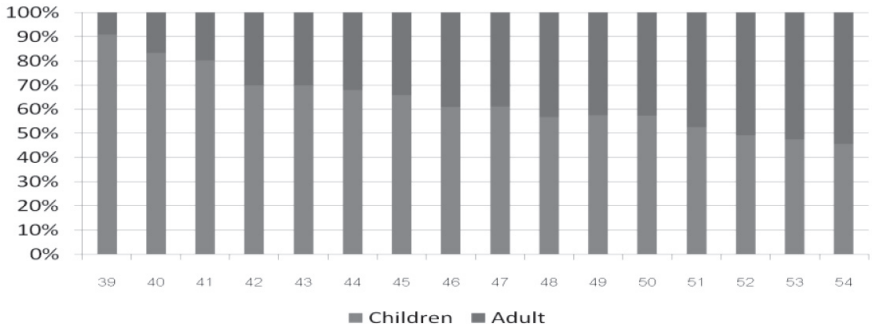
Clinical manifestations of dengue in adults are almost the same as in children. There are DF, DHF, DSS and EDS. The majority of dengue infections in adults are mild, presented as DF. High fever with headache and maculopapular rash is common. Retro-orbital pain, muscle and joint pain are also commonly observed in adults. But many physicians feel that adults have more severe diseases, DSS/ EDS as compare to children. This may be due to the usual very late coming to the hospital of adults. They are very tolerated and come to the hospital after prolonged shock, organ(s) failure and massive bleeding. Some adult cases present with neurological manifestation, usually the result of liver failure. Even these adult cases are severe, in the state of shock/ profound shock, but in the initial presentation to the hospital, they are in good consciousness, just look very weak and complain of tiredness. Besides the late coming for medical attention and treatment, adults have co-morbidities that make DHF/DSS present in unusual manifestations and more difficult to diagnose if the clinicians are not familiar with DHF/DSS. This observation is from Thai experience that adult dengue cases have been increasing dramatically in the past 10 - 15 years. At the very beginning that we saw more adult dengue, the adult doctors had no experience in DHF/DSS treatment, because it is believed to be the only disease for children less than 15 years of age. Many adult cases were

misdiagnosed and not properly managed at that time. At present, number of adult cases are almost equal to children cases in Thailand (Figure 6) and we have more experience with adult cases with the training and practicing according to the current and updated national dengue guidelines which is based on the WHO guidelines 1975, 1986, 1997 and 2011 (WHO SEARO). The management is the same because the clinical course of DHF remains the same, except that adult cases seem to be more severe because of the above reasons; late coming with prolonged shock and organ failure and co-morbidities. Only the rate of IV fluid is different, especially during critical period because adults have less surface areas compare to children.

## *Early clinical diagnosis of dengue infections*

Dengue is suspected in patients with high fever (mostly no localizing signs) in dengue endemic areas with 2 of the followings*:

- o Headache
- o Retro-orbital pain
- o Myalgia




Source: Epidemiology Bureau, MOPH, Thailand

**Figure 6** Percentage of children and adults dengue reported cases: 1996 - 2011

- o Arthralgia/ bone pain
- o Rash
- o Bleeding manifestations: petechiae, epistaxis, gum bleeding, coffee-ground vomiting, hematemesis, melena or at least Tourniquet test positive**
- o Leukopenia (WBC ≤ 5,000 cells/cumm.)
- o Rising Hct 10-15%
- o Platelet count < 150,000 cells/cumm.

● These criteria for suspected cases are very sensitive but less specific.

Recommended practical diagnosis is:

**Tourniquet test positive (or petechiae)** + Leukopenia**

The above 2 criteria for clinical suspected dengue has been used as the surveillance clinical case definition in Thailand and proved to have the high positive predictive value ranging from 70-80%.

**Tourniquet test (Winthrobe Technique)

The tourniquet test is performed by inflating a blood pressure cuff to a point midway between the systolic and diastolic pressures for five minutes. The test is considered positive when 10 or more petechiae per sq. inches are observed. In DHF, the test usually gives a definite positive result with 20 petechiae or more. The test may be negative or only mildly positive in obese patients and during the phase of profound shock. It usually becomes positive, sometimes strongly positive after recovery from shock.

## Differential diagnosis of dengue infections

● Arboviruses: Chikungunya virus (this has often been mistaken for dengue in South-East Asia)

● Other viral diseases: Measles, Rubella and other viral exanthem, Epstein-Barr Virus (EBV), Enteroviruses, Influenza, Hepatitis A, Hantavirus

• Bacterial diseases: Meningococcemia, Leptospirosis, Typhoid, Mellioidosis, Rickettsial diseases, Scarlet fever

• Parasitic diseases: Malaria

## *WHO criteria for clinical diagnosis of DHF/ DSS*

**Clinical manifestations:**

1. Fever: acute onset, high and continuous, lasting 2 to 7 days in most cases.

2. Any of the following hemorrhagic manifestations including a positive tourniquet test (the most common), petechiae, purpura (at venipuncture sites), ecchymoses, epistaxis, gum bleeding, and hematemesis and/or melena.

3. Enlargement of the liver (hepatomegaly) is observed at some stage of the illness in 70-80% of children. The frequency varies with time and/or the observer.

4. Shock, manifested by tachycardia, poor tissue perfusion with weak pulse and narrowed pulse pressure (20 mmHg or less) or hypotension with the presence of cold, clammy skin and/or restlessness.

**Laboratory findings:**

• Thrombocytopenia (100,000 cells/cumm. or less)

• Hemoconcentration; hematocrit (Hct) increase of ≥20%[1] from the baseline of patient or population of the same age

The first two clinical criteria, plus thrombocytopenia and hemoconcentration or a rising Hct, are sufficient to establish a clinical diagnosis of DHF. The presence of liver enlargement in addition to the first two clinical criteria is suggestive of DHF before the onset of plasma leakage.

The presence of pleural effusion (chest X-ray or ultrasound) is the most objective evidence of plasma leakage while hypoalbuminemia (albumin ≤ 3.5 gm%) provides supporting evidence. This is particularly useful for diagnosis of DHF in the following patients:

- Anemia
- Severe hemorrhage
- Where no baseline hematocrit
- Rise in hematocrit to < 20% because of early intravenous therapy.

In cases with shock, a high Hct (usually about 25-30% of the baseline Hct) and marked thrombocytopenia support the diagnosis of DSS. A low erythrocyte sedimentation rate (ESR < 10 mm/hr) during shock differentiates DSS from septic shock.

For easier and friendly use of the clinical criteria for classify patients as DHF where there are limited resources; human, equipment and laboratory (especially complete blood count - CBC), patients with fever and evidence of plasma leakage are most likely to be classified as DHF cases. Strict 4 criteria (Fever, bleeding manifestation, plasma leakage and thrombocytopenia of ≤ 100,000 cells/cumm. to classify as DHF as in the previous version of WHO 1997 may be not necessary.

## *WHO criteria for grading severity of DHF*

DF is different from DHF/DSS in that there is no plasma leakage. More than half of DF patients may have thrombocytopenia.

DHF Grade I - Fever and plasma leakage, without spontaneous bleeding

DHF grade II - Fever, plasma leakage plus spontaneous bleeding

DHF grade III - DHF grade I or II plus evidence of shock

DHF grade IV - DHF grade I or II plus evidence of profound shock; no blood pressure or palpable pulse

DHF grade I and II may be called as DHF, while DHF grade III and IV may be called together as DSS.

Majority of EDS cases have plasma leakage but EDS can be found in DF cases.

