

**CLINICAL PRACTICE GUIDELINES**

September 2015

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**MANAGEMENT OF DENGUE INFECTION IN ADULTS  
(THIRD EDITION)**



Ministry of Health  
Malaysia



Academy of  
Medicine Malaysia

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### **STATEMENT OF INTENT**

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

These guidelines were issued in 2015 and subject to be reviewed in minimum 4 years time or in the advent of any significant change in management of patient. When it is due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed.

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<b>LEVELS OF EVIDENCE</b>
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Level	Study design
<b>I</b>	Evidence from at least one properly randomised controlled trial
<b>II -1</b>	Evidence obtained from well-designed controlled trials without randomisation
<b>II-2</b>	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
<b>II-3</b>	Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
<b>III</b>	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

**SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001**

In line with the current development in CPG methodology, the CPG Unit of MaHTAS is in the process of incorporating Grading Recommendations, Assessment, Development and Evaluation (GRADE) in its work process. The quality of each retrieved evidence and its effect size are carefully assessed/reviewed by the CPG Development Group. In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:-

- Overall quality of evidence
- Balance of benefits vs harms
- Values and preferences
- Resource implications
- Equity, feasibility and acceptability

## GUIDELINES DEVELOPMENT AND OBJECTIVES

### GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for these Clinical Practice Guidelines (CPG) were from the Ministry of Health (MoH). There was also active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A literature search was carried out using the following electronic databases: Guidelines International Network (G-I-N); Medline via Ovid, Pubmed and Cochrane Database of Systemic Reviews (CDSR) (refer to **Appendix 1** for **Search Strategy**). The inclusion criteria are all literature on dengue infection regardless of study design. The search was limited to literature published in the last five years, on humans and in English. In addition, the reference lists of all retrieved literature and guidelines were searched to further identify relevant studies. Experts in the field were also contacted to identify relevant studies. In certain situations, pivotal papers beyond the scope of search were used in the CPG. All searches were conducted from 26 May 2015 to 24 July 2015. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

The previous edition of CPG (2010) was used as the basis in updating these present guidelines. Reference was also made to other guidelines on dengue infection in adults as well as handbooks from WHO such as Dengue Guidelines for Diagnosis, Treatment, Prevention and Control (2009) and Handbook for Clinical Management of Dengue (2012).

A total of 18 clinical questions were developed under different sections. Members of the DG were assigned individual questions within these sections. (Refer to **Appendix 2** for **Clinical Questions**) The DG members met 5 to 7 times throughout the development of these guidelines. The literature retrieved was appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meetings. All statements and recommendations formulated after that were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. Any differences in opinion were resolved consensually. The CPG was based largely on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The literature used in these guidelines was graded using the US/Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendation was done using the principles of GRADE (refer to the preceding page).

On completion, the draft of the CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG, and the HTA and CPG Council MoH Malaysia for review and approval.

## **OBJECTIVES**

### **GENERAL OBJECTIVES**

To provide evidence-based guidance in the management of dengue infection in adult patients.

### **SPECIFIC OBJECTIVES**

- To improve recognition and diagnosis of dengue cases and provide appropriate care to the patients.
- To improve on early and accurate notification of dengue cases for prompt public health intervention.
- To identify severe dengue and carry out more focused close monitoring and prompt appropriate management.
- To provide guidance on appropriate and timely fluid management and the use of blood and blood products.
- To create awareness on early detection of dengue infection with complications.

### **CLINICAL QUESTIONS**

Refer to **Appendix 2**

### **TARGET POPULATION**

Adult patients with dengue fever and severe dengue.

### **TARGET GROUP/USER**

This CPG is intended to guide those involved in the management of dengue infection in adults particularly healthcare professionals in primary and secondary/tertiary care namely:-

- a. Physicians and specialists from related disciplines
- b. Family Health Specialists
- c. Medical officers and general practitioners
- d. Allied health professionals
- e. Pharmacists
- f. Students (medical postgraduates and undergraduates, and allied health students)
- g. Patients and carers

### **HEALTHCARE SETTINGS**

Outpatient, inpatient and community settings inclusive of private healthcare facilities.

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The draft guideline was reviewed by a panel of experts from both public and private sectors. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the guidelines.

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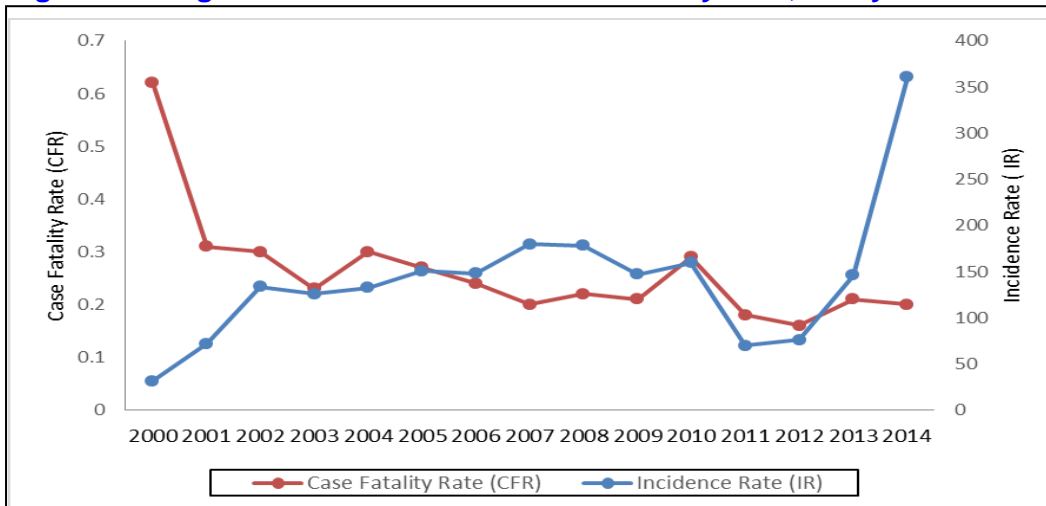
## 1. EPIDEMIOLOGY

Dengue is one of the most important arthropod-borne viral diseases in terms of public health problem with high morbidity and mortality. It affects tropical and subtropical regions around the world, predominantly in urban areas.

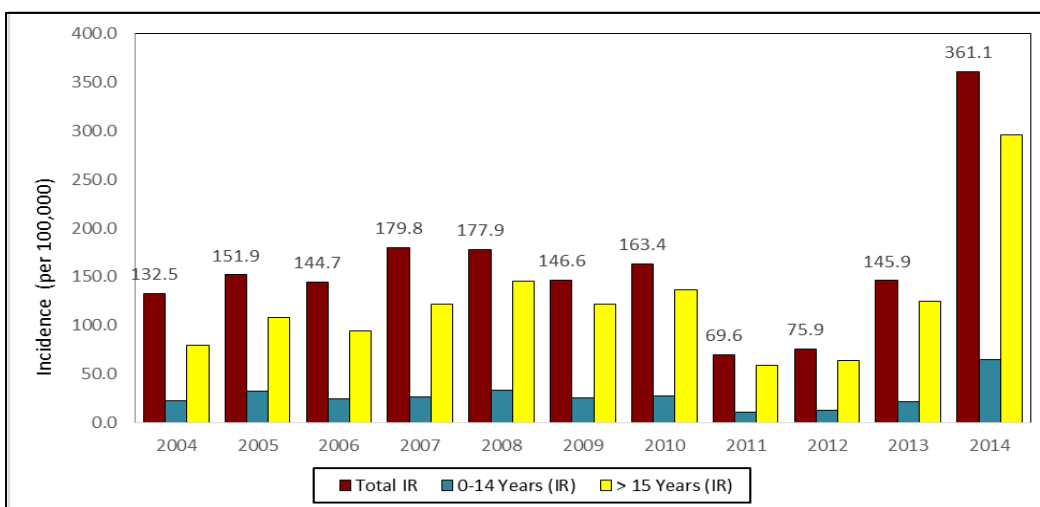
The global increase of dengue incidence is also experienced by Malaysia. Since the year 2000, the dengue incidence in Malaysia continues to increase from 32 cases per 100,000 populations to 361 cases per 100,000 populations in 2014 (Figure 1). The dengue incidence rate is higher in the age group of 15 to 49 years (Figure 2). Most of the dengue cases reported were from urban areas (70 – 80%) where factors such as high density population and rapid development favour dengue transmission.

With regards to case fatality rate, the national target is less than 0.2%. The case fatality rate has been reduced from 0.6% in year 2000 to 0.2% in year 2014 (Figure 1). Most of the dengue death has been observed higher in the age group of 15 years and above (Figure 3) and the highest has been observed in 2014.

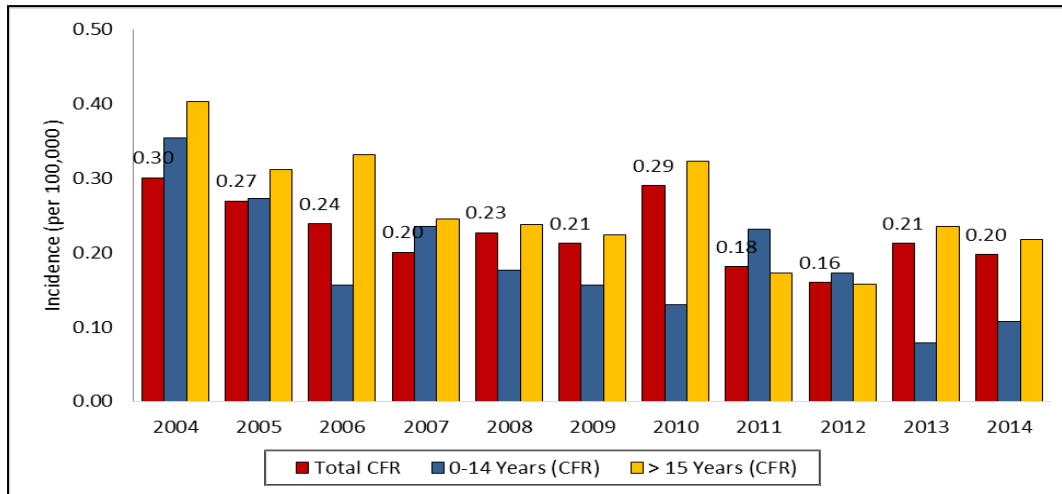
**Figure 1: Dengue Incidence Rate And Case Fatality Rate, Malaysia 2000-2014**



**Figure 2: Dengue Incidence Rate (IR) By Age Group In Malaysia, 2004-2014**



**Figure 3: Dengue Case Fatality Rate (CFR) By Age Group In Malaysia, 2004-2014**

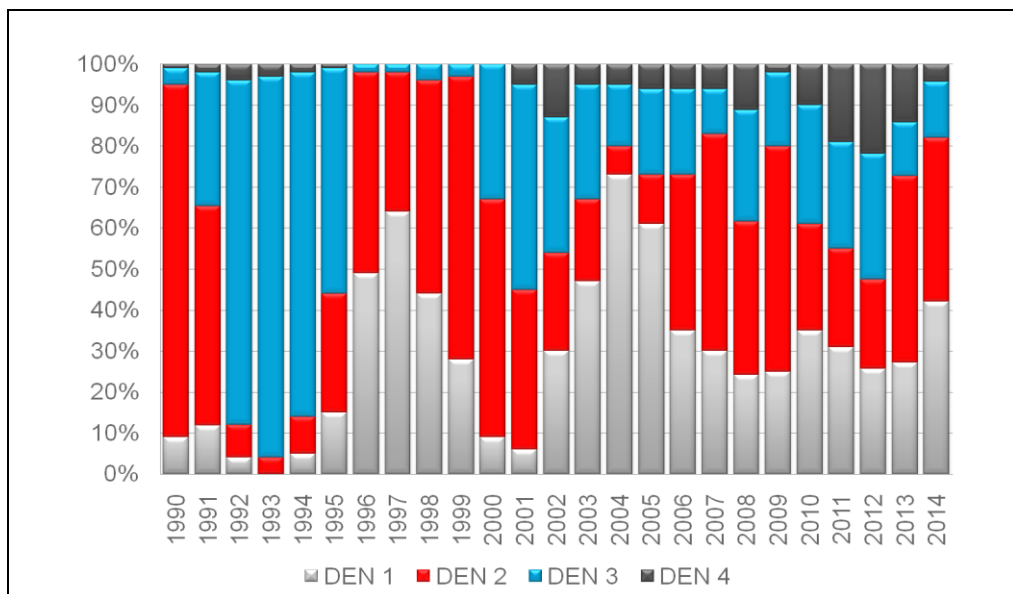


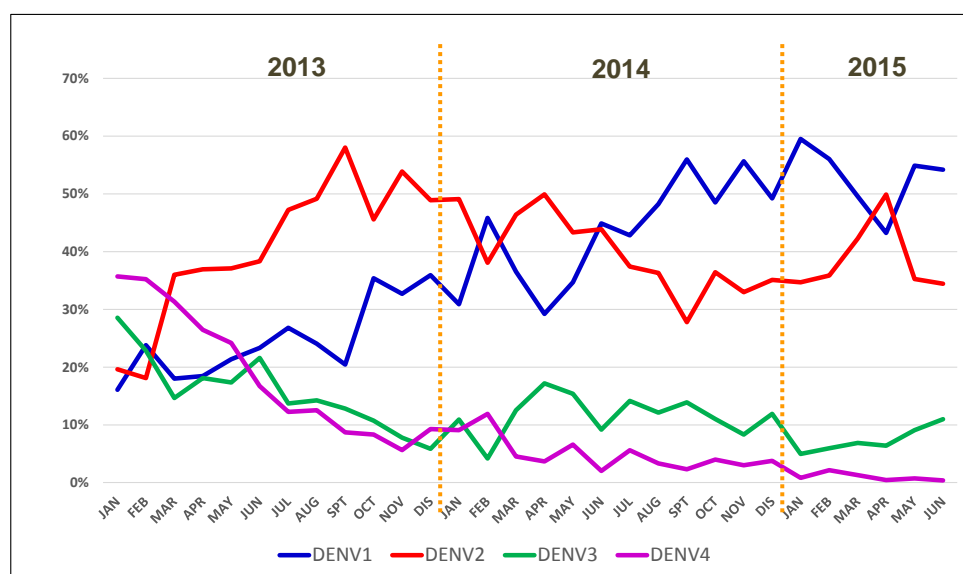
**2. DENGUE VIRUS AND SEROTYPE TRENDS IN MALAYSIA**

Dengue infection is caused by dengue virus which is a mosquito-borne flavivirus. It is transmitted by *Aedes aegypti* and *Aedes albopictus*. There are four distinct serotypes, DENV-1,2,3 and 4. Each episode of infection induces a life-long protective immunity to the homologous serotype but confers only partial and transient protection against other serotypes. Secondary infection is a major risk factor for severe dengue due to antibody-dependent enhancement. Other important contributing factors are viral virulence, host genetic background, T-cell activation, viral load and auto-antibodies.

In Malaysia, all four serotypes can be isolated at any one time. However, a particular dengue virus serotype can predominate for at least two years before it is replaced by another serotype (Figure 4). In year 2013-2014, the predominant serotype had switched twice from DENV-2 to DENV-1 in February and June 2014 (Figure 5).

**Figure 4: Dengue Serotypes in Malaysia (1990-2014)**



**Figure 5: Dengue Serotypes in Year 2013, 2014 and 2015 (Jan-June)**

### 3. CLINICAL MANIFESTATIONS AND PATHOPHYSIOLOGY

#### 3.1 SPECTRUM OF DENGUE INFECTION

The incubation period for dengue infection is 4-7 days (range 3-14).<sup>1</sup> It may be asymptomatic or may result in a spectrum of illness ranging from undifferentiated mild febrile illness to severe disease, with or without plasma leakage and organ impairment. Symptomatic dengue infection is a **systemic and dynamic** disease with clinical, haematological and serological profiles changing from day to day. These changes accelerate within hour or even minutes during the critical phase, particularly in those with plasma leakage (refer to section 3.3).

Understanding the systemic and dynamic nature of dengue disease as well as its pathophysiological changes during each phase of the disease will produce a rational approach in the management of dengue infection.

#### 3.2 CLINICAL COURSE OF DENGUE INFECTION

After the incubation period, the illness begins abruptly and will be followed by 3 phases: febrile, critical and recovery phase (refer Figure 6).<sup>2,3</sup>

##### i. Febrile Phase

Patients develop high grade fever suddenly and usually last 2-7 days. It often accompanied by facial flushing, rash, generalised body ache, vomiting and headache.<sup>2,3</sup> Some patients may have sore throat, injected pharynx and conjunctival injection.

Mild haemorrhagic manifestations like petechiae and mucosal membrane bleeding may be seen during the illness.<sup>4,5</sup> Per vaginal bleeding may occur in females but rarely massive. Gastrointestinal bleeding is not uncommon.<sup>5,6</sup> The findings of an enlarged and tender liver are warning signs of dengue infection.

The earliest abnormality in the full blood count is a progressive decrease in total white cell count followed by platelet reduction. This should alert the physician to a high index of suspicion of dengue infection. This disease should be notified as early as possible for preventive measures.

