MANAGEMENT OF DENGUE IN CHILDREN (SECOND EDITION)
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.

UPDATING THE CPG

These guidelines were issued in 2020 and will be reviewed in a minimum period of four years (2024) or sooner if there is a need to do so. 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. Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on the websites mentioned above.
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KEY RECOMMENDATIONS

The following recommendations were highlighted by the CPG Development Group as the key clinical recommendations that should be recognised for implementation.

Diagnosis and Notification

- Children suspected of dengue infection should be tested with a combination of NS1 Antigen/IgM/IgG rapid test (dengue rapid combo test).
  - Rapid test of NS1 Antigen alone may be used on day 1 to day 5 of illness.

- Notification should be done for all suspected dengue cases from private and public health facilities by telephone/fax/e-notification to the nearest health office within 24 hours of diagnosis. This should be followed by written notification using the standard notification form.

Treatment

- All children with dengue infection who are treated as outpatient:
  - should have daily clinical and laboratory monitoring until resolution of critical phase
  - should be provided with dengue monitoring card and dengue home care leaflet

- Isotonic crystalloid solutions should be used in resuscitation and maintenance therapy in children with dengue.
  - Colloid solutions may be used in persistent shock despite resuscitation with the crystalloid solutions.

- Close monitoring and frequent reassessment should be done to guide appropriate fluid management of children with dengue shock.
  - They should be managed by senior staff in hospitals with paediatrician.
  - Those with decompensated shock should be admitted to the high-dependency or intensive care unit.

- Blood transfusion should be given in life-threatening condition and given as soon as severe bleeding is recognised (overt) or suspected (occult) in children with dengue.
  - It must be given cautiously to avoid fluid overload especially in neonates or infants.

- Dengue infection in infant should be managed in hospital with paediatric services.
LEVELS OF EVIDENCE

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<td>II-2</td>
<td>Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group</td>
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<td>II-3</td>
<td>Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence</td>
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<td>III</td>
<td>Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees</td>
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SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

FORMULATION OF RECOMMENDATION

In line with new development in CPG methodology, the CPG Unit of MaHTAS is in the process of adapting 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 versus 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 CPG were from the Ministry of Health (MoH) and Ministry of Education (MoE). There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A systematic literature search was carried out using the following electronic databases/platforms: mainly Medline via Ovid and Embase. Refer to Appendix 1 for Example of Search Strategy. The inclusion criteria are all children with suspected and confirmed dengue infection regardless of study design. The search was limited to literature published in the last 14 years and on humans specifically children with unspecified age and in English. In addition, the reference lists of all retrieved literature and guidelines were searched and experts in the field contacted to identify relevant studies. All searches were conducted from 30 October 2018 to 7 November 2018. Literature search was repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 7 February 2020 to be included. 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.

References were also made to other guidelines on dengue in children as listed below:

- Paediatric Protocols for Malaysian Hospitals (Fourth Edition) (Ministry of Health Malaysia, 2019)
- Dengue Guidelines for Diagnosis, Treatment, Prevention and Control (World Health Organization, 2009)

A total of 12 main 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 14 times throughout the development of these guidelines. All literatures retrieved were 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 are 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 literatures used in these guidelines were 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). The writing of the CPG follows strictly the requirement of Appraisal of Guidelines for Research and Evaluation (AGREE II).

On completion, the draft 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 Health Technology Assessment (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/moh/resources/CPG_MANUAL_MAHTAS.pdf?mid=634)
OBJECTIVES

The objectives of the CPG are to provide evidence-based recommendations on management of dengue in children on the following aspects:

- diagnosis
- treatment
- monitoring and follow-up
- referral
- prevention

CLINICAL QUESTIONS

Refer to Appendix 2.

TARGET POPULATION

Inclusion Criteria
- Children with suspected and confirmed dengue infection

TARGET GROUP/USER

This document is intended to guide healthcare providers and relevant stakeholders in primary and secondary/tertiary care in the management of dengue in children including:

- doctors
- allied health professionals
- trainees and medical students
- patients and their advocates
- professional societies

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The draft CPG 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 CPG.

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Algorithm 1: Dengue Laboratory Diagnosis

Clinically Suspected Dengue

Dengue Rapid Combo Test
**Algorithm 2. Fluid Management of Children with Dengue Warning Signs**

- Assess airway, breathing and circulation
- Establish that patient not in shock but having only warning signs
- Secure intravenous (IV) access
- Obtain reference haematocrit (HCT), renal profile and liver function test if possible
- Commence Normal Saline at 5 - 7 ml/kg over 1 hour

**NS1 Ag/IgM/IgG negative**

- NS1 Ag positive/IgM positive
- NS1 Ag positive/IgM negative
- NS1 Ag negative/IgM positive (regardless of the IgG result)

**NS1 Ag negative/IgM negative/IgG positive**

- Probable secondary dengue infection or past dengue infection

**Acute or recent dengue infection**

- ≤5 days
  - NS1 Ag (Rapid/ELISA)*

**≥5 days**

- NS1 Ag Negative
  - Dengue IgM/IgG Serology (ELISA)

  - Dengue IgM positive & Dengue IgG positive
    - Recent dengue infection OR secondary dengue infection
  - Dengue IgM positive & Dengue IgG negative
    - Recent dengue infection
  - Dengue IgM negative & Dengue IgG positive
    - Probable secondary dengue infection or past dengue infection
  - Dengue IgM negative & Dengue IgG negative
    - No dengue infection

*Alternatively, Dengue Rapid Combo Test may be repeated

PCR should be sent if serology/NS1 Ag negative in suspected severe dengue or mortality cases.

ELISA - enzyme-linked immunosorbent assay
IgG - Immunoglobulin G
IgM - Immunoglobulin M
NS1 Ag - Non-structural protein 1 Antigen
PCR - polymerase chain reaction
Algorithm 3. Fluid Management of Compensated Dengue Shock in Children

- Stabilise airway, breathing and circulation
- Give high flow oxygen
- Secure intravenous (IV)/intraosseous access within 5 minutes
- Obtain reference haematocrit (HCT) and blood for cross match
- Commence Normal Saline/Hartmann’s solution/Ringer’s Lactate at 10 - 20 ml/kg over an hour

Modified:
Reassessment of haemodynamic status

Reversal of shock

Crystalloid solutions reduced to
1. 5 - 7 ml/kg/hr for 1 - 2 hours
2. 3 - 5 ml/kg/hr for 2 - 4 hours
3. 2 - 3 ml/kg/hr for 24 - 48 hours
If oral fluid intake improves, IV fluid can be reduced

Further fluid boluses of 10 - 20 ml/kg are required if shock recurs

Stop IV fluid if patient shows signs of reabsorption, usually 48 hours after entering critical phase

Check HCT

HCT high

Give further bolus of crystalloid/colloid at 10 - 20 ml/kg over 1 hour

Transfuse fresh packed red cells/fresh whole blood at 10 - 20 ml/kg over 1 hour

HCT low

• consider occult bleeding

HCT low

Reduce crystalloid solutions to 7 - 10 ml/kg

Reversal of shock

Yes

No

Modified:

Algorithm 4. Fluid Management of Decompensated Dengue Shock in Children

- Stabilise airway, breathing and circulation
- Give high flow oxygen
- Secure intravenous (IV)/intraosseous access within 5 minutes
- Obtain reference haematocrit (HCT) and blood for cross match
• Commence Normal Saline/Hartmann’s solution/Ringer’s Lactate or colloid solutions at 20 ml/kg over 15 - 30 minutes*
• Monitor vital signs and hourly urine output (with an indwelling catheter)
• Correct hypoglycaemia/hypocalcaemia if present

Reassessment of haemodynamic status

Reversal of shock

Yes

Check HCT

HCT high

Give further bolus of crystalloid/colloid at 10 - 20 ml/kg over 30 - 60 minutes or faster if patient remains hypotensive

HCT low

• consider occult bleeding

Transfuse fresh packed red cells/fresh whole blood at 10 - 20 ml/kg over 1 hour or faster if profuse bleeding

Reversal of shock

No

Further fluid boluses of 10 - 20 ml/kg are required if shock recurs

Stop IV Fluid if patient shows signs of reabsorption, usually 48 hours after entering critical phase

Crystalloid solutions reduced to
1. 10 ml/kg/hr for 1 hour
2. 5 - 7 ml/kg/hr for 1 - 2 hours
3. 3 - 5 ml/kg/hr for 2 - 4 hours
4. 2 - 3 ml/kg/hr for 24 - 48 hours

If oral fluid intake improves, IV fluid can be reduced

Modified:

*Give fresh packed red cells/fresh whole blood during initial resuscitation when patient presents with overt bleeding e.g. haematemesis/melaena

In refractory shock (patient remains in shock despite 40 - 60 ml/kg of crystalloid/colloid solutions or fresh packed red cells/fresh whole blood), especially when HCT remain unchanged, consider:
• intubation to secure airway and ventilation
• concurrent bleeding and leaking
  ○ Look for source if clinically not apparent yet
  ○ Transfuse fresh packed red cells/fresh whole blood or blood components
• septic shock (co-infection)
  ○ Take blood culture and start IV antibiotics (cefotaxime or ceftriaxone)
  ○ Consider inotropes (adrenaline or noradrenaline)
• cardiac dysfunction
  ○ Perform echocardiogram if available
  ○ Consider inotropes (adrenaline or dobutamine)
• correction of electrolytes imbalances and acidosis
• monitoring of intra-abdominal pressure (IAP) - control ascitic fluid drainage with great caution if IAP elevated

In refractory shock (patient remains in shock despite 40 - 60 ml/kg of crystalloid/colloid solutions or fresh packed red cells/fresh whole blood), especially when HCT remain unchanged, consider:
1. INTRODUCTION

1.1 Epidemiology

Dengue fever (DF) is a common and serious mosquito-borne viral disease. It is caused by dengue virus (DENV) which has four serotypes (Den 1, Den 2, Den 3 and Den 4). All serotypes are found in Malaysia and the predominant serotype changes from year to year.

The vector for DENV is mosquito from the genus Aedes which has biting preference for certain time of the day i.e. morning and late afternoon hours. *A. aegypti* is considered as the principal species as it only feeds on humans and can adapt to cohabit with humans in both urban and rural environments. *A. albopictus* on the other hand is less efficient to spread DENV since it feeds on both human and animal blood.

The incidence of dengue has grown dramatically around the world in recent decades. The actual numbers of dengue cases are underreported and many are misclassified. World Health Organization (WHO) reports a modelling estimate of 390 million dengue infections per year (95% CI 284 to 528), with 96 million (95% CI 67 to 136) manifesting clinically (with any severity of the disease).\(^\text{WHO, level III}\)

In Malaysia, the number of dengue cases and incidence rate (IR) continue to increase with the highest number ever reported was in 2019. In that year, a total of 130,101 dengue cases were reported which was equivalent to IR of 390.4 cases per 100,000 population.