## *Rapid diagnostic tests (RDT)*

There are commercial available RDT that need only 5-10 minutes to get the results. At least there are 2 RDT to be used:

***1. NS1Ag test*** - This is for early diagnosis of dengue infection. It is positive during the febrile phase. The overall sensitivity of the test ranges from 40-70% depends on different companies. The percentage of positivity of the test is highest in the first day of fever (may reach 90%), and then decreases as day goes on. After 5 days, the test is likely to be negative. In addition, this test is likely to be positive more in primary than in secondary dengue infections that patients are likely to develop more severe disease DHF/DSS.

We have to be aware that the negative NS1Ag test does not mean that the patients do not have dengue, still they may have dengue and we have to follow them because the test is not sensitive enough.

This test is to be used only for surveillance purpose. It is also recommended in unusual/ complicated or death cases to help confirm dengue infections. This test does not guide the clinical management and replace CBC, it only confirms dengue infection.

***2. IgG/ IgM test***

This test has to be done after 5 days of fever, so it is not for the early diagnosis of dengue. It is used to confirm dengue and some cases the tests are positive late in course of illness, may be as late as day 7-14 of illness. If only IgM positive, this suggests acute primary dengue infection. If both IgG and IgM positive, this suggests secondary dengue infection. The duration of IgM positive is 1-2 months. If only IgG positive, this suggests past dengue infection because IgG can persist for years.

There is the combination of these 2 tests in the same kit (Duo or Combo), NS1Ag + IgG/IgM. This duo test is more expensive, but it increases the sensitivity of the test to 90%.

### *High risk patients*

- Infants < 1 year of age, obesity, elderly, pregnancy
- Bleeding
- Prolonged shock (DHF grade IV)
- Encephalopathy
- Behavior change
- Underlying diseases: hemolytic diseases (Glucose-6-Phosphatase Dehydrogenase Deficiency, Thalassemia and other hemoglobinopathies), heart diseases, chronic diseases such as diabetes mellitus, hypertension, ischemic heart disease, chronic renal failure, liver cirrhosis.

There are 3 phases in DHF/DSS illness as in the below figure:

- Febrile phase lasts 2-7 days
- Critical phase 1-2 days: plasma leakage and bleeding tendency
- Convalescence phase 3-5 days: reabsorption of pleural effusion and ascites

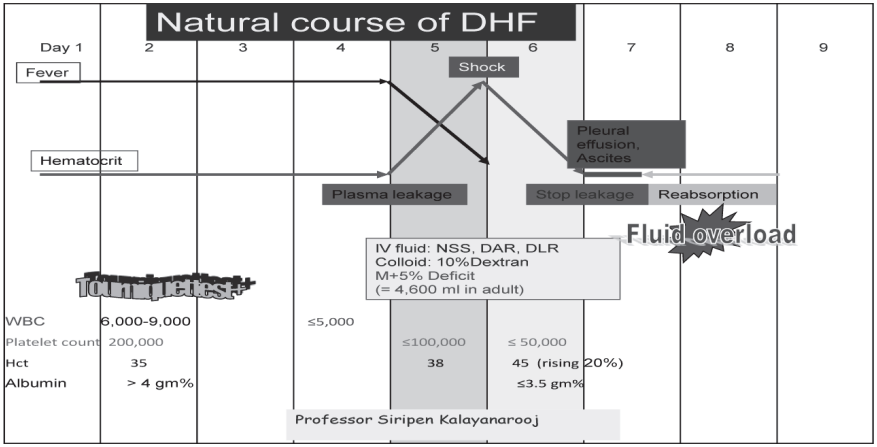



**Figure 7** Natural course of plasma leakage in DHF patients

## *Usefulness of CBC in guiding clinical management of dengue*

**CBC Changes in DHF illness in chronological order:**

o ***Leukopenia*** – WBC ≤ 5,000 cells/cumm. (and relatively lymphocytosis) – within 24 hours there will be no fever which co-incidence with critical period.

o ***Thrombocytopenia*** – Platelet counts ≤ 100,000 cells/cumm. – entering critical period (be aware that about 60% of DF patients can also have thrombocytopenia)

o ***Rising Hct ≥ 20%*** – DHF in critical phase

## *Steps for OPD screening during dengue outbreak*

Parameters that are effectively use to screen more severe dengue cases are:

1. Fever > 3 days. The average duration of fever in DHF/DSS patients is 4 days. The shortest duration of fever in DHF/DSS patients is 2 days.

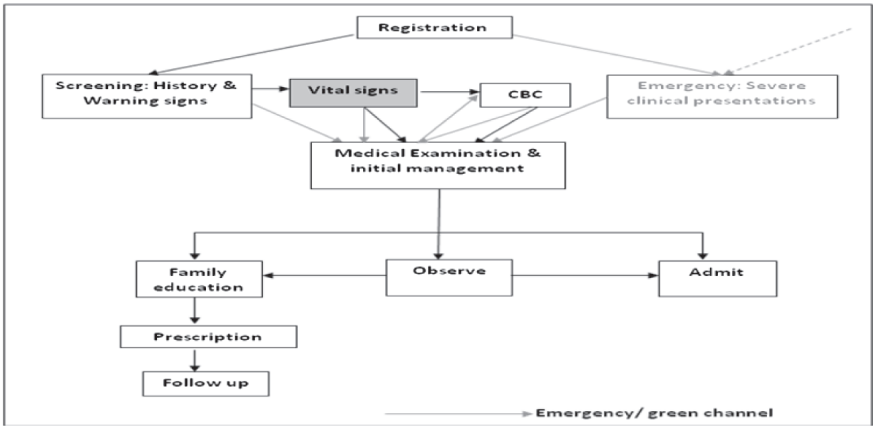



**Figure 8** Screening process in outbreak or high dengue season

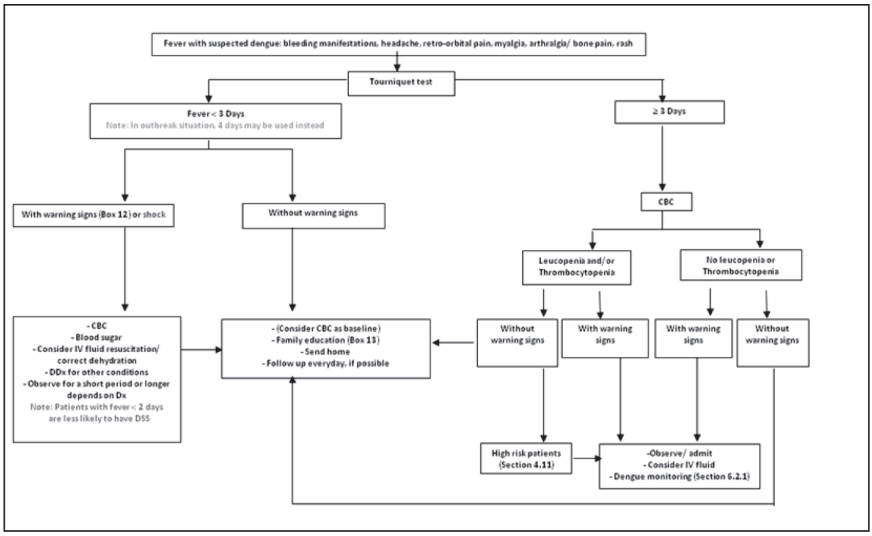



**Figure 9** Suggested triage pathway at the Out-patient Department (OPD)

2. Leukopenia and/ or thrombocytopenia (platelet count ≤ 100,000 cells/cumm.)

3. Warning signs*

***Warning Signs***

- Just before or during the transition to afebrile phase with no improvement in general well-being
- Persistent vomiting, > 3 times in a day
- Severe abdominal pain
- Lethargy and/or restlessness, sudden behavioral changes
- Bleeding: epistaxis, black-colored stools (melena), hematemesis, excessive menstrual bleeding, dark-colored urine (hemoglobinuria) or hematuria
- Giddiness
- Pale, cold clammy hands and feet
- Less/ no urine output for 4-6 hours

## *Management of DF/ DHF/DSS/EDS*

There is no specific treatment of dengue viral infections. Antiviral drugs are still under development. Anti-plasma leakage may be the alternative choice for the management of DHF/DSS with plasma leakage, but until now the pathogenesis and pathophysiologic cannot be clearly demonstrated, so no effective drugs to stop plasma leakage.

