

CLINICAL PRACTICE GUIDELINES

MOH/P/PAK/302.15(GU)

MANAGEMENT OF DENGUE INFECTION IN ADULTS (THIRD EDITION) 2015



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 four (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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LEVELS OF EVIDENCE

Level	Study design
I	Evidence obtained from at least one properly randomised controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence
III	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 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. Details on the CPG development by MaHTAS can be obtained from Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015 (available at <http://www.moh.gov.my/index.php/pages/view/117>).

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 population to 361 cases per 100,000 population in 2014 (Figure 1). The dengue incidence rate is higher in the age group of 15 and above. 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 to be higher in the age group of 15 years and above (Figure 2) and the highest has been observed in 2004.

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

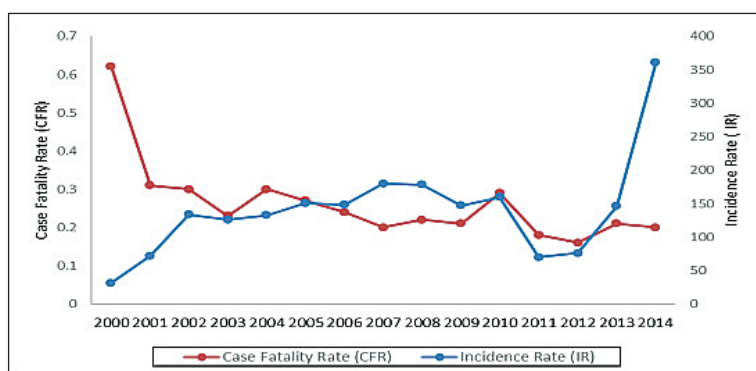
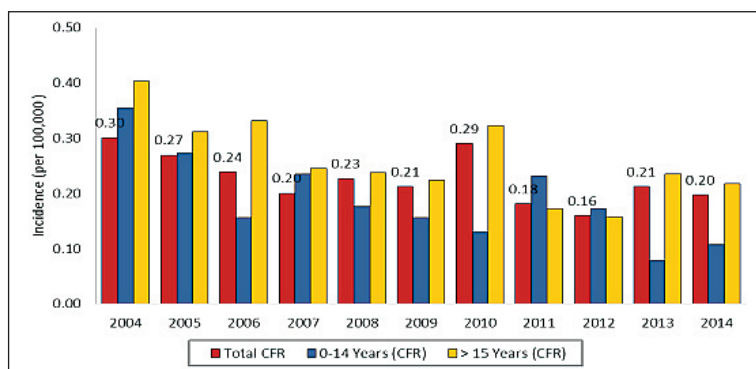


Figure 2: Dengue Case Fatality Rate (CFR) By Age Group In Malaysia, 2004-2014



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 3). In year 2013-2014, the predominant serotype had switched twice from DENV-2 to DENV-1 in February and June 2014 (Figure 4).

Figure 3: Dengue Serotypes in Malaysia (1990-2014)

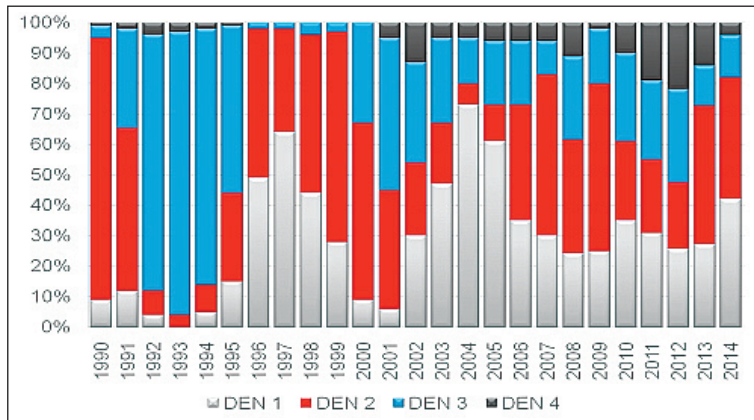
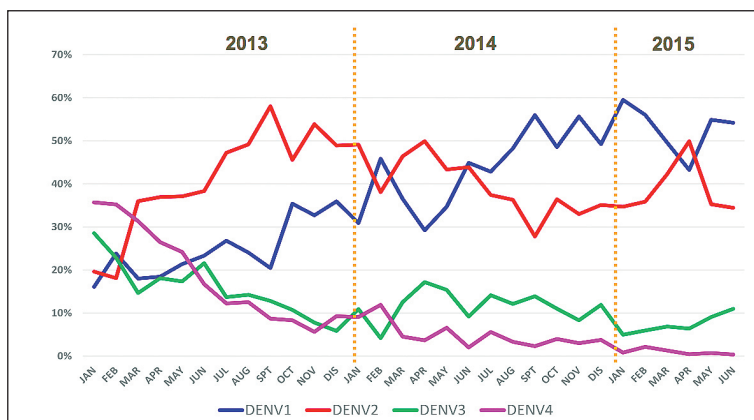


Figure 4: Dengue Serotypes in Year 2013, 2014 and 2015 (Jan-June)



3. CLINICAL MANIFESTATIONS AND PATHOPHYSIOLOGY

3.1 SPECTRUM OF DENGUE INFECTION

The incubation period for dengue infection is 4-7 days (range 3-14).¹ 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 hours or even minutes during the critical phase, particularly in those with plasma leakage (refer to subchapter 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 three phases: febrile, critical and recovery phase (refer to Figure 5).^{2,3}

i. Febrile Phase

Patients develop high grade fever suddenly and usually last 2-7 days. It is often accompanied by facial flushing, rash, generalised body ache, vomiting and headache.^{2,3} 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.^{4,5} Per vaginal bleeding may occur in females but rarely massive. Gastrointestinal bleeding is not uncommon.^{5,6} The findings of 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 third 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.^{2,3,7,8}

The critical phase lasts about 24-48 hours (refer to Figure 5). Varying circulatory disturbances (refer to Table 1) can develop. In less severe cases, these changes are minimal and transient. Many of these patients either recover spontaneously or after a short period of fluid or electrolyte therapy. In more severe forms of plasma leakage, the patients may develop compensated or 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.⁸⁻¹⁰ Organ dysfunctions such as hepatitis, encephalitis and myocarditis usually but not exclusively occur during this phase.

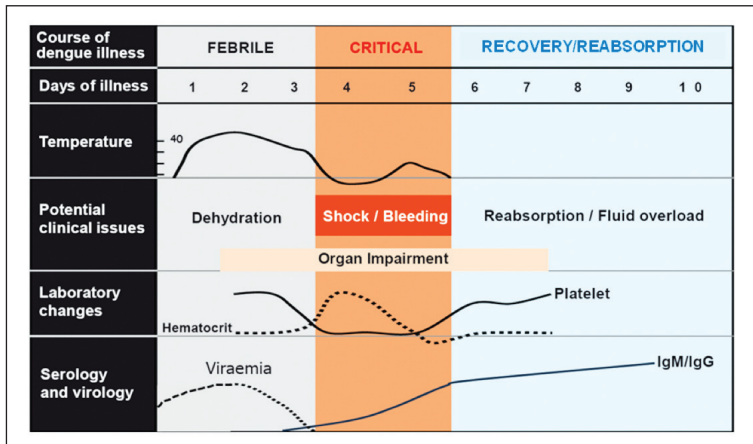
It is important to note that thrombocytopenia and haemoconcentration are usually detectable in this phase. The haematocrit (HCT) level correlates well with plasma volume loss and disease severity. However, interpretation of HCT may be difficult when there are confounding factors such as haemorrhage, 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.²⁻⁴

iii. Recovery/Reabsorption 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.² 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 (hepatitis, encephalitis and intracranial bleed) as the patient enters reabsorption phase.

Figure 5 : Clinical Course of DHF¹¹⁻¹³



- The critical phase often occurs after third 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.^{2,3,14} Hypovolaemia leads to reflex tachycardia and generalised vasoconstriction due to increased sympathetic output.^{15,16} 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.¹⁶

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

The following Table 1 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"> • Clear consciousness • Brisk capillary refill time (<2 sec) • Warm and pink peripheries • Good volume peripheral pulses • Normal heart rate for age • Normal blood pressure for age • Normal pulse pressure for age • Normal respiratory rate for age • Normal urine output 	<ul style="list-style-type: none"> • Clear consciousness - shock can be missed if you do not touch the patient • Prolonged capillary refill time (>2 sec) • Cool extremities • Weak & thready peripheral pulses • Tachycardia • Normal systolic pressure with raised diastolic pressure • Postural hypotension • Narrowing pulse pressure • Tachypnoea • Reduced urine output • Intense thirst 	<ul style="list-style-type: none"> • Change of mental state - restless, combative or lethargy • Mottled skin, very prolonged capillary refill time • Cold, clammy extremities • Feeble or absent peripheral pulses • Severe tachycardia with bradycardia in late shock • Hypotension / unrecordable BP • Narrowed pulse pressure (<20 mmHg) • Metabolic acidosis/ hyperpnoea / Kussmaul's breathing • Oliguria or anuria

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.^{17,18} 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- α , interleukin 2, 6 and 10, interferon- α and histamine are elevated.^{15,19}

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.²⁰⁻²² 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.^{15,19}

3.4 WHO DENGUE CLASSIFICATION

Based on 1997 WHO dengue classification scheme (refer to **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 ^{23, level I}

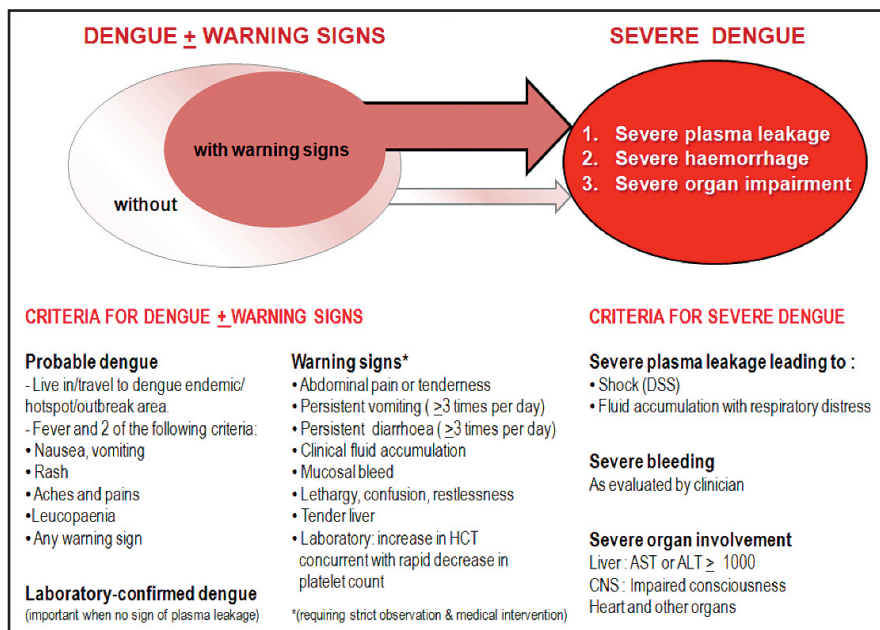
It has been observed that the 1997 WHO classification scheme has several limitations.

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

3.4.2 WHO Classification 2009

This classification addresses the levels of severity of dengue infection which is more practical to be used in the management decision of the patient (Figure 6).

Figure 6: 2009 WHO Dengue Classification and Level of Severity ²⁴



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. Diseases that may mimic dengue infection includes other viral illnesses. Organ dysfunction 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).²⁵

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 or when there is dengue death.

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.²⁶

Dengue mortality audit should be conducted within seven 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 2010.²⁶

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.^{4, level III} The decrease in WCC is accompanied by platelet reduction.

There is no correlation between disease severity and platelet count^{2, level III; 25, level III} and it is not predictive of bleeding.^{28, level I; 29, level II-2; 30-32, level III} 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 median values of normal HCT level among Malaysian populations are:^{33, level II-2}

- male \leq 60 years – 46%
- male > 60 years – 42%
- female (all age groups) – 40%

Other important blood tests in disease monitoring are Liver Function Test (LFT), Renal profile (RP), coagulation profile, lactate and blood gases (Table 6). Special tests such as Troponin and Creatine Kinase (CK) should be discussed with the Specialists/Registrars before performing.

Recommendation 1

- Baseline haematocrit (HCT) and white cell count should be established during the first visit in all patients with suspected dengue infection.
- Serial full blood count and HCT must be monitored as dengue infection 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 the ability to differentiate between dengue and other diseases with similar clinical presentation, 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.^{34-35, level II-2} Generally RCT tests can be read within 15-20 minutes. However, it is important that the tests have to be read according to the manufacturer's recommendation in the product insert.