### **ii. Critical Phase**

The critical phase often occurs after 3rd day of fever (may occur earlier) or around defervescence indicated by a rapid drop in temperature. This coincides with an increase in capillary permeability in some patients. In other viral infections, the patient's condition improves as the temperature subsides, but the contrary happens in severe dengue infection wherein the patient may deteriorate and manifest third space plasma leakage or organ dysfunction.<sup>2,3,7,8</sup>

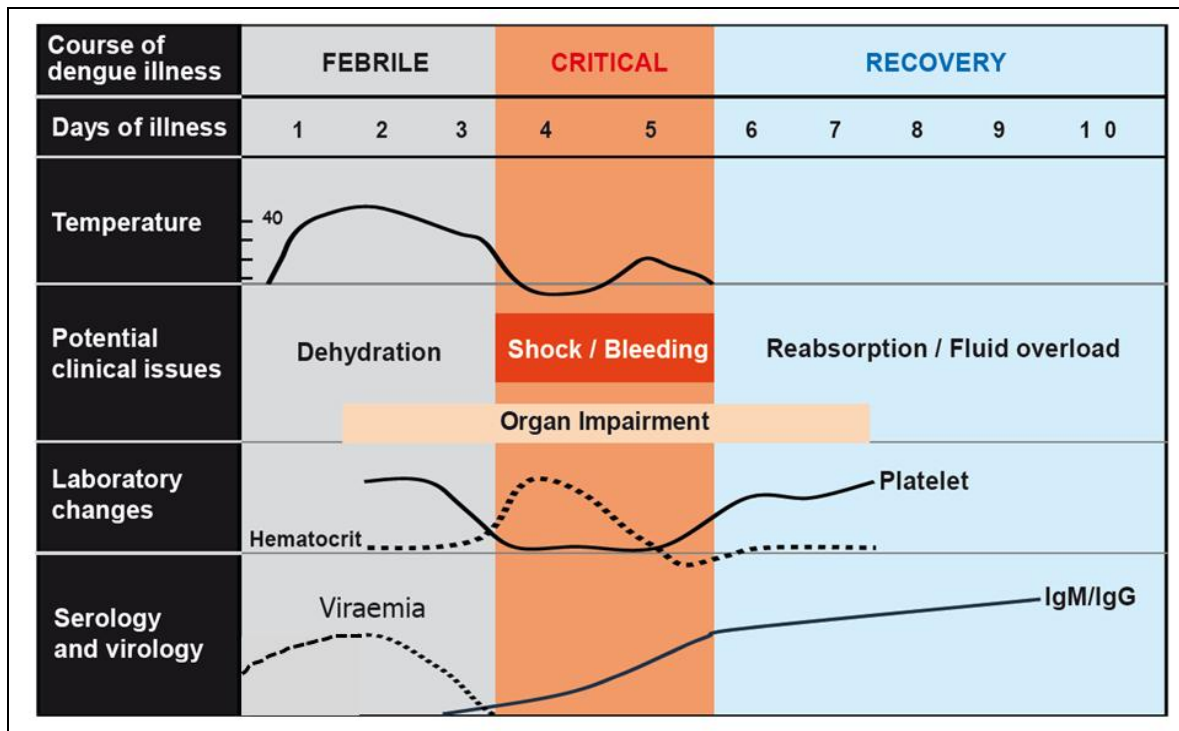
The critical phase lasts about 24-48 hours (refer Figure 6). Varying circulatory disturbances (refer to Table 1) can develop. In less severe cases, these changes are minimal and transient. Many of these patients recover spontaneously, or after a short period of fluid or electrolyte therapy. In more severe forms of plasma leakage, the patients may develop compensated and decompensated shock (Table 1). Abdominal pain, persistent vomiting and/or diarrhoea, restlessness, altered conscious level, clinical fluid accumulation, mucosal bleed or tender liver are the clinical warning signs of dengue infection with high possibility of complications.<sup>8-10</sup> Organ dysfunctions such as hepatitis, encephalitis and myocarditis usually but not exclusively occur during this phase.

It is important to note that thrombocytopenia and haemoconcentration are usually detectable in this phase. The haematocrit (HCT) level correlates well with plasma volume loss and disease severity. However, interpretation of HCT may be difficult when there are confounding factors such as haemorrhage, excessive fluid replacement or in haemodilutional state.

Leucopenia with relative lymphocytosis, clotting abnormalities, elevation of transaminases [typically the level of aspartate aminotransaminase (AST) is higher than the level of alanine aminotransaminase (ALT)], hypoproteinaemia and hypoalbuminaemia are usually observed.<sup>2-4</sup>

### **iii. Recovery Phase**

After 24-48 hours of critical phase, usually plasma leakage stops followed by reabsorption of extravascular fluid. Patient's general well being improves, appetite returns, gastrointestinal symptoms improve, haemodynamic status stabilises and diuresis ensues. Some patient may have a classical rash of "isles of white in the sea of red" with generalised pruritus.<sup>2</sup> It is important to note that during this phase, HCT level stabilises and drops further due to haemodilution following reabsorption of extravascular fluid. The recovery of platelet count is typically preceded by recovery of white cell count (WCC). In some instances, organ dysfunctions may worsen (liver, encephalitis and intracranial bleed) as the patient enters reabsorption phase.

Figure 6 : Clinical Course of DHF <sup>11-13</sup>

- The critical phase often occurs after 3rd day of fever (may occur earlier) or around defervescence with a rapid drop in temperature.
- Clinical deterioration often occurs during the critical phase with plasma leakage or organ dysfunction.
- Evidence of plasma leakage includes raised HCT, haemodynamic instability, fluid accumulation in extravascular space or hypoproteinaemia.
- Abdominal pain, persistent vomiting and/or diarrhoea, restlessness, altered conscious level, clinical fluid accumulation, tender liver or mucosal bleed are the clinical warning signs of dengue infection with high possibility of rapid progression to severe dengue.

### 3.3 PATHOPHYSIOLOGY OF PLASMA LEAKAGE IN SEVERE DENGUE INFECTION

The primary pathophysiological abnormality seen in dengue infection is an acute increase in vascular permeability that leads to leakage of plasma into the extravascular compartment, resulting in haemoconcentration and hypovolaemia or shock.<sup>2,3,14</sup> Hypovolaemia leads to reflex tachycardia and generalised vasoconstriction due to increased sympathetic output.<sup>15,16</sup> Clinical manifestations of vasoconstriction in various systems are as follows :

- Skin - coolness, pallor and delayed capillary refill time
- Cardiovascular system - raised diastolic blood pressure and a narrowing of pulse pressure
- Renal system - reducing urine output
- Gastrointestinal system - persistent vomiting, persistent diarrhoea and abdominal pain
- Central nervous system – lethargy, restlessness, apprehension, reduced level of consciousness
- Respiratory system – tachypnoea (respiratory rate >20/min)

Inadequate perfusion of the tissue leads to increased anaerobic glycolysis and lactic acidosis. If the hypovolaemia is not corrected promptly, the patient will progress to a refractory shock state. By then, the tissue perfusion would not respond to vasopressor drugs, even if the blood pressure and intravascular volume were to be restored and cardiac output would remain depressed. The resultant lactic acidosis further depresses the myocardium and worsens the hypotension.<sup>16</sup>

The common late complications of prolonged shock are massive bleeding, disseminated intravascular coagulopathy (DIC) and multi-organ failure which are often fatal. In organ dysfunction, the pathophysiology will be described in chapter 7.6.

The following table is the summary of the continuum of various pathophysiological changes in a patient who progresses from normal circulatory state to hypovolaemic shock.

**Table 1: A continuum of pathophysiological changes from normal circulation to compensated and decompensated/hypotensive shock**

Normal Circulation	Compensated Shock	Decompensated / Hypotensive Shock
<ul style="list-style-type: none"> <li>• Clear consciousness</li> <li>• Brisk capillary refill time (&lt;2 sec)</li> <li>• Warm and pink peripheries</li> <li>• Good volume peripheral pulses</li> <li>• Normal heart rate for age</li> <li>• Normal blood pressure for age</li> <li>• Normal pulse pressure for age</li> <li>• Normal respiratory rate for age</li> <li>• Normal urine output</li> </ul>	<ul style="list-style-type: none"> <li>• Clear consciousness - shock can be missed if you do not touch the patient</li> <li>• Prolonged capillary refill time (&gt;2 sec)</li> <li>• Cool extremities</li> <li>• Weak &amp; thready peripheral pulses</li> <li>• Tachycardia</li> <li>• Normal systolic pressure with raised diastolic pressure</li> <li>• Postural hypotension</li> <li>• Narrowing pulse pressure</li> <li>• Tachypnoea</li> <li>• Reduced urine output</li> <li>• Intense thirst</li> </ul>	<ul style="list-style-type: none"> <li>• Change of mental state - restless, combative or lethargy</li> <li>• Mottled skin, very prolonged capillary refill time</li> <li>• Cold, clammy extremities</li> <li>• Feeble or absent peripheral pulses</li> <li>• Severe tachycardia with bradycardia in late shock</li> <li>• Hypotension / unrecordable BP</li> <li>• Narrowed pulse pressure (&lt;20 mmHg)</li> <li>• Metabolic acidosis / hyperpnoea / Kussmaul's breathing</li> <li>• Oliguria or anuria</li> </ul>

**Adapted** : Ganong WF. Cardiovascular homeostasis in health and disease. In: Review of Medical Physiology. 22nd Edition. London: McGraw-Hill; 2005:p.630-46.



The pathogenetic mechanism responsible for the increased vascular permeability in severe dengue infection is not known. Post-mortem findings revealed perivascular oedema and loss of integrity of endothelial junctions with endothelial dysfunction.<sup>17,18</sup> Abnormal immune response involving the production of cytokines or chemokines, activation of T-lymphocytes and disturbances of haemostatic system are the major changes seen in severe dengue infection. Mediators including C3a, C5a, tumour necrosis factor- $\alpha$ , interleukin 2, 6 and 10, interferon- $\alpha$  and histamine are elevated.<sup>15,19</sup>

Secondary infection with a heterotypic dengue virus is associated with increased risk of developing severe dengue infection. It is believed to be due to the antibody-dependent enhancement phenomenon.<sup>20-22</sup> The sub-neutralising concentration of the cross-reacting antibody from the previous infection may opsonise the virus and enhance its uptake and replication in the macrophage or mononuclear cells. The level of T-cell activation is also enhanced. Profound T-cell activation with cell death during acute dengue infection may suppress or delay viral elimination, leading to the higher viral loads and increased immunopathology found in patients with severe dengue infection.<sup>15,19</sup>

### **3.4 WHO DENGUE CLASSIFICATION**

Based on 1997 WHO dengue classification scheme (refer **Appendix 3**), the key differentiating feature between DF and DHF is the presence of plasma leakage in DHF. However, in the early febrile phase of dengue infection, the symptoms can overlap and one cannot differentiate DF and DHF.

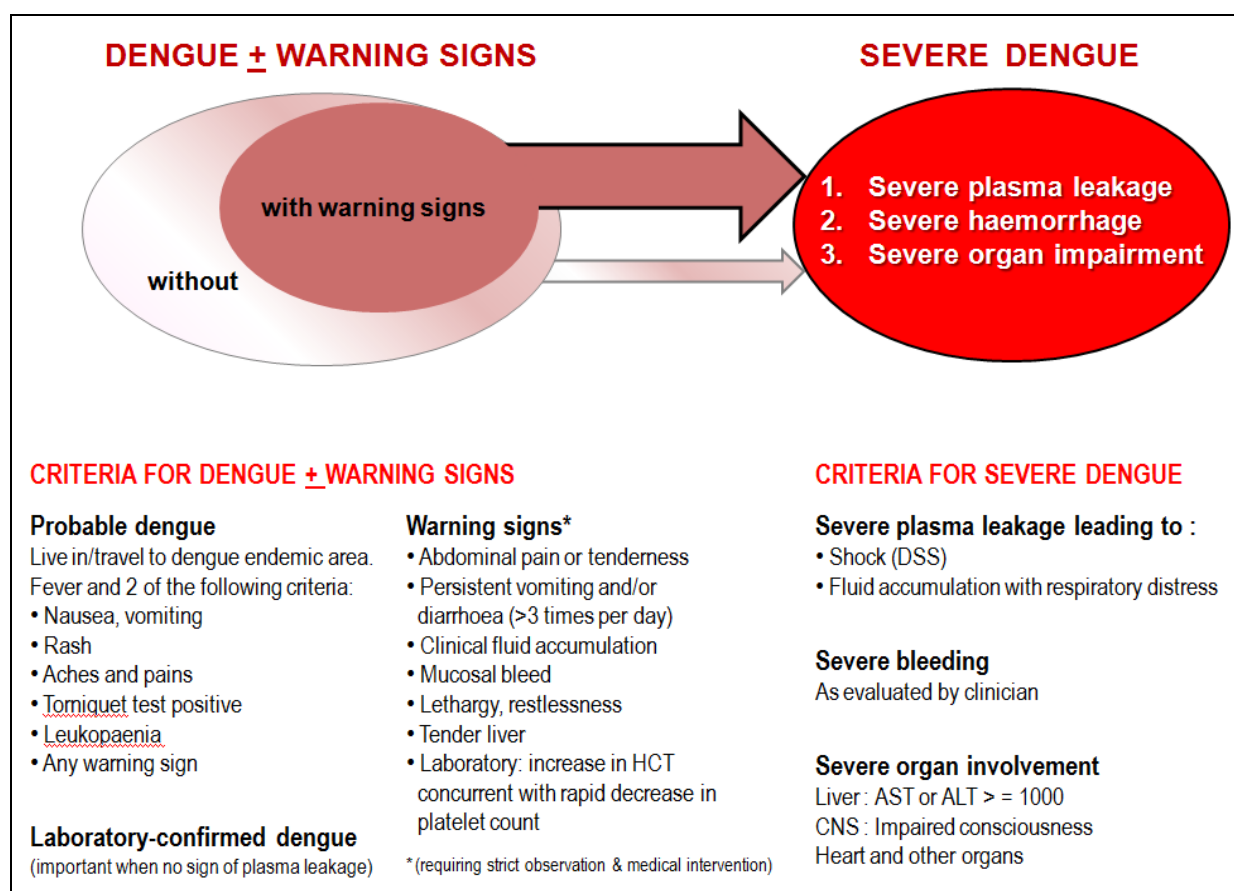
#### **3.4.1 Limitations of 1997 WHO classification**<sup>23, level I</sup>

It has been observed that the 1997 WHO classification scheme has several limitations.

- i. Dengue with shock without fulfilling all the 4 criteria for DHF
- ii. Severe organ impairment without shock
- iii. The 1997 classification scheme does not address the entire spectrum of the disease.

#### **3.4.2 WHO Classification 2009**

This classification into levels of severity of dengue infection is more practical to be used in the management decision of the patient (Figure 7).

Figure 7: 2009 WHO Dengue Classification and Level of Severity<sup>24</sup>

**Adapted:** World Health Organization. Dengue Guidelines for Diagnosis, Treatment, Prevention and Control - New Edition 2009. WHO: Geneva; 2009

### 3.5 DIAGNOSTIC CHALLENGES

Clinical features of dengue infection are rather non-specific and mimic many other diseases, therefore can be easily misinterpreted. A high index of suspicion and appropriate history taking, particularly with regards to a recent stay in dengue hotspots or clusters of fever in neighbourhood, are useful for early and accurate diagnosis of dengue infection.

In addition, a dengue patient may have a co-infection with another pathogen. Other diagnoses that may mimic dengue infection includes other viral illnesses. Organ dysfunctions can occur in other diseases apart from dengue infection and should be investigated.

## 4. DISEASE NOTIFICATION

All suspected dengue cases from private and public health facilities must be notified by telephone/fax/e-notification to the nearest health office within 24 hours of diagnosis, followed by written notification using the standard notification format. Failure to notify is liable to be compounded under the Prevention and Control of Infectious Diseases Act, 1988 (Act 342).<sup>25</sup>

Any delay in notification will increase the risk of dengue transmission in the locality of the residence. It is also important to update the notification if there is a change in severity of dengue infection, when dengue death occurred or change in diagnosis.

Notified cases will be followed up by the health authorities for the verification of case definition and preventive measures. Since 2014, the Ministry of Health Malaysia has set up new criteria for dengue cases registration, whereby all registered dengue cases must be confirmed by laboratory investigations.

All dengue deaths need to be notified as soon as possible by the treating doctor in the hospital to the district health office and/or State Health Director and must be investigated by District Health Officer or Epidemiology Officer.<sup>26</sup>

Dengue mortality audit should be conducted within 7 days after the dengue death has occurred at hospital level followed by state level, chaired by Hospital Director and State Health Director respectively. The complete dengue death report should be sent to Communicable Diseases Division, Ministry of Health within one week via State Vector Officer. The implementation of dengue case management and death should comply to the Director General of Health Malaysia Circular No.15/2010 dated 24 May 2010.<sup>26</sup>

## 5. INVESTIGATIONS

### 5.1 DISEASE MONITORING TESTS

#### i. White cell count (WCC) and Platelet count:

In the early febrile phase WCC and platelet count are usually normal but will decrease rapidly as the disease progresses.<sup>4, level III</sup> The decrease in WCC is accompanied by platelet reduction.

There is a significant negative correlation between disease severity and platelet count<sup>2, level III; 25, level III</sup> but it is not predictive of bleeding.<sup>28, level I; 29, level II-2; 30-32, level III</sup> In recovery phase, the WCC normalises followed by platelet.

#### ii. Haematocrit (HCT):

A rising HCT is a marker of plasma leakage in dengue infection. The normal HCT level among Malaysian populations are:<sup>33, level II-2</sup>

- male  $\leq$  60 years - 46
- male > 60 years - 42
- female (all age group) - 40

Other important blood tests in disease monitoring are Liver Function Test (LFT), Renal function test, coagulation profile, Creatine Kinase (CK), lactate and blood gases (Table 6).

#### Recommendation 1

- The baseline HCT and WCC should be established as early as possible in all patients with suspected dengue infection.
- Serial FBC and HCT must be monitored as the disease progresses.