Dengue vaccine is not available by now but it is on the way. Sanofi Pasteur has published in Lancet this year 2014, that the chimeric dengue vaccines from the phase 3 trial in healthy children in Asia, has vaccine efficacy of 55 % (95% CI 47 to 62 percent) and the vaccine efficacy against DHF is 80 % (95% CI 53 to 92 percent) after one or more doses and 89 % (95% CI 58 to 98 percent) after three injections. Vaccine efficacy varies by serotype (50 % for serotype 1, 35 % for serotype 2, 78 %for serotype 3 and 75 % for serotype 4); vaccine efficacy for serotype 2 was not statistically significant. Hopefully we will soon have safe and effective dengue vaccines to all dengue serotypes available. There are also some other dengue vaccines development in either phase 1 or phase 2 development.

The treatment is only supportive and symptomatic and the management is according to the phase of the DHF/DSS patients, i.e. febrile phase, critical phase or leakage phase and convalescence phase. In febrile phase, the main objective is to reduce the height of fever, nutritional support, and other supportive / symptomatic treatment. Follow up is necessary for differentiation DHF from DF patients. Detection of early indicators for plasma leakage that usually concurrent with defervescence by early warning signs or changing in blood cells parameters; WBC, platelet counts and Hct are the most important. When DHF/DSS patients are identified, the main management is mainly IV fluid administration and correct common complications during this phase that lasts 24-48 hours. Steroid has proved by many randomized-control trials that it cannot prevent shock. DF patients

will have spontaneous recovery, especially in children soon after fever is coming down. Adult patients may have prolonged convalescence that may take weeks or months. In convalescence phase, management is mainly stop IV fluid and look for possible complications especially in those patients who have received a large amount of IV fluid. The management in different phases is as follow.

## *Management in the febrile phase*

**OPD management of suspected dengue cases**

1. Reduction of fever: Recommend only paracetamol. The dosage in children is 10 mg/kg/dose every 4-6 hours when T > 38.5 degree Celsius. In adult 1 tablet of 500 mg every 4-6 hours and not exceeding 5-8 tablets per day. Aspirin, NSAID (Ibuprofen) and steroid are not recommended, because they may cause gastritis with massive GI bleeding and hepatic injury. If the fever is not reduced, tepid sponge with warm water is recommended. Warm shower in older children and adults can replace sponging. Increase fluid intake also helps in reduction of body temperature.

2. Nutritional support: balanced and nutritious, soft diet. Avoid red, brown or black- colored for fear of misleading of blood when the patients throw up. Milk, fruit/ fruit juice or ORS are recommended, if cannot take solid food, poor appetite.

3. Supportive/ symptomatic treatment: anti-emetic, anti-convulsant, antacid, H2-bloker or proton-pump inhibitor,...

4. Follow up every day (if possible) with CBC.

5. Advice about home management and emphasize on warning signs to come back to the hospital ASAP as in the below hand-out given to families of suspected dengue patients.

Handout for homecare of dengue patients *(information to be given to patient/ family member(s) at outpatient department)*

## Home care advice (family education)

- Adequate bed rest.
- Soft diet. High intake of fluids, milk, fruit juice, isotonic electrolyte solution (ORS) and barley/rice water.
- Keeping body temperature below 39 °C, if temperature goes beyond 39 °C, giving patients paracetamol. (Paracetamol is available in 325 mg or 500 mg per tablet or 120 mg per 5 ml syrup. The recommended dose is 10 mg/kg/dose, not more than 4 to 6 times in 24 hours). However, too much paracetamol should be avoided. *[Aspirin or NSAID is not recommended].*
- Tepid sponging of forehead, armpits and extremities. Luke warm shower or bath for adults.

## Watch out for: Warning signs as above:

***Indication for admission:***

o Shock/ impending shock:

o Narrowing of pulse pressure (≤ 20 mmHg) – usually due to plasma leakage

o Hypotension – systolic BP < 80 mmHg in children > 5 years/ adults or < [70 + (age in year X 2)] mmHg (think of bleeding, may be internal or concealed GI bleeding) or orthostatic hypotension (commonly seen in older children and adults)

o Clinical signs of shock: delayed capillary refill time > 2 seconds, rapid and weak pulse, cold clammy skin, irritable/ restlessness, pass no urine > 4–6 hours

o Leukopenia and/or thrombocytopenia with poor appetite especially in patients with warning signs or high risk patients

o Clinical deterioration when fever subsides

o Changes of consciousness

o Live very far or not convenient to come to the hospital

o Family's anxiety or too much concern

### *Referral and transportation*

More severe/ complicated cases should be managed in hospitals, where almost all laboratory investigations, equipments, medicines and blood bank facilities are available. The medical and nursing personnel should be more experienced in the care of these critically ill dengue patients. The following patients should be referred for closer monitoring and probably special treatment in the higher level of hospital care:

- Infants < 1 year old, elderly patients, pregnant women
- Obese patients
- Profound/ prolonged shock
- Significant bleeding
- Repeated shock 2-3 times during treatment
- Patients who seem not to respond to conventional fluid therapy
- Patients who continue to have rising Hct and no colloidal solution is available
- Patients with known underlying diseases: DM, hypertension, heart diseases, hemolytic diseases,...
- Patients with signs and symptoms of fluid overload
- Patient with isolated/ multiple organ involvement
- Patients with neurologic manifestations: change of consciousness, semi-coma, coma, convulsion,

### Referral process

- Discussion with the families.
- Prior contact with the referral hospital; communicating with doctors and nurses in charge.
- Stabilizing patients before transfer.
- Ensuring that referral letter/form must contain information about

clinical conditions, monitoring parameters (Hct, vital signs, intake/ output), progression of disease including all important laboratory findings.

● Taking care during transportation. Rate of IV fluid is important during this time. It is preferable to be given at a slower rate, about 5 ml/kg/ hr, to prevent fluid overload. A nurse should accompany with the patient.

● Review of referred patients by a specialist as soon as they arrive at the referral hospital.

## *Management in the critical phase*

**Dengue corner/ dengue unit (ward)**

Suspected dengue patients should be put together in the same areas or wards with mosquito-free environment for 2 purposes:

1. Prevent nosocomial transmission of dengue, especially those patients in the febrile phase who have dengue viremia

2. For proper monitoring and evaluation of clinical and other parameter especially those with shock or in critical period.

**Monitoring of DHF patients during critical period**

The critical period of DHF refers to the period of plasma leakage, which starts around the time of defervescence or the transition from febrile to afebrile phase. Thrombocytopenia is a sensitive indicator of plasma leakage but may also be observed in patients with DF. A rising hematocrit of 10-15% above baseline is an early objective indicator of plasma leakage.

The following parameters should be monitored during critical period (24-48 hours):

● General conditions: appetite, vomiting, bleeding, capillary refilled time (normal < 2 seconds)

● Vital signs: T, PR, RR, BP every 2-3 hours in non-shock patients, every hour in shock patients and in profound shock every 15 minutes until BP is restored.