During the period 2000 - 2019, the annual number and the incidence rate of dengue cases in Malaysia varied substantially, from the lowest value of 7,103 cases (30/100,000 population) in 2000, reaching a peak of 120,836 cases (390/100,000 population) in 2015. After the peak, there was downward trend in 2016, 2017, 2018 with yearly reduction of 16.1%, 17.3% and 3.9% of cases respectively. However, in 2019, there was an increase of 61.4% dengue cases. Refer to Figure 1.

![Figure 1. Annual number and incidence rate of dengue in Malaysia, 2000 - 2019](source: Analysis of dengue cases in Malaysia. Disease Control Division, Ministry of Health Malaysia. 2020 (unpublished document).)
DENV affects all age groups worldwide. Thus, children are also not spared from dengue infection and their management proves to be challenging. It’s been estimated by WHO that 500,000 people with severe dengue require hospitalisation each year with a large proportion of whom are children. Bhatt S et al., 2013, level III; WHO, 2009, level III

In majority of children (0 - 12 years old), dengue causes flu-like illness which might be difficult to differentiate from other febrile illness (OFI) and seldom causes death. The severe form that leads to plasma leakage and shock is the cause of death among children in some Asian and Latin America countries. WHO, 2009, level III

In Malaysia, the annual percentage of cases among children has increased from 2014 to current percentage of about 20% in 2019 (refer to Figure 2).

![Figure 2. Annual dengue cases among children and adults in Malaysia](image)

**Source:** Analysis of dengue cases in Malaysia. Disease Control Division, Ministry of Health Malaysia. 2020 (unpublished document).

### 1.2 Classification

Dengue classification had undergone major changes since 2009. The previous 1997 classification of DF and dengue hemorrhagic fever (DHF) had many criticisms since the case definition of DHF was too rigid and not applicable in primary care or resource-limited settings. Another issue was that the old case definition failed to identify a significant proportion of dengue cases that were severe in nature involving certain target organs. Severe manifestations e.g. central nervous system (encephalopathy) and hepatic failure were not included in the old definition. The emphasis of the old classification was more on bleeding manifestations, hence the nomenclature of DF and DHF were used. Findings from a multicentre study by DENCO study group led to the new clinical classification. Alexander N et al., 2011, level II-2; Manock SR et al., 2009, level III

Malaysia had adopted these new classifications for use in clinical management and clinical audit of mortality cases. New terms like dengue with/without warning signs and severe dengue are used to emphasise that not only bleeding causing problem in dengue but increase vascular permeability leading to leakage tips an individual to severe form of dengue. Refer to Figure 3.
1.3 Severity

Dengue infection may be asymptomatic or present with a broad range of clinical manifestations [mild febrile illness (known as DF) to life-threatening shock syndrome]. Numerous viral, host and vector factors are thought to impact risk of infection and disease severity.

There are four closely related but serologically distinct DENV types. Generally, infection with one DENV serotype confers protection to infection with that serotype only. Thus, individuals are susceptible to secondary infections with other serotypes. They are at greater risk of severe dengue. Therefore, children and adults living in dengue endemic area like Malaysia where all serotypes co-circulating are at risk for primary/secondary infections with any DENV.\textsuperscript{1} Wahala WM et al., 2011, level III; Rothman AL, 2011, level III; Halstead SB, 2007, level III

Dengue infection in children is often difficult to differentiate from OFI hence appropriate management cannot be instituted in timely manner. Children generally present with non-specific clinical features of OFI.\textsuperscript{1} Wahala WM et al., 2011, level III

Among the different paediatric age groups, infants are at high-risk of getting severe dengue. The age specific incidence of infant DHF is 0.5/1000 person over the age of 3 to 8 months in South East Asia.\textsuperscript{1} Infants with primary infection may develop severe dengue when the mothers have prior DENV immunity.\textsuperscript{1} Capeding MR et al., 2010, level III
2. CLINICAL MANIFESTATIONS AND PATHOPHYSIOLOGY

Dengue in children has a wide spectrum of clinical presentation ranging from non-severe to life-threatening. Refer to Figure 3 for common symptoms and signs of the condition.

Dengue illness begins abruptly after 1 - 4 days of an incubation period (range 3 - 14 days). It encompasses three phases as discussed below.

a. Febrile phase
This phase usually lasts 2 - 7 days. Common features include:
- abrupt high-grade fever
- facial flushing, skin erythema, generalised body ache, myalgia, arthralgia, retro-orbital pain, photophobia, rubelliform exanthema and headache
- anorexia, nausea and vomiting

These features are also present in OFI which might be difficult to differentiate from DF. Refer to Table 2.

The earliest abnormality in full blood count (FBC) is a gradual drop in white cell counts, which should alert the doctor to a high probability of dengue. Haematological manifestations are mild e.g. petechiae, mucosal membrane bleeding (nose, gum), easy bruising or bleeding at venepuncture sites,\textsuperscript{WHO, 2012, level III}

Complications e.g. dehydration and febrile seizures may occur during this phase.

b. Critical phase
This phase usually begins after the third (or earlier) day of illness but can be as late as day eight of illness. It typically occurs around the time of defervescence (temperature drops to and remains below 38°C). Plasma leakage may occur as a result of increased capillary permeability and is manifested by warning signs (refer to yellow box below). This set of clinical parameters usually precedes manifestations of shock.\textsuperscript{WHO, 2012, level III}

### Warning signs of Dengue

- Abdominal pain - abdominal tenderness and continuous pain (not intermittent)\textsuperscript{Narvaez F et al., 2011, level III}
- Persistent vomiting - (≥2 episodes of vomiting that amounts to fatigue or requires intravenous (IV) fluids)\textsuperscript{Sreenivasan, 2018, level II-3}
- Mucosal bleed - bleeding from nose, gums, conjunctiva, vagina, gastrointestinal/respiratory/urinary tract\textsuperscript{Narvaez F et al., 2011, level III}
- Lethargy, restlessness\textsuperscript{WHO, 2012, level III}
- Liver enlargement >2 cm\textsuperscript{WHO, 2012, level III}
- Clinical fluid accumulation - pleural effusion and ascites\textsuperscript{Narvaez F et al., 2011, level III}
- Laboratory: increase in haematocrit (HCT) concurrent with decrease in platelet - HCT raised by 20% from the baseline value with concurrent decrease in platelet count ≤100 x 10\textsuperscript{3} cells/mm\textsuperscript{3}\textsuperscript{WHO, 2012, level III; Narvaez F et al., 2011, level III}

*Refer to Table 6 on Range of Haematocrit in Different Age Groups.*

Significant critical phase usually lasts 24 - 48 hours, mostly worst around defervescence. Some children may enter this phase before defervescence. The initiation of plasma leakage is signalled by an elevated HCT and rapid onset of thrombocytopenia or warning signs. HCT level is well associated with loss of plasma volume and the higher the level of haemoconcentration, the greater the severity of the disease.\textsuperscript{ Kittigul L et al., 2007, level III} However, majority of children recover spontaneously or after a short period of fluid therapy.
Continuous vascular permeability and plasma leakage give rise to hypovolaemia and shock. Severe plasma leakage leads to dengue shock syndrome (DSS). Severe organ involvement may develop e.g. severe hepatitis, encephalitis and myocarditis, and/or severe bleeding even without obvious plasma leakage or shock.

- **Pathophysiology of plasma leakage and shock in dengue**
  Increased capillary permeability is the main pathophysiological abnormality seen in dengue infection which results in plasma leakage into the extravascular compartment. This results in haemoconcentration and hypovolaemia or shock. Shock in dengue is a physiological continuum, from asymptomatic capillary leakage to compensated shock, then hypotensive shock and eventually cardiac arrest. The mechanisms that lead to severe dengue are not well established.

  During earlier stage of shock, the body compensates to maintain normal systolic blood pressure (BP). Hypovolaemia leads to reflex tachycardia and widespread vasoconstriction due to increased sympathetic activity. Refer to Appendix 3 on Systemic Manifestation of Peripheral Vasoconstriction.

Parameters to be monitored during haemodynamic assessment are shown in **Table 1**.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal Circulation</th>
<th>Compensated shock*</th>
<th>Decompensated / Hypotensive shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consciousness level</td>
<td>Clear and alert</td>
<td>Clear and alert</td>
<td>Change of mental state (restless, combative)</td>
</tr>
<tr>
<td>Extremities</td>
<td>Warm and pink extremities</td>
<td>Cool extremities</td>
<td>Cold, clammy extremities</td>
</tr>
<tr>
<td>Capillary refill time (CRT)</td>
<td>Brisk (&lt;2 sec)</td>
<td>Prolonged (&gt;2 sec)</td>
<td>Very prolonged, mottled skin</td>
</tr>
<tr>
<td>Peripheral pulse volume</td>
<td>Good volume peripheral pulses</td>
<td>Weak &amp; thready peripheral pulses</td>
<td>Feeble or absent peripheral pulses</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Normal heart rate for age</td>
<td>Tachycardia</td>
<td>Severe tachycardia with bradycardia in late shock</td>
</tr>
</tbody>
</table>
| BP | Normal BP for age | • Normal systolic pressure with raised diastolic pressure  
• Postural hypotension | Hypotension/ unrecordable BP |
| Pulse pressure | Normal pulse pressure for age | Narrowed pulse pressure (≤20 mmHg) | Unrecordable |
| Respiratory rate | Normal respiratory rate for age | Tachypnoea | Metabolic acidosis/ hyperpnoea |
| Urine output | Normal | Reducing trend | Oliguria/anuria |

*unless the child is touched, parameters of shock will be missed e.g. cold extremities, weak peripheral pulses, prolonged CRT


### c. Recovery phase
Most cases of severe dengue will enter the convalescent phase 24 - 48 hours after the onset of plasma leakage. This is followed by gradual reabsorption of extravascular compartment in the next 48 - 72 hours.

**WHO, 2012, level III**
Improvement of patient’s general condition is shown by gradual return of appetite, disappearance of gastrointestinal symptoms, stabilisation of haemodynamic status and commencement of diuresis. Some patients may develop a confluent erythematous or petechial rash with small areas of normal skin over the extremities described as “isles of white in the sea of red”. WHO, 2012, level III

- In recovery phase, important signs to be considered are:
  - general condition improves
  - HCT may decrease due to dilutional effect which does not warrant further action
  - new onset respiratory distress due to fluid overload

During recovery phase, cardiac manifestations may include bradycardia and hypertension. WHO, 2012, level III; MoH, 2004 The HCT normalises or decreases due to the dilutional effect of reabsorbed fluid. Soon after defervescence, there is an increase of white blood cell (WBC) count followed by recovery of platelet count. WHO, 2012, level III

The clinical course of dengue illness is shown in **Figure 4**.

![Figure 4. The Course of Dengue Illness](image)

**Figure 4. The Course of Dengue Illness**


3. **DIAGNOSIS**

3.1 **Clinical Diagnosis**

Accurate diagnosis of dengue is essential for early detection and management of severe dengue, and timely institution of preventive measures. High index of suspicion is important in
arriving at the diagnosis e.g. history of recent fogging in locality, recent family history of dengue, etc. Definitive diagnosis requires laboratory confirmation.