## 5.2 DIAGNOSTIC TESTS

Diagnostic tests include point of care testing such as dengue NS1 antigen test and rapid combo tests (NS1 antigen and dengue IgM/IgG antibodies). Other laboratory tests include NS1 antigen test, dengue antibody detection tests including IgM and IgG ELISA, dengue genome detection assay (real time RT-PCR) and dengue viral isolation assay. Specifications for an ideal dengue test include able to differentiate between dengue and other diseases with similar clinical presentation, able to detect during the acute stage of infection, provides rapid results, inexpensive and easy to use. However, the interpretation of diagnostic results should be done with the clinical context.

### 5.2.1 Rapid Combo Test (RCT)

Rapid combo tests are assays that can detect the presence of virus as well as antibodies simultaneously.<sup>34-35,level II-2</sup> The results can be obtained within 15-20 minutes. **False positive result may be related to delay in reading the test (refer to product insert).**

Interpretation of the results is through the presence or absence of bands dedicated for dengue NS1 antigen and dengue IgM and IgG antibodies.<sup>34-35,level II-2</sup> The test has a longer detection window as it can detect both the virus and antibodies, thus reducing possibility of false negative. Hence the test is useful during the early phase of onset when there is viraemia as well as later stage of onset when antibodies against dengue began to rise. Suitable samples that can be used for testing include whole blood, serum and plasma. The sensitivity is 93.9% and specificity is 92%.<sup>36,level II-2</sup>

### 5.2.2 Dengue Antigen and Serology Tests by ELISA

Both antigen and serological tests are more commonly used to diagnose dengue infections. The tests include antigen detection (NS1) or antibody detection. Usually different pattern of antibody response are seen in primary dengue infection as compared to secondary dengue infection.<sup>37,level II-2</sup>

#### i. Non-Structural Protein-1 (NS1 Antigen)

NS1 antigen is a highly conserved glycoprotein that seems to be essential for virus viability. Secretion of the NS1 protein is a hallmark of flavivirus infecting mammalian cells and can be found in dengue infection as well as in yellow fever and West Nile virus infection. False positive results have been reported in chronic diseases and haematological malignancy.<sup>38,level III</sup>

The detection rate is much better in acute sera of primary infection (75% - 97%) when compared to the acute sera of secondary infection (60% - 70%).<sup>39-41,level III</sup> The sensitivity of NS1 antigen detection drops from day 4-5 of illness onwards and usually becomes undetectable in the convalescence phase.<sup>40-42,level III</sup>

The presence of NS1 detection after day 5 may predict severe dengue.<sup>44,level II-2</sup>

#### ii. Dengue IgM test

The IgM capture enzyme-linked immunosorbent assay (ELISA) is the most widely used serological test. The antibody titre is significantly higher in primary infections compared to secondary infections. Once the IgM is detectable, it rises quickly and peaks at about 2 weeks after the onset of symptoms, and it wanes to undetectable levels by 90 days.

In primary dengue infection, anti-dengue IgM can be detected after 5 days of illness approximately in 80% of the cases.<sup>37,level II-2</sup> Almost 93% - 99% of cases will have detectable IgM from day 6 through day 10. In the event of a negative IgM result, a repeat serum should be collected after 5 days.

However, in secondary dengue infections, IgM was detected in among 78% of patients after day 7.<sup>45,level II-2</sup> IgM appears earlier or at the same time frame but usually at lower titres compared to primary dengue. This is possibly due to appearance of high levels of anti-dengue IgG before or sometimes simultaneously with the IgM response. Thus, 28% of all secondary dengue infections were undiagnosed when only IgM was the only assay performed.<sup>46-48,level III</sup>

### iii. Dengue IgG test

In primary and secondary dengue infection, dengue IgG was detected in 100% of patients after day 7 of onset of fever. Therefore, dengue IgG is recommended if dengue IgM is still negative after day 7 with the negative IgG in the initial test sample.<sup>45,level II-2; 47, level III</sup>

### iv. Differentiation between primary and secondary dengue infection

Detection of elevated IgG antibodies to dengue virus by ELISA is very useful for identification of secondary dengue infections.<sup>49-50,level II-2</sup> There are commercially available ELISA kits which can be used to differentiate between primary and secondary dengue infections as the kits have incorporated *in-house* threshold levels of IgG. For example, Panbio has incorporated a cut off of more than 22 Panbio Units which is equivalent to HAI level of 1:2560, and thus indicative of secondary dengue infections.<sup>51</sup>

#### **Note: False positive dengue serology**

Serological tests for dengue have been shown to cross-react with:

- other flavivirus – Japanese Encephalitis<sup>48,level III; 52, level III</sup>
- non-flavivirus – malaria, leptospirosis, toxoplasmosis, syphilis<sup>53-54, level III</sup>
- connective tissue diseases – rheumatoid arthritis<sup>55, level III</sup>

### 5.2.3 Dengue Viral RNA Detection

Dengue viral RNA detection is a molecular method that utilises reagents that will target specific genome of the virus to enable amplification and detection of the target. The method is useful only during the viraemic stage of the disease and can detect the viral RNA target up to 5 days after onset of the symptoms.<sup>56-57,level II-2</sup> The test is useful for determination of circulating dengue serotypes in the country.

Limitations of RT- PCR are:

- a) This test is only available in a few centres with facilities and trained personnel (e.g. IMR, National Public Health Laboratory, Public Health Laboratories and University Malaya Medical Centre).
- b) The test is expensive.
- c) The specimen requires special storage temperatures and short transportation time between collection and extraction (refer **Appendix 4**).

### 5.2.4 Virus Isolation

Dengue virus isolation is carried out in Institute for Medical Research (IMR), National Public Health Laboratory and University Malaya Medical Centre for research, surveillance and genotyping purposes.

Please refer to **Appendix 4** on details of sample collection for diagnostic tests.

As clinical diagnosis of dengue lacks specificity, a definitive diagnosis of dengue infections requires laboratory confirmation. There are many targets for laboratory confirmation of dengue which have been listed in **Appendix 5** with information on sensitivity and specificity of each target and the recommended days to use after onset of symptoms.

**Appendix 6** summarises the type of tests recommended for patients presented with clinical history and their interpretation. This serves as laboratory guidelines for the clinicians who are managing dengue patients.

#### Recommendation 2

- Dengue rapid combo test or NS1 Ag should be taken as soon as the disease is suspected.
- Dengue IgM is usually positive after day 5-7 of illness. Therefore a negative IgM taken before day 5-7 of illness does not exclude dengue infection.
- If dengue IgM is negative before day 7, a repeat sample must be taken in recovery phase.
- If dengue IgM is still negative after day 7, dengue IgG is recommended for diagnostic confirmation.

## 6. INVESTIGATION OF POST MORTEM CASE

Suitable samples for virus isolation and PCR can be obtained from most of the organs however, the best tissue sample for investigation is the liver.<sup>58;59,level III</sup> If patient had encephalitis, CSF should also be included as samples for investigation. The liver should be placed in sterile containers and moistened with viral transport media or sterile normal saline. CSF should be submitted in sterile bijou bottle. Both should be refrigerated if there is delay in transportation. Specimen for viral investigation should be transported in ice to IMR and National Public Health Laboratory.

*Caution: Massive blood transfusion may affect the test results mentioned above.*

#### Recommendation 3

- A repeat dengue serology should be obtained at the time of death.
- Suitable specimens for viral isolation and/RT-PCR and/ NS1 antigen detection are recommended for confirmation of dengue.

## 7. MANAGEMENT OF DENGUE INFECTION

### 7.1 OUTPATIENT MANAGEMENT

The management of dengue infection is symptomatic and supportive. An approach to outpatient evaluation is as suggested in Table 2.

Management issues vary according to the 3 phases of the clinical course (refer to section 7.4). It is crucial to recognise plasma leakage, early shock or severe organ dysfunction. This can be achieved by frequent clinical and laboratory monitoring during the early febrile phase of dengue infection.

Dengue patients who are managed in the outpatient setting should be provided with an outpatient dengue monitoring record (refer to **Appendix 7**) to ensure that relevant informations are available for continuity of care by health care providers.

- Primary care providers with no immediate haematocrit facilities and/or point of care tests should refer patient to the nearest health facility for further management.
- Point of care tests (RCT or NS1 antigen) should be done when dengue infection is suspected.

**Table 2: Approach to Outpatient Evaluation of Dengue Infection** <sup>1-3</sup>

It is important to evaluate every patient for the following:

### Overall assessment

1. History
  - Date of onset of fever/ illness
  - Oral intake
  - Assess for warning signs – Refer to Table 3
  - Diarrhoea
  - Change in mental state/seizure/dizziness
  - Urine output (frequency, volume and time of last voiding)
  - Other important relevant histories:
    - Family or neighbourhood history of dengue
    - Jungle trekking and swimming in waterfall (consider leptospirosis, typhus, malaria)
    - Travelling
    - Recent unprotected sexual or drug use behaviour (consider acute HIV seroconversion illness)
    - Co-morbidities (consider sepsis particularly in patients with diabetes mellitus)
2. Physical examination
  - i. Assess mental state and GCS score
  - ii. Assess hydration status
  - iii. Assess haemodynamic status
    - Skin colour (C), capillary filling time (normal < 2 seconds) (C), cold/ warm extremities (T), pulse volume (V) and rate (R) - **CCTVR**
    - Blood pressure and pulse pressure
  - iv. Look out for tachypnoea/ acidotic breathing/ pleural effusion
  - v. Check for abdominal tenderness/ hepatomegaly/ ascites
  - vi. Examine for bleeding manifestation
3. Investigation
  - i. FBC and HCT
  - ii. Point of care test for dengue (RCT or NS1 antigen)

### Diagnosis, disease staging and severity assessment

Based on evaluations in history, physical examination ± FBC, HCT and point of care test the clinicians should be able to determine:

1. Likelihood of dengue infection
2. The phase of dengue infection (febrile/critical/recovery)
3. Severity of the illness

### Plan of management

1. Dengue assessment checklist must be filled (**Appendix 8**)
2. Notify the district health office (refer to Chapter 4 on disease notification) followed by disease notification form
3. If admission is indicated (Refer to admission criteria)
  - Stabilise the patient at primary care before transfer (refer to intravenous fluid regime)
  - Communicate with the receiving hospital/ Emergency Department before transfer
4. If admission is not indicated (Refer to **Table 4**)
  - Daily follow up is necessary especially from day 3 of illness onwards until the patient becomes afebrile for at least 24 - 48 hours without antipyretics.
  - Refer to Home Care Advice Leaflet for Dengue in **Appendix 9**



**Table 3: Warning Signs**

- **Any abdominal pain / tenderness**
  - **Persistent vomiting / diarrhoea (  $\geq$  3 times over 24 hours)**
  - **Third space fluid accumulation (such as ascites, pleural and pericardial effusion)**
  - **Spontaneous bleeding tendency**
  - **Lethargy / restlessness / confusion**
  - **Tender liver**
  - **Raised HCT with rapid drop in platelet:**
    - **HCT male  $\leq$  60 years - 46**
    - **HCT male  $>$  60 years - 42**
    - **HCT female (all age group) - 40**
- \*median value of normal HCT in Malaysia population<sup>33,level II-2.</sup>

**Adapted** : World Health Organization. Dengue Guidelines for Diagnosis, Treatment, Prevention and Control - New Edition 2009. WHO: Geneva; 2009

**Table 4 : Clinical and Laboratory Criteria for Patients Who Can Be Treated at Home<sup>60-62</sup>**

1. Able to tolerate orally well, good urine output and no history of bleeding
2. Absence of warning sign (refer Table 3)
3. Physical examination:
  - Haemodynamically stable
  - No tachypnoea or acidotic breathing
  - No hepatomegaly or abdominal tenderness
  - No bleeding manifestation
  - No sign of third space fluid accumulation
  - No alterations in mental state
4. Investigation:
  - Stable serial HCT
5. No other criteria for admission (i.e. co-morbidities, pregnancy, social factors)

## 7.2 PATIENT TRIAGING AT EMERGENCY AND OUTPATIENT DEPARTMENT

The purpose of triaging patients is to determine whether they require urgent attention. This is to avoid critically ill patients being missed upon arrival.<sup>60,level III; 63-64,level III</sup>

### Triage Checklist at Registration Counter:

1. History of fever
2. Abdominal Pain
3. Vomiting
4. Dizziness/ fainting
5. Bleeding

### Vital parameters to be taken:

Mental state, blood pressure, CCTVR

## 7.3 CRITERIA FOR HOSPITAL REFERRAL / ADMISSION

### 7.3.1 Referral from Primary Care Providers to Hospital

The decision for referral and admission must not be based on a single clinical parameter but should depend on the **Total Assessment** of the patient.

### Referral from primary care providers to hospital

1. Symptoms:
  - Warning signs (refer to Table 3)
  - Bleeding manifestations
  - Inability to tolerate oral fluids
  - Reduced urine output
  - Seizure
2. Signs:
  - Dehydration
  - Shock (refer to Table 1)
  - Bleeding
  - Any organ failure
3. Special situations:
  - Patients with co-morbidity e.g. Diabetes, Hypertension, Ischaemic Heart Disease, Coagulopathies, Morbid Obesity, Renal failure, Chronic Liver disease, COPD
  - Elderly more than 65 years old
  - Patients who are on anti-platelet and/or anticoagulants
  - Pregnancy
  - Social factors that limit follow-up e.g. living far from health facility, no transport, patient living alone, etc.
4. Laboratory criteria: Rising HCT accompanied by reducing platelet count

### 7.3.2 Referral from Hospitals Without Specialist To Hospitals With Specialists

Nearest physician should be consulted for all severe dengue, those who are pregnant and patients with comorbidities.

#### Prerequisites for transfer

1. All efforts must be taken to optimise the patient's condition before and during transfer.
2. The Emergency Department and/or Medical Department of the receiving hospital must be informed prior to transfer.
3. Adequate and essential information must be sent together with the patient that includes fluid chart, monitoring chart and investigation results.

### 7.3.3 Intervention in Emergency Department

Proactive ongoing clinical reassessment of airway, breathing and circulatory status must be done.

### 7.3.4 Laboratory tests in the Emergency Department

These tests must be done immediately in cases with suspected dengue infection :

- FBC and HCT
- Point of care testing e.g. Rapid combo test (RCT) or NS1 antigen
- When indicated (suspect severe dengue) :
  - Blood gases and serum lactate
  - LFT/AST and renal function test
  - Creatine kinase (CK) to detect myocarditis and rhabdomyolysis
  - GSH (Group, screen and hold)

### 7.3.5 Imaging Investigations in the Emergency Department for Patients Requiring Admission

Chest x-ray and ultrasound (when available) are required in patients suspected to have vascular leakage. However, it should not delay admission.

Ultrasonography may be performed by trained personal to look for evidence of:

- i. Third space fluid loss such as the presence of pleural effusion, pericardial effusion, gallbladder wall oedema and intraperitoneal fluid collection.
- ii. Collapsibility of the inferior vena cava (IVC) as an indirect indicator of adequacy of the intravascular fluid compartment & response to intravenous fluids.

#### Recommendation 4

- All patients requiring admission should be **immediately** started on an appropriate fluid therapy (oral or intravenous).
- When indicated, intravenous fluid therapy should be initiated and adjusted accordingly.
- Serial monitoring of vital signs must be done and documented.
- Strict monitoring of ongoing fluid losses and hourly fluid input/output i.e. "I/O charting" must be done.
- Patients with deteriorating vital signs must be uptriaged accordingly.

## 7.4 DISEASE MONITORING

### 7.4.1 Principles of Disease Monitoring

- i. During critical phase, monitoring of patients need to be intensified and frequent adjustments in the fluid regime may be required.
- ii. Recognition of onset of reabsorption phase is also important because intravenous fluid regime needs to be progressively reduced/discontinued at this stage.

### 7.4.2 Inpatient Disease Monitoring

Immediately after admission every patient with suspected dengue infection should be reviewed thoroughly using the dengue assessment checklist (**Appendix 8**). The plan of management and monitoring should be based on the phase and severity of the disease. The clinical findings must also be documented in the Inpatient Dengue Monitoring Chart (**Appendix 10**).

Table 5 and 6 summarises the issues, the parameters and frequency of monitoring according to the different phases of the illness.

