CLINICAL PRACTICE GUIDELINES

2020

MOH/P/PAK/443.20(GU)-e

Management of Dengue in Children

(Second Edition)

Ministry of Health Malaysia

Academy of Medicine Malaysia

Published by:
Malaysia Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Federal Government Administrative Centre
62590 Putrajaya, Malaysia

e-ISBN: 978-967-19299-1-9

Available on the following websites:
http://www.moh.gov.my
http://www.acadmed.org.my

Also available as an app for Android and IOS platform: MyMaHTAS

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.

TABLE OF CONTENTS

TABLE OF CONTENTS

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 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 paediatricians.
  - Those with prolonged and/or decompensated shock should be admitted to the high-dependency or intensive care unit.
- Blood transfusion should be given in life-threatening conditions 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 infants should be managed in a hospital with paediatric services.

LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	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
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

FORMULATION OF RECOMMENDATION

In line with new development in CPG methodology, the CPG Unit of MaHTAS is 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 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 first search was limited to literature published in the last 14 years (2004 - 2018) 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)
- Handbook for Clinical Management of Dengue
- Dengue Guidelines for Diagnosis, Treatment, Prevention and Control

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

HEALTHCARE SETTINGS

Primary, secondary and tertiary care

DEVELOPMENT GROUP

Chairperson

Dr. Thahira A. Jamal Mohamed
Consultant Paediatrician (Infectious Disease)
Hospital Tunku Azizah, Kuala Lumpur

Members (alphabetical order)

Dr. Dianah Abd. Hadi
Paediatrician
Hospital Tunku Azizah, Kuala Lumpur

Ms. Koay Hooi Hoon
Pharmacist
Hospital Tunku Azizah, Kuala Lumpur

Dr. Mohamad Azlan Hamdan
Paediatrician
Hospital Tunku Azizah, Kuala Lumpur

Dr. Mohd. Aminuddin Mohd. Yusof
Head of CPG Unit & Public Health Physician
Cawangan Penilaian Teknologi Kesihatan
Kementerian Kesihatan Malaysia, Putrajaya

Dr. Nik Khairulddin Nik Yusoff
Consultant Paediatrician (Infectious Disease)
Hospital Raja Perempuan Zainab II, Kelantan

Dr. Nor Hafizah Ahmad
Transfusion Medicine Specialist
Pusat Darah Negara, Kuala Lumpur

Dr. Nur Izati Mustapa
Medical Microbiologist
Hospital Sungai Buloh, Selangor

Dr. Pon Kah Min
Consultant Paediatric Intensivist
Hospital Pulau Pinang, Pulau Pinang

Dr. Rahmat Dapari
Senior Medical Lecturer & Public Health Physician
Universiti Putra Malaysia, Selangor

Dr. Shamsuriani Md Jamal
Senior Lecturer & Emergency Physician
Pusat Perubatan Universiti Kebangsaan Malaysia, Kuala Lumpur

Pn. Siti Aisah Fadzilah
Senior Principal Assistant Director
Cawangan Penilaian Teknologi Kesihatan
Kementerian Kesihatan Malaysia, Putrajaya

Dr. Suhaimi Mahmud
Consultant Emergency Physician
Hospital Tuanku Jaafar, Negeri Sembilan

Dr. Suhaimi Mohd Isa
Family Medicine Specialist
Klinik Kesihatan Ayer Keroh, Melaka

Dr. Vickneswari Ayadurai
Consultant Family Medicine Specialist
Klinik Kesihatan Taman Medan, Selangor

REVIEW COMMITTEE

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.

Chairperson

Dr. Hishamshah Mohd Ibrahim
Deputy Director General of Health (Research & Technical Support) and
Senior Consultant Paediatric Haematolo-oncologist
Kementerian Kesihatan Malaysia, Putrajaya

Members (alphabetical order)

Dr. Choong Pheik Sian
Consultant Paediatric Intensivist
Hospital Sultanah Bahiyah, Kedah

Dr. Ho Bee Kiau
Consultant Family Medicine Specialist
Klinik Kesihatan Bandar Botanik, Selangor

Dr. Junainah Sabirin
Deputy Director
Cawangan Penilaian Teknologi Kesihatan
Kementerian Kesihatan Malaysia, Putrajaya

Professor Dr. Lucy Lum Chai See
Consultant Paediatric Intensivist
Pusat Perubatan Universiti Malaya, Kuala Lumpur