- The criteria for a provisional diagnosis of dengue infection are as below: WHO, 2012, level III
  - Live in/travel to dengue endemic area
  - Fever and TWO of the following
    - nausea or vomiting
    - rash
    - aches and pains
    - leukopenia
    - any warning signs
  These criteria are well outlined in dengue classification (Figure 3).

Features well associated with laboratory-confirmed dengue in children are nausea or vomiting, absence of upper respiratory infection symptoms, liver enlargement, thrombocytopenia (platelet count <100,000 /µL) and leukopenia (leukocyte count <4000 /µL). Cavailler P et al., 2016, level III

Differential diagnosis for dengue in children is shown in Table 2.

### Table 2. Differential Diagnosis for Dengue in Children

<table>
<thead>
<tr>
<th>CONDITIONS THAT MIMIC THE FEBRILE PHASE OF DENGUE INFECTION (OFI)</th>
<th>CONDITIONS THAT MIMIC THE CRITICAL PHASE OF DENGUE INFECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu-like syndromes</td>
<td>infectious mononucleosis, human immunodeficiency virus (HIV) seroconversion illness</td>
</tr>
<tr>
<td>Illnesses with a rash</td>
<td>rubella, measles, scarlet fever, meningococcal infection, chikungunya, drug reactions</td>
</tr>
<tr>
<td>Diarrhoeal diseases</td>
<td>rotavirus, other enteric infections</td>
</tr>
<tr>
<td>Illnesses with neurological manifestations</td>
<td>febrile seizures, meningitis, encephalitis, meningoencephalitis</td>
</tr>
<tr>
<td>Infectious</td>
<td>acute gastroenteritis, malaria, leptospirosis, typhoid, typhus, viral hepatitis, bacterial sepsis, septic shock, acute HIV seroconversion illness</td>
</tr>
<tr>
<td>Malignancies</td>
<td>acute leukaemia and other malignancies</td>
</tr>
<tr>
<td>Other clinical pictures</td>
<td>acute abdomen, diabetic ketoacidosis, lactic acidosis, leukopenia and thrombocytopenia ± bleeding, platelet disorders, renal failure, respiratory distress (Kussmaul’s breathing), Systemic Lupus Erythematosus</td>
</tr>
</tbody>
</table>


### 3.2 Laboratory Diagnosis

Dengue infection can be diagnosed by
- detection of the dengue virus protein by non-structural protein 1 antigen (NS1 Ag) - rapid test/ enzyme-linked immunosorbent assay (ELISA)
- antibody detection of immunoglobulin M (IgM)/immunoglobulin G (IgG) (serology) - rapid test/ELISA
- combination of NS1 Ag with IgM/IgG rapid test (dengue rapid combo test)
- genome detection - real time reverse transcriptase-polymerase chain reaction (RT-qPCR)
- virus isolation

NS1 Ag test has a high specificity for dengue infection (86 - 99%) but with lower sensitivity (67% - 71%). Shan X et al., 2015, level III; Zhang H et al., 2014, level III

Dengue rapid test is a good tool for detection of DENV IgM in acute dengue infection (AUC=0.91). Blacksell SD et al., 2006, level II-2

Combination of NS1 Ag with an IgM/IgG rapid test in acute dengue infection results in an increased sensitivity to Fry SR et al., 2011, level III
- 89% for combination of NS1 Ag with anti-IgM
- 93% for combination of NS1 Ag, anti-IgM and anti-IgG

Refer to Figure 5, Table 3 and Table 4 on appropriate test to be done during different phases of dengue infection.
Figure 5. Timeline of dengue biomarker appearance in patients experiencing primary and secondary infection

**Source:** Muller DA, Depelsenaire AC, Young PR. Clinical and Laboratory Diagnosis of Dengue Virus Infection. J Infect Dis. 2017;215 (suppl_2): S89-S95

In primary infection (top panel), both NS1 and virus can be detected from the onset (day 1) of disease, with IgM appearing around day 3 of illness and IgG appearing towards the end of the acute period. Secondary infections (bottom panel) are characterised by the presence of IgG early in the acute phase of disease and a shorter duration of NS1 and virus detection. Note the onset of severe dengue (DHF/DSS), primarily in secondary infections and at a time when virus and NS1 levels are falling. Muller DA et al., 2017, level III
Table 3. Dengue Diagnostics and Sample Characteristics

<table>
<thead>
<tr>
<th>Laboratory tests</th>
<th>Clinical sample</th>
<th>Diagnostic method</th>
<th>Methodology</th>
<th>Laboratory Turnaround Time (TAT)</th>
<th>Laboratory Service</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of DENV and its components</td>
<td>Acute serum (1 - 5 days of fever) and post-mortem tissues</td>
<td>Viral isolation</td>
<td>Mosquito cell culture inoculation</td>
<td>One week or more</td>
<td>IMR/MKAK</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nucleic acid detection</td>
<td>RT-qPCR</td>
<td>1 - 7 days</td>
<td>IMR/MKA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antigen detection</td>
<td>NS1 Ag rapid test</td>
<td>Minutes</td>
<td>Primary health care</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NS1 Ag ELISA</td>
<td>2 - 5 days</td>
<td>Hospitals</td>
</tr>
<tr>
<td>Serological response</td>
<td>Paired sera (acute serum from 1 - 5 days and second serum 15 - 21 days after)</td>
<td>IgM or IgG sero-conversion</td>
<td>ELISA</td>
<td>2 - 5 days</td>
<td>Hospitals</td>
</tr>
<tr>
<td></td>
<td>Serum after day 5 of fever</td>
<td>IgM detection (recent infection)</td>
<td>IgM ELISA</td>
<td>2 - 5 days</td>
<td>Hospitals</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rapid tests</td>
<td>Minutes</td>
<td>Primary health care and hospitals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IgG detection</td>
<td>IgG ELISA</td>
<td>2 - 5 days</td>
<td>Hospitals</td>
</tr>
<tr>
<td>Detection of DENV components and serological response (Combo Test)</td>
<td>Whole blood (anytime dengue suspected)</td>
<td>NS1 Antigen, IgM and IgG detection</td>
<td>NS1 Ag, IgM and IgG rapid test</td>
<td>Minutes</td>
<td>Primary health care and hospitals</td>
</tr>
</tbody>
</table>


Table 4. Confirmed and Probable Dengue Diagnosis, Interpretation of Results and Sample Characteristics

<table>
<thead>
<tr>
<th>Laboratory diagnosis</th>
<th>Method</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed dengue infection</td>
<td>Virus isolation</td>
<td>Virus isolated</td>
</tr>
<tr>
<td></td>
<td>Genome detection</td>
<td>Positive RT-qPCR</td>
</tr>
<tr>
<td></td>
<td>Antigen detection</td>
<td>Positive NS1 Ag</td>
</tr>
<tr>
<td></td>
<td>IgM</td>
<td>From negative IgM to positive IgM in paired sera</td>
</tr>
<tr>
<td></td>
<td>IgG</td>
<td>From negative IgG to positive IgG in paired sera</td>
</tr>
<tr>
<td>Probable dengue infection</td>
<td>IgM</td>
<td>Positive IgM</td>
</tr>
<tr>
<td></td>
<td>IgG</td>
<td>Positive IgG</td>
</tr>
</tbody>
</table>

Refer to **Algorithm 1** on Dengue Laboratory Diagnosis.

All laboratory results should be interpreted by taking into consideration the clinical features and timing of test.

In local setting, for severe dengue or mortality cases, serotyping should be sent to reference laboratory.

### Recommendation 1
- Children suspected of dengue infection should be tested with a combination of NS1 Antigen/IgM/IgG rapid test (dengue rapid combo test).
  - Rapid test of NS1 Antigen alone may be used on day 1 to day 5 of illness.
- Laboratory results should be correlated with clinical presentation of children suspected of dengue.
- Dengue serotyping should be done for severe dengue or mortality cases in children.

#### 3.3 Post-Mortem Cases

Tissue samples of suspected dengue infection from post-mortem cases should be sent for viral isolation and PCR. Tissue samples of choice are from the liver, spleen and lymph nodes. WHO, 2012, level III The tissues should be placed in sterile containers and moistened with sterile normal saline (NS). Bone marrow samples should be collected in ethylenediamine tetraacetic acid (EDTA) tube. In patients suspected of having dengue encephalitis, cerebrospinal fluid (CSF) samples should be submitted in sterile bijou bottles. These samples should be transported on ice to the referral laboratory. All samples should be refrigerated if there is delay in transportation. MoH, 2015

### Recommendation 2
- Tissue samples of suspected dengue infection from post-mortem cases should be sent for viral isolation and polymerase chain reaction test.

#### 3.4 Notification

- Under the Prevention and Control of Infectious Diseases Act, 1988 (Act 342), notification of dengue is mandatory and failure to notify is compoundable.

Any delay in notification will increase the risk of dengue transmission in the locality of the residence. Any change in diagnosis or severity should be re-notified. 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 Department and must be investigated by the District Health Officer or Epidemiology Officer.

Health authorities will investigate all notified cases for the verification of case definition and preventive measures. Ministry of Health Malaysia has set up new criteria since 2014 whereby all registered dengue cases must be laboratory confirmed. MoH, 2017, level III

### Recommendation 3
- Notification should be done for all suspected dengue cases from private and public health facilities by telephone/fax/e-notification to the nearest health office within 24 hours.
of diagnosis. Except for e-notification, other types of notification should be followed by written notification using the standard notification form.

4. RISK FACTORS FOR SEVERE DENGUE

Risk factors for severe dengue need to be identified to improve dengue management in children. From the eight warning signs listed by WHO in 2009 guidelines, only these listed below are significantly associated with severe dengue:

- lethargy
- abdominal pain
- bleeding tendencies
- hepatomegaly
- haemoconcentration of >22% of baseline
- thrombocytopenia of <100,000 /μL

Other predictors of dengue severity in children are:

- demographic: female sex, age group >5 years old, obesity
- epidemiology: secondary infection by DENV, infection by DENV-2
- clinical signs: pulse pressure <20 mmHg, systolic BP <90 mmHg
- laboratory parameters: WBC >5,000 /μL, haemoglobin (Hb) <9 g/dL, prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT), low fibrinogen level
- imaging: gallbladder wall thickening >5 mm, presence of pleural effusion, ascites and/or gallbladder wall thickening

5. TREATMENT

5.1 Febrile Phase

Children may present with acute febrile illnesses which may be difficult to differentiate from dengue infection at the initial stage. During the first encounter, appropriate history taking and examination should be performed to arrive at the diagnosis. For paramedics who attend the child before doctor, use the Checklist for Initial Assessment Dengue in Children for Paramedics to avoid missing diagnosis (refer to Appendix 4).

For children who do not require admission, advice should be given on temperature and fluid management (refer to Appendix 5).