**Table 5: Issues of Monitoring According to Different Phases of Dengue Illness**

Phases of illness	Issues
<b>Febrile</b>	<ul style="list-style-type: none"> <li>- Differentiation of dengue illness from other febrile illnesses.</li> </ul>
<b>Critical</b>	<ul style="list-style-type: none"> <li>- Plasma leakage occurs as patient progresses to late febrile phase or as temperature begins to defervesce (<math>T &lt; 38.0\text{ }^{\circ}\text{C}</math>).</li> <li>- Clinical deterioration occurs during this phase due to plasma leakage.</li> <li>- Plasma leakage results in haemoconcentration and hypovolaemia/shock.</li> <li>- Excessive plasma leakage due, in part, to intravenous fluid therapy may cause respiratory distress.</li> <li>- Bleeding can be precipitated by prolonged shock and shock can be perpetuated by bleeding.</li> <li>- Organ dysfunction may occur.</li> <li>- May mimic acute abdomen of other causes.</li> <li>- May be confused with septic shock or other forms of shock.</li> </ul>
<b>Reabsorption</b>	<ul style="list-style-type: none"> <li>- Cessation of plasma leakage.</li> <li>- Reabsorption of fluid from extravascular compartment.</li> <li>- Haemodilution occurs following fluid reabsorption.</li> <li>- Fluid overload and pulmonary oedema if intravenous fluid therapy is continued.</li> </ul>

**Table 6 : Parameters and Frequency of Monitoring According to Different Phases of Dengue Illness**

Parameters for monitoring	Frequency of monitoring		
	Febrile phase	Critical phase	Reabsorption phase
<b>Clinical Parameters</b>			
General well being Appetite / oral intake Warning signs	Daily or more frequently towards late febrile phase	At least twice a day and more frequently as indicated	Daily or more frequently as indicated
Haemodynamic status <ul style="list-style-type: none"> <li>CCTVR</li> <li>BP</li> <li>Pulse pressure</li> </ul> Respiratory status <ul style="list-style-type: none"> <li>RR</li> <li>SpO<sub>2</sub></li> </ul> Neurological Status <ul style="list-style-type: none"> <li>conscious level</li> <li>restlessness</li> <li>seizures</li> </ul>	4-6 hourly depending on clinical status	2-4 hourly depending on clinical status <b>In shock</b> Every 15-30 minutes till stable then 1-2 hourly	4-6 hourly
Urine output	4 hourly	2-4 hourly <b>In shock</b> : hourly	4-6 hourly
Parameters for monitoring	Frequency of monitoring		
	Febrile phase	Critical phase	Reabsorption phase
<b>Laboratory Parameters</b>			
<b>* All investigations done at ED must be reviewed immediately upon ward admission</b>			
FBC	Daily or more frequently if indicated	4-12 hourly depending on clinical status <b>In shock</b> Repeated before and after each fluid resuscitation and as indicated	Daily
BUSE/Creatinine LFT + AST RBS Creatine Kinase	As clinically indicated	At least daily or more frequently as indicated <b>In shock</b> Crucial to monitor ABG, lactate closely	As clinically indicated
ABG, lactate Coagulation profile CRP Troponin or CKMB Fibrinogen, LDH, ferritin, triglyceride Echocardiogram Ultrasound	As clinically indicated	As clinically indicated	As clinically indicated

**Adapted** : World Health Organization. Dengue Guidelines for Diagnosis, Treatment, Prevention and Control - New Edition 2009. WHO: Geneva; 2009

## 7.5 FLUID MANAGEMENT

### 7.5.1 Non-Shock Patients (DF with Warning Signs)

#### Common pitfalls in fluid therapy:

- Treating patient with unnecessary fluid bolus based on raised HCT as the sole parameter without considering other clinical parameters.
- Excessive and prolonged fixed fluid regime in stable patients.
- Infrequent monitoring and adjustment of infusion rate.
- Continuation of intravenous fluid during the recovery phase.
- Inappropriate fluid therapy in patients with co-morbidities (such as heart disease and renal disease).

In non shock dengue patients, increased oral fluid intake may be sufficient in those who are haemodynamically stable and not vomiting. Inappropriate intravenous fluid therapy had been shown to prolong hospitalisation with a tendency to develop more fluid accumulation.<sup>65,level II-3</sup> However IV fluid (0.9% saline is recommended) is indicated in patients with increasing HCT with evidence of ongoing plasma leakage, despite increased oral intake. IV fluid therapy should also be considered in patients who are vomiting, severe diarrhoea and not tolerating orally.<sup>60,level III; 66,level III</sup>

The normal maintenance requirement for IV fluid therapy in such patients could be calculated based on the formula in Table 7. Frequent adjustment of maintenance fluid regime is needed during the critical phase. Often 1.2 to 1.5 times the maintenance will be required during the critical phase. Patients may be able to take oral fluids after a few hours of IV therapy. If the fluid infusion rate exceeds more than the maintenance requirement, the infusion rate should be reviewed within 4 to 6 hours.

A rising HCT indicates on-going plasma leakage and will require an increase in the IV fluid infusion rate (see management of dengue with warning sign). If patients deteriorate and progress to shock, refer to the section on fluid resuscitation.

Reduce or consider discontinuation of IV fluid therapy when patients begin to show signs of recovery (usually after 24-48 hours of defervescence, or the HCT drops in a stable patient).

**Table 7 : Calculations for maintenance of intravenous fluid infusion**

<p><b>Non-obese and non-overweight patients</b></p> <ul style="list-style-type: none"> <li>• <b>Maintenance fluid can be calculated based on the following formula :</b> <ul style="list-style-type: none"> <li>- 1.2 - 1.5 ml/kg/hour</li> </ul> </li> </ul> <p>* <b>Adapted</b> : National Clinical Guideline Centre (UK). Intravenous Fluid Therapy: Intravenous Fluid Therapy in Adults in Hospital [Internet]. London: Royal College of Physicians (UK); 2013 Dec. Available from <a href="http://www.ncbi.nlm.nih.gov/books/NBK247761/">http://www.ncbi.nlm.nih.gov/books/NBK247761/</a></p>
<p><b>Obese and overweight patients</b></p> <ul style="list-style-type: none"> <li>• <b>Maintenance fluid can be calculated based on adjusted body weight</b></li> <li>• <b>Adjusted bodyweight (ABW) can be calculated using this formula.</b> <ul style="list-style-type: none"> <li>○ <math>ABW = IBW + 0.4(\text{actual weight} - IBW)^*</math></li> <li>○ <b>Ideal bodyweight (IBW) can be estimated based on the following formula.</b><sup>72, level III</sup> <ul style="list-style-type: none"> <li>➤ Female: <math>45.5 \text{ kg} + 0.91(\text{height} - 152.4) \text{ cm}</math></li> <li>➤ Male: <math>50.0 \text{ kg} + 0.91(\text{height} - 152.4) \text{ cm}</math></li> </ul> </li> </ul> </li> </ul> <p>*<b>Adapted</b> : GlobalRPH 2015, calculator adjusted body weight (available at <a href="http://www.globalrph.com/ibw_calc.htm">http://www.globalrph.com/ibw_calc.htm</a>)</p>
<p><b>CAUTION : Input of fluid and output urine must be reviewed and adjusted according to clinical response. Use of volumetric pumps is encouraged, especially in patients requiring close fluid monitoring.</b></p>

**Table 8 : Graded Regime for Dengue with Warning Signs without Shock**

<ul style="list-style-type: none"> <li>• Obtain a baseline HCT before fluid therapy.</li> </ul>
<ul style="list-style-type: none"> <li>• Give crystalloids solution (such as 0.9% saline).</li> </ul>
<ul style="list-style-type: none"> <li>• Start with 5 ml/kg/hour for 1–2 hours, then reduce to 3 ml/kg/hr for 2–4 hours, and then reduce to 2 ml/kg/hr or less according to the clinical response.</li> </ul>
<ul style="list-style-type: none"> <li>• If the clinical parameters are worsening and HCT is rising, increase the rate of infusion.</li> </ul>
<ul style="list-style-type: none"> <li>• Reassess the clinical status, repeat the HCT and review fluid infusion rates accordingly.</li> </ul>

**Recommendation 5**

- In patients without co-morbidities who can tolerate orally, adequate oral fluid intake of two to three litres daily should be encouraged. This group of patients may not require intravenous fluid therapy.
- Intravenous fluid is indicated in patients with :-
  - vomiting, unable to tolerate oral fluids or severe diarrhoea.
  - increasing HCT (with other signs of ongoing plasma leakage) despite increased oral intake.
- Crystalloid should be the fluid of choice for non-shock patients.

### 7.5.2 Dengue Shock Syndrome (DSS)

Dengue shock syndrome is a medical emergency. Recognition of shock in its early stage (compensated shock) and prompt fluid resuscitation will give a good clinical outcome.<sup>67,level 1</sup> Refer Table 1 for details. However, failure to recognise the phase of compensated shock will ultimately lead to decompensated (hypotensive) shock with a more complicated disease course and organ failures.

Pulse pressure of < 20 mmHg and systolic pressure < 90 mmHg are late signs of shock in adults.

All patients with dengue shock should be managed in high dependency or intensive care units. Fluid resuscitation must be initiated promptly and should not be delayed while waiting for admission to ICU or high dependency unit. Following initial resuscitation there may be recurrent episodes of shock because capillary leakage can continue for 24 to 48 hours.

IV fluid therapy is the mainstay of treatment for dengue shock. To date, only four randomised controlled trials studying different types of fluid regime in DSS in children aged from 5 to 15 years are available.<sup>67-70,level 1</sup> Our recommendations are extrapolated from these studies. From these studies of colloids versus crystalloids, there is no clear advantage of using any of the colloids over crystalloids in terms of the overall outcome and mortality.<sup>67-69, level 1; 71,level 1</sup> However colloid may be preferable as the fluid of choice in patients with intractable shock in the initial resuscitation.

**Colloids** seem to restore the cardiac index and reduce the level of HCT faster than crystalloids in patients with intractable shock.<sup>68-69,level 1</sup> The choice of colloids in these studies included gelatin solution and hydroxyethyl starch (HES) solution. In the recent meta-analysis, HES in non-dengue critically ill patients with sepsis was associated with an increase in the rate of renal replacement therapy and coagulation abnormalities.<sup>72,level 1</sup>

Colloid should be used mainly for resuscitation. Prolonged use of colloid as sole maintenance fluid should be avoided. HES solution is contraindicated in patients with severe hepatic dysfunction, fluid overload (e.g. pulmonary oedema and congestive cardiac failure), renal failure and patients receiving dialysis.

**Albumin** as resuscitation fluid in DSS has not been studied, however from extensive use in critically ill patients, 4%-5% albumin is comparable to crystalloid and may be better in subgroup of septic patients.<sup>70,level 1;72,level 1</sup>

**Hypertonic sodium lactate** in DSS has shown positive results in only one study.<sup>73,level 1</sup> However, there is lack of clear evidence to support the use of this solution and furthermore, the product is not available in this country.

### 7.5.3 Principles for Fluid Resuscitation

The volume of initial and subsequent fluid resuscitation depends on the degree of shock and can vary from 10-20 ml/kg adjusted body weight. The volume and rate of fluid replacement should be carefully titrated to the clinical response to maintain an effective circulation while avoiding an over-replacement.

Adequate and effective fluid resuscitation will leads to improvement in the following parameters in Table 9.



**Table 9 : Fluid Responsiveness Parameters**

<p><b>A. Clinical response parameters</b></p> <ul style="list-style-type: none"> <li>✓ Improvement of general well being/ mental state</li> <li>✓ Warm peripheries</li> <li>✓ Capillary refill time &lt;2sec</li> <li>✓ BP stable</li> <li>✓ Improving pulse pressure</li> <li>✓ Reducing tachycardia</li> <li>✓ Improving urine output</li> <li>✓ Less tachypnoea</li> </ul>
<p><b>B. Laboratory parameters</b></p> <ul style="list-style-type: none"> <li>✓ Appropriate decrease in HCT</li> <li>✓ Improvement in metabolic acidosis and lactate clearance</li> </ul>
<p><b>C. Imaging parameters (recommended but not mandatory)</b></p> <ul style="list-style-type: none"> <li>✓ Improvement of IVC collapsibility index (spontaneous breathing patient)</li> </ul> <p style="text-align: center;"> <math display="block">\frac{\text{IVC expiratory diameter} - \text{IVC inspiratory diameter}}{\text{IVC expiratory diameter}} \times 100 = \text{Caval index (\%)}</math> </p> <p>*Caval index close to 100% is indicative of almost complete collapse, therefore volume depletion and 0% suggests minimal collapse i.e. likely volume overload. &gt;40% collapse will be fluid responsive.<sup>72</sup></p> <p><b>Adapted :</b> Goldflam K, Saul T and Lewiss R. Focus on: inferior vena cava ultrasound. ACEP News 6. 2011. pp 24-25. (available at : <a href="http://www.acep.org/Content.aspx?id=80791">http://www.acep.org/Content.aspx?id=80791</a>)</p>
<p><b>CAUTION : IVC assessment should be performed by trained personnel and not to be interpreted in isolation.</b></p>

### 7.5.3 Non-responders to Initial Resuscitation (Refer Algorithm A and B)

If the first two cycles of fluid resuscitation (about 40 ml/kg) fails to establish a stable haemodynamic state and HCT remains high, further bolus of colloids should be considered for the third cycle.<sup>1:60,level III</sup> (refer to **Algorithm A** and **Algorithm B**)

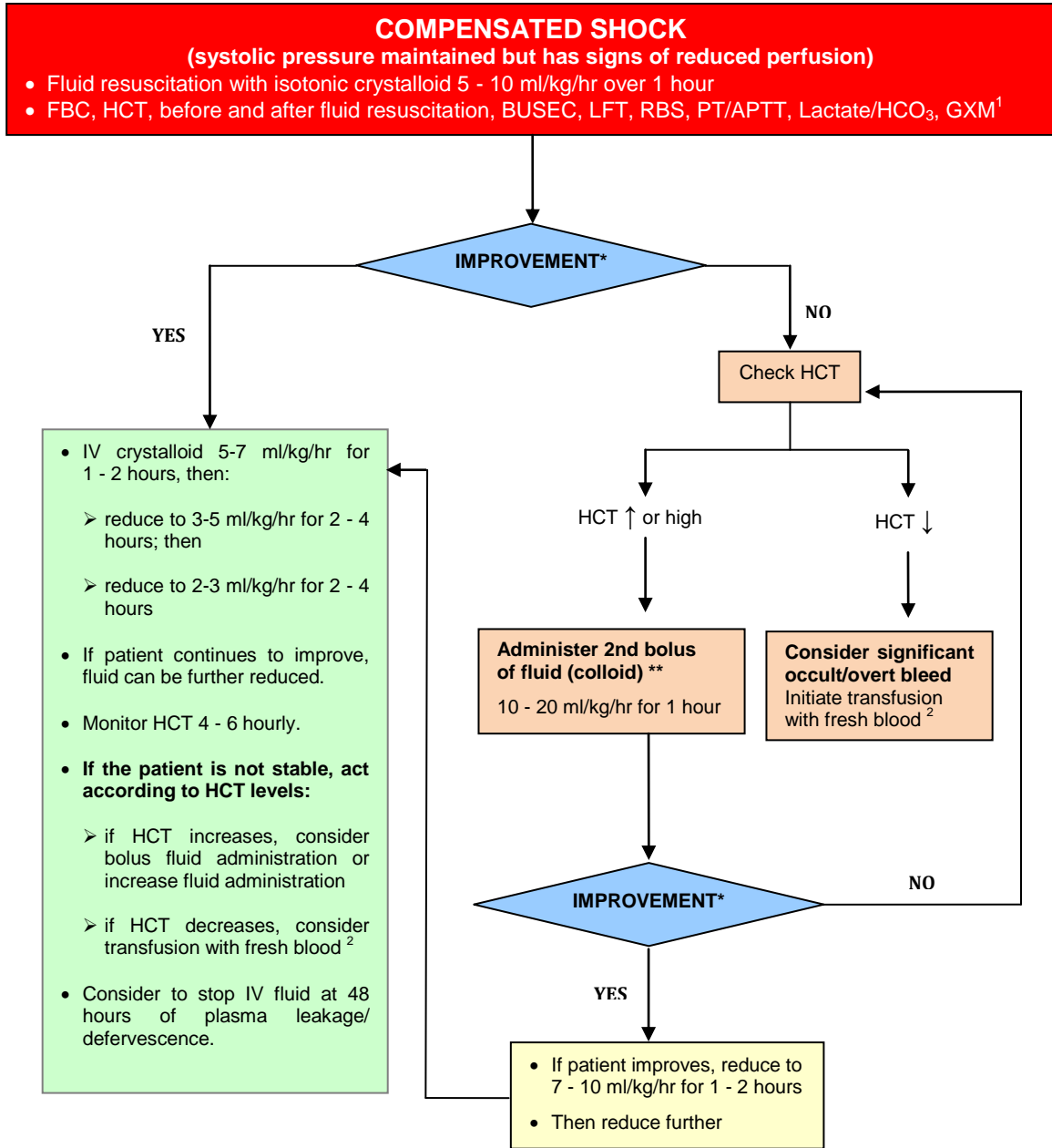
If the repeat HCT drops after two cycles of fluid resuscitation and the patient remains in shock, one should suspect significant bleed (often occult) for which blood ± blood products transfusion needs to be instituted promptly. (refer to **Algorithm A** and **Algorithm B**)

Other possible causes of persistent shock include: (refer to **Algorithm C**)

- ✓ sepsis
- ✓ cardiogenic shock (due to myocarditis, cardiomyopathy, RV/LV dysfunction, pericardial effusion or cardiac ischaemia),
- ✓ cytokine storm (a vasodilated state due to release of inflammatory mediators)
- ✓ liver failure with lactic acidosis.

Fluid therapy has to be judiciously controlled to avoid fluid overload which could result in massive pleural effusion, pulmonary oedema or ascites.<sup>69,level I</sup>

**ALGORITHM A - FLUID MANAGEMENT IN COMPENSATED SHOCK**



\* Reassess the patient's clinical condition, vital signs, pulse volume, capillary refill time, urine output and temperature of extremities.