● Hct every 4 to 6 hours in uncomplicated cases and more frequent

in unstable patients or those with suspected/ massive bleeding.

* Urine output every 8 hours in uncomplicated cases and hourly in patients with profound/ prolonged shock or those cases with fluid overload. The expected amount of urine output is 0.5 ml/kg/hr (based on ideal body weight).

**Indication for IV fluid administration:**

o Febrile phase: only in cases with severe vomiting and moderate to severe dehydration, otherwise try oral fluid intake, fruit juice or ORS.

o Critical phase: when there is thrombocytopenia and patients cannot have adequate oral intake. Plain water is contra-indicated because it may cause electrolyte imbalance, especially hyponatremia that may lead to convulsion or massive plasma leakage.

o Generally no IV fluid during convalescence phase.

## General principle of IV fluid management during critical period of plasma leakage:

● Isotonic crystalloid solutions should be used throughout the critical period except in the very young infants < 6 months, in whom 0.45% sodium chloride (5%N/2) may be used.

● Hyper-oncotic colloid solutions or plasma expander (Osmolarity >300 mOsm/L) such as 10% dextran-40 in NSS should be used in patients with massive plasma leakage, and those not responding to the minimum volume of crystalloid (as recommended below). Iso-oncotic colloid or plasma substitute solutions such as plasma, hemaccel are not effective because they have the same osmolarity as plasma.

● A minimum volume of maintenance + 5% dehydration (M + 5%D) should be given to maintain a "just adequate" intravascular volume and circulation. This volume includes both IV and oral intake. Usually maximum body weight used for adults is 50 kgs. In older children > 10 years old whose ideal body weight are _ 35 kgs, may use adult rate of IV fluid to

prevent fluid overload.

- The duration of intravenous fluid therapy should not exceed 24 to 48 hours for those with shock. For non-shock, the duration of intravenous fluid therapy may have to be longer, but not more than 60 to 72 hours.
- In obese patients, the ideal body weight should be used as a guide to calculate the fluid volume. Weight for age is preferred than weight for height for it is less that goes along with the principle of minimum IV fluid to maintain intra-vascular circulation.

**Table 1** Requirement of fluid based on ideal body weight (IBW)

| Ideal Body Weight (Kgs) | Maintenance (ml) | M + 5% Deficit (ml) | Ideal Body Weight (Kgs) | Maintenance (ml) | M + 5% Deficit (ml) |
|---|---|---|---|---|---|
| 5 | 500 | 750 | 35 | 1,800 | 3,550 |
| 10 | 1,000 | 1,500 | 40 | 1,900 | 3,900 |
| 15 | 1,250 | 2,000 | 45 | 2,000 | 4,250 |
| 20 | 1,500 | 2,500 | 50 | 2,100 | 4,600 |
| 25 | 1,600 | 2,850 | 55 | 2,200 | 4,950 |
| 30 | 1,700 | 3,200 | 60 | 2,300 | 5,300 |

**Table 2** Rate of IV fluid in children and adults

| Note | Children Rate (ml/kg/hour) | Adult Rate (ml/hour) |
|---|---|---|
| Half the maintenance M/2 | 1.5 | 40-50 |
| Maintenance (M) | 3 | 80-100 |
| M + 5% Deficit | 5 | 100-120 |
| M + 7% Deficit | 7 | 120-150 |
| M + 10% Deficit | 10 | 300-500 |

Rate of intravenous fluids should be adjusted according to the 4 parameters monitored as above. The rate of IV fluid differs in adults and children are not the same.

## Rate of infusion in non-shock cases

In non-shock case, the rate of IV fluid depends on the time after the beginning of plasma leakage which can be estimated by 2 parameters, platelet counts (degree of thrombocytopenia) and % rising Hct.

o First day of plasma leakage: Platelet 50,000-100,000 cells/ cumm. and rising Hct 5-10%

o Second day of plasma leakage: Platelet count < 50,000 cells/ cumm. and rising Hct >10-20%

The rate is shown in the below figure 10.

## Rate of infusion in DSS case (Figure 11)

***IV fluid Resuscitation in DSS patients is completely different from other kind of shock.*** In DHF grade III, the rate is only 10 ml/kg/hr (or 500 ml/hr in adult) and the rate has to be reduced as in the figure below. In DHF grade IV, the initial fluid resuscitation is increasing to 20 ml/kg/hr, but

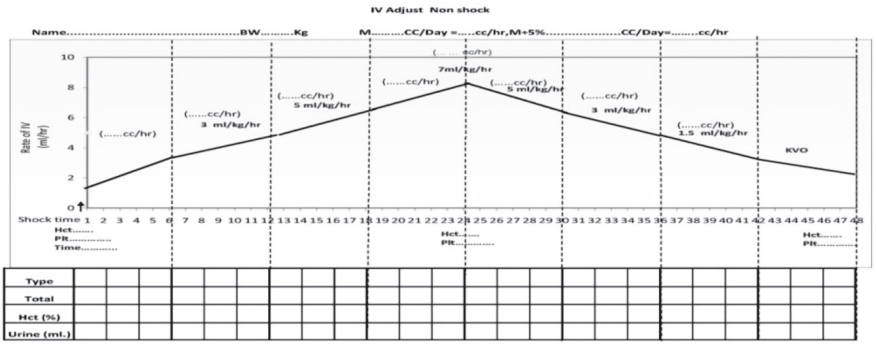
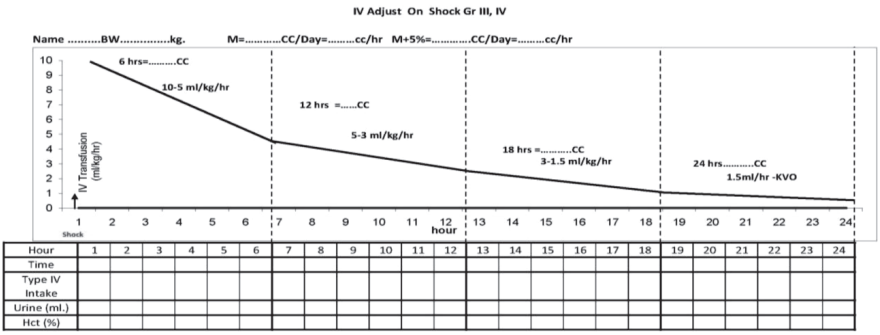



**Figure 10** Suggested rate of IV fluid in non-shock DHF cases




| Hour | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time | | | | | | | | | | | | | | | | | | | | | | | | |
| Type IV Intake | | | | | | | | | | | | | | | | | | | | | | | | |
| Urine (ml.) | | | | | | | | | | | | | | | | | | | | | | | | |
| Hct (%) | | | | | | | | | | | | | | | | | | | | | | | | |

**Figure 11** Suggested rate of IV fluid in DSS patients

when the BP can be restored, the rate should be reduced to 10 ml/kg/hr immediately, usually after 15-30 minutes. If the volume of resuscitation is too much, the patients will have more pleural effusion and ascites which may result in respiratory distress later.

So the diagnosis of DSS is very important and should be made as early as possible by doing CBC. DSS patients will have rising Hct >20-30% and thrombocytopenia. In complicated DSS cases with significant bleeding, rising Hct may not be clearly seen or the rising of Hct may be minimal as < 10 %, or some cases dropping of Hct is seen instead. But marked thrombocytopenia will be seen. In shock cases, leukopenia may not be seen. Leukocytosis may replace leukopenia, due to body stressful situation. Normal ESR may be used to differentiate DSS from septic shock.