Prof. Dr. Muhammad Yazid Jalaludin
Head of Department &
Consultant Paediatric Endocrinologist
Pusat Perubatan Universiti Malaya, Kuala Lumpur

Dr. Noryati Abu Amin
Senior Consultant Transfusion Medicine &
Director
Pusat Darah Negara, Kuala Lumpur

Dr. Ravindran Thayan
Head of Virology Unit
Institut Penyelidikan Perubatan, Kuala Lumpur

Dr. Ridzuan Mohd Isa
Consultant Emergency Physician
Hospital Ampang, Selangor

Dr. Rose Nani Mudin
Head of Vector Borne Disease Sector
Bahagian Kawalan Penyakit
Kementerian Kesihatan Malaysia, Putrajaya

Ms. Subasyini Sivasupramaniam
Senior Pharmacist
Hospital Tunku Azizah, Kuala Lumpur

Dr. Susan Pee
Consultant Paediatric Nephrologist
Hospital Sultan Ismail, Johor

Dr. Zubaidah Abdul Wahab
Senior Consultant Medical Microbiologist
Hospital Selayang, Selangor

EXTERNAL REVIEWERS (alphabetical order)

Dr. Aziani Hashim
General Practitioner
Klinik Aziani, Cheras, Selangor

Dr. Hon Sai Kit
Consultant Paediatrician
Pantai Hospital Ampang, Kuala Lumpur

Dato' Dr. Hussain Imam Muhammad Ismail
Senior Consultant Paediatric Neurologist
Hospital Pulau Pinang, Pulau Pinang

Dr. Lee Jan Hau
Senior Consultant Paediatric Intensivist
Children's Intensive Care Unit
KK Women's & Children's Hospital
Singapore

Dr. Lee Siew Wah
Pediatric Intensivist
Hospital Sultanah Aminah, Johor

Datuk Dr. Mahathar Abd. Wahab
Head of Department &
Consultant Emergency Physician
Hospital Kuala Lumpur, Kuala Lumpur

Dr. Noraini Ismail
Consultant Medical Microbiologist
Hospital Sultanah Bahiyah, Kedah

Professor Dr. Rujipat Samransamruajkit
Consultant Paediatrician &
Chief of Paediatric Intensive Care Unit
Chulalongkorn University, Thailand

Dr. Salmiah Md Sharif
Family Medicine Specialist
Klinik Kesihatan Seremban
Negeri Sembilan

Dr. Sheila Gopal Krishnan
Consultant Paediatrician
Hospital Seri Manjung, Perak

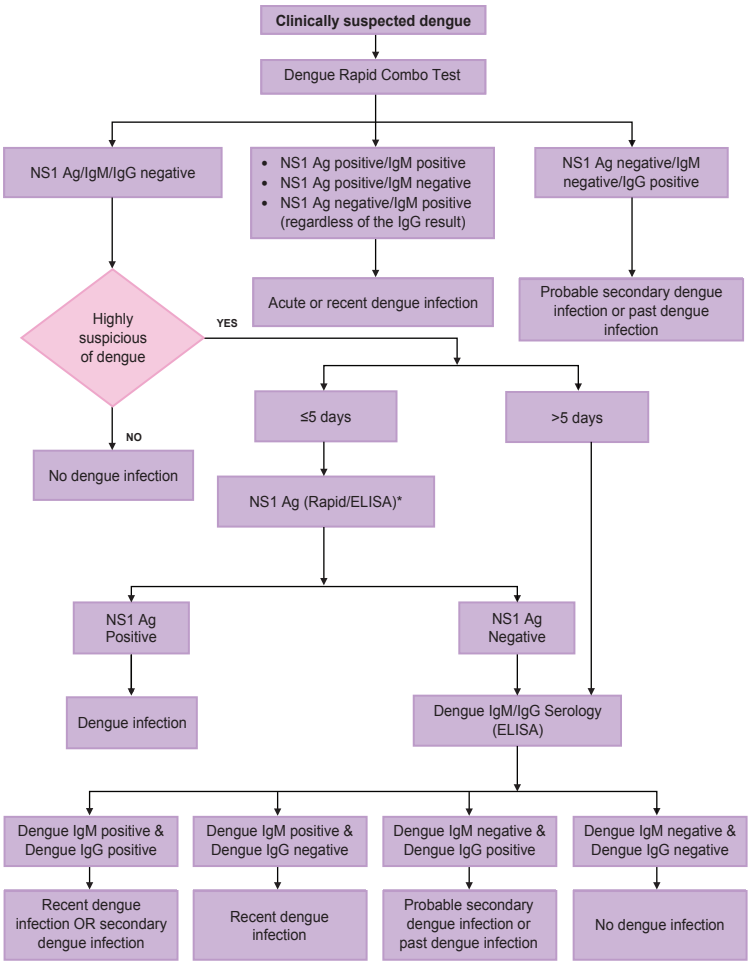
Dr. Tang Swee Fong
Senior Consultant Paediatric Intensivist
Pusat Perubatan Universiti Kebangsaan
Malaysia, Kuala Lumpur