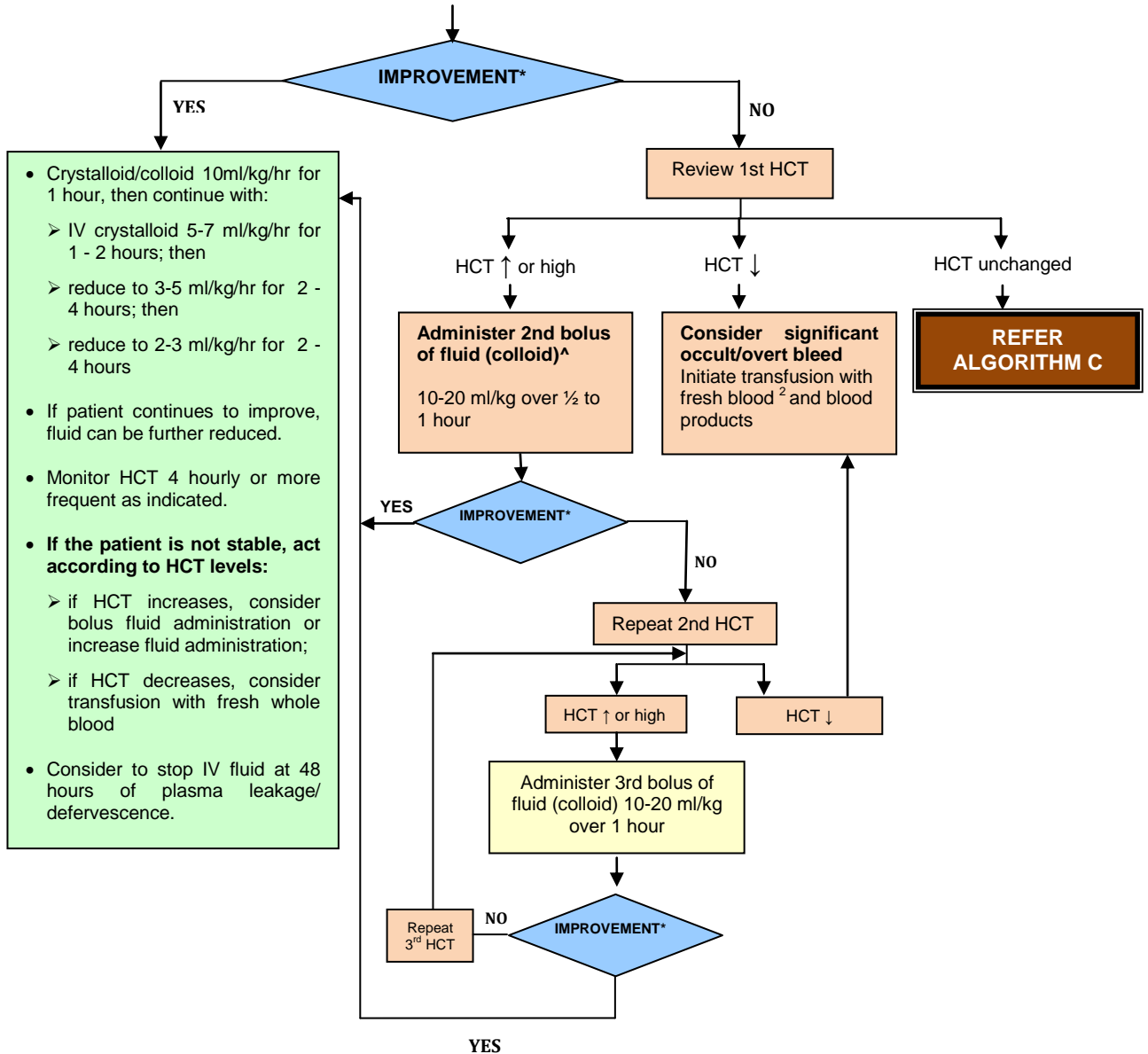
\*\* Colloid is preferable if the patient has already received previous bolus of crystalloid

IV = intravenous ; HCT = haematocrit  
 ↑ = increased ; ↓ = decreased  
<sup>1</sup>GXM: require 1st stage cross match or emergency O  
<sup>2</sup>fresh blood : less than 5 days, either packed cells or whole blood

**ALGORITHM B - FLUID MANAGEMENT IN DECOMPENSATED SHOCK**

**DECOMPENSATED SHOCK**

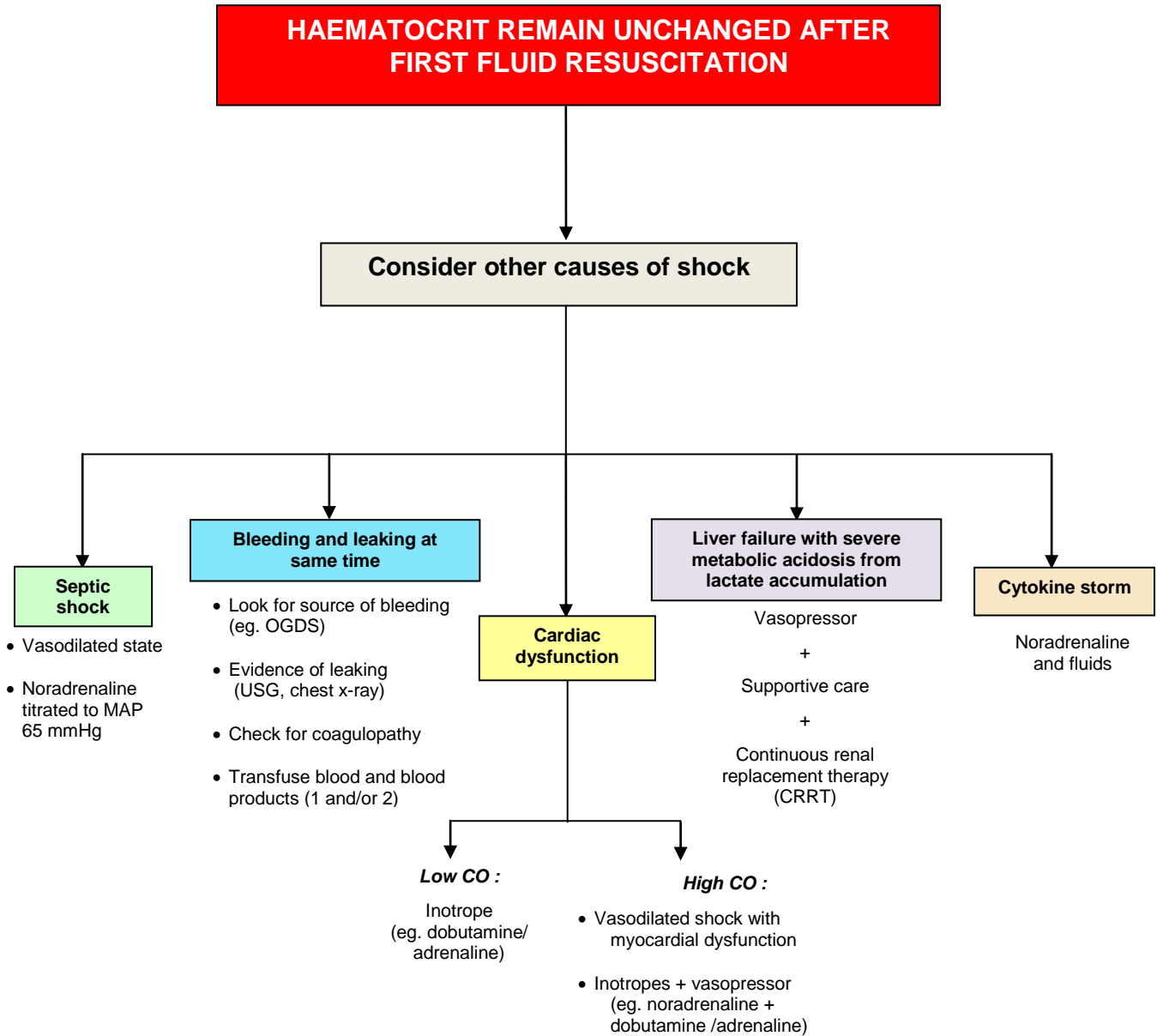
- Fluid resuscitation with 20 ml/kg/hr colloid\*\* over 15 – 30 minutes.
- Try to obtain a HCT level before fluid resuscitation
- FBC, HCT, before and after fluid resuscitation, BUSEC, LFT, RBS, PT/APTT, Lactate/HCO<sub>3</sub>, GXM<sup>1</sup>



\* Reassess the patient’s clinical condition, vital signs, pulse volume, capillary refill time and temperature of extremities.  
 ^ Colloid is preferable if the patient has already received previous boluses of crystalloid  
 \*\*In absence of colloid, crystalloid can be used.

IV = intravenous ; HCT = haematocrit  
 ↑ = increased ; ↓ = decreased  
<sup>1</sup>GXM: require 1st stage cross match or emergency O  
<sup>2</sup>fresh blood : less than 5 days, either packed cells or whole blood

**ALGORITHM C - FLUID MANAGEMENT IN DECOMPENSATED SHOCK  
(WITH PRESENCE OF BLEEDING & LEAKING OR OTHER CAUSES OF SHOCK)**



All the above types of shocks need to be supported by echocardiography and non-invasive cardiac output monitoring and treatments tailor to each patient.

HCT = haematocrit ; MAP = mean arterial pressure ; CO = cardiac output;  
OGDS = oesophagogastroduodenoscopy ; USG = ultrasonography

↑ = increased ; ↓ = decreased

<sup>1</sup>GXM: require 1st stage cross match or emergency O

<sup>2</sup>fresh blood : less than 5 days

### 7.5.4 Metabolic acidosis

Patient could be in shock even with normal blood pressure as the leakage happens slowly over hours and body compensates well by peripheral vasoconstriction to maintain the mean arterial pressure. Thus, **compensated metabolic acidosis** is an early sign of shock due to leakage or bleeding. Lactic acidosis due to tissue hypoxia and hypoperfusion is the most common cause of metabolic acidosis in dengue shock.

Monitoring of blood lactate levels is commonly carried out in patients with severe dengue. A lactate level of <2 mmol/L in a critically ill patient generally implies that the patient has adequate tissue perfusion, although higher levels are not necessarily the result of tissue hypoxia.

Correction of shock and adequate fluid replacement will correct the metabolic acidosis. If metabolic acidosis remains uncorrected by this strategy, one should suspect severe bleeding, liver failure, acute kidney injury, sepsis, cardiac dysfunction, drugs (e.g. beta2 agonists, metformin) and hyperchloraemic metabolic acidosis.

Hyperchloraemia, caused by the administration of large volumes of 0.9% sodium chloride solution (chloride concentration of 154 mmol/L), may cause metabolic acidosis with normal lactate levels and presents as a normal anion gap metabolic acidosis. If serum chloride levels increase, change the fluid to balanced solution such as sterofundin or Hartmann's.<sup>73</sup>  
level III This improves chloride related acidosis.

Sodium bicarbonate for metabolic acidosis caused by tissue hypoxia is not recommended for pH  $\geq$ 7.10. Bicarbonate therapy is associated with sodium and fluid overload, an increase in lactate and pCO<sub>2</sub> and a decrease in serum ionised calcium.

A delay in lactate clearance or persistent lactate elevation is associated with poor outcome. Persistent lactic acidosis contributes to myocardial depression, arrhythmias, vasodilatation, increase in respiratory muscle workload, reduced oxygen delivery, decreased ATP production and multi-organ failure.

A likely more useful parameter for guiding therapy is **lactate clearance**. Lactate clearance is calculated as follows:<sup>76</sup>

$$\frac{\text{lactate}_{\text{initial}} - \text{lactate}_{\text{subsequent}}}{\text{lactate}_{\text{initial}}} \times 100\%$$

A 20% clearance in 2 hours improves survival.

### 7.5.5 Arterial blood gases

Arterial blood gas (ABG) analysis is frequently done (2-4 hourly) in patients with shock mainly for detection of worsening acidosis by looking at base excess, bicarbonate, CO<sub>2</sub> and lactate.

Mixed respiratory alkalosis with metabolic acidosis (CO<sub>2</sub> lower than expected) commonly seen in liver failure, dengue encephalitis and sepsis. This also can be seen in patients with pleural effusion and moderate ascites as they are tachypnoeic.

Hypoxaemia is a guide to warn us of fluid overload, pleural effusion and interstitial oedema.

### 7.5.6 Electrolyte and acid-base imbalances

All patients with severe dengue should be monitored for electrolytes imbalances such as **hyponatraemia** and **hyperkalaemia**. Presence of hyponatraemia is a common observation in severe dengue and a marker of disease severity.<sup>77-78,level III</sup>

Other electrolytes that need to be monitored are :-

- serum calcium
- serum phosphate
- serum magnesium

#### Recommendation 6

- Crystalloids should be the preferred choice in compensated DSS.
- Compensated DSS who do not respond to initial crystalloid resuscitation should receive colloids as the second fluid bolus.
- In decompensated DSS, colloids should be the initial solution for resuscitation.
- In persistent shock, other causes of shock should be aggressively looked for.

## 7.6 MANAGEMENT OF COMPLICATIONS IN DENGUE INFECTION

### 7.6.1 MANAGEMENT OF BLEEDING / HAEMOSTASIS

#### i. Haemostatic Abnormalities in Dengue Infection

The haemostatic changes that occur in dengue infection are a result of endothelial activation.<sup>79,level II-3;80-81,level III</sup> This leads to thrombocytopenia and coagulation activation which are an intrinsic part of the disease.<sup>79,level II-3;80-81,level III</sup>

Thrombocytopenia and coagulation abnormalities do not reliably predict bleeding in dengue infection.<sup>82,level I;83,level II-2;84,level III</sup>

Markers of endothelial activation such as elevated levels of thrombomodulin, tissue factor and Von Willebrand factor are more often seen in severe dengue.<sup>85-86,level II-2</sup> Increased levels of these proteins may promote microvascular thrombosis and end-organ damage.<sup>87,level III</sup>

#### ii. How to Recognise Significant Occult Bleeding?

Bleeding is considered significant when it results in haemodynamic instability. Bleeding from the gums or per vagina, epistaxis and petechiae are common but will usually cease spontaneously and are often not significant.<sup>88,level II-3</sup> Significant bleeding or disseminated intravascular coagulation usually occurs following prolonged shock and acidosis.<sup>89,level III</sup>

**Suspect significant occult bleeding in the following situations:**

- HCT not as high as expected for the degree of shock to be explained by plasma leakage alone.<sup>89, level III</sup>
- A drop in haematocrit without clinical improvement despite adequate fluid replacement (40-60 ml/kg).<sup>89, level III; 61</sup>
- Severe metabolic acidosis and end-organ dysfunction despite adequate fluid replacement.<sup>89, level III</sup>

**iii. Management of Bleeding in Dengue Infection**

Transfusion of blood and blood components in dengue is indicated when there is evidence of significant bleeding.<sup>89, level III</sup> Oxygen delivery at tissue level is deemed optimal only with fresh packed red cells or whole blood because of higher levels of 2, 3 diphosphoglycerate (2,3 DPG). However, recently published studies done in non-dengue critically ill patients and patients undergoing cardiac surgery have not shown any difference in patient outcomes when transfused fresh blood < 8 days old compared to blood stored longer (> 21 days).<sup>90-91, level I</sup>

**Transfusion of blood in patients with significant bleeding**

- Transfuse blood (5–10ml/kg of packed red cells or 10–20 ml/kg of whole blood) and observe the clinical response.
- Consider repeating the blood transfusion if there is further blood loss or no appropriate rise in HCT after blood transfusion.

**Recommendation 7**

- Patients with mild bleeding such as from the gums or per vagina, epistaxis and petechiae do not require blood transfusion.
- Transfusion with blood (preferably less than 5 days) ± blood component is indicated in significant bleeding.

**iv. Management of Upper Gastrointestinal Bleeding**

Gastrointestinal bleeding is one of the most common haemorrhagic manifestations in dengue infection and it often associated with high mortality.<sup>88, level II-3</sup> The common reasons of gastrointestinal haemorrhage in dengue are haemorrhagic (and/or erosive) gastritis, peptic ulcer and oesophageal ulcer.<sup>92, level II-2; 93, level III</sup>

Fluid therapy, transfusion of fresh blood and blood products and administration of proton pump inhibitor are fundamental in management of gastrointestinal haemorrhage in dengue infection.<sup>94, level II-2</sup> Endoscopy in dengue patient with gastrointestinal haemorrhage is indicated if the patient has persistent bleeding despite optimum medical therapy.<sup>95-97, level III</sup>

In general, endoscopic therapy is recommended in patient with peptic ulcers with recent haemorrhage including active arterial bleeding, nonbleeding visible vessels, nonbleeding adherent clots or persistent oozing. However, endoscopic injection therapy is not recommended in dengue infection with gastrointestinal haemorrhage.<sup>92, level II-2</sup>

## v. Role of Prophylactic Transfusions in Dengue Infection

Prophylactic transfusion with platelets and fresh frozen plasma do not produce sustained changes in the coagulation status and platelet count in patients with severe dengue infection.<sup>98-99, level III</sup>

Inappropriate transfusion of blood components increases the risk of pulmonary oedema and respiratory embarrassment.<sup>98, level III</sup>

There is no role for prophylactic transfusion with platelets and plasma in dengue.

## vi. The Role of Adjunctive Therapy in Dengue Infection

There is insufficient evidence to support the use of recombinant activated factor VII in dengue patients with significant bleeding.<sup>100, level I; 101, level III</sup> The coagulation system is activated in dengue and infusion of activated factor concentrates may increase the risk of thrombosis.<sup>102, level III</sup>

## 7.6.2 MANAGEMENT OF HEPATITIS IN DENGUE INFECTION

### i. Clinical Features and Biochemical Profiles

Clinical features suggesting dengue related hepatic involvement includes abdominal pain (18%-63%), nausea and vomiting (49%-58%), anorexia, presence of hepatomegaly and elevated transaminases.<sup>103-105, level II-2; 106, level III</sup> Acute liver failure are uncommon (5.2 %).<sup>107, level II-2; 108, level III</sup>

Raised AST has been seen in 63-97% of patients while raised ALT levels in 45-96%. More than 10 fold rise has been seen in 3-15 % cases.<sup>105, level II-2; 109, level III</sup> In a majority of studies elevation of AST is more than ALT during the first week of infection, with a tendency to decrease to normal levels within three weeks.