Reading too late gives false results.

Interpretation of the results is through the presence or absence of bands for dengue NS1 antigen and dengue IgM and IgG antibodies.^{34-35,level II-2} These tests have a longer detection window as they can detect both the virus and antibodies, thus reducing the possibility of false negative results. Hence these tests are useful during the early phase of onset when there is viraemia as well as at a later stage when antibodies against dengue begin 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%.^{36,level II-2}

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 patterns of antibody response are seen in primary dengue infection as compared to secondary dengue infection.^{37,level II-2}

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 malignancies.^{38,level III}

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%).^{39-41,level III} The sensitivity of NS1 antigen detection drops from day 4-5 of illness onwards and usually becomes undetectable in the convalescence phase.^{40-42,level III}

The presence of NS1 detection after day five may predict severe dengue.^{44,level II-2}

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 two 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 five days of illness in approximately 80% of the cases.^{37,level II-2} 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 five days.

However, in secondary dengue infections, IgM was detected in among 78% of patients after day seven.^{45,level II-2} 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.^{46-48,level III}

iii. Dengue IgG test

In primary and secondary dengue infection, dengue IgG was detected in 100% of patients after day seven of onset of fever. Therefore, a repeat dengue IgG is recommended if dengue IgM is still negative after day seven with the negative IgG in the initial test sample. ^{45, level II-2; 47, level III}

iv. Differentiation between primary and secondary dengue infection

Detection of significant elevation of IgG antibodies to dengue virus by ELISA is very useful for identification of secondary dengue infections. ^{49-50, level II-2} 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. ⁵¹

Note: False positive dengue serology

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

- other flavivirus – Japanese Encephalitis ^{48, level III; 52, level III}
- non-flavivirus – malaria, leptospirosis, toxoplasmosis, syphilis ^{53-54, level III}
- connective tissue diseases – rheumatoid arthritis ^{55, level III}

5.2.3 Dengue Viral RNA Detection (Real time RT-PCR)

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 five days after onset of the symptoms. ^{56-57, level II-2} 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, State 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 to **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 when to do after the 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.

- 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.

Recommendation 2

- Dengue rapid combo test or non-structural protein 1 antigen (NS1 Ag) should be taken as soon as dengue infection is suspected.
- If dengue IgM is negative before day seven, a repeat sample must be taken in recovery phase.
- If dengue IgM is still negative after day seven, dengue IgG should be done for diagnostic confirmation of secondary dengue infection.

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

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.^{58-59,level III} 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 bijoux 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.

Recommendation 3

- A repeat dengue serology should be obtained at the time of dengue death.
- Suitable specimens for viral isolation and/or real time reverse transcriptase polymerase chain reaction (RT-PCR) and/or non-structural protein 1 (NS1) antigen detection should be done for confirmation of dengue infection.

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 three phases of the clinical course (refer to section 7.4). It is crucial to recognise plasma leakage, early shock and 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 Infection¹⁻³

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
- 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 intravenous drug user (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 refill 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 by the attending doctor (**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 is afebrile for at least 24-48 hours without antipyretics.
 - Provide the patient with Outpatient Dengue Monitoring Record (**Appendix 7**) and Home Care Advice Leaflet for Dengue Patients (**Appendix 9**)

Table 3: Warning Signs

- **Any abdominal pain/tenderness**
 - **Persistent vomiting (≥ 3 times over 24 hours)**
 - **Persistent diarrhoea (≥ 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 ≤ 60 years – 46%
 - HCT male > 60 years – 42%
 - HCT female (all age groups) – 40%
- *median values of normal HCT in Malaysian population^{33,level II-2.}

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 Home⁶⁰⁻⁶²

1. Able to tolerate orally well, good urine output and no history of bleeding
2. Absence of warning signs (refer to Table 3)
3. Physical examination:
 - Haemodynamically stable
 - No tachypnoea or acidotic breathing
 - No tender liver 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.^{60,level III; 63-64,level III}

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 and respiratory rate

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, Coagulopathy, 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 cases of 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, ICU and 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 of suspected dengue infection :

- FBC and HCT
- Point of care testing e.g. Rapid combo test (RCT) or NS1 antigen

In suspected severe dengue, the following investigations should be done:

- Blood gases and serum lactate
- LFT/AST and RP
- Creatine kinase (CK) to detect myocarditis and rhabdomyolysis
- GXM

7.3.5 Imaging Investigations in the Emergency Department for Patients Requiring Admission

Chest x-ray and ultrasound (where 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

- Dengue assessment checklist should be filled by the attending doctor for all patients with suspected dengue infection (refer to **Appendix 8**).
- All dengue patients requiring admission should be **immediately** started on an appropriate fluid therapy [oral or intravenous (IV)].
 - o When indicated, IV fluid therapy should be initiated and adjusted accordingly.
- In monitoring of dengue patients, the following must be done and documented:
 - o serial monitoring of vital signs
 - o strict monitoring of ongoing fluid losses and hourly fluid input/output charting
- Dengue 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 by the attending doctor (**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 summarise the issues, 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
Febrile	<ul style="list-style-type: none"> - Differentiation of dengue illness from other febrile illnesses.
Critical	<ul style="list-style-type: none"> - Plasma leakage occurs as patient progresses to late febrile phase or as temperature begins to defervesce (T <38.0 °C). - Clinical deterioration occurs during this phase due to plasma leakage. - Plasma leakage results in haemoconcentration and hypovolaemia/ shock. - Excessive plasma leakage due, in part, to intravenous fluid therapy may cause respiratory distress. - Bleeding can be precipitated by prolonged shock and shock can be perpetuated by bleeding. - Organ dysfunction may occur. - May mimic acute abdomen from other causes. - May be confused with septic shock or other forms of shock.
Reabsorption	<ul style="list-style-type: none"> - Cessation of plasma leakage. - Reabsorption of fluid from extravascular compartment. - Haemodilution occurs following fluid reabsorption. - Fluid overload and pulmonary oedema if intravenous fluid therapy is continued.

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
Clinical Parameters			
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 • CCTVR • BP • Pulse pressure	4-6 hourly depending on clinical status	2-4 hourly depending on clinical status	4-6 hourly
Respiratory status • RR • SpO ₂		In shock Every 15-30 minutes till stable then 1-2 hourly	
Neurological Status • conscious level • restlessness • seizures			
Urine output	4 hourly	2-4 hourly In shock : Hourly	4-6 hourly
Parameters for monitoring	Frequency of monitoring		
	Febrile phase	Critical phase	Reabsorption phase
Laboratory Parameters and Imaging			
All investigations done at ED must be reviewed immediately upon ward admission			
FBC	Daily or more frequently as indicated	4-12 hourly depending on clinical status In shock 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 In shock Crucial to monitor ABG and lactate closely	As clinically indicated
ABG, lactate Coagulation profile CRP Troponin or CKMB Fibrinogen, LDH, ferritin, triglyceride ECG 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 patients with unnecessary fluid boluses based on raised HCT or warning signs 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.
- Excessive 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.^{65,level II-3} 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.^{60,level III; 66,level III}

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. In dengue patients without co-morbidities who can tolerate orally, adequate oral fluid intake of two to three litres daily should be encouraged (often 1.2-1.5 times the normal 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 2-4 hours.

In patients with persistent warning signs with increasing or persistently high HCT, the graded fluid bolus may be initiated with caution (refer to Table 8). Frequent monitoring of clinical and laboratory parameters must be carried out every 2-4 hours until patients improve. Aim for urine output of 0.5-1.0 ml/kg/hr.

A rising HCT indicates on-going plasma leakage and will require an increase in the IV fluid infusion rate. If patients deteriorate and progress to shock, refer to the section on fluid resuscitation in DSS (subchapter 7.5.2).

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>Non-obese patients</p> <ul style="list-style-type: none"> • 1.2 to 1.5 ml/kg/hour <p>Adapted : 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 http://www.ncbi.nlm.nih.gov/books/NBK247761/</p>
<p>Obese patients (BMI ≥ 27.5 kg/m²)*</p> <p>Maintenance fluid can be calculated based on adjusted body weight</p> <ul style="list-style-type: none"> • Adjusted bodyweight (ABW) can be calculated using the formula. <ul style="list-style-type: none"> ○ $ABW = IBW + 0.4 (\text{actual weight} - IBW)**$ ○ Ideal bodyweight (IBW) can be estimated based on the following formula. ^{72, level III} <ul style="list-style-type: none"> > Female: $45.5 \text{ kg} + 0.91(\text{height in cm} - 152)$ > Male: $50.0 \text{ kg} + 0.91(\text{height in cm} - 152)$ <p>Adapted : * Malaysian Society for the Study of Obesity. Clinical Practice Guidelines: Management of Obesity. Ministry of Health, Malaysia;2004</p> <p>** GlobalRPH 2015, calculator adjusted body weight (available at http://www.globalrph.com/ibw_calc.htm)</p>
<p>CAUTION : Fluid intake and urine output must be reviewed and adjusted according to clinical response. Use of volumetric pumps is encouraged, especially in patients requiring close fluid monitoring.</p>

Table 8 : Graded Fluid Bolus Regime

• Obtain a baseline HCT before fluid therapy.
• Give crystalloids solution (such as 0.9% saline).
• 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.
• If the clinical parameters are worsening and HCT is rising, increase the rate of infusion.
• Reassess the clinical status, repeat the HCT and review fluid infusion rates accordingly.

Recommendation 5

- In dengue patients without co-morbidities who can tolerate orally, adequate oral fluid intake of two to three litres daily should be encouraged. These patients may not require intravenous (IV) fluid therapy.
- IV fluid should be instituted in dengue patients with:
 - o vomiting, unable to tolerate oral fluids or severe diarrhoea
 - o increasing haematocrit (with other signs of ongoing plasma leakage) despite increased oral intake
- In patients with persistent warning signs with increasing or persistently high HCT, the graded fluid bolus may be initiated with caution.
- Crystalloids solution should be the fluid of choice for non-shock dengue 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.^{67,level 1} Refer to 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 maybe recurrent episodes of shock because capillary leakage can continue for 24-48 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 5-15 years are available.^{67-70,level 1} 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.^{67-69, level 1; 71,level 1} 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.^{68-69,level 1} 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.^{72,level 1}

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.^{70,level 1;72,level 1}

Hypertonic sodium lactate in DSS has shown positive results in only one study.^{73,level 1} 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

A. Clinical response parameters	
✓	Improvement of general well being/mental state
✓	Warm peripheries
✓	Capillary refill time <2sec
✓	BP stable
✓	Improving pulse pressure
✓	Reducing tachycardia
✓	Improving urine output
✓	Less tachypnoea
B. Laboratory parameters	
✓	Appropriate decrease in HCT
✓	Improvement in metabolic acidosis and lactate clearance
C. Imaging parameters (recommended but not mandatory)	
✓	Improvement of IVC collapsibility index (spontaneous breathing patient)
$\frac{\text{IVC expiratory diameter} - \text{IVC inspiratory diameter}}{\text{IVC expiratory diameter}} \times 100 = \text{Caval index (\%)}$	
<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. >40% collapse will be fluid responsive.⁷²</p>	
<p>Adapted : Goldflam K, Saul T and Lewiss R. Focus on: inferior vena cava ultrasound. ACEP News 6. 2011. pp 24-25. (available at : http://www.acep.org/Content.aspx?id=80791)</p>	
<p>CAUTION : IVC assessment should be performed by trained personnel and not to be interpreted in isolation.</p>	

7.5.3 Non-responders to Initial Resuscitation (Refer to 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.^{1,60,level III} (refer to **Algorithm A** and **Algorithm B**)