- Acetaminophen (paracetamol) may be used for the treatment of fever and pain. The dose in dengue needs to be adjusted since there is theoretical risk of liver injury. The recommended dose is 10 mg/kg/dose, not more than 3 - 4 times in 24 hours in children. WHO, 2012, level III
- Perform tepid sponging if the patient still has a high fever. WHO, 2012, level III
- Do not prescribe acetylsalicylic acid (aspirin), ibuprofen or other non-steroidal anti-inflammatory agents (NSAIDs) or intramuscular injections, as these aggravate gastritis or bleeding. WHO, 2012, level III
5.1.1 Outpatient monitoring and treatment
Outpatient monitoring is recommended for children with dengue infection who do not require admission and they are as listed below: WHO, 2012, level III
- daily vital signs monitoring i.e. temperature, pulse rate/volume, BP and CRT
- daily FBC monitoring specifically HCT and platelet count. Initial HCT can be used as a baseline during the monitoring. Critical phase of plasma leakage is preceded by decreasing WBC count, platelet count and increasing HCT. Thus, daily FBC is recommended until the critical phase has resolved.
- daily fluid intake and urine output. Caregivers should be advised to record oral fluid intake and urine output. Urine output of 4 - 6 times/day signifies adequate fluid intake.
- caregivers should bring the child for reassessment by healthcare providers if the child’s condition worsens i.e. presence of warning signs.

Children with dengue infection who are managed as outpatient should be provided with dengue monitoring card and dengue home care leaflet (refer to Appendix 5).

**Recommendation 4**
- All children with dengue infection who are treated as outpatient:
  - should have daily clinical and laboratory monitoring until resolution of critical phase
  - should be provided with dengue monitoring card and dengue home care leaflet

5.1.2 Admission criteria
Most children with dengue infection are asymptomatic. Those with symptoms will generally recover with/without symptomatic treatment. However, approximately 5% of cases will develop severe dengue and require admission. AAP, 2018, level III Refer to Chapter 2 on Clinical Manifestations and Pathophysiology and Chapter 4 on Risk Factors for Severe Dengue.

- The admission criteria for children with dengue infection include: WHO, 2012, level III
  - age <12 months
  - presence of warning signs
  - features of severe dengue
  - presence of co-morbidities
- Admission may be considered based on social factors e.g. difficulty for outpatient monitoring.

Positive NS1 Ag test only is not an indication for admission as majority of non-severe dengue (65.9%) are NS1 Ag positive. Pothapregada S et al., 2016, level III Serological evidence of dengue does not indicate the child needs admission since dengue IgM positivity (93%) is more common in non-severe dengue. Mishra S et.al, 2016, level III

Healthcare providers should use his/her clinical acumen to stabilise patients prior to transfer to appropriate healthcare facilities. Adequate communication to the receiving facility must be made. Refer to Garispanduan Rujukan dan Perpindahan Pesakit di Antara Hospital-hospital Kementerian Kesihatan, MoH, 2009

5.1.3 Inpatient monitoring
As the child progresses through the course of dengue infection, appropriate monitoring is recommended to enable early detection of severe illness. Clinical and laboratory parameters that may predict progression are:
- clinical - increased central to peripheral temperature gradient, bleeding episodes, hepatomegaly, pulse pressure ≤20 mmHg, systolic BP <90 mmHg
- laboratory - white cell count >5,000 /μL, platelet ≤100,000 /μL, high serum lactate base excess

Dynamic prediction model that incorporates signs, symptoms and daily laboratory measurements improves DSS prediction (AUC=0.70). On the other hand, Classification and Regression Tree (CART) that includes HCT, Glasgow Coma Scale (GCS), urinary protein, creatinine and platelet count has a moderate accuracy (64.1%) for predicting the development of severe dengue among children with confirmed DENV infection.

Frequency of monitoring of clinical and laboratory parameters will depend on severity and phase of illness (refer to Table 5).

Documentation of the findings from the monitoring should be done using the Inpatient Dengue Monitoring Chart (refer to Appendix 6).

- Rapid haemodynamic assessment can be performed at bedside using C (skin colour), C (CRT), T (extremities’ temperature), V (pulse volume) and R (pulse rate).

### Table 5. Disease Monitoring for Different Phases of Dengue Illness

<table>
<thead>
<tr>
<th>Parameters for Monitoring</th>
<th>Febrile phase</th>
<th>Critical phase</th>
<th>Recovery phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General well-being</td>
<td>Daily or more frequently towards late febrile phase</td>
<td>At least twice a day and more frequently as indicated</td>
<td>Daily or more frequently as indicated</td>
</tr>
<tr>
<td>Appetite/oral intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting/diarrhoea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warning signs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Haemodynamic status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin Colour (pink/cyanosis)</td>
<td>4 - 6 hourly depending on clinical status</td>
<td>2 - 4 hourly depending on clinical status</td>
<td>4 - 6 hourly</td>
</tr>
<tr>
<td>Capillary refill time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremities (Temperature - cold/warm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse Volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse Rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen saturation (pulse oximeter /SpO₂)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neurological status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consciousness level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signs of bleeding</td>
<td>Daily or more frequently towards late febrile phase</td>
<td>At least twice a day and more frequently as indicated</td>
<td>Daily or more frequently as indicated</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Abdominal tenderness, hepatomegaly</td>
<td>8-hourly</td>
<td>2 - 4 hourly</td>
<td>4 - 6 hourly</td>
</tr>
<tr>
<td>Abdominal tenderness, hepatomegaly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascites, pleural effusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine output</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBC</td>
<td>Daily or more frequently if indicated</td>
<td>4 - 12 hourly depending on clinical status</td>
<td>Daily</td>
</tr>
<tr>
<td>Blood Urea Serum Electrolytes (BUSE)/Creatinine</td>
<td>As indicated</td>
<td>At least once or more frequently as indicated</td>
<td>As indicated</td>
</tr>
<tr>
<td>Liver Function Test (LFT) (including aspartate transaminase (AST)/alanine transaminase (ALT))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood sugar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial Blood Gas (ABG)/Venous Blood Gas (VBG)</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
</tr>
<tr>
<td>Lactate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulation profile</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 5.2 Critical Phase

The three main priorities of managing hospitalised patients with dengue in critical phase are:
- replacement of plasma losses
- early recognition and treatment of haemorrhage
- prevention of fluid overload

Judicious IV fluid therapy is essential and usually is the only intervention required to maintain effective circulation for 24 - 48 hours during the critical phase. For overweight or obese patients, the ideal body weight should be used for calculating fluid infusion rates (refer to Appendix 7).

Fluid resuscitation must be clearly separated from fluid maintenance. Fluid resuscitation of 10 - 20 ml/kg fluid boluses are administered for a limited period of time under close supervision. This rapid fluid boluses to reverse shock is followed by titrated fluid volume to match ongoing losses. Haemodynamic state should be used as a main driver of IV fluid therapy and not HCT alone.
Goals of fluid resuscitation are to:

- improve circulation as evidenced by decreasing tachycardia, improving BP and pulse volume, warm and pink extremities and CRT <2 seconds
- improve end-organ perfusion as evidenced by improving consciousness level and urine output
- achieve appropriate decrease in HCT (refer to Subchapter 5.2.6 on Interpretation of HCT)

Patients with severe dengue who are in critical phase require emergency treatment and urgent referral to a hospital with paediatrician and access to blood transfusion facilities (refer to Figure 3 for Criteria of Severe Dengue). All shock patients should have their blood group taken and a cross-match carried out.

Criteria for pediatric intensive care unit/high dependency unit referral

Dengue patients should be referred to paediatric intensive care units/high dependency unit in the event of life-threatening situation characterised by one or a combination of the following: WHO, 2012, level III

- prolonged and/or decompensated shock
- severe bleeding with severe disseminated intravascular coagulopathy
- fluid overload
- respiratory distress and failure
- severe organ impairment (hepatic damage, renal impairment, cardiomyopathy, encephalopathy or encephalitis)

5.2.1 Choice of resuscitation fluid

Most children with dengue in shock respond well to judicious treatment with isotonic crystalloid solutions. Hung NT, 2012, level III; Wills BA et al., 2005, level I These fluids should not contain glucose. WHO, 2012, level III Isotonic crystalloid solutions should be used for maintenance therapy. Feld LG et al., 2018, level I; WHO, 2012, level III Early intervention with colloidal solutions is not indicated. Wills BA et al., 2005, level I This is supported by a Cochrane systematic review that included children with DSS which showed no evidence that resuscitation with colloids reduced the risk of death compared with crystalloids. Perel P, 2012, level I

In the case of persistent shock despite resuscitation with crystalloid solutions, colloid solutions can be considered. MoH, 2004 Clinicians should use colloid solutions based on their personal experience, familiarity with particular products, local availability and cost.

Colloid solutions have been advocated for fluid resuscitation in severe dengue for both adults and children. Among the colloids used, hydroxyethyl starch (HES) is the most controversial. In a randomised controlled trial (RCT) on children with dengue, minor advantages in initial recovery were shown with HES while significantly more allergic adverse reactions were associated with dextran. Wills BA et al., 2003, level I However, a recent systematic review of paediatric population with shock of various aetiology showed concern on safety issues with HES used for resuscitation. They included increased creatinine level, decreased platelet count and increased length of intensive care unit stay. Thus, HES was not recommended for paediatric patients. Li L et al., 2015, level I

Recommendation 5

Isotonic crystalloid solutions should be used in resuscitation and maintenance therapy in children with dengue.
5.2.2 Treatment of warning signs
In children with dengue presenting with warning signs or signs of dehydration, judicious volume replacement with IV fluid therapy from this early stage may modify the course and severity of disease. Refer to Algorithm 2.

5.2.3 Treatment of compensated shock
Treatment plan for patients with compensated shock is as follows (refer to Algorithm 3):WHO, 2012, level III

- Obtain a reference HCT before starting IV fluid therapy.
- Secure IV access within five minutes. If unsuccessful, attempt intraosseous (IO) access.
- Start IV fluid resuscitation with isotonic crystalloid solutions at 10 - 20 ml/kg/hour over one hour.
- Reassess the patient’s condition (vital signs, CRT, HCT and urine output).
- If the condition of the patient improves, reduce IV fluid accordingly.
- If oral fluid intake improves, IV fluid can be reduced earlier.
- Stop IV fluid if patient shows signs of reabsorption, usually 48 hours after entering critical phase.
- If vital signs are still unstable (i.e. shock persists), check HCT urgently after the first fluid bolus.
- If the HCT increases or still high with evidence of shock, repeat crystalloid solution at 10 - 20 ml/kg over an hour.
- Consider changing to colloidal solution at 10 - 20 ml/kg after resuscitation with 40 ml/kg of crystalloid solution.
- Decreasing HCT with unstable vital signs indicates bleeding which may be occult. Transfuse patient with fresh whole blood or packed cells.
- Boluses of crystalloid or colloidal solutions may need to be repeated if shock recurs.

Children with compensated shock should be closely monitored in hospitals with paediatrician and managed by senior staff.

5.2.4 Treatment of decompensated (hypotensive) shock
All dengue children with decompensated shock should be managed more vigorously. The treatment plan is as mentioned in treatment of shock earlier except the following:WHO, 2012, level III

- Initiate IV fluid resuscitation with crystalloid solution at 20 ml/kg as a bolus over 15 - 30 minutes for quick shock reversal.
- Colloids may be considered if the BP has to be restored urgently, i.e. in those with pulse pressure <10 mmHg. It has been shown to reduce the level of HCT faster than crystalloids in intractable shock, however the effect is transient.Wills BA et al., 2005, level I
- IO route should be attempted if peripheral venous access cannot be obtained within five minutes for immediate resuscitation.
- Monitor vital signs closely and urine output hourly with an indwelling catheter.
- Children with decompensated shock should be admitted to the high-dependency or intensive care area and managed by senior staff.