### ii. Pathogenesis

The pathogenesis of liver involvement during dengue infection is poorly understood. The potential mechanism of liver injury include direct effects of the virus, immunology injury due to dysregulated immune response to the virus, ischaemic injury due to hypotensive episodes and hepatotoxic effect of medications such as acetaminophen or herbal remedies.<sup>104, level II-2; 108, level III</sup> Hepatocyte injury including necrotic changes commonly involve midzonal area followed by centrilobular area.<sup>104, level II-2</sup>

### iii. Management and Use of N-Acetylcysteine (NAC)

Dengue hepatitis is usually a self limiting disease. The management of acute liver failure (as defined by coagulopathy, usually INR > 1.5 and any degree of mental alteration in a patient without preexisting cirrhosis) includes appropriate fluid management, monitoring of haemodynamics and metabolic parameters.<sup>110</sup> Avoidance of other potential hepatotoxic drugs is crucial.

There are reported case studies on use of NAC in acute liver failure secondary to dengue infection.<sup>108, level III; 111-114, level III</sup> However up to now, there is insufficient evidence to support the use of NAC in the management of dengue associated hepatitis.



Liver transplantation is difficult because of haemodynamic instability, bleeding manifestation, and organ dysfunction caused by infection itself, and may not be a viable treatment option. Artificial and bioartificial liver support systems have not been conclusively shown to be beneficial for acute liver failure.

### 7.6.3 MANAGEMENT OF CARDIAC COMPLICATIONS IN DENGUE INFECTION

Cardiac dysfunction is increasingly recognised as a component of shock in dengue infection and it can also manifest as arrhythmias, functional myocardial impairment and myocarditis.<sup>115-116,level II-2;117,level III</sup> Functional myocardial impairment can be caused by subclinical myocarditis, myocardial oedema, or circulating myocardial depressant factors.<sup>118,level III</sup> Possible mechanisms include regional vulnerability to coronary hypoperfusion, cytokine storm, direct myocardial inflammation and altered calcium homeostasis.

Cardiac complications of dengue should be suspected in those with fluid refractory shock or haemodynamic compromise disproportionate to capillary leakage/HCT increase (**Refer to Algorithm C**). In such patients, it is recommended to do ECG, cardiac biomarkers and echocardiography.

#### i. Investigations :

- *Cardiac markers*
  - Cardiac biomarkers (CK / CKMB or Troponin) have limited sensitivity and could be normal.<sup>118,level III</sup>
- *ECG*
  - ECG alterations reported in dengue infection are often transient. ECG changes might be the only sign of cardiac involvement with normal biomarker levels and echocardiograms.<sup>119,level II-2</sup> Common ECG changes reported are :
    - Sinus bradycardia
    - Atrioventricular block
    - Atrial fibrillation
    - T wave and ST-segment abnormalities

#### ii. Echocardiography

The available data on role of echocardiography in assessing cardiac function of dengue infected patients is limited and predominantly in paediatric population.<sup>116,level II-2;120-121,level III</sup> There is evidence of significantly low ejection fraction during the critical stage of severe dengue fever.<sup>121,level III;122,level II-2;123,level III</sup>

Measurement of ejection fraction is difficult to interpret as it is influenced by changes in preload and afterload. In severe dengue infection, there may be evidence of systolic and diastolic dysfunction with possible segmental wall abnormalities of the septum as well as right ventricular wall.<sup>116,level II-2;122,level II-2</sup>

#### iii. Treatment:

Management of dengue infection in such patient should primarily be focused on cautious fluid resuscitation, aiming to give just sufficient intravenous fluid therapy to maintain adequate tissue perfusion.

There has been no evidence to support the use of antiviral and immunomodulatory treatments such as beta interferon, corticosteroids and intravenous immunoglobulins for dengue myocarditis.<sup>118,level III</sup>

**Recommendation 8**

- Cardiac complications of dengue infection should be suspected in those with fluid refractory shock or haemodynamic compromise disproportionate to capillary leakage/HCT increase.
- Adequate fluid resuscitation is a pre-requisite before myocardial dysfunction can be diagnosed.

**7.6.4 MANAGEMENT OF NEUROLOGICAL COMPLICATIONS IN DENGUE INFECTION**

The proportion of hospitalised dengue patients in Southeast Asia developing neurological complications ranges between 0.5%–5.4%.<sup>125,level II-2;126-127,level III</sup> Dengue infection results in a wide spectrum of neurological complications such as encephalopathy, encephalitis, intracranial bleed, meningitis and meningoencephalitis.<sup>127,level III;128-129,level II-2</sup> Immune-mediated syndromes that include myelitis, acute disseminated encephalomyelitis (ADEM), and Guillain–Barré syndrome (GBS), myositis and various neuro-ophthalmic complications have been reported.<sup>127,level III</sup>

**i. Dengue Encephalopathy**

This is the most commonly reported neurological complication in dengue infection. Encephalopathy in dengue may be the result of prolonged shock, hypoxia, cerebral oedema, acute liver failure, acute renal failure, hyponatraemia and cerebral haemorrhage.

**ii. Dengue Encephalitis**

Dengue encephalitis is the next commonly reported neurological complication especially in secondary dengue infection. It classically presents with fever, headache, seizures, altered consciousness and focal neurological signs after 5-7 days of onset of fever.<sup>129-131,level II-2</sup> The most common abnormality on neuroimaging is cerebral oedema. MRI is the imaging modality of choice. However, the MRI can be normal.<sup>125,level II-2</sup>

If possible, lumbar puncture should be done. The CSF should be analysed for dengue virus-specific IgM antibodies, NS1 antigen, dengue virus RNA, depending on available laboratory facilities. CSF analysis can be normal or they can reveal pleocytosis and high protein.<sup>131,level II-2;132,level III</sup> In general, the sensitivity of serological techniques and RT-PCR is low.<sup>132,level III</sup>

The treatment modality for management of dengue encephalitis is supportive. Symptoms suggestive of raised intracranial pressure (ICP) which include headache, vomiting and depress consciousness should be looked for. Standard interventions for the management of raised ICP should then be instituted. The outcome of dengue encephalitis is variable with many studies showing good recovery.<sup>131,level II-2;133,level II-2</sup>

**iii. Acute Transverse Myelitis**

Acute transverse myelitis can occur within the first week of illness due to direct virus invasion or 1-2 weeks later as an immune-mediated phenomenon.

**iv. Muscle Involvement**

Extent of muscle involvement in dengue infection can vary from transient myalgia, rhabdomyolysis, quadriparesis to respiratory muscle weakness. In most cases spontaneous recovery happens within 1-2 weeks.

**v. Ocular Manifestations**

Ocular manifestations of dengue infection include maculopathy, retinal oedema, retinal haemorrhages, optic neuropathy and vitritis.<sup>127,level III</sup>

**Adjuvant Treatment**

- *Corticosteroids*

The effectiveness of corticosteroids in neurological complications of dengue remains to be proven. However, some recommend IV methylprednisolone in dengue myelitis and ADEM.  
<sup>127,level III</sup>

- *Immunoglobulin*

High doses of intravenous immunoglobulin might be useful to treat post-dengue Guillain-Barré syndrome.  
<sup>127,level III</sup>

- *Plasmapheresis*

No evidence to show effectiveness of plasmapheresis in management of neurological complications in dengue infection.

**Recommendation 9**

- In patients with altered sensorium, the common causes for encephalopathy must be ruled out.
- In patients with suspected encephalitis, symptoms and signs suggestive of raised intracranial pressure should be looked for.

**7.6.5 MANAGEMENT OF RENAL COMPLICATIONS IN DENGUE INFECTION**

Dengue infection has been associated with a variety of renal disorders. Transient proteinuria and haematuria have been reported in dengue infection <sup>134-135,level III</sup> and usually normalise within 3- 4 weeks of illness.

Acute renal failure (ARF) occasionally complicates severe dengue infection. It is usually due to acute tubular necrosis as a result of hypotension, haemolysis, disseminated intravascular coagulation <sup>136,level II-2</sup> and rhabdomyolysis. <sup>137,level III</sup> ARF in such setting carries a high mortality rate. <sup>136, level II-2;138,level II-2</sup>

Treatment of ARF in dengue infection follows standard management. It involves volume optimisation, treatment of electrolyte abnormalities and dialysis if indicated (eg. severe metabolic acidosis, hyperkalaemia, fluid overload etc). Peritoneal dialysis is not recommended as there is a high risk of bleeding.

**7.6.6 MANAGEMENT OF HAEMOPHAGOCYTTIC SYNDROME IN DENGUE INFECTION**

Haemophagocytic syndrome (HPS) is a potentially fatal syndrome of pathologic extreme immune activation leading to cytokine storm. There is increased IL-2, TNF- $\alpha$ , IL-6, IL-8, interferon  $\gamma$  generated by uncontrolled activation of histiocytes and T-cells. <sup>139-140,level III;141-142</sup>

The clinical course is generally severe and may mimic sepsis. It commonly presents with an unexplained persistent fever or resurgence of high grade fever after an initial defervescence. Other presentations are hepatosplenomegaly, rash, bleeding, CNS manifestations and jaundice (Refer Table 10). <sup>143,level III</sup>

Laboratory findings of HPS presented in forms of bicytopenia or pancytopenia, coagulopathy, hypertriglyceridaemia, hypofibrinogenaemia, hyperferritinaemia, transaminitis, hyperbilirubinaemia, hypoalbuminaemia and hyponatraemia. <sup>139,level III;142;144,level III</sup> Dengue associated HPS had been increasingly reported. <sup>144-159,level III</sup>

Currently, there are three well-accepted diagnostic classifications for haemophagocytic lymphohistiocytosis (HLH): Diagnostic criteria for HLH used in HLH-2004 trial;<sup>143,level III</sup> Proposed HLH diagnostic criteria, 2009<sup>141</sup> and HScore 2014.<sup>160,level II-2</sup> Former two were not validated in adult while the latter was validated for macrophage activation syndrome in adult.

The lack of validated HPS classification system for dengue should not discourage clinicians to attempt to diagnose HPS. Since HPS is a progressive systemic disease, the lack of enough criteria at one juncture does not exclude the diagnosis.

Haemophagocytosis demonstrated in bone marrow biopsy is the hallmark of the diagnosis but it is non-specific. It has been reported from day 5 till day 32 after the onset of illness. The absence of haemophagocytic activities in marrow in the early phase does not exclude the diagnosis.

Serum ferritin of >10,000 was not pathognomonic of HPS in adults<sup>161,level III</sup> even though it is highly sensitive and specific in paediatric population.<sup>162,level III</sup> The level does not correlate with severity but the trend is more important as it relates with disease activity. Often there is a sudden exponential rise of ALT, AST and LDH which could occur in less than 12 hours.

The mainstay of management is mainly supportive.<sup>146-147,level III;152,level III;159,level III</sup> Milder forms of HPS can recover spontaneously. For severe HPS, specific therapy with IV methylprednisolone or dexamethasone (with or without IVIg) may sometimes be helpful if started early and promptly.<sup>147,level III;152-153,level III;158,level III</sup> Steroids should be tapered off rapidly as patients improve clinically and biochemically. High dose steroid should be avoided when suspected bacterial sepsis and in the presence of active gastrointestinal bleeding.

**Table 10 : Pathophysiologic Manifestation of Haemophagocytic Syndrome**

Category 2: Significant immune activation	Category 3: Abnormal immunopathology
<ul style="list-style-type: none"> <li>• Fever</li> <li>• Splenomegaly/hepatomegaly</li> <li>• Elevated ferritin (&gt;300ng/mL)</li> <li>• Elevated sCD25</li> <li>• Elevated sCD163</li> </ul>	<ul style="list-style-type: none"> <li>• Cytopenias</li> <li>• Decreased fibrinogen or increased triglycerides</li> <li>• Haemophagocytosis</li> <li>• Hepatitis</li> <li>• CNS involvement</li> </ul>

**Adapted** : Henter JI, Horne A, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for haemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007 Feb;48(2):124-31

## 7.7 INTENSIVE CARE MANAGEMENT OF DENGUE INFECTION

Management of severe dengue in the intensive care unit (ICU) follows the general principles of a critically ill patient. Indications for intensive care referral can be categorised into organ systems as in Table 11.

**Table 11 : Indications for Intensive Care Referral**

<b>Respiratory</b>	
1.	Acute respiratory distress with the following clinical signs: <ul style="list-style-type: none"> <li>- RR &gt; 30/min</li> <li>- Dyspnoea</li> <li>- Use of accessory muscles</li> <li>- Agitation, confusion</li> </ul>
2.	High levels of supplemental oxygen (O <sub>2</sub> concentration $\geq$ 50% to maintain oxygen saturation >90% )
3.	Risk of respiratory compromise with large volume resuscitation e.g. congestive heart failure, chronic kidney disease
4.	Massive haemoptysis
5.	Potential need for non-invasive/ invasive ventilation
<b>Cardiovascular</b>	
1.	Haemodynamic instability due to hypovolaemia, haemorrhage, myocarditis or other cause
2.	Complex cardiac dysrhythmias requiring close monitoring/ intervention
3.	Underlying cardiac disease with risk of cardiorespiratory compromise e.g. unstable ischaemic heart disease, fixed cardiac output states
<b>Neurologic</b>	
1.	Seizures
2.	CNS depression
<b>Gastrointestinal</b>	
1.	Acute gastrointestinal bleeding with hypotension, continuous bleeding
2.	Severe acute hepatitis
<b>Haematologic</b>	
1.	Severe coagulopathy
2.	Significant bleeding
<b>Renal</b>	
1.	Acute kidney injury
2.	Acute rhabdomyolysis with renal insufficiency

### 7.7.1 Respiratory Support:

The main objectives of respiratory support are to:

1. support pulmonary gas exchange based on alveolar ventilation and arterial oxygenation.
2. reduce the metabolic cost of breathing by unloading the ventilatory muscles.

Indications for mechanical ventilation in severe dengue include:

- persistent shock
- acute respiratory failure secondary to massive pleural effusion  $\pm$  ascites, fluid overload
- severe metabolic acidosis
- airway protection

Patients who are alert, cooperative and haemodynamically stable with or without mild metabolic acidosis may benefit from non-invasive ventilation.<sup>163,level I</sup>

Intubation and ventilation in patients with severe dengue are not without risks. Initiation of positive pressure ventilation will further decrease the cardiac output by reducing venous return. In patients with pleural effusion and ascites, haemodynamics will be further compromised when higher airway pressure is applied to achieve adequate ventilation and oxygenation. Care must be taken to avoid trauma to the airway during intubation, which may cause bleeding.

In patients with metabolic acidosis, respiratory support should be considered despite preservation of relatively normal arterial blood pH. When the actual  $P_a\text{CO}_2$  is higher than the expected to compensate for the acidosis, consider intubation and mechanical ventilation.

**Formula to calculate expected  $P_a\text{CO}_2 = 1.5 (\text{Actual } [\text{HCO}_3] \text{ mmol/L}) + 8 (\pm 2 \text{ mmHg})$**

When a patient with metabolic acidosis is on invasive mechanical ventilation, set the ventilator settings so that the  $P_a\text{CO}_2$  remains low, at the expected  $P_a\text{CO}_2$  level. Failure to do so may cause further deterioration as the acidosis markedly worsens, resulting in depression of myocardial contractility, hypotension and arrhythmias.

### 7.7.2 Haemodynamic Support

Fluid resuscitation is crucial and should be initiated early as per guidelines in the section on fluid management. The causes of persistent shock and treatment in severe dengue are outlined in **Algorithm C**.

The role of inotropic and vasopressor agents in dengue shock has not been investigated in clinical trials. Vasopressors may be able to maintain the blood pressure but do not improve tissue perfusion if the intravascular volume has not been restored.

The use of inotropic and vasopressor agents should be limited to the following clinical situations (Refer **Algorithm C**):

1. As a **temporary measure to prevent life-threatening hypotension** while aggressive fluid resuscitation is being carried out or during induction for intubation.<sup>164-167,level I</sup>
2. **Cardiogenic shock**  
In the case of cardiac dysfunction, it is appropriate to use inotropic agents such as dobutamine or adrenaline in combination with a vasopressor.<sup>168,level I</sup>
3. **Concomitant septic shock**  
Noradrenaline is preferred to other vasopressors as first-line therapy.<sup>164,level I</sup>

### 7.7.3 Renal Replacement Therapy

Renal replacement therapy may be indicated in severe dengue with acute kidney injury (Refer chapter on Management of Renal Complications in Dengue Infection).

### 7.7.4 Guide on Safety and Risk of Invasive Procedures

#### i. Central venous catheter (CVC) insertion

In any condition that requires fluid resuscitation, rapid and large volume of fluids can be infused via a large bore peripheral venous catheter. A well sited proximal peripheral venous catheter is sufficient if it is expected that vasopressor is required for only short duration (1-2 hours).<sup>169</sup>

The commonly available CVCs are long and multi-lumens with relatively smaller individual lumen. The need for CVC arise:

- inadequate peripheral venous access<sup>170, level III</sup>
- patient requires an infusion of vasopressor for prolonged period.<sup>170, level III</sup>

Apart from the above indications, CVC should not be inserted solely for monitoring of CVP. CVP is not reliable to predict left ventricular filling volume or to predict haemodynamic response to fluid challenge.<sup>171, level I; 172, level II-2</sup> Thus, CVP should not be used to guide fluid management in dengue.