Professor Dr. Tan Kah Kee
Lead in Paediatrics
Perdana University - RCSI, Kuala Lumpur

Ms. Vanessa Liang LuWen
Clinical Pharmacist
Hospital Tunku Azizah, Kuala Lumpur

Dr. Yap Hsiao Ling
Paediatrician (Paediatric Emergency
Medicine)
Hospital Tunku Azizah, Kuala Lumpur

Algorithm 1: Dengue Laboratory Diagnosis

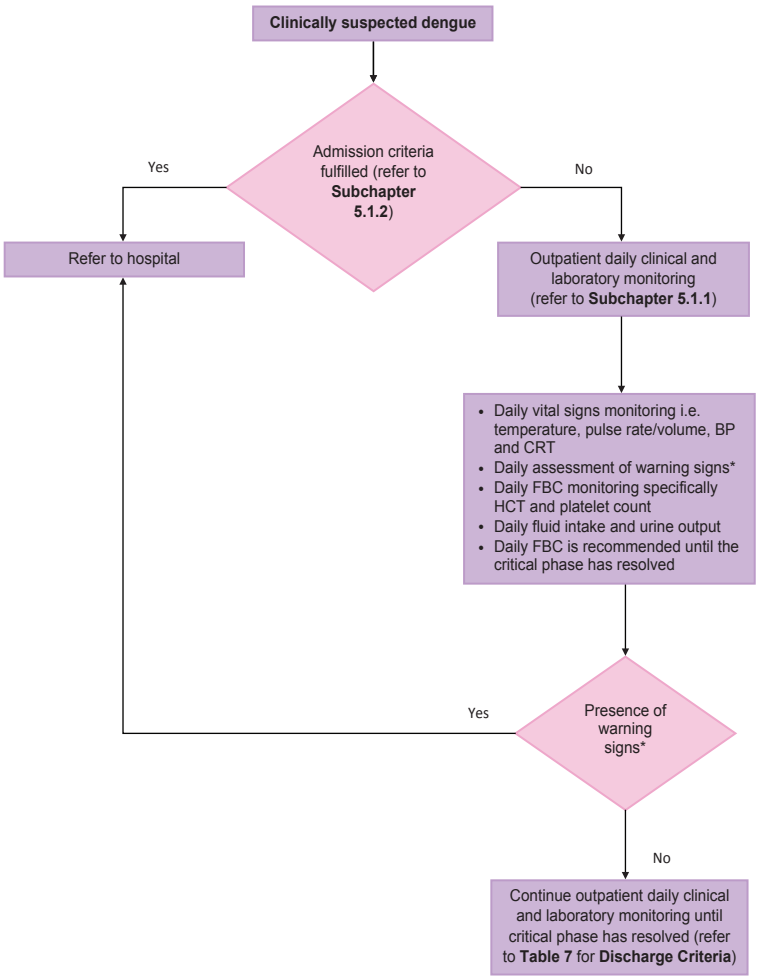


*Alternatively, Dengue Rapid Combo Test may be repeated

- PCR should be sent if NS1 Ag/serology is negative in suspected severe dengue or mortality cases.
- ELISA for dengue may be used in centres where combo test is not offered.