Refer to Algorithm 4.
Recommendation 6

- Close monitoring and frequent reassessment should be done to guide appropriate fluid management of children with dengue shock.
  - They should be managed by senior staff in hospitals with paediatrician.
  - Those with decompensated shock should be admitted to the high-dependency or intensive care unit.

5.2.5 Monitoring of dengue patients in shock

Patients with dengue shock should be monitored frequently until the critical phase is over. Parameters to be monitored include:WHO, 2012, level III

- consciousness level
- vital signs
- peripheral perfusion (every 15 - 30 minutes until the patient is out of shock, then 1 - 2 hourly)
- continuous electrocardiogram (ECG) and pulse oximetry monitoring is advisable in unstable patients

Refer to Table 5 for the frequency of monitoring in critical phase.

- The higher the fluid infusion rate, the more frequent the patient should be monitored and reviewed in order to avoid fluid overload while ensuring adequate volume replacement.WHO, 2012, level III
- In local setting, children with shock should have continuous ECG and pulse oximetry monitoring. IV fluid should be administered using infusion/syringe pumps.

A detailed fluid balance of all inputs and outputs should be maintained. Urine output should be checked regularly (each hour until the patient is out of shock; then every 1 - 2 hours). A continuous bladder catheter is essential in close monitoring of urine output. An acceptable urine output would be at least 0.5 - 1 ml/kg/hour. Input/output ratio should not be used as sole determinant in fluid resuscitation as input is typically much greater than output during critical phase. WHO, 2012, level III

If previously not detectable, pleural effusion and ascites are usually detectable after fluid boluses. Monitoring with bedside ultrasonography may be used if available. More importantly, monitor their effects on breathing and assess the need of respiratory support. WHO, 2012, level III

If blood gas machine is available, HCT, lactate and acidosis level should be repeatedly analysed using capillary or venous blood to monitor changes in the circulation. HCT should be monitored before and after fluid boluses until stable, then 4 - 6 hourly. WHO, 2012, level III

An arterial line has certain advantages but its placement can be hazardous because of the risk of bleeding from failed attempts. The advantage of an arterial line is that in profound and persistent/recurrent shock states, it allows for continuous and accurate BP measurements and frequent blood sampling. If arterial line insertion is attempted, it should be done in critical care setting. WHO, 2012, level III

In addition, patients with severe dengue should be monitored for:WHO, 2012, level III

- blood glucose (before fluid resuscitation and repeat as indicated)
- other organ functions (e.g. renal, liver and coagulation profiles) before resuscitation and as indicated
5.2.6 Interpretation of Haematocrit

- Baseline HCT on the first three days of illness is a useful reference point. The rise of HCT level beyond 20% of the baseline during critical phase indicates significant plasma leakage and the need for IV fluid therapy. WHO, 2012, level III

It is important to note that during fluid therapy, HCT level should be taken pre- and post-fluid resuscitation or when there are changes in the fluid infusion rate.

- HCT alone is not the driver for fluid therapy. The interpretation of HCT will be most meaningful if the corresponding haemodynamic state and response to fluid therapy are known at the time of blood sampling. WHO, 2012, level III
  - A rising or persistently high HCT with unstable vital signs indicates active plasma leakage and the need for a further bolus of fluid resuscitation.
  - A rising or persistently high HCT in patients with stable vital signs and adequate urine output does not require extra IV fluid. Continue to monitor closely and usually the HCT will start to fall within the next 24 - 48 hours as plasma leakage stops.
  - A decrease in HCT with signs of shock may indicate major occult haemorrhage and urgent transfusion with fresh packed red cells/fresh whole blood is needed. Occult bleeding may take several hours to become apparent and the patient’s HCT will continue to decrease without achieving haemodynamic stability.
  - A decrease in HCT with stable vital signs and adequate urine output, indicates haemodilution or reabsorption of extravasated fluids. This signifies the start of recovery phase and IV fluids must be discontinued immediately to avoid pulmonary oedema.

The following table shows the normal range of HCT in different age groups.

<table>
<thead>
<tr>
<th>Age</th>
<th>HCT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord blood</td>
<td>45 - 65</td>
</tr>
<tr>
<td>2 weeks</td>
<td>42 - 66</td>
</tr>
<tr>
<td>3 months</td>
<td>31 - 41</td>
</tr>
<tr>
<td>6 months - 6 years</td>
<td>33 - 42</td>
</tr>
<tr>
<td>7 - 12 years</td>
<td>34 - 40</td>
</tr>
<tr>
<td>Adult male</td>
<td>42 - 52</td>
</tr>
<tr>
<td>Adult female</td>
<td>37 - 47</td>
</tr>
</tbody>
</table>


5.2.7 Glucose control

Both hyperglycaemia and hypoglycaemia may occur in the same dengue patient at different periods during the critical phase through several mechanisms. WHO, 2012, level III

Hyperglycaemia, WHO, 2012, level III
- is the result of a neuroendocrine stress response, occurs in diabetes mellitus and results from inappropriate large quantities of glucose-fluids administered in resuscitation
- causes osmotic diuresis which worsens the hypovolaemic shock and gives a false impression of a “good urine output”
- is also associated with increased morbidity and mortality in critically ill paediatric patients; most cases of hyperglycaemia will resolve with appropriate (isotonic, non-glucose) and adequate fluid resuscitation
However, if hyperglycaemia persists, undiagnosed diabetes mellitus or impaired glucose tolerance should be considered and IV insulin therapy initiated. Subcutaneous insulin should be avoided in shock state as absorption is unreliable.

Hypoglycaemia;
- occurs due to starvation in young children, diabetic patients on hypoglycaemic agents and severe liver impairment
- may cause seizures, mental confusion and increased sympathetic drive
- should be treated as an emergency with a bolus of 2 ml/kg of dextrose 10%

Frequent glucose monitoring should be carried out and euglycemia maintained with glucose-isotonic solution [NS dextrose 5% running at maintenance rate according to Holliday Segar formula (refer to Table 7)] and enteral feeding if possible. This maintenance fluid should be included as part of fluid therapy according to the Algorithm 2, 3 and 4.

Table 7. Holliday-Segar calculator

<table>
<thead>
<tr>
<th>Weight</th>
<th>Total fluids</th>
<th>Infusion rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 10 kgs</td>
<td>100 ml/kg</td>
<td>4 ml/kg/hour</td>
</tr>
<tr>
<td>Subsequent 10 kgs</td>
<td>50 ml/kg</td>
<td>2 ml/kg/hour</td>
</tr>
<tr>
<td>All additional kg</td>
<td>20 ml/kg</td>
<td>1 ml/kg/hour</td>
</tr>
</tbody>
</table>


If oral intake is still inadequate, blood glucose should be monitored frequently during the critical and recovery phase.

5.2.8 Electrolytes and acid-base imbalances
Hyponatraemia is a common observation in severe dengue but the underlying mechanism is not fully understood. It could be related to gastrointestinal losses through vomiting and diarrhoea or the use of hypotonic solutions for resuscitation and correction of dehydration. The use of isotonic solutions for fluid resuscitation and maintenance will prevent and correct this condition. \(^{\text{WHO, 2012, level III}}\)

Hyperkalaemia;
- is observed in association with severe metabolic acidosis or acute kidney injury (AKI). Appropriate fluid resuscitation will reverse the metabolic acidosis and associated hyperkalaemia
- in life-threatening situation, hyperkalaemia should be managed with infusions of calcium gluconate, sodium bicarbonate and/or insulin-dextrose; potassium binder e.g. sodium polystyrene sulfonate and beta agonist are useful adjunctive treatment. Refer to Malaysian Paediatric Protocol Fourth Edition (page 34) \(^{\text{MoH, 2019, level III}}\)
- in failed medical treatment, renal replacement therapy (RRT) should be considered if patient’s haemodynamic status is stable

Hypokalaemia;
- is often associated with gastrointestinal fluid losses and stress-induced hypercortisol state
- usually happens towards the later part of the critical phase
- should be corrected with potassium supplements in the IV fluids

Serum calcium levels should be monitored in critically ill patients. Hypocalcaemia is common following large amount of blood transfusion and should be corrected.
5.2.9 Metabolic acidosis
Compensated metabolic acidosis is an early sign of hypovolaemia and shock. Lactic acidosis due to tissue hypoxia and hypoperfusion is the most common cause of metabolic acidosis in critically ill dengue patients. Correction of shock and adequate fluid replacement will reverse the metabolic acidosis. If metabolic acidosis remains uncorrected by this strategy, one should suspect severe bleeding, check the HCT and transfuse fresh packed red cells/fresh whole blood urgently.\textsuperscript{WHO, 2012, level III}

Differential diagnosis of high lactate (>2.2 mmol/L) includes acute renal failure and acute liver failure secondary to severe dengue. Other causes are co-infections e.g. leptospirosis, salmonellosis or other superimposed bacterial sepsis.

Sodium bicarbonate for metabolic acidosis caused by tissue hypoxia is not recommended for pH ≥7. Bicarbonate therapy is associated with sodium and fluid overload, increase in lactate, hypercarbia and decrease in serum ionised calcium. A left shift in the oxyhaemoglobin dissociation curve due to sodium bicarbonate administration may aggravate the tissue hypoxia.\textsuperscript{WHO, 2012, level III}

Hyperchloraemia, caused by the administration of large volumes of 0.9% sodium chloride solution (chloride concentration of 154 mmol/L), may cause hyperchloraemic acidosis with normal lactate levels. If serum chloride levels increase, use Hartmann’s solution or Ringer’s lactate as crystalloid. These do not worsen the lactic acidosis.\textsuperscript{WHO, 2012, level III}

5.2.10 Treatment for dengue with neurological involvement
Prevalence of neurological involvement in children admitted with dengue infection varies at 0.5 - 9.5%.\textsuperscript{Shokeen P et al., 2018, level III; Kamel MG et al., 2017, level III; Carod-Artal FJ et al., 2013, level III} A wide-spectrum of neurological manifestations have been described including encephalopathy, encephalitis, immune-mediated syndromes and muscular dysfunctions.\textsuperscript{Li GH et al., 2017, level III; Carod-Artal FJ et al., 2013, level III}

Acute encephalopathy is the most common neurological complication with prevalence at 0.5 - 5.1%.\textsuperscript{Shokeen P et al., 2018, level III; Carod-Artal FJ et al., 2013, level III} Affected children usually present with reduced level of consciousness which may be caused by multiple underlying factors, including prolonged shock, hypoxia, cerebral oedema, bleeding, metabolic abnormalities and acute liver or kidney failure. Analysis of the CSF is usually normal. Prognosis is variable and dependent on underlying contributing factors. Management is usually supportive with emphasis on corrections of underlying metabolic and haemodynamic abnormalities.\textsuperscript{Carod-Artal FJ et al., 2013, level III; Witayathawornwong P, 2004, level III}

Children with encephalitis can present with reduced consciousness, headache, altered mental status and seizures. Clinical features may be indistinguishable from encephalopathy. Presence of DENV by PCR, NS1 Ag or dengue IgM antibody in CSF is helpful to differentiate the condition from encephalopathy. Neuroimaging features are diverse and nonspecific, with cerebral oedema being the most common finding. Supportive management is recommended. Outcome is variable.\textsuperscript{Carod-Artal FJ et al., 2013, level III}

Immune-mediated neurological syndrome associated with dengue infection has been described in paediatric population. Acute transverse myelitis, acute disseminated encephalomyelitis and Guillain-Barre Syndrome usually follow their natural course. Standard management as per the disorder is recommended.\textsuperscript{Carod-Artal FJ et al., 2013, level III}

• Acute encephalopathy is the most common neurological complication of dengue. Its management is usually supportive with emphasis on corrections of underlying metabolic and haemodynamic abnormalities.
5.2.11 Treatment for dengue with liver involvement
Liver involvement is commonly seen in children with dengue infection with prevalence ranges from 38.7% to 87%. Prevalence is generally higher in the more severe category of dengue infection (dengue with warning signs and severe dengue). The exact mechanisms on liver injury are still not fully understood.