**Additional laboratory tests for DHF grade IV and severe complicated cases**

- Complete Blood Count (CBC)
- Blood glucose
- Blood gas analysis, lactate (if available)
- Serum electrolytes
- Serum calcium
- Liver function tests

- BUN, Creatinine, Uric acid
- Coagulation profile (if available)
- Right lateral decubitus chest radiograph (optional)
- Grouping and matching for fresh whole blood (FWB) or packed red cells (PRC)
- Cardiac enzymes or ECG if indicated, especially in adults
- Serum amylase and ultrasound if abdominal pain does not resolve with fluid therapy

Complications commonly seen in DHF/DSS cases, especially cases with prolonged shock or fluid overload are acidosis, bleeding (internal or concealed), hypoglycemia, hypocalcemia and organ(s) failure (liver, kidney, respiratory, heart). Practical laboratory investigations (ABCS) in cases with prolonged shock (DHF grade IV), repeated shock or cases not response to conventional IV fluid management as recommend) are blood gas (capillary or venous), LFT, BUN, Creatinine, Hct (or CBC), electrolyte including Ca and iCa, blood sugar which are shown in Table 3.

During critical period, if the patients have signs of fluid overload: puffy eyelids, abdominal distention or when there is persistent high Hct for more than 6 hours (>25-30% of baseline) and the IV fluid cannot be reduced, switch from crystalloid to colloid solutions (plasma expander) as bolus fluids. Dextran-40 is effective as 10 ml/kg/dose bolus infusions or 500 ml/hr in adults, but the dose is restricted to 30 ml/kg/day because of its renal effects. ***Dextran-40 in a bolus dose can bring the Hct down by 10 points, but not below the baseline Hct.*** If Hct drops > 10 points, think of bleeding. Hct should be done before and after dextran-40 infusion to guide further management. Do not recommend to administer in a more rapid rate than 10 ml/kg/hr or 500 ml/hr for it may cause sudden increase in the plasma osmolarity that may precipitate neurological complication. Dextran-40 is excreted in the urine and will affect the urine osmolarity. Patients may

**Table 3** Practical laboratory investigations (ABCS) in cases with prolonged shock (DHF grade IV) or severe / complicated cases or cases with no clinical and vital sign improvement despite adequate volume replacement

| Abbreviation | Laboratory investigations | Note |
|---|---|---|
| A-Acidosis | Blood gas (capillary or venous) | Indicate prolonged shock. Organ involvement should also be looked for; Liver function and BUN, Creatinine. |
| B-Bleeding | Hematocrit | If dropped compared to the previous value or not rising, cross match for rapid blood transfusion. |
| C-Calcium | Electrolyte, Ca++ | Hypocalcemia is found in almost all cases of DHF but asymptomatic. Ca supplement in more severe/ complicated cases is indicated. The dosage is 1 ml/kg dilute 2 times IV push slowly, maximum dose 10 ml of Ca gluconate. |
| S-Blood sugar | Serum sugar (Dextrostix) | Most severe DHF cases have poor appetite together with vomiting. Those with impaired liver function may have hypoglycemia. Some cases may have hyperglycemia. |

experience "sticky" urine because of the hyper-oncotic nature of Dextran-40 molecules (osmolarity about 2-3 times of plasma). Other colloidal solutions (plasma substitute): Hemaccel, 6% Hetastarch (Voluven) including plasma (FFP) are not effective in treating DHF/DSS patients with massive plasma leakage.

If intravenous access cannot be obtained urgently, try oral electrolyte solution if patient is conscious and co-operate. Central venous catheter insertion or intra-osseous route (need experienced clinicians) is indicated in patients with alteration of consciousness or not-co-operate. The central venous catheter insertion or intra-osseous access are life-saving and should

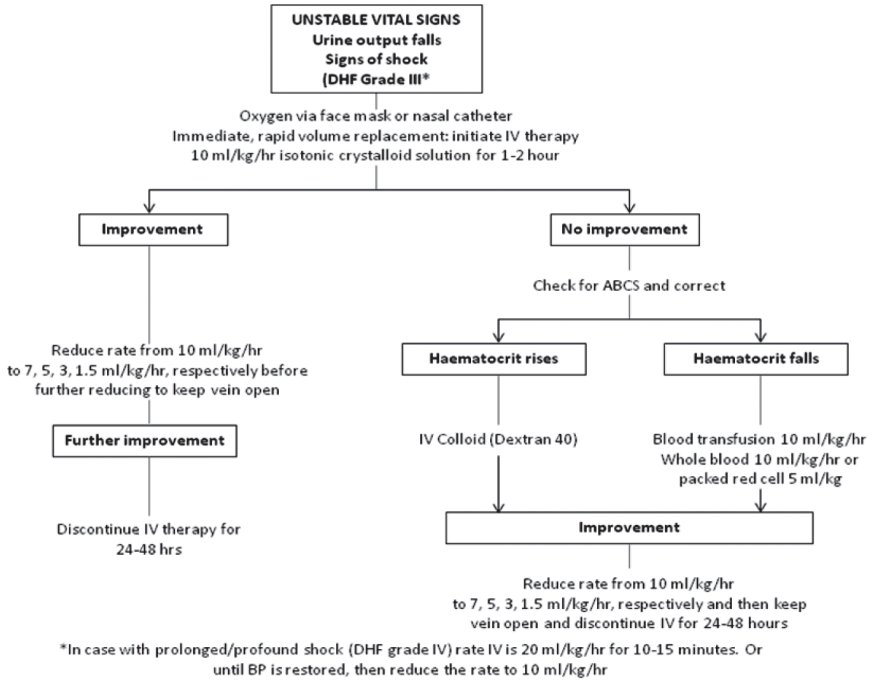



**Figure 12** Volume replacement flow chart for DSS patients

be attempted after 2–5 minutes, or 2 failed attempts at peripheral venous access, or failed oral route. Venous cut down is recommended if the above techniques are not available.

**Indications for blood transfusion:**

- Clinical bleeding of >10% total blood volume, 6–8 ml /kg (IBW) or 300 ml in adults.
- DSS patients who have rising Hct < 20% or dropping Hct at the time of shock.
- DHF/DSS patients who have dropping of Hct from the previous value without clinical and vital signs improvement despite adequate volume replacement. The most common bleeding found is upper GI bleeding which often takes time before the patients pass as melena (concealed or internal

bleeding).

Dengue patients whom significant bleeding is suspected and requires blood grouping/matching and probably blood transfusion later include:

- DSS patients Grade IV or prolong shock.
- DHF patients who have persistent abdominal pain or history of peptic ulcer especially in adults.
- DF/DHF/DSS who had taken aspirin, NSAID, steroid as antipyretic or to relieve headache or bodyache or who have underlying peptic ulcer.
- Women who have menstruation or abnormal vaginal bleeding.
- Patient with hemoglobinopathy, Thalassemia, G-6-PD deficiency who may have hemoglobinuria.

**Amount of blood to be transfused:**

- Equal to the amount estimated.
- If cannot estimate, give FWB 10 ml/kg or PRC 5 ml/kg at a time (or 1 Unit of FWB or PRC in adults) and evaluate if another amount is required. This will make Hct increase by 5 points in children and 3-4 points in adults.

It is mandatory to do the Hct before and after transfusion in order to assess the bleeding whether it is still active or not. If the Hct does not rise to the expected value, bleeding is still active and more blood transfusion is needed.

**Type of blood**

Choice of FWB or PRC to be transfused depends on the condition of the patients and the availability of blood. Ideally, in uncomplicated cases, FWB is preferred. In cases with signs of fluid overload, PRC is the choice to be transfused.