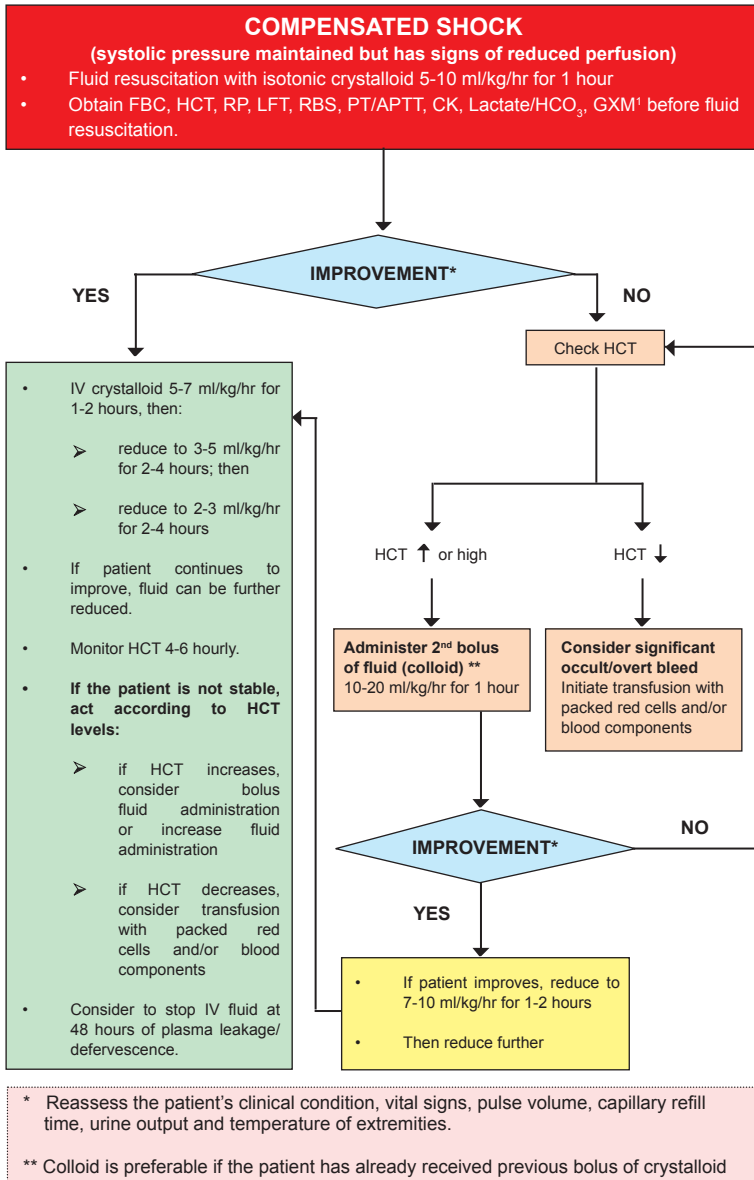
If the repeat HCT drops after two cycles of fluid resuscitation and the patient remains in shock, one should suspect significant bleed (often occult) for which blood ± blood products transfusion needs to be instituted promptly. (refer to **Algorithm A** and **Algorithm B**)

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.^{69,level I}

ALGORITHM A - FLUID MANAGEMENT IN COMPENSATED SHOCK



IV = intravenous ; HCT = haematocrit

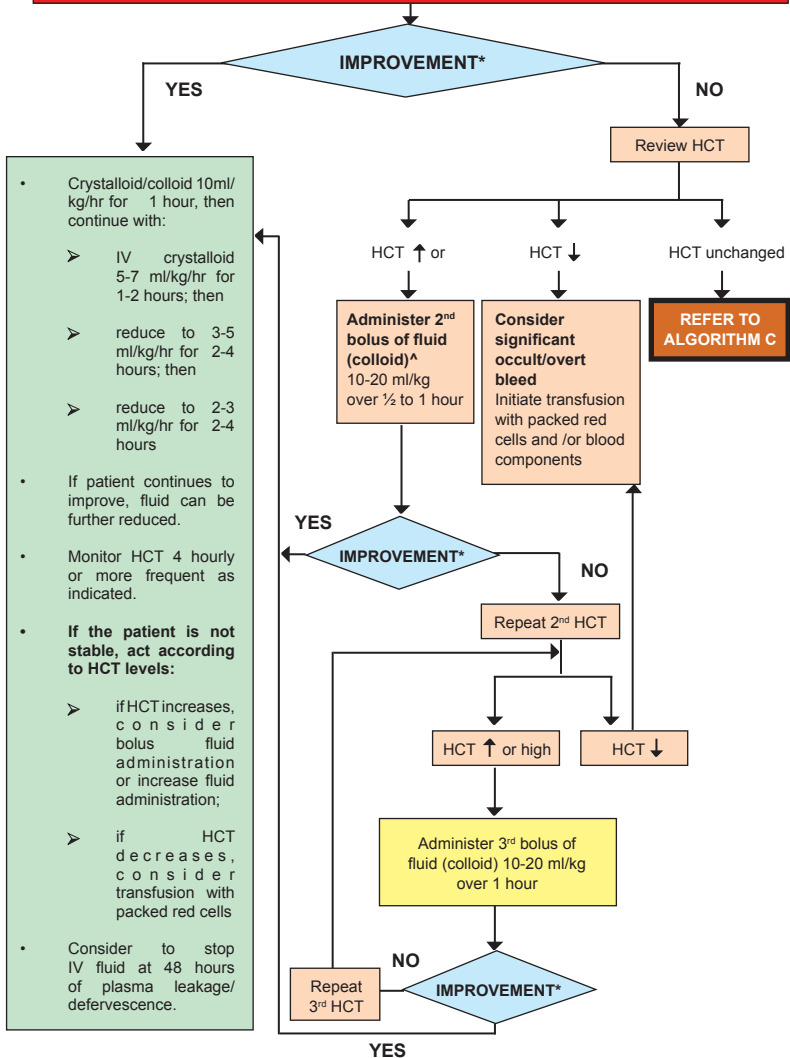
↑ = increased ; ↓ = decreased

¹GXM: emergency cross-match

ALGORITHM B - FLUID MANAGEMENT IN DECOMPENSATED SHOCK

DECOMPENSATED SHOCK

- Fluid resuscitation with 20 ml/kg colloid / crystalloid within 15 - 30 minutes
- Obtain HCT/FBC, RP, LFT, RBS, PT/APTT, CK, Lactate/HCO₃, GXM¹ before fluid resuscitation.



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

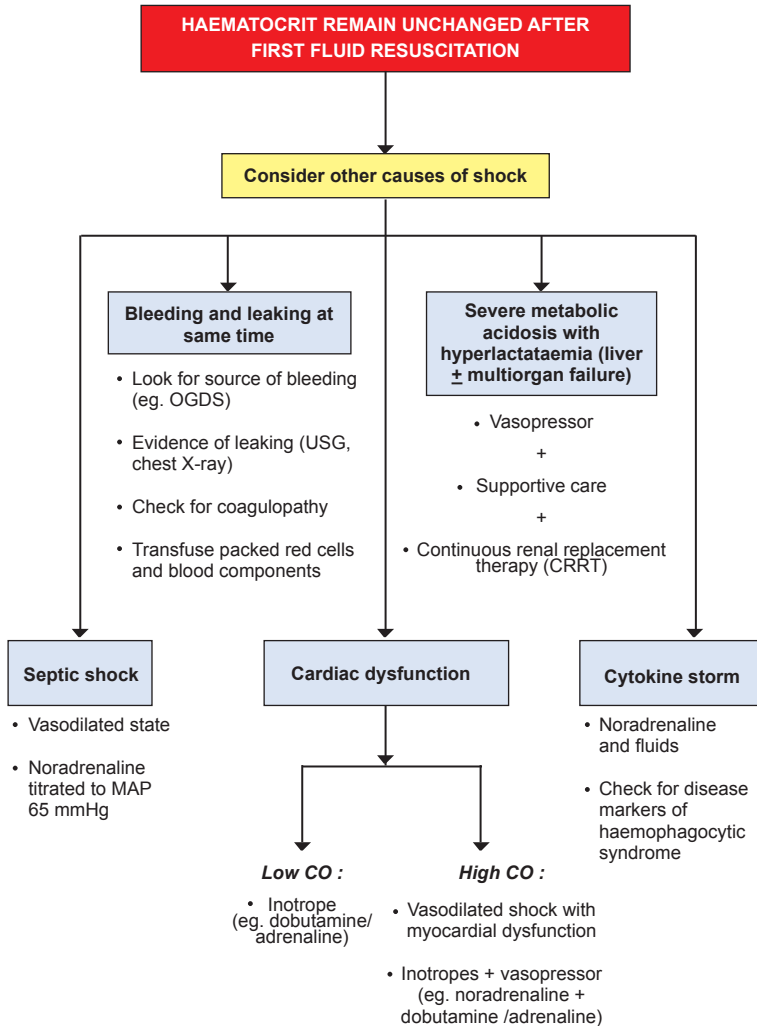
[^] Colloid is preferable if the patient has already received previous bolus of crystalloid.

IV = intravenous ; HCT = haematocrit

↑ = increased ; ↓ = decreased

¹GXM: emergency cross-match

**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

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 present as a normal anion gap metabolic acidosis. If serum chloride levels increase, change the fluid to balanced solution such as sterofundin or Hartmann's.^{73, level III} This improves chloride-related acidosis.

Sodium bicarbonate for metabolic acidosis caused by tissue hypoxia is not recommended for pH ≥ 7.10 . Bicarbonate therapy is associated with sodium and fluid overload, an increase in lactate and pCO₂ 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:⁷⁶

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

A 20% clearance in two 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, CO₂ and lactate.

Mixed respiratory alkalosis with metabolic acidosis (CO₂ lower than expected) commonly seen in liver failure, dengue encephalitis and sepsis. This is 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 electrolyte imbalances such as **hyponatraemia** and **hyperkalaemia**. Presence of hyponatraemia is a common observation in severe dengue and a marker of disease severity.^{77-78,level III}

Other electrolytes that need to be monitored are :-

- serum calcium
- serum phosphate
- serum magnesium

Recommendation 6

- Crystalloids solution is be the preferred choice in Dengue Shock Syndrome (DSS).
- Patients with DSS who do not respond to initial crystalloid resuscitation should receive colloids as the second fluid bolus.
- In DSS with persistent shock, other causes of shock should be aggressively looked for and treated accordingly.

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 is a result of endothelial activation.^{79,level II-3;80-81,level III} This leads to thrombocytopaenia and coagulation activation which are an intrinsic part of the disease.^{79,level II-3;80-81,level III}

Thrombocytopaenia and coagulation abnormalities do not reliably predict bleeding in dengue infection.^{82,level I;83,level II-2;84,level III}

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

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.^{88,level II-3} Significant bleeding or disseminated intravascular coagulation usually occurs following prolonged shock and acidosis.^{89,level III}

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.^{89, level III}
- A drop in HCT without clinical improvement despite adequate fluid replacement (40-60 ml/kg).^{89, level III; 61}
- Severe metabolic acidosis and end-organ dysfunction despite adequate fluid replacement.^{89,level III}

iii. Management of Bleeding in Dengue Infection

Transfusion of blood and blood components in dengue is indicated when there is evidence of significant bleeding.^{89,level III} Recently published studies done in critically ill patients and patients undergoing cardiac surgery have not shown any difference in clinical outcomes and lactate recovery when transfused with shorter-term storage packed cells (7-10 days) compared to longer-term storage packed cells (21-28 days).^{90-92,level I}

Transfusion of blood in patients with significant bleeding

- Transfuse blood (5–10ml/kg of packed red cells) and observe the clinical response. Consider blood components if required.
- Consider repeating the blood transfusion if there is further blood loss or no appropriate rise in HCT after blood transfusion.
- No significant difference in clinical outcomes and lactate recovery when transfused with shorter-term storage packed cells compared with longer-term storage packed cells.

Recommendation 7

- Dengue patients with mild bleeding do not require blood transfusion.
- Transfusion with packed cells and/or blood component should be administered in dengue patients with significant bleeding.

iv. Management of Upper Gastrointestinal Bleeding

Gastrointestinal bleeding is one of the most common haemorrhagic manifestations in dengue infection and it is often associated with high mortality.^{88,level II-3} The common causes are haemorrhagic (and/or erosive) gastritis, peptic ulcer and oesophageal ulcer.^{93,level II-2; 94, level III}

Fluid therapy, transfusion of packed cells and blood products, and administration of proton pump inhibitor are fundamental in the management of gastrointestinal haemorrhage in dengue infection.^{95,level II-2} Endoscopy is indicated if these patients have persistent bleeding despite optimum medical therapy.^{96-98,level III}

Endoscopic therapy is also recommended in patients with history of 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.^{93,level II-2}

v. 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.^{99-100, level III}

Prophylactic transfusion of packed cells and/or blood components is only indicated when invasive procedure or an operation is decided. The transfusion of platelet is recommended within one hour and FFP within 30 minutes prior to the procedure. Inappropriate transfusion of blood components increases the risk of pulmonary oedema, respiratory depression and transfusion-transmitted infection.^{99,level III}

- There is no role for routine prophylactic transfusion with platelets and plasma in dengue infection.
- Prophylactic transfusion of packed cells and/or blood components is only indicated when invasive procedure or an operation is decided.

vi. Adjunctive Therapy in Dengue Infection

There is insufficient evidence to support the use of recombinant activated factor VII in dengue patients with significant bleeding.^{101,level I;102,level III} The coagulation system is activated in dengue and infusion of activated factor concentrates may increase the risk of thrombosis.^{103,level III}

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, hepatomegaly and elevated transaminases.^{104-106,level II-2;107,level III} In a single-centered study done in Malaysia, 5.2% of acute liver failure was attributed to dengue infection.^{108,level II-2;109,level III}

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.^{106,level II-2;110,level III} 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.^{104-106,level II-2}

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.^{105,level II-2; 109,level III} Hepatocyte injury including necrotic changes commonly involve midzonal area followed by centrilobular area.^{105,level II-2}

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 haemodynamic and metabolic parameters.¹¹¹ Avoidance of other potential hepatotoxic drugs is crucial.