Spectrum of liver involvement ranges from mild elevation of liver enzymes, AST and ALT levels to acute and fulminant liver failure. In most children, the liver dysfunctions are mild with transient elevation of AST and ALT levels (range 84.4% - 95.9%) and often asymptomatic. Acute liver failure is rare (range 1.1% - 5.8%).

AST level is usually higher than ALT level in contrast to other causes of viral hepatitis. This was postulated to be caused by the release of AST from injured myocytes. The liver enzyme levels usually return to normal values within 2 - 4 weeks after illness.

- Supportive management is recommended in dengue infection with liver involvement and the prognosis is generally good.
- Those with acute or fulminant liver failure should be closely monitored in critical care settings.
  - Emphasis should be put on early recognition of severe liver involvement, stabilisation of haemodynamic status, avoidance of hepatotoxic medications, close monitoring of neurological parameters and management of hepatic encephalopathy.

There is no strong evidence to support the routine use of N-Acetyl cysteine (NAC) in children with DF associated acute liver failure.

5.2.12 Treatment for dengue with cardiac involvement
Clinically significant cardiac involvement including myocarditis is uncommon in children with dengue.

In an observational study on 181 hospitalised children with dengue, left ventricular systolic and diastolic dysfunction was seen in relation to severity of plasma leakage. However, it was transient and resolved spontaneously. Thus, treatment should mainly be focused on fluid resuscitation to maintain adequate tissue perfusion.

5.2.13 Treatment for dengue with kidney involvement
The kidney is one of the major organs affected during dengue infection in children. The exact mechanism and prevalence remain unclear. Proteinuria is more often detected between day 5 and day 7 after onset of fever, and usually normalises as the patients recover.

Some children with dengue may develop AKI following prolonged shock due to inadequate fluid resuscitation. The treatment for this condition is mainly supportive. If RRT is required, it should commence only in haemodynamically stable patients. Continuous veno-venous haemodialysis (CVVH) is the preferred mode of RRT. Peritoneal dialysis may be considered if CVVH is not available, but it is associated with high risk of bleeding. When RRT is not available or cannot be carried out yet, the succeeding hyperuricaemia, hyperkalaemia and hyperphosphataemia should be managed with allopurinol, potassium binders (e.g. sodium polystyrene sulfonate, calcium polystyrene sulfonate) and calcium carbonate respectively.
5.2.14 Blood transfusion
Blood transfusion is only indicated in patients with:

- massive bleeding
- occult bleeding with shock as evidenced by HCT decreasing compared to baseline with unstable vital signs. Refer to Algorithm 3 and 4.

Internal bleeding may be difficult to recognise in the presence of haemoconcentration.

- Decision to transfuse should be taken by senior clinicians to avoid unnecessary transfusion which can lead to fluid overload especially in neonates and infants.
  - Do not wait for HCT level to drop too low before making the decision.
  - Consider to repeat blood transfusion if there is further overt blood loss or no appropriate rise in HCT after blood transfusion in an unstable patient.

The following blood and blood components are recommended for transfusion:

i) red cells or whole blood
   - for children, give 10 - 20 ml/kg/dose of fresh packed red cells or fresh whole blood
   - for neonates, give aliquots of 5 - 10 ml/kg of fresh packed red cells or 10 - 20 ml/kg of fresh whole blood at an appropriate rate
   The rate depends on the patient's condition. The patient should be monitored carefully to avoid fluid overload.

ii) platelet and fresh frozen plasma
   - should be considered in invasive and surgical procedures if severe bleeding is anticipated

There is no evidence to support the practice of transfusing platelet and fresh frozen plasma for severe bleeding in dengue.

- However, the transfusion may be indicated based on clinical judgement and if the patient does not respond to initial fresh packed red cells or fresh whole blood transfusion.

Observational studies showed that platelet concentrates and fresh frozen plasma transfusion in dengue were not able to sustain the platelet counts and coagulation profile. It can also lead to fluid overload in massive bleeding patient.

**Recommendation 7**

- Blood transfusion should be given in life-threatening condition and given as soon as severe bleeding is recognised (overt) or suspected (occult) in children with dengue.
  - Selection of blood components is based on patient's clinical condition or type of bleeding.
  - It should be given cautiously to avoid fluid overload especially in neonates or infants.

5.3 Recovery Phase

If excessive IV fluids have been given, there is a risk of fluid overload during critical and/or recovery phase e.g. respiratory distress from massive pleural effusion and ascites, pulmonary oedema or congestive heart failure. To avoid these complications, IV fluids should be discontinued early.

To prevent nosocomial infection, venofix/branula or peripheral inserted central catheter (PICC) need to be removed once there is no indication for further IV therapy.
The treatment of fluid overload is dependent on the patient's haemodynamic stability, intravascular volume status and the timing of this event with respect to the critical phase. Small doses of IV frusemide 0.1 - 0.5 mg/kg/dose twice or thrice daily or a continuous infusion of frusemide 0.1 mg/kg/hour may be indicated for patients who are out of the critical phase.\textsuperscript{WHO, 2012, level III}

6. **SPECIAL GROUPS**

6.1 **Neonates**

Neonates can acquire DENV through vertically transmission or at the time of delivery. They may be asymptomatic and the clinical manifestations vary from mild to severe illness.\textsuperscript{WHO, 2012, level III}

Symptomatic and supportive treatment under close observation is the mainstay of treatment in neonates with dengue infection.\textsuperscript{WHO, 2012, level III} Consultation with neonatologists is advisable.

6.2 **Infants**

In general, dengue in infants is due to primary infection but the manifestations could be severe as infants might have received dengue antibodies transplacentally from their mother.\textsuperscript{WHO, 2012, level III}

Clinical presentation of dengue in infants is similar to older children.\textsuperscript{WHO, 2012, level III} They may present with coryza symptoms e.g. cough, nasal congestion and runny nose. However, presence of febrile convulsion, vomiting, diarrhoea and petechial rash are significantly associated with dengue among infants. Most of the infants with dengue are 4 - 10 months of age.\textsuperscript{WHO, 2012, level III; Chau TN et al., 2010, level III}

It is often not possible to differentiate between dengue and other infections in infants (e.g. pneumonia, bacterial sepsis, meningoencephalitis, other viral exanthems, rotavirus infections, etc.) at the febrile stage.\textsuperscript{WHO, 2012, level III}

Compared to those with acute undifferentiated febrile illness, infants with dengue infection more likely to have:\textsuperscript{Chau TN et al., 2010, level III}
- petechiae, bruises, hepatomegaly and clinical evidence of systemic leakage
- lower WBC count and platelet nadirs
- higher liver transaminases and HCT level

- Infants have relatively low normal value of HCT (28 - 42%) compared with older children and may be even lower in iron deficiency anaemia.\textsuperscript{WHO, 2012, level III}
  - Any increment of ≥20% from baseline HCT is considered haemoconcentration. Refer to \textbf{Table 6 on Range of Haematocrit in Different Age Groups}.\textsuperscript{WHO, 2012, level III}

Shock occurs because of severe plasma leakage and often preceded by warning signs with subnormal body temperature. However, some infants may still have fever at the onset of shock, thus differential diagnosis of septic shock need to be considered.\textsuperscript{WHO, 2012, level III}

Infants with dengue infection should be referred for in hospital management.\textsuperscript{WHO, 2012, level III}

**Recommendation 8**
- Dengue infection in infant should be managed in hospital with paediatric services.
6.3 Red Cells Disorder

Haemolysis can be triggered during acute dengue illness. This manifests in both early and late febrile stage of thalassemia. It may also occur in other haemoglobinopathies and glucose-6-phosphate dehydrogenase (G6PD) deficiency. Chuansummrit A et al., 2012, level III

- Haemoconcentration during plasma leakage may be missed in anaemic patients with dengue due to low baseline HCT level. Chuansummrit A et al., 2012, level III
- Healthcare providers should use patients’ baseline Hb level to calculate degree of haemoconcentration.

Fresh packed red cells or fresh whole blood should be given if significant haemolysis is suspected. Chuansummrit A et al., 2012, level III; WHO, 2012, level III

7. DISCHARGE CRITERIA

Patients who have been monitored for dengue may be discharged if they fulfil all of the following clinical and laboratory criteria as shown in Table 7.

Table 7. Discharge Criteria

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Laboratory criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No fever for 24 - 48 hours</td>
<td>• Increasing trend of platelet count</td>
</tr>
<tr>
<td>• Improvement in clinical status (general well-being, appetite, haemodynamic status, urine output)</td>
<td>• Stable HCT without IV fluids</td>
</tr>
<tr>
<td>• Absence of respiratory distress</td>
<td>• Resolution or recovery of organ dysfunction</td>
</tr>
</tbody>
</table>

Adapted:

8. TRADITIONAL AND COMPLEMENTARY MEDICINE

Traditional and complementary medicines (TCM) e.g. papaya leaf extracts and crab soup are often used in dengue infection as part of Malaysian cultural practices.

- There is no evidence on the safety and efficacy of TCM to support its use in the treatment of dengue in children.

9. PREVENTION STRATEGIES

9.1 Vaccination

Three multicentre placebo-controlled RCTs looked into the efficacy and safety of CYD-TDV vaccine against dengue in children.