**Rate of blood transfusion**

Rate of blood transfusion depends on the patients' conditions. If in

shock state, IV push or free flow is recommended. If no signs of shock, the preferred rate is 5 ml/kg/hr or 3 ml/kg/hr in cases with signs of fluid overload. Blood has to be transfused ASAP to increase red cells to carry oxygen to all tissues to correct hypoxia/ shock.

**Platelet transfusion**

Platelet transfusion is indicated in cases that need blood transfusion. But if those patients have signs and symptoms of fluid overload, it is contra-indicated because larger volume of platelet concentrate will precipitate acute pulmonary edema or heart failure. If platelet is not available, only blood transfusion is enough. Platelets may help stop bleeding but not help correct hypoxia/ shock because they carry no oxygen to tissues to correct hypoxia and shock.

Platelet prophylaxis is not recommended in children for thrombocytopenia, no matter how low the platelet count. It may be considered in adults with underlying hypertension, heart disease, or those with anti-coagulant or anti-platelet aggregation therapy,...and have marked thrombocytopenia (less than 10,000 cell/ cumm.).

## *Management of high risk DHF patients*

**Obese patients**

Obese patients have less respiratory reserves and care should be taken to avoid excessive intravenous fluid infusions. The ideal body weight should be used to calculate fluid resuscitation and replacement. Colloids (Dextran - plasma expander) should be considered in the early stages of fluid therapy. Once stabilized, furosemide may be given to induce diuresis. Adolescents or children, whose ideal body weight is > 35 kgs. should use the adult rate for IV fluid administration.

**Infants**

Infants also have less respiratory reserve and more susceptible to liver impairment and electrolyte imbalance. They may have a shorter dura-

tion of plasma leakage, usually 12-24 hours (not 24-28 hours like in older children and adults). Convulsion and diarrhea (a few loose stool) is common unusual clinical presentations in these young infants that may lead to other clinical diagnosis like CNS or system infections. Rising Hct and thrombocytopenia will help in clinical diagnosis of DHF. Leukopenia may not be found in infants in the early febrile phase because the average WBC is higher in infants. They usually respond quickly to fluid resuscitation. Infants should therefore be evaluated more frequently for oral fluid intake and urine output.

**Pregnant women**

Pregnant women with suspected dengue infections should be admitted early for close monitoring and carefully detect the earliest signs of plasma leakage. Multi-disciplinary care among obstetrics, internal medicine and pediatrics specialties is essential. Family counseling is necessary in severe cases. Early DHF in pregnant woman may be misdiagnosed with HELLP (Hemolysis, Elevation of Liver enzyme and low Platelet) Syndrome.

There are increasing reports of dengue infections in pregnant women

FRENCH GUIANA: 1992-2006
CELIA BASURKO ET AL, EUR J OBSTET GYNECOL REPROD BIOL 2009

| Abnormalities | % |
|---|---|
| Premature labor | 41.0 |
| Premature birth | 9.6 |
| Hemorrhage during labour | 9.3 |
| Retro-placental hematoma | 1.9 |
| Prematurity | 20.0 |
| Fetal death in utero | 3.8 |
| Late miscarriage | 3.8 |
| Acute fetal distress during labour | 7.5 |
| Neonatal death (Pseudo aeruginosa? septicemia) | 1.9 |
| Vertical transmission (3/20) | 15 |

**Figure 13** Findings in pregnant women with confirmed dengue infections in French Guiana

and one report from French Guiana reported 53 pregnant dengue infections; 3 cases in the first trimester, 15 cases between 15-27 weeks gestation, and 35 cases in more than 28 weeks of gestation. The results are in the below Figure 13.

## Perinatal dengue/ Vertical transmission of dengue

Perinatal dengue infections, the result of vertical transmission from mothers to offspring is also increasing in reports. In general, dengue infections in newborn babies are usually mild. DF is more likely but need more studies. Review of 11 reports from Thailand from the year 2000 reveals 25 peri-natal dengue in mothers and children. The age range of mother is between 19-43 years. One mother is below 20 and 2 mothers are above 30 years old. Clinical presentations in mothers are 11 DF (44%), 8 DHF (32%) and 6 DSS (8%) while in newborn (NB) babies, there are 13 DF (52%), 10 DHF (40%) and 2 DSS (8%). Both DSS babies were born from DSS mothers. The age range in babies is before birth - 9 days. Fever is the initial presentation in all babies, except one that had signs and symptoms before birth. Six babies developed fever within the first day of life, while 17 of them had fever from 4-6 days. The other 2 babies developed fever on day 2 and 9 of their lives. Other clinical presentations are petechiae, rash and hepatomegaly. There is no death, but one baby with DSS had intra-ventricular hemorrhage and later has developmental delay. Seventy percent of DHF/DSS mothers had DHF/DSS babies while 18% of DF mother had DHF babies. Management in NB babies is supportive and symptomatic. Role of platelet transfusion in NB with very low platelet has to be further evaluated.

## Patients with hypertension

These patients may be on anti-hypertensive therapy that masks the cardiovascular response in shock. A blood pressure that is perceived to be

normal may in fact be low for these patients. Clinical signs of shock are better to guide clinical diagnosis of DSS than the BP.

## DM patients

Intravenous insulin is required to control when the blood sugar level is > 300 mg% in dengue patients with underlying DM, the dosage is the same as in cases with diabetic hyper-osmolar or ketoacidosis. Non-glucose containing crystalloids should be used when the blood sugar level is > 200 mg%.

## Patients with heart diseases

Discontinue anti-coagulant therapy (anti-platelet aggregation, aspirin, warfarin,..) is generally recommended temporarily for 3-5 days during the critical period. But consultation with cardiologists before stopping these medicines is recommended, because some patients may develop serious effect of acute stroke, or myocardial infarction immediately after discontinuation of these drugs. Congenital and ischemic heart diseases: Fluid therapy should be more cautious as they may have less cardiac reserve.

## Hemolytic diseases and hemoglobinopathies

These patients are at risk of hemolysis and will require blood transfusion. Caution should be taken with overhydration and alkalinisation therapy, which can cause fluid overload and hypocalcemia. In general, there is no need to over-hydrate or giving NaHCO3, because DHF patients usually have hypervolemia during reabsorption period and mild respiratory alkalosis all through their clinical course of DHF/DSS.

## *Management of complications*

The most common complication in DHF/DSS is fluid overload.

## Causes of fluid overload include:

- Early IV fluid administration during febrile phase, usually with hypotonic solutions.
- Administer hypotonic solution during critical period (when platelet count is below or around 100,000 cells/cu mm.)
- Do not adjust rate of IV fluid according to the clinical course of DHF/DSS.
- Patients can drink oral fluid and it is not recorded or include in the management plan. Plain water is contra-indicated, for it may contribute to dilutional effect and cause electrolyte imbalance (hyponatremia). Only ORS or fruit juice are recommended during critical period in those patients who cannot take any solid food.
- Do not use dextran-40 when indicated or not use in a bolus dose. Some may use other iso-oncotic colloid solutions (plasma, hemaccel, gelafudin,...) that are not effective in DHF/DSS with fluid overload.
- Transfuse unnecessary platelet concentrate, FFP or other blood components.
- Continue IV fluid beyond the critical period, especially when the DHF/DSS patients are in reabsorption period.
- Do not correct associated common complications ABCS (acidosis, bleeding, hypocalcemia and hypocalcemia).

## Signs and symptoms of patients with fluid overload

- Early signs and symptoms: Puffy eyelids, distended abdomen (ascites), tachypnea, mild dyspnea.
- Late signs and symptoms: All of the above, moderate to severe respiratory distress, shortness of breath, wheezing (not due to asthma) is an early sign of interstitial pulmonary edema and crepitation, restlessness/agitation and confusion are signs of hypoxia and impending respiratory failure.