There are case studies on use of NAC in acute liver failure secondary to dengue infection.^{109,level III;112-115,level III} However up to now, there is insufficient evidence to support the use of NAC in the management of dengue-associated hepatitis.

The regime for IV N-Acetylcysteine for treatment of acute liver failure in dengue infection remains controversial, but have been suggested as follows:

- 100 mg/kg/day as infusion for five days.^{112,level III}
- 150 mg/kg infusion over 15-60 minutes, followed by 12.5 mg/kg/hour for four hours and then 6.25 mg/kg/hour.^{116,level III}

Liver transplantation is not feasible because of haemodynamic instability, bleeding manifestation and other organ dysfunction caused by dengue infection itself; and thus, may not be a viable treatment option. Artificial and bioartificial liver support systems have not conclusively been shown to be beneficial for dengue-related 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 manifest as arrhythmias, functional myocardial impairment and myocarditis.^{117-118,level II-2;119,level III} Functional myocardial impairment can be caused by subclinical myocarditis, myocardial oedema or circulating myocardial depressant factors.^{120,level III} 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 biomarkers*
 - Cardiac biomarkers (CK/CKMB or Troponin) have limited sensitivity and could be normal.^{120,level III}
- *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.^{121,level II-2} Common ECG changes reported are :
 - o Sinus bradycardia
 - o Atrioventricular block
 - o Atrial fibrillation
 - o 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.^{118,level II-2;122-123,level III} There is evidence of significantly low ejection fraction during the critical stage of severe dengue infection.^{123,level III;124,level II-2;125,level III}

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.^{118,level II-2;124,level II-2}

Echocardiography is indicated in refractory shock despite adequate fluid resuscitation and suspected myocardial dysfunction.

iii. Treatment:

Management of dengue infection in such patients should primarily be focused on cautious fluid resuscitation, aiming to give just sufficient IV 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 IV immunoglobulins for dengue myocarditis.^{120,level III}

Recommendation 8

- Echocardiography is indicated in refractory shock despite adequate fluid resuscitation and in suspected myocardial dysfunction in dengue infection.
- Adequate fluid resuscitation should be ensured before myocardial dysfunction can be diagnosed in dengue infection.

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% and 5.4%.^{127,level II-2;128-129,level III} Dengue infection results in a wide spectrum of neurological complications such as encephalopathy, encephalitis, intracranial bleed, meningitis and meningoencephalitis.^{129,level III;130-131,level II-2} Immune-mediated syndromes that include myelitis, acute disseminated encephalomyelitis (ADEM), and Guillain-Barré syndrome (GBS), myositis and various neuro-ophthalmic complications have been reported.^{129,level III}

i. Dengue Encephalopathy

This is the most commonly reported neurological complication in dengue infection. Encephalopathy in dengue infection 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.^{131-133,level II-2} The most common abnormality on neuroimaging is cerebral oedema. MRI is the imaging modality of choice. However, the MRI can be normal.^{127,level II-2}

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.^{133,level II-2;134,level III} In general, the sensitivity of serological techniques and RT-PCR is was low.^{134,level III}

The treatment modality for management of dengue encephalitis is supportive. Symptoms suggestive of raised intracranial pressure (ICP) which include headache, vomiting and reduced 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.^{133,level II-2;135,level II-2}

iii. Acute Transverse Myelitis

Acute transverse myelitis in dengue infection 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.^{129,level III}

Adjuvant Treatment

- *Corticosteroids*

The effectiveness of corticosteroids in neurological complications of dengue remains to be proven. However, IV methylprednisolone have been recommended in dengue myelitis and ADEM.^{129,level III}

- *Immunoglobulin*

High doses of intravenous immunoglobulin (IVIg) might be useful to treat post-dengue Guillain-Barré syndrome.^{129,level III}

- *Plasmapheresis*

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

Recommendation 9

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

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.^{136-137,level III} 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^{138,level II-2} and rhabdomyolysis.^{139,level III} ARF in such setting carries a high mortality rate.^{138, level II-2;140,level II-2}

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 HAEMOPHAGOCYTIC 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- α , IL-6, IL-8, interferon γ generated by uncontrolled activation of histiocytes and T-cells.^{141-143,level III} 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 to Table 10).^{144,level III}

Laboratory findings of HPS present in forms of bicytopenia or pancytopenia, coagulopathy, hypertriglyceridaemia, hypofibrinogenaemia, hyperferritinaemia, transaminitis, hyperbilirubinaemia, hypoalbuminaemia and hyponatraemia.^{140,level III;143;145,level III} Dengue-associated HPS had been increasingly reported.^{145-160,level III}

Currently, there are three well-accepted diagnostic classifications for haemophagocytic lymphohistiocytosis (HLH): Diagnostic criteria for HLH used in HLH-2004 trial;^{144,level III} Proposed HLH diagnostic criteria, 2009¹⁴² and HScore 2014.^{161,level II-2} Former two were not validated in adults while the latter was validated for macrophage activation syndrome in adults.

The lack of validated HPS classification system for dengue should not discourage clinicians to attempt diagnosing HPS. Since HPS is a progressive systemic disease, the lack of adequate 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 is not pathognomonic of HPS in adults^{162,level III} although it is highly sensitive and specific in paediatric population.^{163,level III} The level does not correlate with severity but the trend is 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.^{147-148,level III;153,level III;160,level III} 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.^{148-149,level III;153-154,level III;159,level III} 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 : Manifestations of Haemophagocytic Syndrome

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

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

Respiratory	
1.	Acute respiratory distress with the following clinical signs: <ul style="list-style-type: none"> - RR >30/min - Dyspnoea - Use of accessory muscles - Agitation, confusion
2.	High levels of supplemental oxygen (O ₂ concentration ≥50% to maintain oxygen saturation >90%)
3.	Risk of respiratory compromise with large volume resuscitation e.g. congestive heart failure, chronic kidney disease, etc.
4.	Massive haemoptysis
5.	Potential need for non-invasive/invasive ventilation
Cardiovascular	
1.	Haemodynamic instability due to hypovolaemia, haemorrhage, myocarditis or other causes
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, etc.
Neurologic	
1.	Seizures
2.	CNS depression
Gastrointestinal	
1.	Acute gastrointestinal bleeding with hypotension, continuous bleeding
2.	Severe acute hepatitis
Haematologic	
1.	Severe coagulopathy
2.	Significant bleeding
Renal	
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.^{164,level I}

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_aCO_2 is higher than the expected to compensate for the acidosis, consider intubation and mechanical ventilation.

Formula to calculate expected $P_aCO_2 = 1.5 (\text{Actual } [HCO_3^-] \text{ mmol/L}) + 8 (\pm 2 \text{ mmHg})$

When a patient with metabolic acidosis is on invasive mechanical ventilation, set the ventilator settings so that the P_aCO_2 remains low, at the expected P_aCO_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 to **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.^{165-168,level I}
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.^{169,level I}
3. **Concomitant septic shock**
Noradrenaline is preferred to other vasopressors as first-line therapy.^{165,level I}

7.7.3 Renal Replacement Therapy

Renal replacement therapy may be indicated in severe dengue with acute kidney injury (refer to 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).¹⁷⁰

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

- inadequate peripheral venous access ^{171,level III}
- patient requires an infusion of vasopressor for prolonged period^{171, level III}

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.^{172,level I;173,level II-2} 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 patients is low,^{174-175,level II-2; 176,level III} A subclavian approach should be avoided as the subclavian artery and vein is not accessible to direct compression.^{176,level III} The use of real-time USG is recommended for CVC insertion if it is available and there is expertise.^{177,level I;178, level II-2}

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.^{179-180;181,level III} If platelets are to be transfused, a CVC should be done within 4 hours following transfusion for a maximum effect.^{182,level II-2} The most recent recommendation by American Association of Blood Banks suggested for transfusion as low as 20,000 prior to CVC insertion.¹⁷⁹

ii. Arterial Catheter Insertion

Intra-arterial cannulation is useful as it enables continuous arterial pressure monitoring and repeated arterial blood gas sampling. Overall, the rate of bleeding complication is low (0.53%-1.58%), lowest in the radial site compared to the femoral.^{183, level I}

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.^{184,level III}

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.^{185,level III}

Recommendation 10

- Non-invasive ventilation may be beneficial in dengue patients 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 in dengue patients.
- Intravenous fluid therapy is the mainstay of treatment in decompensated dengue shock syndrome (DSS), however inotrope and vasopressors may be used as a temporary measure.
- In DSS:
 - central venous pressure should not be used to guide fluid therapy
 - subclavian vein cannulation should be avoided
 - real-time ultrasonography is recommended for central venous cannulation 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:¹⁸⁶

- elevation of HCT in dengue is masked by haemodilution due to increase in plasma volume especially in the second and third 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 platelets
- mild metabolic acidosis and low P_aCO_2 of 32 mmHg (in third 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 DSS. The higher percentage of severe dengue infection occurred among pregnant women compared to non-pregnant women (OR: 3.38; 95% CI: 2.10–5.42, $p=0.0001$).^{187,level II-3} Significant number of pregnant women with dengue infection may present with DSS and mortality rate is about three times higher in this group.^{187-189,}

^{level II-3} A rare complication with pre-eclampsia, eclampsia or dengue encephalopathy have been reported.^{189,level II-3}

A very close monitoring of the vital signs, early signs of shock and bleeding should be sought. Appropriate fluid therapy, and when indicated blood and blood product transfusion, should be instituted.^{188,level II-3} A referral to intensivist and obstetrician should be done early in this group of patients to optimise care.

ii. Maternal Complications in Pregnant Women with Dengue Infection

Pregnant women with dengue who progress to spontaneous vaginal delivery do not have additional risk of adverse outcomes. Maternal complications commonly happen when dengue infection occur during first and third trimester. First trimester infection is associated with abortion and third trimester infection is commonly complicated with preterm birth.^{190,level III} 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 foetal distress and higher chance of surgical interventions.^{189,level II-3 ;191,level III}

iii. Foetal Outcome in Pregnant Women with Dengue Infection

DEN virus can be vertically transmitted to the foetus in utero or to the infant at parturition from infected symptomatic pregnant women.^{187,level II-3} Mothers who are asymptomatic have very low risk of transmission to the foetus.^{192,level II-3} Clinical monitoring and laboratory investigations should be carried out for up to one week of life in the neonates.^{193,level II-3} Positive serology tests for dengue IgM, NS1 antigen or real-time RT-PCR to dengue in neonates confirm the vertical transmission.^{193,level II-3}

Dengue infection during pregnancy may be associated with various complications, including preterm delivery (4.0%-17.9%), foetal death (8.9%-13.6%), low birth weight (4.0%-24.3%) and more frequent miscarriage (RR=3.3).^{188-189,level II-3;193-194,level II-3;195,level III} No long term foetal abnormalities noted among infants with vertical transmission.^{193,level II-3}

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.^{191,level III} However, if premature labour occurs during the acute infection, it is advisable to delay the delivery until the acute infection resolves. The use of tocolytic drugs such as nifedipine and atosiban may be indicated. Close foetal monitoring is required in this group of patients to detect foetal 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.^{190,level III} Deliveries in these patients should be conducted by obstetrician or senior medical officer (in hospital without specialist). Group and cross match (GXM) must be done for all dengue patients in labour. Blood and blood products transfusion is to be given only when indicated.

Instrumental delivery should be avoided where possible and if indicated, the procedures should be done by an obstetrician.^{190,level III} When the decision for instrumental delivery or operative delivery is made, the blood and blood products must be made available.^{190,level III} Active management of third stage of labour in preventing postpartum haemorrhage is required by the use of IV uterotonic agent (avoid intramuscular injection). Platelets transfusion is only recommended when patients have manifestation of bleeding, decided for caesarean section or instrumental delivery.^{190,level III} In this patient, platelets transfusion should be targeted to achieve minimum of 50,000/ml to ensure maternal safety.^{190, level III}

v. Breastfeeding

Transmission of dengue virus through breastfeeding is inconclusive. There is a case report of significant dengue viral load detected in breastmilk during the acute viraemic phase.^{196,level III} Hence, it is advisable to delay breastfeeding during the acute viraemic phase.