In the first RCT, the dengue vaccine was moderately efficacious (54.8%, 95% CI 46.8 to 61.7) in symptomatic, virologically confirmed dengue (VCD) with good safety profile when given as
three injections (months 0, 6 and 12) to children aged 2 - 14 years in endemic areas in Asia. Capeding MR et al., 2014, level I

Pooled analysis of two RCTs showed the dengue vaccine was efficacious in children ≥9 years old against all severity dengue hospitalisation (80.8%, 95% CI 70.1 to 87.7). The result was not in favour in younger children. Analysis on long-term safety was not available then. Hadinegoro SR et al., 2015, level I

Further analysis of three RCTs demonstrated that the risk was higher for hospitalisation in VCD (HR=1.75, 95% CI 1.14 to 2.70) and severe VCD (HR=2.87, 95% CI 1.09 to 7.61) in vaccinated compared with control in seronegative 2 to 16 years old participants. However, the vaccine was efficacious in seropositive participants with HR of 0.32 (95% CI 0.23 to 0.45) and 0.31 (95% CI 0.17 to 0.58) for the same outcomes. Thus, the vaccine was protective in those who had exposure to dengue before vaccination. Sridhar S et al., 2018, level I

- More evidence is warranted especially on long-term safety profile before dengue vaccination can be recommended.

9.2 Prevention of Mosquito Bite

Preventive measures on mosquito bite include the use of: WHO, 2009, level III
- clothing that minimises skin exposure during daylight hours when mosquitoes are most active
- repellents on exposed skin or to clothing in strict accordance with label instructions
- insecticide-treated mosquito nets during sleeping
- household insecticide aerosol products, mosquito coils or other insecticide vapourisers
- household fixtures e.g. window and door screens and air-conditioning

In a local health technology assessment, repellent use was found to be not effective in reducing incidence of dengue. MoH, 2019, level III

10. IMPLEMENTING THE GUIDELINES

Implementation of CPG is important as it helps in providing quality healthcare services based on best, recent available evidence applied to local scenario. Various factors and resource implications should be considered for the success of the uptake in the CPG recommendations.

10.1 Facilitating and Limiting Factors

The facilitating factors in implementing the CPG are:
- availability of CPG to healthcare providers (hardcopies and softcopies)
- conferences and updates on management of dengue in children including those involve professional bodies
- Clinical Audit on Dengue Mortality
- public awareness activities e.g. COMBI (Communication for Behavioural Impact)

Limiting factors in the CPG implementation include:
- limited awareness and knowledge in management of dengue in children among healthcare providers
- variation in treatment practice and preferences among healthcare providers
- insufficient resources especially trained personnel, diagnostic kits and infrastructure
- misconception on the disease and its management by the public
10.2 Potential Resource Implications

To implement the CPG, there must be strong commitments to:

i. ensure widespread distribution of CPG to healthcare providers via printed copies and online accessibility
ii. reinforce training of healthcare providers via regular seminars and workshops
iii. involve multidisciplinary team at all levels of health care
iv. improve the diagnostic and therapeutic facilities
v. train more experts in the field of dengue in children

To assist in the implementation of the CPG, the following are proposed as clinical audit indicators for quality management:

- Percentage of children suspected of dengue infection tested with a combination of NS1 Antigen/IgM/IgG rapid test (Dengue Rapid Combo Test) = \[ \frac{\text{Number of children suspected of dengue infection tested with dengue rapid combo test in a period}}{\text{Number of children suspected of dengue infection within the same period}} \] x 100%

Target of 75%

Implementation strategies will be developed following the approval of the CPG by MoH which include Quick Reference and Training Module.
REFERENCES

1. World Health Organization (WHO). Dengue and severe dengue. (Available at: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue)


APPENDIX 1

EXAMPLE OF SEARCH STRATEGY

Clinical Question: What is the effective and safe treatment for dengue fever in children in febrile phase? - fluid therapy

1. DENGUE/
2. (classical adj2 (dengue* or dengue fever*)).tw.
3. dengue*.tw.
4. (dengue adj1 fever*).tw.
5. 1 or 2 or 3 or 4
6. FEVER/
7. fever*.tw.
8. hyperthermia*.tw.
10. (febrile adj1 phase).tw.
11. febrile.tw.
12. (warning adj1 sign*).tw.
13. warning.tw.
14. or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. THERAPEUTICS/
16. therap*.tw.
17. treatment*.tw.
18. FLUID THERAPY/
19. (fluid adj1 therap*).tw.
20. (oral adj1 rehydration*).tw.
21. (oral adj2 rehydration therap*).tw.
22. rehydration*.tw.
23. SODIUM CHLORIDE/
24. saline solution.tw.
25. sodium chloride.tw.
26. COLLOIDS/
27. colloid*.tw.
28. hydrocolloid*.tw.
29. HYDROXYETHYL STARCH DERIVATIVES/
30. (hydroxyethyl starch adj2 derivative*).tw.
31. hetastarch.tw.
32. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33. 5 and 14 and 32
34. limit 40 to (English language, humans, last 14 years and all child (0 to 18 years))
APPENDIX 2

CLINICAL QUESTIONS

1. What are the clinical criteria and classification used to diagnose dengue fever in children?
2. What are the accurate diagnostic tests for dengue fever in children?
   • full blood count (including haematocrit)
   • rapid test [Combo/Immunoglobulin M/Immunoglobulin G, non-structural protein 1 antigen (NS1 Ag)]
   • enzyme-linked immunosorbent assay ELISA (IgM/IgG)
3. What are the risk factors for severe dengue fever in children?
4. What is the optimal outpatient monitoring and follow-up for dengue fever in children?
5. What are the admission criteria for dengue fever in children?
   • level of platelet counts
   • presence of warning signs
   • duration of illness
   • presence of co-morbidities
6. What is the effective and safe treatment for dengue fever in children in the following aspects?
   • febrile phase
   • warning signs
   • critical phase
   • shock
   • blood and blood products use
   • severe organ involvement
7. What is the effective and safe traditional and complementary medicine for dengue fever in children?
8. What are the effective and safe monitoring in different phases of dengue fever in children in terms of:
   • clinical assessment
   • laboratory assessment
   • radiological assessment
9. What are criteria for high-dependency unit/intensive care unit care for dengue fever in children?
10. What are the discharge criteria for dengue fever in children?
11. What are the effective and safe treatment in dengue fever in the following groups:
    • neonates
    • infants
    • patients with thalassemia
12. What are prevention strategies for dengue fever in children?
    • vaccination
    • repellent
**APPENDIX 3**

**SYSTEMIC MANIFESTATION OF PERIPHERAL VASOCONSTRICTION**

**Initial stage of shock**
- Quiet tachypnoea (tachypnoea without increased effort)
- Cold extremities and delayed capillary refill time (CRT) of >2 seconds
- Weak volume peripheral pulses
- Normal oxygen saturation (SpO₂: 95 - 100%)
- Normal systolic pressure
- Diastolic pressure rises towards systolic pressure and pulse pressure (difference between systolic and diastolic pressures) narrows
- Compensated metabolic acidosis (normal pH, low partial pressure of carbon dioxide (pCO₂) and low bicarbonate level)
- May remain conscious and alert

**Worsening hypovolaemic shock**
- Increasing tachycardia and peripheral vasoconstriction
- Cold and cyanosed extremities and, limbs become mottled, cold and clammy
- Rapid breathing and increases in depth - a compensation for the metabolic acidosis
- Kussmaul's breathing
- Hypotension
- Disappearance of peripheral pulses
- Weak central pulse (femoral)
- Cortical hypoperfusion manifested by poor eye contact, failure to recognise parents or failure to respond to painful stimuli e.g. venepuncture
- Change in mental state (restless, confused, extremely lethargic, seizures)
  *children and young adults have been known to have a clear mental status even in profound shock*

**Prolonged hypotensive shock**
- Severe metabolic acidosis
- Multiple organ failure e.g. acute liver and renal failure, encephalopathy, cardiomyopathy
- Major bleeding*
- Coagulation abnormalities e.g. disseminated intravascular coagulation
  *may occur in the absence of shock if the child is given NSAIDs, acetylsalicylic acid or corticosteroids

**Cardiac arrest**

May take few hours

May take few hours

May take few minutes
APPENDIX 4

CHECKLIST FOR PARAMEDICS ON INITIAL ASSESSMENT OF DENGUE IN CHILDREN

<table>
<thead>
<tr>
<th>Name:</th>
<th>Age:</th>
<th>Identification Card No.:</th>
<th>Date/Time:</th>
</tr>
</thead>
</table>

**1. Presence of fever**

If NO, any history of taking fever medicine e.g. paracetamol

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<thead>
<tr>
<th>YES</th>
<th>NO</th>
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</table>

**2. Living in dengue area**

| ✔ |

**3. Probable dengue criteria: History of fever + ≥2 criteria below**

<table>
<thead>
<tr>
<th>3.1</th>
<th>Rash</th>
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<tbody>
<tr>
<td>3.2</td>
<td>Nausea/vomiting</td>
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<td>3.3</td>
<td>Aches/pains</td>
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<td>3.4</td>
<td>Low white cell count</td>
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<td>3.5</td>
<td>Warning signs:</td>
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<td>Persistent abdominal pain</td>
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<td>Persistent vomiting - &gt;3 episodes of vomiting/24 hours</td>
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<td>Red spot on the skin, bleeding from nose or gums, vomiting blood, black-coloured stool, heavy menses, blood in urine</td>
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<td>Lethargy, poor feeding</td>
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<td>Respiratory distress</td>
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<td></td>
<td>Laboratory: haematocrit (HCT) above 40% and platelet count ≤100 x 10³ cells/mm</td>
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</tbody>
</table>

**4. Special population:**

- Infant (age <12 months old)
- Co-morbidities - any medical illness

**5. Haemodynamic status CCTVR**

- Skin Colour - cyanosis
- Capillary refill time - >2 seconds
- Extremities - Temperature (cold)
- Pulse Volume - weak
- Pulse Rate - abnormal

**6. Diagnosis/management**

<table>
<thead>
<tr>
<th>Health clinic</th>
<th>Emergency Dept., Hospital</th>
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</thead>
<tbody>
<tr>
<td>Probable dengue (1+2+3)</td>
<td>Refer doctor</td>
</tr>
<tr>
<td>Probable dengue in special population (1+2+3+4)</td>
<td>Refer doctor for assessment pre-admission</td>
</tr>
<tr>
<td>Probable dengue with warning signs (1+2+3+3.5)</td>
<td>Refer doctor immediately</td>
</tr>
<tr>
<td>Probable severe dengue (1+2+3+5)</td>
<td>Refer doctor immediately for resuscitation</td>
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</table>
HOME CARE ADVICE FOR CHILDREN WITH DENGUE

WHAT SHOULD BE DONE?

- Adequate bed rest
- Adequate fluid intake 6 - 8 drinks a day

<table>
<thead>
<tr>
<th>Age group</th>
<th>Per drink</th>
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<tr>
<td>&lt;5 years old</td>
<td>100 - 120 ml</td>
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<td>5 - 10 years old</td>
<td>160 - 180 ml</td>
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<tr>
<td>&gt;10 years old</td>
<td>200 - 220 ml</td>
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</tbody>
</table>

- milk, fruit juice, oral rehydration salt (ORS), barley water, coconut water
- Paracetamol as advised by healthcare providers for fever control
- Tepid sponging for fever control
- 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 medicine like non-steroidal anti-inflammatory drugs e.g. aspirin, mefenamic acid, ibuprofen and diclofenac sodium (suppository).
- Steroids should be avoided.
- Antibiotics are not required.