In general, it is a relative contraindication to insert a CVC in patients with thrombocytopenia or coagulation abnormalities. Overall, the risk of bleeding following CVC insertion in these groups is low.<sup>173-174, level II-2; 175, level III</sup> A subclavian approach should be avoided in these patients as the subclavian artery and vein is not accessible to direct compression.<sup>175, level III</sup> The use of real time USG is recommended for CVC insertion if it is available and there is expertise.<sup>176, level I; 177, level II-2</sup>

Routine prophylactic transfusion of platelets and FFP in severe thrombocytopenia prior to insertion of CVC should not be done as there is no clear evidence to support this practice.<sup>178-179; 180, level III</sup> If platelet is to be transfused, a CVC should be done within 4 hours following transfusion for maximum effect.<sup>181, level II-2</sup> The most recent recommendation by American Association of Blood Banks suggested transfusion as low as 20,000 prior to CVC insertion.<sup>178</sup>

#### ii. Arterial Catheter Insertion

Intra-arterial cannulation is useful as it enables continuous arterial pressure monitoring and repeated arterial blood gas sampling. The rate of bleeding complication is low overall (0.53% to 1.58%), lowest in the radial site compared to the femoral.<sup>181, level I</sup>

#### iii. Gastric Tube

If a gastric tube is required, the nasogastric route should be avoided in patients with bleeding disorder. Consider orogastric tube as this is less traumatic.<sup>183, level III</sup>

#### iv. Pleural Tap and Chest Drain

Intercostal drainage of pleural effusions should be avoided as it can lead to severe haemorrhage and sudden circulatory collapse.<sup>184, level III</sup>

**Recommendation 10**

- Non invasive ventilation may be beneficial in those who are alert, cooperative and haemodynamically stable with or without mild metabolic acidosis.
- Caution should be exercised during intubation as sedatives and mechanical ventilation may worsen haemodynamic instability.
- Fluid therapy is the mainstay of treatment in decompensated shock, however inotrope and vasopressors may be used as a temporary measure.
- CVP should not be used to guide fluid therapy.
- Subclavian vein cannulation should be avoided.
- The use of real time USG is recommended for CVC insertion if it is available and there is expertise.

**8. DENGUE INFECTION IN PREGNANCY**

An early diagnosis of dengue infection in pregnancy is usually difficult due to the various physiological changes of pregnancy, which are:<sup>185</sup>

- Elevation of HCT in dengue is masked by haemodilution due to increase in plasma volume especially in the 2<sup>nd</sup> and 3<sup>rd</sup> trimester. Serial HCT measurement is crucial for disease monitoring in pregnancy.
- The detection of third space fluid accumulation is difficult due to the presence of gravid uterus.
- Baseline blood pressure is often lower and pulse pressure wider
- Baseline heart rate may be higher
- Elevated liver enzymes
- Low haemoglobin and platelet
- Mild metabolic acidosis and low PaCO<sub>2</sub> of 32mmHg (in 3<sup>rd</sup> trimester)

**i. Pregnancy Outcomes In Pregnant Women with Dengue Infection**

Significant bleeding due to thrombocytopenia is not common. However, both mother and the newborn with dengue infection may be at an increased risk for haemorrhage in the presence of dengue shock syndrome (DSS). It was observed that higher percentage of severe dengue infection occurred among pregnant women compared to non-pregnant women (OR: 3.38; CI: 2.10–5.42,  $p = 0.0001$ )<sup>186,level II-3</sup>. Significant number of pregnant women with dengue may present with DSS and mortality demonstrated to be about 3 times higher in this group.<sup>186-188, level II-3</sup> A rare complication with pre-eclampsia, eclampsia or dengue encephalopathy have been reported.<sup>188,level II-3</sup>

A very close monitoring of the vital signs and early signs of shock and bleeding should be sought. Appropriate fluid therapy, and when indicated, blood and blood product transfusion should be instituted.<sup>187,level II-3</sup> A referral to intensivist and obstetrician should be done early in this group of patient to optimise care.

**ii. Maternal Complications in Pregnant Women with Dengue Infection**

Pregnant women with dengue who progressed to spontaneous vaginal delivery do not have additional risk of adverse outcomes. Maternal complications commonly happened when infection occur during first and third trimester. First trimester infection is associated with



abortion and third trimester infection commonly complicated with preterm birth.<sup>189,level III</sup> Infection occur during labour can be associated with worse maternal outcomes contributed by massive bleeding due to surgical interventions such as caesarean section and operative vaginal delivery. Acute dengue infection during this stage will increase the risk of fetal distress and higher chance of surgical interventions.<sup>188,level II-3 ;190,level III</sup>

### iii. Fetal Outcome in Pregnant Women with Dengue Infection

DEN virus can be vertically transmitted to the fetus in utero or to the infant at parturition from infected symptomatic pregnant women.<sup>186,level II-3</sup> Mother who are asymptomatic has very low risk of transmission to the fetus.<sup>191,level II-3</sup> Clinical monitoring and laboratory investigations should be carried out for up to 1 week of life in the neonates.<sup>192,level II-2</sup> Positive serology test for dengue IgM, NS1 antigen or RT-PCR to dengue in neonate confirmed the vertical transmission.<sup>192,level II-2</sup>

Dengue infection during pregnancy may be associated with various complications, including preterm delivery (4.0-17.9%), fetal death (8.9-13.6%), low birth weight (4.0-24.3%) and more frequent miscarriage (RR= 3.3).<sup>187-188,level II-3;192-193,level II-2;194,level III</sup> No long term fetal abnormalities noted among infants with vertical transmission.<sup>192,level II-2</sup>

### iv. Mode and Timing of Delivery

Dengue infection is not an indication for elective delivery. Majority of patients can be allowed to progress to spontaneous vaginal delivery.<sup>190,level III</sup> However, if premature labour occurs during the acute infection, it is advisable to delay the delivery until acute infection resolve. The use of tocolytic drugs such as nifedipine and atosiban may be indicated. Close fetal monitoring is required in this group of patients to detect fetal distress and decision for delivery can be made by the obstetrician. All pregnant mothers with dengue should be co-managed in hospitals by physician, anaesthetist and obstetrician.<sup>189,level III</sup> Deliveries in this patient group should be conducted by obstetrician or senior medical officer (in hospital without specialist).

Instrumental delivery should be avoided where possible and if indicated, the procedures should be done by an obstetrician.<sup>189,level III</sup> When the decision for instrumental delivery or operative delivery is made, the blood and blood products must be made available.<sup>189,level III</sup> Active management of third stage of labour in preventing postpartum haemorrhage is required by the use of intravenous uterotonic agent (avoid intramuscular injection). Platelet transfusion is only recommended when patient has manifestation of bleeding, decision for caesarean section or instrumental delivery.<sup>189,level III</sup> In this patient, platelet transfusion should be targeted to achieve minimum of 50,000/ml to ensure maternal safety.<sup>189, level III</sup>

- HCT value in pregnant women is usually lower compared to normal adult due to physiological haemodilution.
- Dengue infection in pregnancy has a higher risk of developing severe dengue and mortality.
- Dengue infection in pregnancy has a higher adverse fetal outcome.
- Routine platelet transfusion is not indicated unless there is presence of bleeding manifestation or patient is planned for operative or instrumental delivery.
- Intramuscular injection must be avoided in pregnant patients with thrombocytopenia.

**Recommendation 11**

- All pregnant mothers with dengue should be managed in hospitals by physician, anaesthetist and obstetrician.
- Blood and blood products should be transfused as indicated when operative delivery is decided.
- Spontaneous vaginal delivery should be the preferred mode of delivery.
- Serology test (Dengue IgM and NS1 antigen) or RT-PCR should be performed in neonates to confirm congenital dengue.

**9. DISCHARGE CRITERIA**

The following should be taken into consideration before discharging a patient.<sup>60,level III; 61</sup>

- Improved general well-being
- Afebrile for 24-48 hours
- Rising white cell count followed by platelet count
- Stable haematocrit
- Resolution/recovery of organ dysfunction

**10. PREVENTION OF DENGUE TRANSMISSION IN HOSPITALS**

Patients are viraemic and hence potentially infectious during the febrile phase.<sup>195-196,level III</sup>  
There are no scientific studies that address the efficacy of mosquito repellents or mosquito netting in reducing dengue transmission in hospitalised patients. However, several community studies have shown that the use of mosquito netting/ screening was efficacious in preventing transmission of dengue in the community.<sup>197,level I; 198, level III</sup>

Generally, repellent products with higher concentrations of DEET (N,Ndiethyl-m-toluamide) were found to have longer repellence times.<sup>199,level III</sup>

**11. VACCINATION**

There are published and ongoing trials on the efficacy of dengue vaccine among the paediatric population.<sup>200-202, level I</sup>

## 12. IMPLEMENTING THE GUIDELINES

It is important to standardise the management of dengue infection in adults at all healthcare levels in Malaysia by using an evidence-based CPG. This aims to prevent mortality and long-term morbidity.

### 12.1 Facilitating and Limiting Factors

Existing facilitators for application of the recommendations in the CPG include:-

- i. wide dissemination of the CPG to healthcare providers (hardcopies and softcopies)
- ii. regular dengue update for healthcare providers

Existing barriers for application of the recommendations of the CPG are:-

- i. inadequate understanding of dengue infection and management among patients/carers and healthcare providers
- ii. insufficient resources especially trained personnel, diagnostic kits and infrastructure
- iii. variation in treatment practice and preferences

### 12.2 Potential Resource Implications

To implement the CPG, there must be strong commitment to:-

- i. ensure widespread distribution of the CPG to healthcare providers
- ii. initiate training (with adequate funding) of healthcare providers ensuring information is up-to-date
- iii. ensure availability of highly specialised diagnostic tools and trained manpower in dengue management including multidisciplinary team at different levels of healthcare
- iv. ensure widespread distribution of updated patient education materials

Implementation strategies such as Quick Reference and Training Module will be developed following the approval of the CPG by MoH.

To assist in the implementation of the CPG, the following is proposed as **clinical audit indicator for quality management**:-

- |   |   |   |        |
|---|---|---|--------|
| i. <b>Case fatality rate of dengue infection</b>                          | = | $\frac{\text{No. of death of dengue infection}}{\text{No. of dengue infection}} \times 100\%$ | X 100% |
| National target < 0.2%  |   |   |        |
| ii. <b>Case fatality rate for severe dengue</b>                           | = | $\frac{\text{No. of death in severe dengue}}{\text{Total no. of severe dengue}} \times 100\%$ | X 100% |
| iii. <b>Clinical audit surveillance on outcome of Dengue in Pregnancy</b> | : | Maternal and fetal outcomes in each trimester   |        |

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**CLINICAL QUESTIONS**

1. What is the current epidemiological data and notification system for dengue?
2. What are the serotyping patterns of dengue infection in Malaysia?
3. What are the clinical criteria or classification used to diagnose dengue infection?
4. What are the effective tools/investigations in diagnosis of dengue?
5. What are the effective investigations in diagnosing dengue?
6. What are the effective/safe management of patients with dengue infection at primary care or outpatient department?
7. What are the effective/safe risk stratification and management of patient that can be treated at home?
8. What are the effective/safe management of patients with dengue infection in emergency department/during triaging?
9. What are the effective/safe management of patients with dengue infection before transferring from ED to the ward?
10. What are the effective/safe management of patients with dengue infection who requires hospitalisation?
11. What are the effective/safe tools and management for inpatient disease monitoring?
12. What are the effective/safe fluid management in patients with dengue infection?
13. What are the complications of dengue infection and the effective/safe management of these complications?
14. What are the criteria for intensive care referral of dengue infection?
15. What are the effective/safe intensive care management for dengue infection?
16. What are the effective/safe management of dengue infection in pregnancy?
17. What are the discharge criteria for patients with dengue infection?
18. What are the effective/safe preventive measures for dengue transmission in hospital?

## SEARCH STRATEGY

The following MeSH terms or free text terms were used either singly or in combination. Search was limited to English, human and last five years. These are some of the examples of search strategy used for the clinical questions. The details are available upon request from the CPG Secretariat.

**Emergency management**

- 1 dengue/
- 2 severe dengue/
- 3 dengue\*.tw.
- 4 (dengue adj1 fever).tw.
- 5 ((breakbone or break-bone or break bone) adj1 fever).tw.
- 6 (classical adj1 dengue\*).tw.
- 7 classical dengue fever\*.tw.
- 8 (severe adj1 dengue\*).tw.
- 9 hemorrhagic dengue\*.tw.
- 10 (dengue adj1 hemorrhagic fever).tw.
- 11 dengue shock syndrome.tw.
- 12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
- 13 EMERGENCY SERVICE, HOSPITAL/
- 14 ((Emergency or unit\* emergency) adj1 (room\* or ward\* or unit\* or outpatient unit\* or department\*)).tw.
- 15 "accident and emergency department".tw.
- 16 ((hospital emergenc\* or emergenc\* hospital) adj1 service\*).tw.
- 17 (hospital adj1 (emergenc\* service\* or services emergenc\*)).tw.
- 18 13 or 14 or 15 or 16 or 17
- 19 Clinical laboratory techniques/
- 20 ((Clinical laboratory or laboratory) adj1 (technique\* or diagnos\* or technique\* clinical)).tw.
- 21 ((Laboratory or diagnos\*) adj test\*).tw.
- 22 "diagnos\* and laboratory examinations".tw.
- 23 19 or 20 or 21 or 22
- 24 12 and 18 and 23

**Diagnostic test (1)**

- 15 IMMUNOGLOBULIN M/
- 16 Immunoglobulin M.tw.
- 17 IMMUNOGLOBULIN G/
- 18 7s gamma globulin.tw.
- 19 gamma globulin 7s.tw.
- 20 igg2b.tw.
- 21 igg2a.tw.
- 22 immunoglobulin g.tw.
- 23 polyglobin.tw.
- 24 igg1.tw.
- 25 igg2.tw.
- 26 igg3.tw.
- 27 igg4.tw.
- 28 igg.tw.
- 29 igg t.tw.
- 30 Primary infection.tw.
- 31 Secondary infection/
- 32 Secondary infection.tw.
- 33 COINFECTION/
- 34 (infection\* adj1 mixed).tw.
- 35 (infection\* adj1 secondary).tw.
- 36 co\*infection\*.tw.
- 37 (infection\* adj1 polymicrobial).tw.

**Fluid management**

- 1 dengue/
- 2 severe dengue/
- 3 dengue\*.tw.
- 4 (dengue adj1 fever).tw.
- 5 ((breakbone or break-bone or break bone) adj1 fever).tw.
- 6 (classical adj1 dengue\*).tw.
- 7 classical dengue fever\*.tw.
- 8 (severe adj1 dengue\*).tw.
- 9 hemorrhagic dengue\*.tw.
- 10 (dengue adj1 hemorrhagic fever).tw.
- 11 dengue shock syndrome.tw.
- 12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
- 13 Rehydration\*.tw.
- 14 Fluid adj1 (therap\* or management or replacement or resuscitation or administration).tw.
- 15 Starch-based intravenous fluid.tw.
- 16 (Starch\* or derivatives or starch derivatives) adj1 (hydroxyethyl\* or hydroxyethyl starch).tw.
- 17 Colloid\*.tw.
- 18 Hydrocolloid\*.tw.
- 19 Gelatine.tw.
- 20 Gelafusal.tw.
- 21 gel?fusine.tw.
- 22 Dextrans/
- 23 Dextran\*.tw.
- 24 Isotonic Solutions/
- 25 Isotonic adj1 solutions.tw.
- 26 Saline Solution, Hypertonic/
- 27 solution\* adj1 (hypertonic saline or saline hypertonic).tw.
- 28 sodium chloride solution\* hypertonic.tw.
- 29 Ringer's lactate.tw.
- 30 Albumins/
- 31 Albumins.tw.
- 32 Prealbumin.tw.

**Diagnostic test (2)**

- 1 Rapid combo test.tw.
- 2 Duo test.tw.
- 3 ANTIBODIES, VIRAL/
- 4 (viral adj1 antibodies).tw.
- 5 REAGENT KITS, DIAGNOSTIC/
- 6 in vitro diagnostic medical device\*.tw.
- 7 (diagnostic adj1 test kit\*).tw.
- 8 (reagent adj1 kit\* diagnostic).tw.
- 9 diagnostic reagent kit\*.tw.
- 10 in vitro diagnostic device\*.tw.
- 11 non-structural protein 1/
- 12 Non-structural protein 1.tw.
- 13 VIRAL NONSTRUCTURAL PROTEINS/
- 14 ((nonstructural or non-structural) adj1 protein\* viral).tw.
- 15 (protein\* adj1 viral ns).tw.

**Complications**

- 1 dengue/
- 2 severe dengue/
- 3 dengue\*.tw.
- 4 (dengue adj1 fever).tw.
- 5 ((breakbone or break-bone or break bone) adj1 fever).tw.
- 6 (classical adj1 dengue\*).tw.
- 7 classical dengue fever\*.tw.
- 8 (severe adj1 dengue\*).tw.
- 9 hemorrhagic dengue\*.tw.
- 10 (dengue adj1 hemorrhagic fever).tw.
- 11 dengue shock syndrome.tw.
- 12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
- 13 Cardiac complication\*.tw.
- 14 Heart complication\*.tw.
- 15 h?emophagocytic syndrome adj (infection associated or infection-associated).tw.
- 16 infection-associated h?emophagocytic syndrome.tw.
- 17 h?emophagocytic syndrome\*.tw.
- 18 h?emophagocytic adj1 lymphohistiocytos?s.tw.
- 19 reactive adj1 (h?emophagocytic syndrome).tw.
- 20 lymphohistiocytos?s hemophagocytic.tw.
- 21 rhabdomyolys?s.tw.
- 22 Hepatitis/
- 23 Hepatitis.tw.
- 24 Hepatitides.tw.
- 25 Encephalopathy.tw.
- 26 Encephalitis/
- 27 encephalitis.tw.
- 28 (brain adj1 inflammation\*).tw.
- 29 (infectious adj1 encephaliti\*).tw.
- 30 Meningitis/
- 31 Meningitis.tw.
- 32 Meningitides.tw.
- 33 Renal impairment.tw.
- 34 Renal Insufficiency/
- 35 (insufficienc\* adj1 (renal or kidney)).tw.
- 36 (failure\* adj1 (kidney or renal)).tw.
- 37 Acute Kidney Injury/
- 38 (acute adj1 (kidney failure\* or renal failure\* or renal injur\* or kidney injur\*)).tw.
- 39 (acute adj1 (kidney insufficienc\* or renal insufficienc\*)).tw.