- HCT value in pregnant women is usually lower compared to normal adults 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 foetal 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 infection should be managed in hospitals by a multidisciplinary team (physician, anaesthetist and obstetrician).
- Intrapartum management in pregnant dengue patients are:
 - spontaneous vaginal delivery is the preferred mode of delivery
 - group and cross match must be done. Blood and blood products transfusion to be given only when indicated
 - blood and blood products should be transfused as indicated when instrumental or operative delivery is decided
- Serology tests (Dengue IgM and non-structural protein 1 [NS1] antigen) or reverse transcriptase polymerase chain reaction should be performed in neonates when congenital dengue infection is suspected.

9. DISCHARGE CRITERIA

The following should be taken into consideration before discharging a dengue patient:^{60,level III; 61}

- 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.^{197-198,level III} 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 had shown that the use of mosquito netting/screening was efficacious in preventing transmission of dengue in the community.^{199,level I; 200, level III}

Generally, repellent products with higher concentrations of DEET (N,Ndiethyl-toluamide) have longer repellence times.^{201,level III}

11. VACCINATION

There are published and ongoing trials on the efficacy of dengue vaccine among the paediatric population.^{202-204, level I}

12. FOOD AND SUPPLEMENTS

Food and supplements such as *Carica papaya* leave juice/extract, cactus extract, crab or padi frog soup, bitter gourd soup, porcupine bezoar stone, Tawa-tawa and Pegaga leaves and commercial isotonic drink have not been proven scientifically with robust evidence in preventing complications, expediting the recovery or curing dengue infection. It is important to note that the main problem that needs to be dealt with in dengue infection is the plasma leakage and/or immune activation issues, not only about the low platelet count. Manipulation of platelet count alone does not alter the clinical course of the disease as it is just a surrogate marker of disease progression or evolution. Plasma leakage and organ dysfunction should be the main focus of management.

13. 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.

13.1 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

13.2 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. **Case fatality rate of dengue infection**
National target < 0.2% = $\frac{\text{No. of death of dengue infection}}{\text{No. of dengue infection}} \times 100\%$
- ii. **Case fatality rate for severe dengue** = $\frac{\text{No. of death in severe dengue}}{\text{Total no. of severe dengue}} \times 100\%$

REFERENCES

1. World Health Organization. Dengue Guidelines for Diagnosis, Treatment, Prevention and Control - New Edition 2009. WHO: Geneva; 2009
2. Nimmannitya S. Clinical spectrum and management of dengue haemorrhagic fever. *Southeast Asian J Trop Med Pub Hlth.* 1987; 18(3):392-7.
3. Gubler DJ. Dengue and Dengue Haemorrhagic Fever. *Clin Microbio Review.* 1998; 11(3):480-96.
4. Kalayanarooj S, Vaughn DW, Nimmannitya S, et al. Early clinical and laboratory indicators of acute dengue illness. *J Infect Dis.* 1997 Aug; 176(2):313-21.
5. Balmaseda A, Hammond SN, Perez MA, et al. Short report: assessment of the World Health Organization scheme for classification of dengue severity in Nicaragua. *Am J Trop Med Hyg.* 2005 Dec; 73(6):1059-62.
6. Hammond SN, Balmaseda A, Perez L, et al. Differences in dengue severity in infants, children, and adults in a 3-year hospital-based study in Nicaragua. *Am J Trop Med Hyg.* 2005; 73:1063-170.
7. Guzman MG, Alvarez M, Rodríguez R, et al. Fatal dengue hemorrhagic fever in Cuba, 1997. *Int J Infect Dis* 1999; 3:130-5.
8. Rigau-Perez JG, Laufer MK. Dengue-related deaths in Puerto Rico, 1992-1996: diagnosis and clinical warning signs. *Clin Infect Dis.* 2006 May 1;42(9):1241-6.
9. Ong A, Sandar M, Chen MI, Sin LY. Fatal dengue haemorrhagic fever in adults during a dengue epidemic in Singapore. *International Journal of Infectious Diseases.* 2007 May;11(3):263-7.
10. Wichmann O, Hongsiriwon S, Bowonwatanuwong C, et al. Risk factors and clinical features associated with severe dengue infection in adults and children during the 2001 epidemic in Chonburi, Thailand. *Trop Med Int Health.* 2004 Sep;9(9):1022-9.
11. Simmons CP, et al. Current concepts: Dengue. *N Engl J Med.* 2012 Apr;366:1423-32.
12. Tricou V, Minh NN, Farrar J, et al. Kinetics of viremia and NS1 antigenemia are shaped by immune status and virus serotype in adults with dengue. *PLoS Negl Trop Dis.* 2011 Sep;5(9):e1309. doi: 10.1371/journal.pntd.0001309.
13. Duyen HT, Ngoc TV, Ha do T, et al. Kinetics of plasma viremia and soluble nonstructural protein 1 concentrations in dengue: differential effects according to serotype and immune status. *J Infect Dis.* 2011 May 1;203(9):1292-300. doi: 10.1093/infdis/jir014.
14. Cohen SN, Halstead SB. Shock associated with dengue infection. I. Clinical and physiologic manifestations of dengue hemorrhagic fever in Thailand, 1964. *J Pediat* 1966; 68:448-56.
15. Pongpanich B. Pathogenetic mechanism in dengue hemorrhagic fever: Report of an international collaborative study. *Bull World Hlth.* 1973; 48:117.
16. Ganong WF. Cardiovascular homeostasis in health and disease. In: *Review of Medical Physiology.* 22nd Edition. London: McGraw-Hill; 2005:p.630-46.
17. Bhamarapravati N, Tuchinda P, Boonyapaknavik V. Pathology of Thailand haemorrhagic fever: a study of 100 autopsy cases. *Anna Trop Med Parasitol.* 1967;61:500-10.
18. Sahaphong S, Riengrojpitak S, Bhamarapravati N, et al. Electron microscopic study of the vascular endothelial cell in dengue haemorrhagic fever. *Southeast Asian J Trop Med Public Health* 1980;11:194.
19. Chuansumrit A, Tangnaratchak K. Pathophysiology and management of dengue hemorrhagic fever. *Transfusion Alternatives In Transfusion Medicine.* 2006;8 (Suppl 1):3-11.
20. Halstead SB. Observations related to pathogenesis of dengue hemorrhagic fever. VI. Hypotheses and discussion. *Yale J Biol Med.* 1970 Apr;42(5):350-62.

21. Sangkawibha N, Rojanasuphot, S, Ahandriks, et al. Risk factors in dengue shock syndrome: a prospective epidemiologic study in Rayong, Thailand. I. The 1980 outbreak. *Am. J. Epidemiol.* 1984;120:653-669.
22. Guzman MG, Kouri G, Bravo J, et al. Enhanced severity of secondary dengue-2 infections: death rates in 1981 and 1997 Cuban outbreaks. *Rev Panam Salud Publica*, 2002 Apr;11:223-7.
23. Badyopadhyay S, Lum LCS, Kroeger A. Classifying dengue: a review of the difficulties in using the WHO case classification for dengue haemorrhagic fever. *Tropical Medicine and International Health.* 2006; 11(8):1238-55.
24. World Health Organization, & UNICEF. Handbook for clinical management of dengue. 2012.
25. Prevention and Control of Infectious Disease Act 1988 (Act 342). Kuala Lumpur: Percetakan Nasional Malaysia Berhad, 2001.
26. Surat Pekeliling Ketua Pengarah Kesihatan Malaysia Bil 15/2010. Pelaksanaan Pengurusan Kes dan Kematian Denggi.
27. Malavige GN, Velanthanthiri VG, Wijewickrama ES, et al. Patterns of disease among adults hospitalized with dengue infections. *QJM.* 2006 May;99(5):299-305.
28. Mairuhu AT, Mac Gillavry MR, Setiati TE. Is clinical outcome of dengue-virus infections influenced by coagulation and fibrinolysis? A critical review of the evidence. *Lancet.* Jan 2003;3:33-41.
29. Krishnamurti C, Kalayanarooj S, Cutting MA, et al. Mechanisms of hemorrhage in dengue without circulatory collapse. *Am J Trop Med Hyg.* 2001 Dec;65(6):840-7.
30. Lum LC, Goh AY, Chan PW, et al. Risk factors for hemorrhage in severe dengue infections. *J. Pediatr* 2002 May;140:629-31.
31. Chuansumrit A, Philmothares V, Tardtong P, et al. Transfusion requirements in patients with dengue hemorrhagic fever. *Southeast Asian J Trop Med Public Health.* 2000;3:10-14
32. Chaudhary R, Khetan D, Sinha S, et al. Transfusion support to dengue patients in a hospital-based blood transfusion service in north India. *Transfusion and Apheresis Science.* 2006 Dec; 35:239-44.
33. Ambayya A, Su AT, Osman NH, et al. Haematological reference intervals in a multiethnic population. *PLoS One.* 2014 Mar 18;9(3):e91968. doi: 10.1371/journal.pone.0091968. eCollection 2014.
34. Tontulawat P, Pongsiri P, Thongmee C, et al. Evaluation of rapid immunochromatographic NS1 test, anti-dengue IgM test, semi-nested PCR and IgM ELISA for detection of dengue virus. *Southeast Asian J Trop Med Public Health.* 2011 May;42(3):570-8.
35. Wang SM, Sekaran SD. Early diagnosis of Dengue infection using a commercial Dengue Duo rapid test kit for the detection of NS1, IGM, and IGG. *Am J Trop Med Hyg.* 2010 Sep;83(3):690-5. doi: 10.4269/ajtmh.2010.10-0117.
36. Gan VC, Tan LK, Lye DC, et al. Diagnosing dengue at the point-of-care: utility of a rapid combined diagnostic kit in Singapore. *PLoS One.* 2014 Mar 19;9(3):e90037. doi: 10.1371/journal.pone.0090037.
37. Peeling RW, Artsob H, Pelegriano JL, et al. Evaluation of diagnostic tests: dengue. *Nat Rev Microbiol.* 2010 Dec;8(12 Suppl):S30-8.
38. Chung SJ, Krishnan PU, Leo YS. Two cases of false-positive dengue non-structural protein 1 (NS1) antigen in patients with hematological malignancies and a review of the literature on the use of NS1 for the detection of Dengue infection. *Am J Trop Med Hyg.* 2015 Feb;92(2):367-9. doi:10.4269/ajtmh.14-0247.
39. Kumarasamy V, Wahab AH, Chua SK, et al. Evaluation of a commercial dengue NS1 antigen-capture ELISA for laboratory diagnosis of acute dengue virus infection. *J Virol Methods.* 2007 Mar;140(1-2):75-9.