THE DANGER SIGNS OF DENGUE INFECTION

If any of the following are observed, please go immediately to the nearest healthcare facilities for further management:

- Lethargy or poor feeding
- Bleeding i.e. red spots on the skin, bleeding from nose or gums, vomiting blood, black-coloured stool, heavy menstruation, vaginal bleeding
- Frequent vomiting (≥2 times)
- Persistent abdominal pain
- Drowsiness, irritability or seizure
- Pale, cold or clammy skin
- Difficulty in breathing
- Reduced urine output
## Dengue Monitoring Record

<table>
<thead>
<tr>
<th>Date</th>
<th>Day of fever</th>
<th>Last dose paracetamol</th>
<th>Temp. (°C)</th>
<th>BP (mmHg)</th>
<th>PR (min)</th>
<th>Hb (g/dL)</th>
<th>HCT (%)</th>
<th>WBC (x10³/µL)</th>
<th>Platelet (x10³/µL)</th>
<th>Attending Clinic/ Tel. No</th>
<th>Next Appointment</th>
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</table>
## INPATIENT DENGUE MONITORING CHART

(24-Hours Clinical, Laboratory and Fluid Monitoring)  
Name: _______________  
RN: _______________  
Age: _______________  
Actual BW: _____ kg  
Ideal BW: _____ kg  

Date of onset of fever: _______________  
Date and approximate time of onset of warning signs: _______________

*Laboratory results should be tabulated under the time of blood sampling, not time of results being available.

**Place a (X) when patient developed shock.

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CALCULATION OF IDEAL BODY WEIGHT (IBW) FOR OBESE CHILDREN

If patient’s height is within 5th and 95th centile of age, use Moore method as below:
• the IBW is the weight for age on the same percentile as height.

For example, a child with a height at the 10th centile can have his IBW determined by looking at the growth chart and finding the weight at the 10th centile for his age.

If patient’s height exceeds 95th centile for age, use McLaren method as below:
• weight at the 50th centile for height age chart

Use steps as below for IBW:
i. plotting the child’s height for age
ii. extending a line horizontally to the 50th centile height-for-age line
iii. extending a line vertically from the 50th centile height-for-age to the corresponding 50th centile weight and note this IBW

Refer to the growth chart below for method of plotting.
# SIGNS OF DEHYDRATION

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<tr>
<th>Assess:</th>
<th>Mild Dehydration</th>
<th>Moderate Dehydration</th>
<th>Severe Dehydration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Look at child’s general condition</td>
<td>Well, alert</td>
<td>Restless or irritable</td>
<td>Lethargic or unconscious</td>
</tr>
<tr>
<td>Look for sunken eyes</td>
<td>No sunken eyes</td>
<td>Sunken eyes</td>
<td>Sunken eyes</td>
</tr>
<tr>
<td>Offer the child fluid</td>
<td>Drinks normally</td>
<td>Drinks eagerly, thirsty</td>
<td>Not able to drink or drinks poorly</td>
</tr>
<tr>
<td>Pinch skin of abdomen</td>
<td>Skin goes back immediately</td>
<td>Skin goes back slowly</td>
<td>Skin goes back very slowly (&gt;2 seconds)</td>
</tr>
<tr>
<td>Classify</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treat</td>
<td>Plan A</td>
<td>Plan B</td>
<td>Plan C</td>
</tr>
<tr>
<td></td>
<td>Give fluid and food to treat diarrhoea at home</td>
<td>Give fluid and food for some dehydration</td>
<td>Give fluid for severe dehydration. Provide food as soon as child tolerates.</td>
</tr>
</tbody>
</table>

*% of body weight (in g) loss in fluid (Fluid Deficit) e.g. a 10 kg child with 5% dehydration has loss 5/100 x 10000 g = 500 ml of fluid deficit

**IMCI:** Management of the child with a serious infection or severe malnutrition

**Source:** Ministry of Health Malaysia. Paediatric Protocol for Malaysian Hospitals. Putrajaya: MoH; 2019
## CHARACTERISTICS OF COMMON CRYSTALLOID/COLLOIDS SOLUTIONS AVAILABLE IN MALAYSIA

### CRYSTALLOID SOLUTIONS

<table>
<thead>
<tr>
<th>Content</th>
<th>Human plasma</th>
<th>Normal saline (0.9% saline)</th>
<th>Ringer’s lactate</th>
<th>Hartmann’s solution</th>
<th>Sterofundin ISO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mmol/L)</td>
<td>136 - 145</td>
<td>154</td>
<td>130</td>
<td>131</td>
<td>145</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.5 - 5.0</td>
<td>4</td>
<td>5.0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>98 - 106</td>
<td>154</td>
<td>109</td>
<td>111</td>
<td>127</td>
</tr>
<tr>
<td>Others (mmol/L)</td>
<td></td>
<td>Lactate: 28</td>
<td>Lactate: 29</td>
<td></td>
<td>Acetate: 24 Malate: 5</td>
</tr>
<tr>
<td>Osmolarity (mosmol/L)</td>
<td>291</td>
<td>308</td>
<td>273</td>
<td>278</td>
<td>309</td>
</tr>
<tr>
<td>Common adverse effects</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperchloraemic metabolic acidosis</td>
<td>Hyperglycaemia</td>
<td>Caution in patients with depressed myocardial function</td>
<td></td>
</tr>
</tbody>
</table>

### COLLOIDS SOLUTIONS

<table>
<thead>
<tr>
<th>Content</th>
<th>Human plasma</th>
<th>Succinylated gelatin 4% (e.g. Gelafundin/Infusol)</th>
<th>Hydroxyethyl starch 6% (HES) (e.g. Voluven)</th>
<th>Albumin 5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mmol/L)</td>
<td>136 - 145</td>
<td>154</td>
<td>154</td>
<td>130 - 160</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>98 - 106</td>
<td>120</td>
<td>154</td>
<td>130 - 160</td>
</tr>
<tr>
<td>Osmolarity (mosmol/L)</td>
<td>291</td>
<td>308</td>
<td>308</td>
<td>309</td>
</tr>
<tr>
<td>Serious adverse effects</td>
<td>NA</td>
<td>Hyperallactoid reaction of various severity including shock</td>
<td>Anaphylactoid reaction of various severity including shock</td>
<td>Anaphylactoid reaction of various severity including shock</td>
</tr>
</tbody>
</table>

**Source:** Product insert of the respective solution.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABG</td>
<td>arterial blood gas</td>
</tr>
<tr>
<td>AKI</td>
<td>acute kidney injury</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine transaminase</td>
</tr>
<tr>
<td>APTT</td>
<td>activated partial thromboplastin time</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate transaminase</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>BUSE</td>
<td>blood urea serum electrolytes</td>
</tr>
<tr>
<td>CART</td>
<td>Classification and Regression Tree</td>
</tr>
<tr>
<td>COMBI</td>
<td>Communication for Behavioural Impact</td>
</tr>
<tr>
<td>CPG</td>
<td>clinical practice guidelines</td>
</tr>
<tr>
<td>CRT</td>
<td>capillary refill time</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>CVVH</td>
<td>continuous veno-venous haemodialysis</td>
</tr>
<tr>
<td>DENV</td>
<td>dengue virus</td>
</tr>
<tr>
<td>DF</td>
<td>dengue fever</td>
</tr>
<tr>
<td>DHF</td>
<td>dengue haemorrhagic fever</td>
</tr>
<tr>
<td>DSS</td>
<td>dengue shock syndrome</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogramme</td>
</tr>
<tr>
<td>EDTA</td>
<td>ethylenediamine tetraacetic acid</td>
</tr>
<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>FBC</td>
<td>full blood count</td>
</tr>
<tr>
<td>g</td>
<td>gramme</td>
</tr>
<tr>
<td>GCS</td>
<td>Glasgow Coma Scale</td>
</tr>
<tr>
<td>G6PD</td>
<td>glucose-6-phosphate dehydrogenase</td>
</tr>
<tr>
<td>Hb</td>
<td>haemoglobin</td>
</tr>
<tr>
<td>HCT</td>
<td>haematocrit</td>
</tr>
<tr>
<td>HDU</td>
<td>high dependency unit</td>
</tr>
<tr>
<td>HES</td>
<td>hydroxyethyl starch</td>
</tr>
<tr>
<td>HI</td>
<td>Haemagglutination Inhibition</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>hr</td>
<td>hour</td>
</tr>
<tr>
<td>IAP</td>
<td>intra-abdominal pressure</td>
</tr>
<tr>
<td>IBW</td>
<td>ideal body weight</td>
</tr>
<tr>
<td>ICU</td>
<td>intensive care unit</td>
</tr>
<tr>
<td>IgG</td>
<td>immunoglobulin G</td>
</tr>
<tr>
<td>IgM</td>
<td>immunoglobulin M</td>
</tr>
<tr>
<td>IMR</td>
<td>Institute of Medical Research</td>
</tr>
<tr>
<td>IO</td>
<td>intraosseous</td>
</tr>
<tr>
<td>IR</td>
<td>incidence rate</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>kg</td>
<td>kilogramme</td>
</tr>
<tr>
<td>L</td>
<td>litre</td>
</tr>
<tr>
<td>LFT</td>
<td>liver function test</td>
</tr>
<tr>
<td>ml</td>
<td>millilitre</td>
</tr>
<tr>
<td>mmol</td>
<td>milimoles</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>mosmol</td>
<td>miliosmole</td>
</tr>
<tr>
<td>NA</td>
<td>not applicable</td>
</tr>
<tr>
<td>NAC</td>
<td>N-acetyl cysteine</td>
</tr>
<tr>
<td>NPHL</td>
<td>National Public Health Laboratory</td>
</tr>
<tr>
<td>PHL</td>
<td>Public Health Laboratory</td>
</tr>
<tr>
<td>NS</td>
<td>normal saline</td>
</tr>
<tr>
<td>NS1 Ag</td>
<td>non-structural protein 1 antigen</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>OFI</td>
<td>other febrile illness</td>
</tr>
<tr>
<td>ORS</td>
<td>oral rehydration salts</td>
</tr>
<tr>
<td>pCO₂</td>
<td>partial pressure of carbon dioxide</td>
</tr>
<tr>
<td>PICC</td>
<td>peripheral inserted central catheter</td>
</tr>
<tr>
<td>PR</td>
<td>pulse rate</td>
</tr>
<tr>
<td>PT</td>
<td>prolonged prothrombin time</td>
</tr>
<tr>
<td>RCT(s)</td>
<td>randomised controlled trial(s)</td>
</tr>
<tr>
<td>RN</td>
<td>registered number</td>
</tr>
<tr>
<td>RRT</td>
<td>renal replacement therapy</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>reverse transcriptase-polymerase chain reaction</td>
</tr>
<tr>
<td>SpO₂</td>
<td>oxygen saturation</td>
</tr>
<tr>
<td>TCM</td>
<td>traditional and complementary medicines</td>
</tr>
<tr>
<td>VBG</td>
<td>venous blood gas</td>
</tr>
<tr>
<td>VCD</td>
<td>virologically-confirmed dengue</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood count</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</tbody>
</table>
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- Matron Wong on retrieval of evidence
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