**WORLD HEALTH ORGANIZATION CLASSIFICATION OF DF AND DHF (1997)****CASE DEFINITION FOR DENGUE FEVER**

Given the variability in the clinical illness associated with dengue infection, it is not appropriate to adopt a detailed clinical definition of dengue fever. Rather, the need for laboratory confirmation is emphasised.

The following classifications are proposed:

- Probable – an acute febrile illness with two or more of the following manifestations:
  - headache
  - retro-orbital pain
  - myalgia
  - arthralgia
  - rash
  - haemorrhagic manifestations
  - leucopenia

**AND**

- Supportive serology (a reciprocal haemagglutination-inhibition antibody titre  $\geq 1280$ , a comparable IgG enzyme-linked immunosorbent assay (ELISA) titre or a positive IgM antibody test on a late acute or convalescent-phase serum specimen)

**OR**

- Occurrence at the same location and time as other confirmed cases of dengue fever
  - Confirmed – a case confirmed by laboratory criteria (see below)
  - Reportable – any probable or confirmed case should be reported

Laboratory criteria for confirmation of dengue fever are

- Isolation of the dengue virus from serum or autopsy samples; or
- Demonstration of a fourfold or greater change in reciprocal IgG or IgM antibody titres to one or more dengue virus antigens in paired serum samples; or
- Demonstration of dengue virus antigen in autopsy tissue, serum or cerebrospinal fluid samples by immune histochemistry, immune fluorescence or ELISA;

**OR**

- Detection of dengue virus genomic sequences in autopsy tissue serum or cerebrospinal fluid samples by polymerase chain reaction (PCR).

**CASE DEFINITION FOR DENGUE HAEMORRHAGIC FEVER**

The following must ALL be present :

- Fever, or history of acute fever, lasting 2–7 days, occasionally biphasic.
- Haemorrhagic tendencies, evidenced by at least one of the following:
  - a positive tourniquet test
  - petechiae, ecchymoses or purpura
  - bleeding from the mucosa, gastrointestinal tract, injection sites or other locations
  - haematemesis or melaena
- Thrombocytopenia (100,000 cells per mm<sup>3</sup> or less).
- Evidence of plasma leakage due to increased vascular permeability, manifested by at least one of the following:
  - a rise in the HCT equal to or greater than 20% above average for age, sex and population;
  - a drop in the HCT following volume-replacement treatment equal to or greater than 20% or baseline;
  - signs of plasma leakage such as pleural effusion, ascites and hypoproteinaemia

**CASE DEFINITION FOR DENGUE SHOCK SYNDROME**

All of the above four criteria for DHF must be present, plus evidence of circulatory failure manifested by:

- Rapid and weak pulse, and
- Narrow pulse pressure [ $<20\text{mmHg}$  (2.7 kPa)]  
OR manifested by:
  - Hypotension for age, and
  - Cold, clammy skin and restlessness

Grade I : Fever accompanied by non-specific constitutional symptoms; the only haemorrhagic manifestation is a positive tourniquet test and / or easy bruising.

Grade II : Spontaneous bleeding, in addition to the manifestations of Grade I patients, usually in the form of skin or other haemorrhages.

\*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 :* \* i. Grades III and IV are classified as Dengue Shock Syndrome  
ii. The WHO Classification has been reviewed and revised.

## METHODS OF SAMPLE COLLECTION

### 1. Rapid Combo Test (bed side test)

- i. Draw 1 ml of blood into a plain tube without anti-coagulants.
- ii. Set-up the rapid combo test device on suitable surface area.
- iii. Proceed to perform the test according to the procedure, using whole blood.
- IV. Read the results within the stipulated time and discard the device and other clinical waste in biohazard bag.

### 2. Dengue Serology (ELISA)

- i. Draw 3-5 ml of blood into a plain tube without anti-coagulants.
- ii. Clot at ambient temperature
- iii. Dispatch to the laboratory within 4 hours of collection for serum separation by centrifugation.

Note : Haemolysed or icteric or lipaemic specimens invalidate certain test. If such specimens are received, the samples will be rejected to assure results are of clinical value.

### 3. Viral Genome Detection (PCR)

#### a) Blood

- i. Collect 3-5 ml of blood into plain tube.
- ii. Send directly to virology lab within 2 hours of sampling. If this is delayed, centrifuge and aliquot serum into sterile tube. Keep the sample in a freezer at -70°C and put in ice when sending to Virology laboratory the next day.

#### b) Cerebrospinal fluid (CSF)

- i. Collect a minimum of 0.5 ml (5 drops) of CSF into sterile bijou bottle.
- ii. Pack in ice for transport.
- iii. Send directly to virology lab within 2 hours after being taken.
- iv. Send together with serum sample.

#### c) Post-mortem tissue sample

Tissue specimens should be placed in a sterile container containing either viral transport media (VTM) or normal saline (NS) and sent immediately to the laboratory which can perform dengue real time RT-PCR.

### 4. Viral Isolation

#### a) Blood

- i. Draw 3-5 ml of blood into a plain tube without anti-coagulants

#### b) CSF

- i. Collect at least 1 ml of CSF specimen in a sterile plain screw capped container (universal or Bijou Bottle). Do not add in VTM or freeze.
- ii. Pack the specimen individually in biohazard plastic bag and keep in 4°C or in cold box with ice.
- iii. Send to the lab within 24 hours after collection.

#### c) Tissue or post mortem tissue

- i. Put the tissue in sterile container containing viral transport media or normal saline and screw capped tight.
- ii. Packed the specimen individually in biohazard plastic bag and keep in 4°C or in cold box with ice.
- iii. Send to the laboratory within 24 hours after collection
  - Inform the laboratory processing the samples that the case was fatal

- Obtain a blood sample to attempt virus isolation and serology
- Obtain tissue samples for separate tests of virus isolation and immunohistochemistry

**TYPE OF TESTS FOR DENGUE DIAGNOSIS AND RECOMMENDED USE**

Type of test	Technique	Recommended Time To Use	Sensitivity (%)	Specificity (%)
1. Antibody Detection	IgM Detection	4 days after onset of symptoms and up to 3 months in primary dengue. 3 days after onset of symptoms and sometimes hindered by large scale IgG production in secondary dengue	61.5-100	52.0-100
	IgG Detection	10 days after onset of symptom in primary dengue and 3 days after onset of symptoms in secondary dengue	46.3-99.0	80.0-100
	Rapid IgM Detection (Strips)	5 days after onset of symptoms and up to 2 months	20.5-97.7	76.6-90.6
2. Antigen/ Antibody Combined Detection	NS1 and IgM Combo Kit	As this is a combo test, useful in early stage of infection (day 3 onwards) and up to sero conversion period (up to two weeks onwards)	89.9-92.9	75.0 – 100
	NS1 and IgM/IgG Combo kit	As this is a combo test, useful in early stage of infection (day 3 onwards) and up to sero conversion period (up to two weeks onwards). In the event of both NS1 and IgM are non reactive and IgG is reactive, case can be interpreted as secondary dengue.	93.0	100
3. Viral Detection	Virus Isolation (cell culture)	1-5 days of onset of symptoms in Primary Dengue and 1-4 days after onset of symptoms in secondary dengue	40.5	100
	Virus Isolation (mosquitoes)	- same as above-	71.5-84.2	100
	Viral RNA RT-PCR (Conventional)	- same as above-	48.4-100	100
	Viral RNA RT-PCR (Real Time)	- same as above-	58.9-100	100
	Viral Antigen (NS1)	1-7 days of onset of symptoms in Primary Dengue and 1-5 days after onset of symptoms in secondary dengue	54.2-93.4	92.5-100

**TYPE OF DENGUE TESTS RECOMMENDED BASED ON CLINICAL HISTORY**

Clinical History	Test	Result	Interpretation
History of fever less than 5 days	Dengue NS1 Ag or RCT	Positive	Acute dengue infection.
		Negative	Dengue infection still cannot rule out. Suggest to send second sample for Dengue IgM after day 5 of fever
History of fever more than 5 days	Dengue IgM	Positive	Presence of detectable IgM antibody. Suggestive of recent dengue infection
		Indeterminate	Advice to repeat the test.
		Negative	The result does not rule out dengue infection. Advice to send repeat sample for dengue IgM after day 7 of fever or ask for Dengue IgG test.
History of fever more than 5 days and Dengue IgM and /or NS1 was negative	Dengue IgG	Positive	Elevated IgG levels are seen in acute or past infections. A titre of equal or more than 1:2560 is consistent with acute secondary infection.
		Indeterminate	Advice to repeat the test if clinically indicated.
		Negative	No detectable elevated IgG antibody. The absence of elevated IgG is presumptive evidence that the patient does not have secondary dengue infection.



**DENGUE ASSESSMENT CHECKLIST**

**DENGUE ASSESSMENT CHECKLIST**

RECOGNITION			
CRITERIA	Yes	No	Details
Fever	<input type="checkbox"/>	<input type="checkbox"/>	
Aches & pains	<input type="checkbox"/>	<input type="checkbox"/>	
Nausea and/or vomiting	<input type="checkbox"/>	<input type="checkbox"/>	
Rash	<input type="checkbox"/>	<input type="checkbox"/>	
Leucopenia	<input type="checkbox"/>	<input type="checkbox"/>	
Any Warning Signs	<input type="checkbox"/>	<input type="checkbox"/>	
Warning Signs	Yes	Details	
Persistent vomiting/ diarrhoea ( $\geq 3x$ over last 24h)	<input type="checkbox"/>		
Any abdominal pain/ tenderness	<input type="checkbox"/>		
Lethargy/ restlessness/ confusion	<input type="checkbox"/>		
Tender liver	<input type="checkbox"/>		
Third space fluid accumulation	<input type="checkbox"/>		
Spontaneous bleeding tendencies	<input type="checkbox"/>		
Raised Hct with rapid drop in platelet	<input type="checkbox"/>	<i>(In the absence of baseline values)</i>	
<i>Male <math>\leq 60</math>: Hct <math>&gt; 46</math></i>			
<i>Male <math>&gt; 60</math>: Hct <math>&gt; 42</math></i>			
<i>Female all ages: Hct <math>&gt; 40</math></i>			
Other criteria for admission	Yes	Details	
Syncope	<input type="checkbox"/>		
Diarrhoea	<input type="checkbox"/>		
Social factor	<input type="checkbox"/>		
Special group	Yes	Details	
Obese	<input type="checkbox"/>		
Pregnant	<input type="checkbox"/>		
Heart failure/ CKD/ CLD	<input type="checkbox"/>		
DM	<input type="checkbox"/>		
HPT	<input type="checkbox"/>		
IHD	<input type="checkbox"/>		
COPD	<input type="checkbox"/>		
Age $> 65$	<input type="checkbox"/>		
<b>ADMIT if ANY WARNING SIGNS present or presence of other criterion for admission.</b> <b>CONSIDER admission for patients in the special group even in the absence of warning signs.</b>			
Instructions			
1. Please notify			

PATIENT DETAILS			
Name :			
IC No / MRN :			
WCC:	Temp:		
Hb:	BP/MAP:		
Hct:	HR:		
Plt:	CRT:		
	RR:		
SEVERE DENGUE		Yes	Details
Hypotension SBP $<90$ or MAP $<60$ or SBP drop $>40$ mmHg from known baseline		<input type="checkbox"/>	
Shock index: HR $>$ SBP or impaired perfusion		<input type="checkbox"/>	
Third space fluid accumulation with respiratory distress		<input type="checkbox"/>	
Disturbed conscious level		<input type="checkbox"/>	
Any bleed GI/ non-mucosal and non-cutaneous/ supra-physiological		<input type="checkbox"/>	
Specific organ dysfunction <i>(pls specify)</i>		<input type="checkbox"/>	
CRITICAL CARE REVIEW & FAST-TRACK			
Instructions			
1. Review features of severe dengue present. 2. Specify start and end time of fluid regime			
Date & Time of:			
Fever onset:			
Critical phase onset:			
Phase:			
Febrile	<input type="checkbox"/>	Critical	<input type="checkbox"/>
		Recovery	<input type="checkbox"/>
DIAGNOSIS			
DENGUE FEVER WITHOUT WARNING SIGNS			<input type="checkbox"/>
DENGUE FEVER <b>WITH WARNING SIGNS</b>			<input type="checkbox"/>
<b>SEVERE DENQUE</b>			<input type="checkbox"/>
Dr:			
Date:			

**HOME CARE ADVICE LEAFLET FOR DENGUE PATIENTS****Front View**

**HOME CARE ADVICE FOR DENGUE PATIENTS**

**WHAT SHOULD BE DONE?**

- Adequate bed rest
- Adequate fluid intake (more than 8 glasses or 2 litres for an average person).
  - Milk, fruit juice (caution with diabetes patient) and isotonic electrolyte solution (ORS) and barley water.
  - Plain water alone is not sufficient and may cause electrolyte imbalance.
- Take paracetamol (not more than 4 gram per day).
- Tepid sponging.
- If possible, use mosquito repellent or rest under a mosquito net even during day time to prevent mosquito bites.
- Look for mosquito breeding places in and around the home and eliminate them.

**WHAT SHOULD BE AVOIDED?**

- Do not take non steroidal anti-inflammatory (NSAIDS) eg. aspirin / mefenamic acid (ponstan) or steroids. If you are already taking these medications, please consult your doctor.
- Antibiotics are not required
- Do not take injection
- Do not do massage / cupping / quasa

**Back View**

**THE DANGER SIGNS OF DENGUE INFECTION  
(IF ANY OF THESE ARE OBSERVED, PLEASE GO IMMEDIATELY TO THE NEAREST  
HOSPITAL / EMERGENCY DEPARTMENT)**

- 1. Bleeding**  
for example :
  - Red spots or patches on the skin
  - Bleeding from nose or gums
  - Vomiting blood
  - Black coloured stools
  - Heavy menstruation / vaginal bleeding
- 2. Frequent vomiting and/or diarrhoea**
- 3. Abdominal pain / tenderness / diarrhea**
- 4. Drowsiness or irritability**
- 5. Pale, cold or clammy skin**
- 6. Difficulty in breathing**

**Adapted :** CPG Management of Dengue Infection in Adults (Revised 2<sup>nd</sup> Edition), 2010



INPATIENT DENGUE MONITORING CHART

**DENGUE CHART** NAME: \_\_\_\_\_ MRSP: \_\_\_\_\_

Date	Time
TEMPERATURE	
BP	X
MAP	•
PR	X
<b>SHOCK INDEX</b>	
PR ≥ SBP	
PR > MAP	
PR ≤ MAP	
WT:	
HT:	
±	Disc:
<input type="checkbox"/> NSL	
<input type="checkbox"/> Ipc	
<input type="checkbox"/> Igt	
RR	
(count over 3 minutes)	
SpO <sub>2</sub>	
>95%	
<95%	
Inspired O <sub>2</sub> %	
<b>FLUIDS</b>	
Date	Time
Out/In	Fluid type
Volume (ml)	Volume (ml)
Line 1 (I)	Fluid type
Volume (ml)	Volume (ml)
Line 2 (I)	Fluid type
Volume (ml)	Volume (ml)
Line 3 (I)	Fluid type
Volume (ml)	Volume (ml)
<b>RUNNING TOTAL</b>	
Urine	
Vom/Inct	
Stools	
<b>TOTAL EXCRETION</b>	
WCC Baseline	
Hb Baseline	
PLT Baseline	
PLT Baseline	
MCOS Baseline	
LACT Baseline	

**LIST OF ABBREVIATIONS**

ABG	Arterial blood gases
ALT	Alanine transaminase
AST	Aspartate aminotransferase
BP	Blood pressure
BUSEC	Blood urea serum electrolyte creatinine
CCTVR	Skin colour, cold/warm extremities, capillary filling time <2 secs, pulse volume and rate
CK	Creatine kinase
CNS	Central nervous system
CRT	Capillary refill time
CSF	Cerebrospinal fluid
CVC	Central venous catheter
CVP	Central venous pressure
DBP	Diastolic blood pressure
DENV	Dengue virus
DF	Dengue fever
DHF	Dengue haemorrhagic fever
DIC	Disseminated intravascular coagulation
DSS	Dengue shock syndrome
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
FBC	Full blood count
FFP	Fresh frozen plasma
GCS	Glasgow Coma Scale
GXM	Group cross match
HCT	Hematocrit
HCO <sub>3</sub>	Bicarbonate
HI	Haemagglutination inhibition
HPS	Haemophagocytic syndrome
ICU	Intensive care unit
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMR	Institute of Medical Research
IV	Intravenous
IVC	Inferior vena cava
LDH	Lactate dehydrogenase
LFT	Liver function test
NAC	N-Acetylcysteine
NS1	Non-structural protein 1
PCR	Polymerase chain reaction
PP	Pulse pressure
PR	Pulse rate
RBS	Random blood sugar
RCT	Rapid combo test
RP	Renal profile
RR	Respiratory rate
RT-PCR	Reverse transcriptase Polymerase chain reaction
SBP	Systolic blood pressure
USG	Ultrasonography
WCC	White cell count
WHO	World Health Organization
WS	Warning signs

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