40. Lapphra K, Sangcharaswichai A, Chokephaibulkit K, et al. Evaluation of an NS1 antigen detection for diagnosis of acute dengue infection in patients with acute febrile illness. *Diagn Microbiol Infect Dis.* 2008 Apr;60(4):387-91. doi:10.1016/j.diagmicrobio.2007.11.010.
41. Blacksell SD, Mammen MP Jr, Thongpaseuth S, et al. Evaluation of the Panbio dengue virus nonstructural 1 antigen detection and immunoglobulin M antibody enzyme-linked immunosorbent assays for the diagnosis of acute dengue infections in Laos. *Diagn Microbiol Infect Dis.* 2008 Jan;60(1):43-9.
42. Sekaran SD, Lan EC, Maheswarappa KB, et al. Evaluation of dengue NS1 capture ELISA assay for the rapid detection of dengue. *Journal of Infections In Developing Countries.* 2007;1(2):182-8.
43. Dussart P, Labeau B, Lagathu G, et al. Evaluation of an enzyme immunoassay for detection of dengue virus NS1 antigen in human serum. *Clin Vaccine Immunol.* 2006 Nov;13(11):1185-9.
44. Paranavitane SA, Gomes L, Kamaladasa A, et al. Dengue NS1 antigen as a marker of severe clinical disease. *BMC Infect Dis.* 2014 Oct 31;14:570. doi: 10.1186/s12879-014-0570-8.
45. Schilling S, Ludolfs D, Van An L, et al. Laboratory diagnosis of primary and secondary dengue infection. *J Clin Virol.* 2004 Nov;31(3):179-84.
46. Gubler DJ. Dengue and dengue hemorrhagic fever. *Clin Microbiol Rev.* 1998 Jul;11(3):480-96. Review.
47. Chanama S, Anantapreecha S, A-nuegonpipat A, et al. Analysis of specific IgM responses in secondary dengue virus infections: levels and positive rates in comparison with primary infections. *J Clin Virol.* 2004 Nov;31(3):185-9.
48. Wichmann O, Stark K, Shu PY, et al. Clinical features and pitfalls in the laboratory diagnosis of dengue in travellers. *BMC Infect Dis.* 2006 Jul 21;6:120.
49. Hawkes RA, Boughton CR, Naim HM, et al. Arbovirus infections of humans in New South Wales. Seroepidemiology of the flavivirus group of togaviruses. *Med J Aust.* 1985 Dec 9-23;143(12-13):555-61.
50. Chen WJ, Hwang KP, Fang AH. Detection of IgM antibodies from cerebrospinal fluid and sera of dengue fever patients. *Southeast Asian J Trop Med Public Health.* 1991 Dec;22(4):659-63.
51. Panbio Dengue IgG Capture ELISA Product Insert Cat No 01PE10 August 2008. Standard Diagnostics Republic of Korea.
52. Cuzzubbo AJ, Vaughn DW, Nisalak A, et al. Comparison of PanBio dengue duo enzyme-linked immunosorbent assay (ELISA) and MRL dengue fever virus immunoglobulin M capture ELISA for diagnosis of dengue virus infections in Southeast Asia. *Clin Diagn Lab Immunol.* 1999 Sep;6(5):705-12
53. Wu SJ, Paxton H, Hanson B, et al. Comparison of two rapid diagnostic assays for detection of immunoglobulin M antibodies to dengue virus. *Clin Diagn Lab Immunol.* 2000 Jan;7(1):106-10.
54. Kit Lam S, Lan Ew C, Mitchell JL, et al. Evaluation of a capture screening enzyme-linked immunosorbent assay for combined determination of immunoglobulin M and G antibodies produced during Dengue infection. *Clin Diagn Lab Immunol.* 2000 Sep;7(5):850-2.
55. Berlioz-Arthaud A. Evaluation of reagents for the serological diagnosis of Dengue EPINET II Workshop. Institut Pasteur de Nouvelle Calédonie. March 2002.
56. Grobusch MP, Niedrig M, Göbels K, et al. Evaluation of the use of RT-PCR for the early diagnosis of dengue fever. *Clin Microbiol Infect.* 2006 Apr;12(4):395-7
57. Seah CLK et al. A comparative, prospective study of serological, virus isolation and PCR amplification techniques for the laboratory diagnosis of dengue infection. *Serodiagnosis and immunotherapy in infectious disease.* 1995;7.2:55-58.
58. Dengue hemorrhagic fever: diagnosis, treatment, prevention and control. 2nd ed. Geneva: World Health Organization: 1997. Available at: <http://w3.who.int/csr/resources/publications/dengue/024-33.pdf>.

59. Ramos C, Sánchez G, Pando RH, et al. Dengue virus in the brain of a fatal case of hemorrhagic dengue fever. *J Neurovirol.* 1998 Aug;4(4):465-8.
60. Kalayanarooj S, Nimmannitya S. Guidelines for DHF Case Management for Workshop on Case Management of Dengue Hemorrhagic Fever, WHO Collaborating Centre for Case Management of Dengue/DHF/DSS June 10 – 15, 2002.
61. Subcommittee of Technical Experts on Clinical Management of DF/ DHF. Guidelines on Clinical Management of Dengue/Dengue Hemorrhagic Fever, Sri Lanka. 2005. Available at <http://www.epid.gov.lk/pdf/Guidelines>
62. MOH, Singapore. Guidelines on Clinical Management of Dengue Fever/Dengue Haemorrhagic Fever 2005.
63. Carlos CC, Oishi K, Cinco, et al. Comparison of Clinical Features and Hematologic CDC. Healthcare Infection Control Practices Advisory Committee. Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings 2007. Administrative responsibilities. Atlanta (GA): Centers for Disease Control and Prevention (CDC);2007 June.
64. Hamod D, Chang H, Wang TL. Dengue Fever versus Bioterrorism. *Ann Disaster Med.* 2002;1 Suppl 1:S 44-58.
65. Lee IK, Lee WH, Yang KD, et al. Comparison of the effects of oral hydration and intravenous fluid replacement in adult patients with non-shock dengue hemorrhagic fever in Taiwan. *Trans R Soc Trop Med Hyg.* 2010 Aug;104(8):541-5. doi: 10.1016/j.trstmh.2010.05.003.
66. WHO Regional Publication SEARO, 29, 1999.
67. Dung NM, Day NP, Tam DT, et al. Fluid replacement in dengue shock syndrome: a randomized, double-blind comparison of four intravenous-fluid regimens. *Clin Infect Dis.* 1999 Oct; 29:787-94.
68. Ngo NT, Cao XT, Kneen R, et al. Acute management of dengue shock syndrome: a randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. *Clin Infect Dis.* 2001; 32:(2) 204-13.
69. Wills BA, Nguyen MD, Ha TL, et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. *N Engl J Med.* 2005 Sep 1; 353(9):877- 89.
70. Akech S, Ledermann H, Maitland K. Choice of fluids for resuscitation in children with severe infection and shock: systematic review. *BMJ.* 2010 Sep 2;341:c4416. doi: 10.1136/bmj.c4416.
71. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev.* 2013 Feb 28;2:CD000567. doi: 10.1002/14651858.CD000567.pub6.
72. Haase N, Perner A, Hennings LI, et al. Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. *BMJ.* 2013 Feb 15;346:f839. doi: 10.1136/bmj.f839.
73. Somasetia DH, Setiati TE, Sjahrodji AM, et al. Early resuscitation of dengue shock syndrome in children with hyperosmolar sodium-lactate: a randomized single-blind clinical trial of efficacy and safety. *Crit Care.* 2014 Sep 5;18(5):466. doi: 10.1186/s13054-014-0466-4.
74. Muller L, Bobbia X, Toumi M, et al. Respiratory variations of inferior vena cava diameter to predict fluid responsiveness in spontaneously breathing patients with acute circulatory failure: need for a cautious use. *Crit Care.* 2012 Oct 8;16(5):R188. doi: 10.1186/cc11672.
75. Skellett S, Mayer A, Durward A, et al. Chasing the base deficit: hyperchloraemic acidosis following 0.9% saline fluid resuscitation. *Archives of Disease in Childhood.* 2000 Dec;83(6):514-6.
76. Jansen TC, van Bommel J, Schoonderbeek FJ, et al; LACTATE study group. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. *Am J Respir Crit Care Med.* 2010 Sep 15;182(6):752-61. doi: 10.1164/rccm.200912-1918OC.

77. Lumpaopong A, Kaewplang P, Watanaveeradej V, et al. Electrolyte disturbances and abnormal urine analysis in children with dengue infection. *Southeast Asian J Trop Med Public Health*. 2010 Jan;41(1):72-6.
78. Mekmullica J, Suwanphatra A, Thienpaitoon H, et al. Serum and urine sodium levels in dengue patients. *Southeast Asian J Trop Med Public Health*. 2005 Jan;36(1):197-9.
79. Sosothikul D, Seksarn P, Pongsewalak S. Activation of endothelial cells, coagulation and fibrinolysis in children with dengue virus infection. *Thromb Haemost*. 2007 Apr;97:627-34
80. Avila-Aguero ML, Avila-Aguero CR, Um SL, et al. Systemic host inflammatory and coagulation response in the Dengue virus primo-infection. *Cytokine*. 2004 Sep 21;27:173-9.
81. Tanomsri S, Suchitra N. Haematology in dengue and dengue haemorrhagic fever. *Bailliere's Clinical Haematology* 2000;13:261-76.
82. Mairuhu AT, Mac Gillavry MR, Setiati TE. Is clinical outcome of dengue-virus infections influenced by coagulation and fibrinolysis? A critical review of the evidence. *Lancet*. Jan 2003;3:33-41.
83. Krishnamurti C, Kalayanarooj S, Cutting MA, et al. Mechanisms of hemorrhage in dengue without circulatory collapse. *Am J Trop Med Hyg*. 2001 Dec;65(6):840-7.
84. Chaudhary R, Khetan D, Sinha S, et al. Transfusion support to dengue patients in a hospital-based blood transfusion service in north India. *Transfusion and Apheresis Science*. 2006 Dec; 35:239-44.
85. Wills BA, Oragui EE, Stephens AC, et al. Coagulation abnormalities in dengue hemorrhagic fever: serial investigations in 167 Vietnamese children with Dengue Shock Syndrome. *Clin Infect Dis*. 2002 Aug; 35(3): 277-85.
86. Perret C, Chanthavanich P, Pengsaa K, et al. Dengue infection during pregnancy and transplacental antibody transfer in Thai mothers. *Journal of Infection*. 2005;51:287-93.
87. Esmon CT. The impact of the inflammatory response on coagulation. *Thrombosis Research*. 2004;114(5-6):321-7.
88. Fariz-Safhan MN, Tee HP, Abu Dzarr GA, et al. Bleeding outcome during a dengue outbreak in 2005 in the East-coast region of Peninsular Malaysia: a prospective study. *Trop Biomed*. 2014 Jun;31(2):270-80.
89. Lum LC, Goh AY, Chan PW, et al. Risk factors for hemorrhage in severe dengue infections. *J. Pediatr* 2002 May;140:629-31.
90. Lacroix J, Hébert PC, Fergusson DA, et al; ABLE Investigators; Canadian Critical Care Trials Group. Age of transfused blood in critically ill adults. *N Engl J Med*. 2015 Apr 9;372(15):1410-8. doi: 10.1056/NEJMoa1500704.
91. Steiner ME, Ness PM, Assmann SF, et al. Effects of red-cell storage duration on patients undergoing cardiac surgery. *N Engl J Med*. 2015 Apr 9;372(15):1419-29. doi: 10.1056/NEJMoa1414219.
92. Dhabangi A, Mworozzi E, Lubega IR, et al. The effect of blood storage age on treatment of lactic acidosis by transfusion in children with severe malarial anaemia: a pilot, randomized, controlled trial. *Malar J*. 2013 Feb 6;12:55. doi: 10.1186/1475-2875-12-55.
93. Chiu YC, Wu KL, Kuo CH, et al. Endoscopic findings and management of dengue patients with upper gastrointestinal bleeding. *Am J Trop Med Hyg*. 2005 Aug;73(2):441-4.
94. Sari EF, Syam AF, Leonard Nainggolan. Cause of Upper Gastrointestinal Tract Bleeding in Dengue Hemorrhagic Fever Patient. *Indones J Gastro, Hepato Dig*. 2008;9:30-4.
95. Chuansumrit A, Phimolthares V, Tardtong P, et al. Transfusion requirements in patients with dengue hemorrhagic fever. *Southeast Asian J Trop Med Public Health*. 2000 Mar;31(1):10-4.
96. Hsu WH, Wu IC. Watermelon stomach in dengue hemorrhagic fever. *Endoscopy*. 2013;45 Suppl 2.