## Management of fluid overload

Review the total intravenous fluid therapy, clinical course and check and correct for ABCS as above. All solutions should be stopped.

If the patients with fluid overload are in the state of shock, or still in the critical period of plasma leakage or in equilibrium period with still no signs of reabsorption,10 ml/kg/hr or 500 ml/hr in adults of hyper-oncotic colloid boluses (dextran-40) should be given before giving furosemide. In shock cases, the blood pressure is usually restored within 10 to 30 minutes of infusion, then administer 1 mg/kg/dose or 40 mg in adults of furosemide IV, and continue with dextran infusion until complete the dose of dextran. Intravenous fluid should be reduced according to the state after the first shock according to the rate given in Figure 11, or in cases with severe fluid overload, IV fluid can be reduced to 1 ml/kg/hr or 20-40 ml/hr in adults until discontinuation. Subsequence IV rate will be adjusted in order to obtain urine of 0.5 ml/kg/hr. If Hct is rising to high value again, Dextran as a bolus dose can be given again with or without furosemide depending on the degree of respiratory distress of the patients. Furosemide may be repeated every 30-60 minutes, if the patients still have signs and symptoms of fluid overload. In the convalescence phase of DHF, patient with fluid overload or those with frank pulmonary edema, furosemide may be given without dextran, if the patient has stable vital signs.

Furosemide is recommended at pharmacologic dose as above, to make sure that if no urine is obtained, that is because the patients do not have adequate intra-vascular volume or the patients may have acute renal failure. Some adult clinicians prefer low dose of furosemide infusion that results in slower rate of recovery from respiratory distress. Vital signs every 15 mins. **for 4 times is routine recommendation** after furosemide IV in every patients for fear of shock again because it will deplete only the intra-vascular volume, not the extra-vascular volume as ascites or pleural effusion. In our experience, when furosemide is given during dextran infusion,

no cases of shock are observed. In patients that are sensitive to furosemide, a large volume of urine, > 10 ml/kg/hr or > 500 ml is obtained in one hour, they may develop shock. The next dose of furosemide is recommended to reduce to half dose, if it is needed again.

The following points of care are needed in DHF/DSS patients with complications of fluid overload:

- These patients should have a urinary bladder catheter insertion to monitor hourly urine output.
- Furosemide should be given during dextran infusion, because the hyper-oncotic nature of dextran will maintain the intravascular volume (less plasma leakage and probably reabsorb back some of the extravasated plasma as ascites and pleural effusion) while furosemide depletes the intravascular compartment.
- If there is no urine output in response to furosemide, check the intravascular volume status (venous cut down, insertion of central venous catheter or arterial line) to measure central venous or arterial pressure. If this is adequate, pre-renal failure is excluded meaning that the patient is in acute renal failure. These patients may require ventilatory support soon. If the intravascular volume is inadequate or the blood pressure is unstable, check the ABCS and other electrolyte imbalances.
- In cases with no response to furosemide (no urine obtained), repeated doses of furosemide and double the dosage are recommended. If oliguric renal failure is established, peritoneal dialysis is to be done as soon as possible by insertion of Tenchkoff catheter and remove as much as possible of the ascitic fluid, because this cause increase in intra-abdominal pressure and compress on inferior vena cava and renal arteries/veins, which result in no venous return and no circulation to the heart and kidneys. Persistent shock with poor circulation and renal failure are commonly seen in these cases. These cases have poor prognosis if cardiac function and renal failure are not reversible. This procedure is highly recommended be-

cause it will dramatically decrease the intra-abdominal pressure as the ascitic fluid is taken out and spontaneous return of the normal hemodynamic conditions of the patients if the timing is not too long.

- Some clinicians may prefer plasmapheresis, hemodialysis, continuous veno-venous hemofiltration (CVVH), continuous arterio-venous hemofiltration (CAVH) or other renal replacement therapy according to their experience and availability.

- If no sophisticated techniques available, pleural and/or abdominal tapping may be indicated and life-saving in cases with severe respiratory distress and failure of the above management. This has to be done with extreme caution because traumatic bleeding is the most serious complication, which will lead to death. Discussion and explanation about the complication and the prognosis with families is mandatory before performing this procedure.

## *Management of convalescence phase*

Convalescence can be recognized by the improvement in clinical parameters (appetite and general well being) and hemodynamic state such as good peripheral perfusion, stable vital signs, decrease of Hct to baseline or below and diuresis. **Intravenous fluid should be discontinued.** In those with massive effusion and ascites, hypervolemia may occur and diuretic therapy may be necessary to prevent pulmonary edema. Hypokalemia may be present due to stress and dieresis, and should be corrected with potassium-rich fruits (banana, orange,...) or supplements.

**Signs of recovery**

- Stable pulse, blood pressure and respiratory rate
- Normal temperature
- No evidence of external or internal bleeding
- Return of appetite
- No vomiting, no abdominal pain

- Good urinary output
- Stable Hct at baseline level
- Convalescent confluent petechiae rash or itching especially on the extremities
- Sinus brady-arrhythmia may be found in some patients who usually need no special treatment except bed rest. There are rare reports of myocarditis; heart block or PVC that need specific treatment in children but more reports in adult patients.

***Criteria for discharging patients***

- Absence of fever for at least 24 hours without the use of antipyretic therapy
- Return of appetite
- Visible clinical improvement
- Good urine output
- Minimum of 2-3 days after recovery from shock
- No respiratory distress minimum of 2-3 days after recovery from shock from pleural effusion and no ascites
- Platelet count of more than 50,000/cumm. and recommend patients to avoid traumatic activities for at least 2 weeks for platelet count to become normal. In > 90% of uncomplicated cases, platelet rises to normal within 7 days. If platelet counts do not increase > 100,000 cells/cumm., consult with hematologists for possible bone marrow aspiration is recommended. Rare complication may be found in some DHF/DSS cases as idiopathic thrombocytopenic purpura (ITP) or infectious associated hemophagocytic syndrome (IAHS). Steroid and/ or intravenous immunoglobulin (IVIG) may be indicated for treatment of these cases

## *Advice before discharge DHF/DSS patients*

- Avoid trauma, sports and aggressive behavior 2 weeks after discharge, for some cases may have low platelet count. Platelets usually rise

spontaneously within 7 days after critical period in >90% of patients

- There is no risk for spread of dengue virus and the patients can go to school. The viremia period is during the febrile phase
- If people in the same house or around the areas are sick with high fever, they are likely to have dengue infections. They should be taken to the hospital for proper diagnosis and management
- Aedes Egypti mosquitoes are the vector of DHF. Advise how to do the prevent and control of dengue for both at home and at school:
  - Prevent mosquitoes bite during daytime
  - Get rid of adult mosquitoes.
  - Get rid of the containers which are the breeding places of Aedes mosquitoes

**Common causes of death in dengue**

- Prolonged shock with multiple organs failure
- Massive bleeding
- Fluid overload

Most of dengue patients who died had 2-3 of the above conditions.