97. Boo YL, Chin PW, Hoo FK, et al. Duodenal hematoma: An unusual presentation of dengue fever. *RMJ*. 2015; 40(2): 248-250. - level III
98. Lee CY, Tsai HC, Lee SS, et al. Dengue hemorrhagic fever presenting with hemorrhagic pancreatitis and an intramural hematoma of the duodenal wall: a case report and review of the literature. *Southeast Asian J Trop Med Public Health*. 2013 May;44(3):400-8. - level III
99. Lum LC, Abdel-Latif Mel-A, Goh AY, et al. Preventive Transfusion in DSS- is it necessary? *J Pediatr*. 2003 Nov;143(5):682-4.
100. Chairulfatah, A, Setiabudi, D., Agoes, et al. Thrombocytopenia and platelet transfusions in dengue haemorrhagic fever and dengue shock syndrome. *Dengue Bulletin*, 2003;27
101. Chuansumrit A, Wangruangsattid S, Lektrakul Y, et al. Dengue Study Group. Control of bleeding in children with DHF using recombinant activated FVII: a randomized, double-blind, placebo-controlled study. *Blood Coagul Fibrinolysis*. 16(8): 549-55.
102. 86 Chuansumrit A, Tangnaratchakiet K, Lektakul Y, et al. The use of recombinant activated FVII for controlling life-threatening bleeding in DSS. *Blood Coagul Fibrinolysis*. 2004 Jun;15:335-42.
103. United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) Guidelines on the selection and use of therapeutic products to treat hemophilia and other hereditary bleeding disorders. *Hemophilia*. 2003;9:1-23.
104. Parkash O, Almas A, Jafri SM, et al. Severity of acute hepatitis and its outcome in patients with dengue fever in a tertiary care hospital Karachi, Pakistan (South Asia). *BMC Gastroenterol*. 2010 May 7;10:43.
105. Trung DT, Thao le TT, Hien TT, et al. Liver involvement associated with dengue infection in adults in Vietnam. *Am J Trop Med Hyg*. 2010 Oct;83(4):774-80.
106. Tristão-Sá R, Kubelka CF, Zandonade E, et al. Clinical and hepatic evaluation in adult dengue patients: a prospective two-month cohort study. *Rev Soc Bras Med Trop*. 2012 Dec;45(6):675-81.
107. Samanta J, Sharma V. Dengue and its effects on liver. *World J Clin Cases*. 2015 Feb 16;3(2):125-31. doi: 10.12998/wjcc.v3.i2.125
108. Ahmad S, Dhar M, Srivastava S, et al. Dengue hepatitis sans dysfunction: experience of a single tertiary referral centre in the north Indian state of Uttarakhand. *Trop Doct*. 2013 Apr;43(2):62-5. doi: 10.1177/0049475513483281.
109. Tan SS, Bujang MA. The clinical features and outcomes of acute liver failure associated with dengue infection in adults: a case series. *Braz J Infect Dis*. 2013 Mar-Apr;17(2):164-9. doi: 10.1016/j.bjid.2012.09.007
110. Thomas L, Brouste Y, Najjioullah F, et al. Predictors of severe manifestations in a cohort of adult dengue patients. *J Clin Virol*. 2010 Jun;48(2):96-9. doi: 10.1016/j.jcv.2010.03.008.
111. Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. *Hepatology*. 2012;55(3):965-967.
112. Habaragamuwa BW, Dissanayaka P. N-acetylcystein in dengue associated severe hepatitis. *Indian J Crit Care Med*. 2014 Mar;18(3):181-2. doi: 10.4103/0972-5229.128712.
113. Senanayake MP, Jayamanne MD, Kankanararachchi I. N-acetylcysteine in children with acute liver failure complicating dengue viral infection. *Ceylon Med J*. 2013 Jun;58(2):80-2. doi: 10.4038/cmj.v58i2.5684.
114. Abeysekera RA, Illangasekera U, Jayalath T, et al. Successful use of intravenous N-acetylcysteine in dengue haemorrhagic fever with acute liver failure. *Ceylon Med J*. 2012 Dec;57(4):166-7. doi: 10.4038/cmj.v57i4.5085.
115. Giri S, Agarwal MP, Sharma V, et al. Acute hepatic failure due to dengue: A case report. *Cases J*. 2008 Oct 2;1(1):204. doi: 10.1186/1757-1626-1-204.

116. Stravitz RT, Kramer AH, Davern T, et al; Acute Liver Failure Study Group. Intensive care of patients with acute liver failure: recommendations of the U.S. Acute Liver Failure Study Group. *Crit Care Med.* 2007 Nov;35(11):2498-508.
117. Miranda CH, Borges Mde C, Matsuno AK, et al. Evaluation of cardiac involvement during dengue viral infection. *Clin Infect Dis.* 2013 Sep;57(6):812-9. doi: 10.1093/cid/cit403.
118. Yacoub S, Griffiths A, Chau TT, et al. Cardiac function in Vietnamese patients with different dengue severity grades. *Crit Care Med.* 2012 Feb;40(2):477-83. doi: 10.1097/CCM.0b013e318232d966.
119. Lee CH, Teo C, Low AF. Fulminant dengue myocarditis masquerading as acute myocardial infarction. *Int J Cardiol.* 2009 Aug 21;136(3):e69-71. doi: 10.1016/j.ijcard.2008.05.023.
120. Yacoub S, Wertheim H, Simmons CP, et al. Cardiovascular manifestations of the emerging dengue pandemic. *Nat Rev Cardiol.* 2014 Jun;11(6):335-45. doi: 10.1038/nrcardio.2014.40.
121. Kularatne SA, Pathirage MM, Kumarasiri PV, et al. Cardiac complications of a dengue fever outbreak in Sri Lanka, 2005. *Trans R Soc Trop Med Hyg.* 2007 Aug;101(8):804-8.
122. Khongphatthanayothin A, Lertsapcharoen P, Supachokchaiwattana P, et al. Myocardial depression in dengue hemorrhagic fever: prevalence and clinical description. *Pediatr Crit Care Med.* 2007 Nov;8(6):524-9.
123. Khongphatthanayothin A, Suesawalak M, Muangmingsook S, et al. Hemodynamic profiles of patients with dengue hemorrhagic fever during toxic stage: an echocardiographic study. *Intensive Care Med.* 2003 Apr;29(4):570-4.
124. Sengupta SP, Nugurwar A, Jaju R, et al. Left ventricular myocardial performance in patients with dengue hemorrhagic fever and thrombocytopenia as assessed by two-dimensional speckle tracking echocardiography. *Indian Heart J.* 2013 May-Jun;65(3):276-82. doi: 10.1016/j.ihj.2013.04.017.
125. Wali JP, Biswas A, Chandra S, et al. Cardiac involvement in Dengue Haemorrhagic Fever. *Int J Cardiol.* 1998 Mar 13;64(1):31-6.
126. Charron C, Caille V, Jardin F, et al. Echocardiographic measurement of fluid responsiveness. *Current opinion in critical care.* 2006 Jun;12(3):249-54.
127. Cam BV, Fonsmark L, Hue NB, et al. Prospective case control study of encephalopathy in children with dengue hemorrhagic fever. *Am J Trop Med Hyg* Dec 2001 Dec;65(6):848-51.
128. Hendarto SK, Hadinegoro SR. Dengue encephalopathy. *Acta Paediatr Jpn* 1992 Jun;34(3):350-7.
129. Carod-Artal FJ, Wichmann O, Farrar J, et al. Neurological complications of dengue virus infection. *Lancet Neurol.* 2013 Sep;12(9):906-19.
130. Araújo FM, Araújo MS, Nogueira RM, et al. Central nervous system involvement in dengue: a study in fatal cases from a dengue endemic area. *Neurology.* 2012 Mar 6;78(10):736-42.
131. Soares CN, Cabral-Castro MJ, Peralta JM, et al. Review of the etiologies of viral meningitis and encephalitis in a dengue endemic region. *J Neurol Sci.* 2011 Apr 15;303(1-2):75-9.
132. Jackson ST, Mullings A, Bennett F, et al. Dengue infection in patients presenting with neurological manifestations in a dengue endemic population. *West Indian Med J.* 2008 Sep;57(4):373-6.
133. Rao SM, Pradeep M, Dnyaneshwar M, et al. Dengue Encephalitis - Clinical spectrum and outcome. *Intern Med Inside.* 2013;1:8.
134. Soares CN, Faria LC, Peralta JM, et al. Dengue infection: neurological manifestations and cerebrospinal fluid (CSF) analysis. *J Neurol Sci.* 2006 Nov 1;249(1):19-24.
135. Sahu R, Verma R, Jain A, et al. A Neurologic complications in dengue virus infection: a prospective cohort study. *Neurology.* 2014 Oct 28;83(18):1601-9.
136. Vasanwala FF, Puvanendran R, Ng JM, et al. Two cases of self-limiting nephropathies secondary to dengue haemorrhagic fever. *Singapore Med J.* 2009 Jul;50(7):e253-5.

137. Abeyskera RA, Illangasekera U, Jayalath, T, et al. A Case of Mixed Nephrotic-Range Proteinuria–Microscopic Hematuria After Dengue Hemorrhagic Fever. *Infectious Diseases in Clinical Practice*. 2013;21(6):386-388.
138. Lee IK, Liu JW, Yang KD. Clinical characteristics, risk factors, and outcomes in adults experiencing dengue hemorrhagic fever complicated with acute renal failure. *Am J Trop Med Hyg*. 2009 Apr;80(4):651-5
139. Repizo LP, Malheiros DM, Yu L, et al. Biopsy proven acute tubular necrosis due to rhabdomyolysis in a dengue fever patient: a case report and review of literature. *Rev Inst Med Trop Sao Paulo*. 2014 Jan-Feb;56(1):85-8.
140. Khalil MA, Tan J, Khalil MA et al. Predictors of hospital stay and mortality in dengue virus infection-experience from Aga Khan University Hospital Pakistan. *BMC Res Notes*. 2014 Jul 27;7:473. doi:10.1186/1756-0500-7-473.
141. Schram AM and Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. *Blood*. 2015;125(19):2908-14.
142. Filipovich, AH. Hemophagocytic lymphohistiocytosis (HLH) and related disorders. *ASH Education Program Book*. Cincinnati Children's Hospital Medical Center;2009.p127-131.
143. Weitzman S. Approach to hemophagocytic syndromes. *ASH Education Program Book*. Division of Hematology/Oncology, The Hospital for Sick Children University Avenue Toronto;2011.p178-183.
144. Henter JL, Home A, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007 Feb;48(2):124-31.
145. Rajagopala S, Singh N, Agarwal R, et al. Severe hemophagocytic lymphohistiocytosis in adults-experience from an intensive care unit from North India. *Indian J Crit Care Med*. 2012 Oct;16(4):198-203. doi: 10.4103/0972-5229.106501.
146. Pal P, Giri PP, Ramanan AV. Dengue associated hemophagocytic lymphohistiocytosis: a case series. *Indian Pediatr*. 2014 Jun;51(6):496-7.
147. Jain D, Singh T. Dengue virus related hemophagocytosis: a rare case report. *Hematology*. 2008 Oct;13(5):286-8. doi: 10.1179/102453308X316095.
148. Srichaikul T, Punyagupta S, Kanchanapoom T, et al. Hemophagocytic syndrome in Dengue hemorrhagic fever with severe multiorgan complications. *J Med Assoc Thai*. 2008 Jan;91(1):104-9.
149. Sorakhunpipitkul L, Punyagupta S, Srichaikul T, et al. Thai adult dengue hemorrhagic fever during 2008–2010: seven cases presented with severe multiorgan failure and successfully treated with high dose of corticosteroids and intravenous immunoglobulin G. *J Infect Dis Antimicrob Agents*. 2011; 28(2):99-103.
150. Rajagopala S, Singh N. Diagnosing and treating hemophagocytic lymphohistiocytosis in the tropics: systematic review from the Indian subcontinent. *Acta Med Acad*. 2012;41(2):161-74. doi: 10.5644/ama2006-124.49.
151. Mitra S, Bhattacharyya R. Hemophagocytic syndrome in severe dengue Fever: a rare presentation. *Indian J Hematol Blood Transfus*. 2014 Sep;30(Suppl 1):97-100. doi: 10.1007/s12288-013-0273-0.
152. Morel Z, Ramirez A. Autoimmune response in children with dengue. *Case reports. Reumatol Clin*. 2014 Jul-Aug;10(4):257-9. doi: 10.1016/j.reuma.2013.07.005.
153. Tan LH, Lum LC, Omar SF, Kan FK. Hemophagocytosis in dengue: comprehensive report of six cases. *J Clin Virol*. 2012 Sep;55(1):79-82. doi: 10.1016/j.jcv.2012.06.005.
154. Asli RA, Abdullah MA, Telisinghe PU, et al. Haemophagocytic lymphohistiocytosis: a rare manifestation of dengue fever. *Brunei Int Med J*. 2013;9(5):334-337.
155. Vijayalakshmi AM, Ganesh VR. Hemophagocytic syndrome associated with dengue hemorrhagic fever. *Indian Pediatr*. 2009 Jun;46(6):545.

156. Ray S, Kundu S, Saha M, Chakrabarti P. Hemophagocytic syndrome in classic dengue fever. *J Glob Infect Dis.* 2011 Oct;3(4):399-401. doi: 10.4103/0974-777X.91068.
157. Rathore R, Daniyal SM, Iqbal A, et al. Hemophagocytic Syndrome—A Rare Complication of Dengue Fever. *Annals of King Edward Medical University.* 2013;18(1).
158. Kapdi M, Shah I. Dengue and haemophagocytic lymphohistiocytosis. *Scand J Infect Dis.* 2012 Sep;44(9):708-9. doi: 10.3109/00365548.2011.652667.
159. Ribeiro E, Kassab S, Pistone T, et al. Primary dengue fever associated with hemophagocytic syndrome: a report of three imported cases, Bordeaux, France. *Intern Med.* 2014;53(8):899-902.
160. Kobayashi K, Hikone M, Sakamoto N, et al. Dengue-associated hemophagocytic syndrome in a Japanese traveler: a case report. *J Travel Med.* 2015 Jan-Feb;22(1):64-6. doi: 10.1111/jtm.12158.
161. Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol.* 2014 Sep;66(9):2613-20. doi: 10.1002/art.38690.
162. Schram AM, Campigotto F, Mullally A, et al. Marked hyperferritinemia does not predict for HLH in the adult population. *Blood.* 2015 Mar 5;125(10):1548-52. doi: 10.1182/blood-2014-10-602607.
163. Allen CE, Yu X, Kozinetz CA, et al. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer.* 2008 Jun;50(6):1227-35.
164. Cam BV, Tuan DT, Fonsmark L, et al. Randomized Comparison of Oxygen Mask Treatment vs. Nasal Continuous Positive Airway Pressure in Dengue Shock Syndrome with Acute Respiratory Failure. *J Trop Pediatr.* 2002;48:335–339.
165. Annane D, Vignon P, Renault A, et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. *Lancet* 2007;370: 676–84.
166. De Backer D, Biston P, Devriendt J, et al. Comparison of Dopamine and Norepinephrine in the Treatment of Shock. *N Engl J Med* 2010; 362:779-789.
167. Havel C, Arrich J, Losert H, et al. Vasopressors for hypotensive shock (Review). *Cochrane Database of Systematic Reviews* 2011, Issue 5.
168. Myburgh JA, Higgins, A, Jovanovska A, et al. A comparison of epinephrine and norepinephrine in critically ill patients *Intensive Care Medicine* 2008;34:2226-2234.
169. Levy B , Perez P, Perny J et al. Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. *Crit Care Med* 2011 Mar;39(3):450-5.
170. Djogovic D, MacDonald S, Wensel A, et al. Vasopressor and Inotrope Use in Canadian Emergency Departments: Evidence Based Consensus Guidelines. *CJEM.* 2015 Feb;17 Suppl 1:1-16. doi: 10.1017/cem.2014.77.
171. Taylor Robert W & Palagiri AC. Central Venous Catheterization: Concise Definitive Review. *Critical Care Medicine.* 2007; 35(5):1390-96.
172. Marik PE, Cavallazzi R. Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. *Crit Care Med.* 2013 Jul;41(7):1774-81. doi: 10.1097/CCM.0b013e31828a25fd.
173. Kumar A, Anel R, Bunnell E, et al. Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. *Crit Care Med.* 2004 Mar;32(3):691-9.
174. Mumtaz H, Williams V, Hauer-Jensen M, et al. Central venous catheter placement in patients with disorders of hemostasis. *Am J Surg.* 2000 Dec;180(6):503-5; discussion 506.
175. Kander T, Frigyesi A, Kjeldsen-Kragh J, et al. Bleeding complications after central line insertions: relevance of pre-procedure coagulation tests and institutional transfusion policy. *Acta Anaesthesiol Scand.* 2013 May;57(5):573-9. doi: 10.1111/aas.12075

176. Doerfler ME, Kaufman B, Goldenberg AS. Central venous catheter placement inpatients with disorders of hemostasis. *Chest*. 1996 Jul;110(1):185-8.
177. Calvert N, Hind D, McWilliams RG, et al. The effectiveness and cost-effectiveness of ultrasound locating devices for central venous access: a systematic review and economic evaluation. *Health Technol Assess*. 2003;7(12):1-84.
178. Tercan F, Ozkan U, Oguzkurt L. US-guided placement of central vein catheters in patients with disorders of hemostasis. *Eur J Radiol*. 2008 Feb;65(2):253-6.
179. Kaufman RM, Djulbegovic B, Gernsheimer T, et al; AABB. Platelet transfusion: a clinical practice guideline from the AABB. *Ann Intern Med*. 2015 Feb 3;162(3):205-13. doi: 10.7326/M14-1589.
180. Patel IJ, Davidson JC, Nikolic B, et al; Standards of Practice Committee, with Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Endorsement. Consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. *J Vasc Interv Radiol*. 2012 Jun;23(6):727-36. doi: 10.1016/j.jvir.2012.02.012.
181. Blumberg N, Heal JM, Phillips GL. Platelet transfusions: trigger, dose, benefits, and risks. *F1000 Med Rep*. 2010 Jan 27;2:5. doi: 10.3410/M2-5.
182. Kander T, Tanaka KA, Norström E, et al. The effect and duration of prophylactic platelet transfusions before insertion of a central venous catheter in patients with bone marrow failure evaluated with point-of-care methods and flow cytometry. *Anesth Analg*. 2014 Oct;119(4):882-90. doi: 10.1213/ANE.0000000000000259.
183. Scheer B, Perel A, Pfeiffer UJ. Clinical review: complications and risk factors of peripheral arterial catheters used for haemodynamic monitoring in anaesthesia and intensive care medicine. *Crit Care*. 2002 Jun;6(3):199-204.
184. Metheny NA, Meert KL, Clouse RE. Complications related to feeding tube placement. *Curr Opin Gastroenterol*. 2007 Mar;23(2):178-82.
185. Soni A, Chugh K, Sachdev A, Gupta D. Management of dengue fever in ICU. *Indian J Pediatr*. 2001 Nov;68(11):1051-5.
186. Ministry of Health Malaysia. Management of Dengue Infection in Adults (Revised 2nd Edition). Kuala Lumpur: MoH; 2010.
187. Machado CR, Machado ES, Denis Rohloff R, et al. Is Pregnancy Associated with Severe Dengue? A Review of Data from the Rio de Janeiro Surveillance Information System. *PLoS Negl Trop Dis*. 2013;7(5):5-8.
188. Adam I, Jumaa AM, Elbashir HM, et al. Maternal and perinatal outcomes of dengue in PortSudan, Eastern Sudan. *Virology*. 2010;7:153.
189. Pouliot SH, Xiong X, Harville E, et al. Maternal dengue and pregnancy outcomes: a systematic review. *Obstet Gynecol Surv*. 2010;65(2):107-18.
190. Chitra TV, Panicker S. Maternal and fetal outcome of dengue fever in pregnancy. *J Vector Borne Dis*. 2011;48(4):210-3.
191. Kariyawasam S, Senanayake H. Dengue infections during pregnancy: Case series from a tertiary care hospital in Sri Lanka. *J Infect Dev Ctries*. 2010;4(11):767-75.
192. Mohamed Ismail NA, Wan Abd Rahim WER, Salleh SA, et al. Seropositivity of Dengue Antibodies during Pregnancy. *Sci World J*. Hindawi Publishing Corporation; 2014;2014:1-4.
193. Phongsamart W, Yoksan S, Vanaprappa N, et al. Dengue virus infection in late pregnancy and transmission to the infants. *Pediatr Infect Dis J*. 2008;27(6):500-4.
194. Friedman EE, Dallah F, Harville EW, et al. Symptomatic Dengue Infection during Pregnancy and Infant Outcomes: A Retrospective Cohort Study. *PLoS Negl Trop Dis*. 2014;8(10):e3226.
195. Singla N, Arora S, Goel P, et al. Dengue in pregnancy: an under-reported illness, with special reference to other existing co-infections. *Asian Pac J Trop Med*. Hainan Medical College; 2015;8(3):206-8.

196. Barthel A, Gourinat AC, Cazorla C, et al. Breast milk as a possible route of vertical transmission of dengue virus? *Clin Infect Dis*. 2013 Aug;57(3):415-7. doi: 10.1093/cid/cit227.
197. Brown JL, Wilkinson R, Davidson RN, et al. Rapid diagnosis and determination of duration of viraemia in dengue fever using a reverse transcriptase polymerase chain reaction. *Trans R Soc Trop Med Hyg*. 1996 Mar-Apr;90(2):140-3.
198. Murgue B, Roche C, Chungue E, et al. Prospective study of the duration and magnitude of viraemia in children hospitalised during the 1996-1997 dengue-2 outbreak in French Polynesia. *J Med Virol*. 2000 Apr;60(4):432-8.
199. Ko YC, Chen MJ, Yeh SM. The predisposing and protective factors against dengue virus transmission by mosquito vector. *Am J Epidemiol*. 1992 Jul 15;136(2):214-20.
200. Igarashi A. Impact of dengue virus infection and its control. *FEMS Immunol Med Microbiol*. 1997 Aug;18(4):291-300.
201. Chou JT, Rossignol PA, Ayres JW. Evaluation of commercial insect repellents on human skin against *Aedes aegypti* (Diptera: Culicidae). *Journal of Medical Entomology*. 1997. 34(6): 624-30.
202. Villar L, Dayan GH, Arredondo-García JL, et al; CYD15 Study Group. Efficacy of a tetravalent dengue vaccine in children in Latin America. *N Engl J Med*. 2015 Jan 8;372(2):113-23. doi: 10.1056/NEJMoa1411037.
203. Capeding MR, Tran NH, Hadinegoro SR, et al; CYD14 Study Group. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. *Lancet*. 2014 Oct 11;384(9951):1358-65. doi: 10.1016/S0140-6736(14)61060-6.
204. Hadinegoro SR, Arredondo-García JL, Capeding MR, et al; CYD-TDV Dengue Vaccine Working Group. Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease. *N Engl J Med*. 2015 Jul 27.

APPENDIX 1

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*) adj1 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 Gelifusol.tw
- 21 gel*fusine.tw
- 22 Dextran/
- 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 adj1 (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 encephalit*).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

APPENDIX 2**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?

APPENDIX 3**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 ≥ 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).

APPENDIX 3**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 mm³ 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.

APPENDIX 4

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 laboratory 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 laboratory 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 laboratory within 24 hours after collection

c) Tissue or post mortem tissue

- i. Put the tissue in sterile container containing VTM 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

APPENDIX 5

TYPE OF TESTS FOR DENGUE DIAGNOSIS

Type of test	Technique	When To Test	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 2 weeks)	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 2 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

APPENDIX 6

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.

APPENDIX 8

DENGUE ASSESSMENT CHECKLIST

DENGUE ASSESSMENT CHECKLIST

RECOGNITION				PATIENT DETAILS			
CRITERIA	Yes	No	Details				
Fever	<input type="checkbox"/>	<input type="checkbox"/>		Name :			
Aches & pains	<input type="checkbox"/>	<input type="checkbox"/>		IC No / MRN :			
Nausea and/or vomiting	<input type="checkbox"/>	<input type="checkbox"/>		WCC:		Temp:	
Rash	<input type="checkbox"/>	<input type="checkbox"/>		Hb:		BP/MAP:	
Leucopenia	<input type="checkbox"/>	<input type="checkbox"/>		Hct:		HR:	
Any Warning Signs	<input type="checkbox"/>	<input type="checkbox"/>	(see below for warning signs)	Pit:		CRT:	
Warning Signs		Yes	Details	RR:			
Persistent vomiting $\geq 3\times$ / diarrhoea $\geq 3\times$ (over the last 24h)	<input type="checkbox"/>			SEVERE DENGUE			
Any abdominal pain/ tenderness	<input type="checkbox"/>			Hypotension SBP<90 or MAP<60 or SBP drop >40mmHg from known baseline	<input type="checkbox"/>	Yes	Details
Lethargy/ restlessness/ confusion	<input type="checkbox"/>			Shock index: HR> SBP or abnormal CCTVR	<input type="checkbox"/>		
Tender liver	<input type="checkbox"/>			Third space fluid accumulation with respiratory distress	<input type="checkbox"/>		
Third space fluid accumulation	<input type="checkbox"/>			Altered conscious level	<input type="checkbox"/>		
Spontaneous bleeding tendencies	<input type="checkbox"/>			Any bleed GI/ non-mucosal and non-cutaneous/ non-physiological	<input type="checkbox"/>		
Raised Hct with rapid drop in platelet	<input type="checkbox"/>		(In the absence of baseline values) Male age ≤ 60 : Hct >46 Male age >60: Hct >42 Female all ages: Hct >40	Specific organ dysfunction (p/s specify)	<input type="checkbox"/>		
				CRITICAL CARE REVIEW & FAST-TRACK			
				Instructions			
				1. Review features of severe dengue present.			
				2. Specify start and end times of fluid regimes			
				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 WITH WARNING SIGNS <input type="checkbox"/>			
				SEVERE DENGUE <input type="checkbox"/>			
				Signature/Stamp:			
				Date:			
ADMIT if ANY WARNING SIGNS present or presence of other criteria CONSIDER admission for patients in the special group even in the absence of warning signs. Instructions 1. Please notify as DENGUE INFECTION 2. If admitting, please inform the receiving Dr							

APPENDIX 9

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 / diarrhoea**
4. **Drowsiness or irritability**
5. **Pale, cold or clammy skin**
6. **Difficulty in breathing**

Adapted : CPG Management of Dengue Infection in Adults (Revised 2nd Edition), 2010

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
GSH	Group, screen and hold
GXM	Group cross match
HCT	Hematocrit
HCO ₃	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
IVIg	Intravenous immunoglobulin
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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