*Delayed or misdiagnosed of Dengue/DHF/DSS in the early stage is found in more than 50% of dengue deaths in Thailand.*

## *Unusual presentations of DHF/ DSS/ EDS and management*

In severe/ complicated cases of DHF/DSS/EDS, the initial presentations are not typically like uncomplicated DHF/DSS, so most inexperience doctors often miss the diagnosis of DHF/DSS/EDS. In endemic countries of dengue, it is recommended for the routine practice to *always think of DHF/DSS/EDS when the patients present with thrombocytopenia,* especially when platelet is < 50,000 cells/cumm. High fever is often seen in these complicated cases, so other infections: Leptospirosis, Rickettsial

diseases, Mellioidosis, Malaria,..are in the differential diagnosis. *Evidence of plasma leakage is the most important clue for the diagnosis of DHF/ DSS/EDS.*

The additional presentations of severe complicated DHF/ DSS/ EDS are high fever, leukocytosis, and increase in percentage of PMS so that these cases are commonly mis-diagnosed as sepsis/ septic shock, or other above mentioned infections. So in patients who present with shock, high fever, bleeding manifestations (petechii, epistaxis, gum bleeding, bruise at venipuncture sites), thrombocytopenia, leukocytosis, increased in percentage of PMN, clinicians should look for evidence of plasma leakage other than rising Hct, and portable chest film. Pleural effusion and ascites are better detected by right lateral decubitus chest film (which is usually not possible in severe cases), ultrasound or hypoalbuminemia < 3.5 gm%. Differential diagnosis of these patients include:

- Other infections, not dengue/ DHF/ DSS/ EDS.
- DHF/ DSS/ EDS cases with
  - o Co-infections or super-imposed infections.
  - o Transaminitis or hepatitis or liver dysfunction/ failure.
  - o Significant bleeding or hemolysis.

The above patients with evidence of plasma leakage are likely to have DHF/ DSS/ EDS, and the 3 above conditions have to be managed as early as possible to prevent further deterioration by the below recommendations. Some patients may have all 3 above associated conditions:

- Consider empiric antibiotics to cover another possible or likely co-infections after septic workup and appropriate infectious investigations. ESR may help in differentiating septic shock from DSS because in DSS the ESR is very low (between 0-5 mm/hr) or < 20 mm/hr while it is very high in bacterial infections.
- If AST/ ALT elevation are found especially if AST/ ALT > 1,000 Unit, management as pre-hepatic coma is recommended to prevent

hepatic encephalopathy as in the below management of encephalopathy.

- Transfuse blood, preferred PRC if obvious bleeding is recognized, or in cases with no rising of Hct to explain shock or dropping Hct compare to the previous value. If the Hct is high due to progressive plasma leakage, dextran in bolus dose may be administered to see whether the Hct drop to > 10 points that indicates bleeding or not.

## *Management of DHF/ DSS/ SDS patients with encephalopathy*

More than half of DHF patients who present with encephalopathy (drowsy, confusion, speak fowl language, convulsion, change of consciousness to stupor or coma) are due to hepatic failure from prolonged shock. Other causes of encephalopathy include:

- Electrolyte imbalance:
  - o Hyponatremia; Na level < 125 mEq/L may need treatment and level < 120 mEQ/L needs treatment with 3% NaCl (patients may have convulsion).
  - o Hypocalcemia
- Metabolic disturbance: hypoglycemia

If the above abnormalities are correct early, the prognosis is good with complete recovery.

- Intra-cranial bleeding: not commonly seen, usually found in the later phase of complicated DSS with multiple organ failure, not during the critical phase.
- Encephalitis: rare and so far only one confirmed report of dengue virus in the neurons. Others are not confirmed but found positive dengue virus isolation, PCR positive in the CSF with no CSF pleocytosis.

The principle management of DHF/ DSS/ EDS patients with encephalopathy is the same as management of hepatic encephalopathy, i.e. to prevent increase intra-cranial pressure (ICP) that causes encephalopa-

thy to be worse. The followings are recommendations for supportive therapy for this condition:

1. Maintain adequate airway oxygenation with oxygen therapy to keep oxygen oxygenation > 95%. Intubation may be necessary for those patients who have respiratory failure or in semi-coma/ coma condition

2. Prevent/ reduction of ICP by the following measures:

o Give minimal IV fluid to maintain adequate intra-vascular volume, ideally the total IV fluid should not > 80% maintenance

o Switch to colloidal solution earlier if continue rising Hct and a large volume of IV fluid is needed in cases with severe plasma leakage.

o Administer diuretic if indicated in cases with signs and symptoms of fluid overload.

o Consider steroid to reduce ICP. Dexamethazone 0.5 mg/kg/day IV every 6-8 hours is recommended.

o Hyperventilate

o Semi-prone position

3. Decrease ammonia production:

o Give lactulose 5-10 ml every 6 hours for induction of osmotic diarrhea.

o Local antibiotic, neomycin to get rid of bowel flora. It is not necessary if systemic antibiotics are given.

4. Maintain blood sugar level >60 mg%. Recommend glucose infusion rate between 4-6 mg/kg/hour.

5. Correct acid-base and electrolyte balance, e.g. correct hypo/ hypernatremia, Hypo/ hyperkalemia, hypocalcemia and acidosis.

6. Vitamin K1 IV administration; 3 mg for <1 year old, 5 mg for <5 years old and 10 mg for >5 years old and adults.

7. Anti-convulsant should be given for control of seizures; phenobarbital, dilantin and diazepam IV as indicated.

8. Transfuse blood, preferably fresh packed red cell as indicated.

Other blood components as platelet, fresh frozen plasma may not be given because of limited volume for these patients. Larger volume of IV fluid may cause increased ICP and worsening of neurological signs and symptoms.

9. Empiric antibiotic therapy may be indicated if high fever and superimposed bacterial infections cannot be ruled out.

10. H2-blockers or proton pump inhibitor may be given to alleviate gastro-intestinal bleeding.

11. Avoid unnecessary drugs because most drugs have to be metabolized by the liver.

12. Consider peritoneal dialysis, plasmapheresis or hemodialysis or renal replacement therapy in cases with clinical deterioration.

Some DF/ DHF patients present with unusual manifestations with signs and symptoms of CNS involvement, such as convulsion and/or coma. This has generally been shown to be encephalopathy, not encephalitis, which may be the result of intracranial hemorrhage or occlusion associated with DIC. In recent years however, several cases with CNS infections have been documented by virus isolations from the CSF or brain.

## *Outbreak preparedness for clinical management*

There has been increasing incidence of dengue outbreaks in many countries globally. The following elements are recommended for the preparedness of dengue clinical management:

- Personnel to be recruited, trained and assigned appropriate duties:
  - o Doctors
  - o Nurses
  - o Healthcare workers
  - o Back-office personnel
- Clinical Practice Guidelines (CPG) [The above personnel should undergo a brief training in the use of this CPG]

- **Medicines and solutions**
  - o Paracetamol
  - o Oral rehydration solution
  - o IV fluid
    - Crystalloid : 0.9% and 5%D/NSS, 5%DAR, 5%DLR
    - Colloid-hyper-oncotic (plasma expander) : 10% Dextran-40 in NSS
  - o 20% or 50% glucose
  - o Vitamin K1
  - o Calcium gluconate
  - o KCl solution
  - o Sodium bicarbonate
- **Equipments and Supplies**
  - o IV fluids and vascular access, including scalp vein, medicut, cotton, gauze, 70% alcohol
  - o Oxygen and delivery system
  - o Sphygmomanometer with 3 different cuffs size
  - o Automate CBC machine (Coulter Counter)
  - o Micro-centrifuge (for Hct determination)
  - o Microscope (for platelet count estimation)
  - o Glucometer (for blood sugar level)
- **Laboratory support**
  - o Basic
    - Complete blood count (CBC): Hct, white blood count (WBC), platelet count, differential count
  - o More complicated cases
    - Blood sugar
    - Liver function test
    - Renal function test (BUN, Creatinine)
    - Electrolyte, Calcium

- Blood gas analysis
- Coagulogram: partial thromboplastin time (PTT), prothrombin time (PT), thrombin time (TT)
- Chest x-ray
- Ultrasonography

- **Blood Bank**
  - o Fresh whole blood, packed red cell, (platelet concentrate)