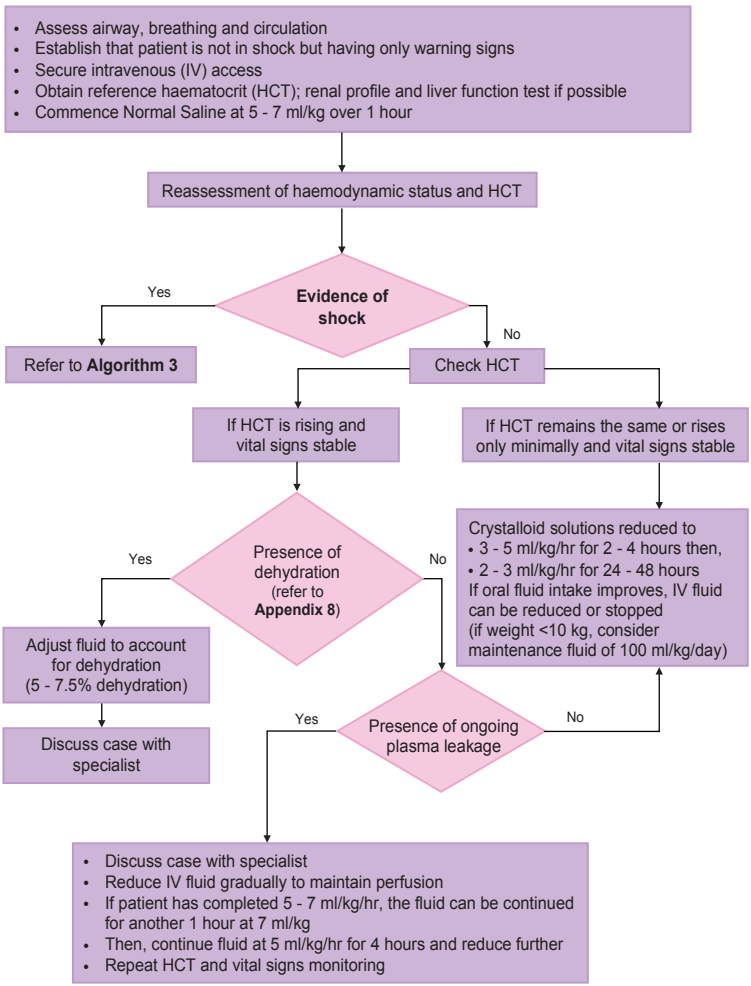
ELISA - enzyme-linked immunosorbent assay
IgG - Immunoglobulin G
IgM - Immunoglobulin M
NS1 Ag - Non-structural protein 1 Antigen
PCR - polymerase chain reaction

Algorithm 2: Outpatient Monitoring of Children with Suspected Dengue



*Refer to **Figure 3**

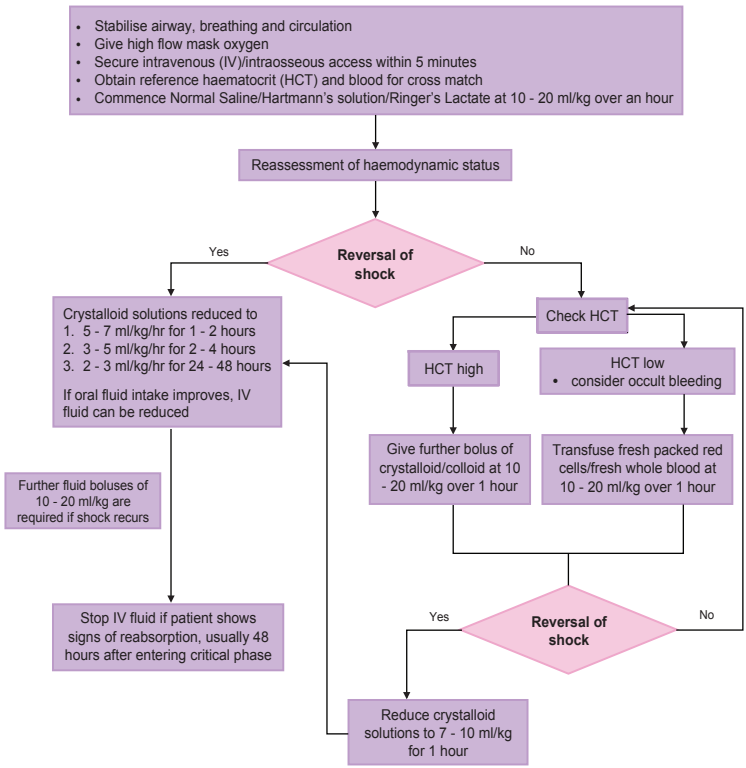
Algorithm 3. Fluid Management of Children with Dengue Warning Signs



Modified:

1. Ministry of Health Malaysia. Paediatric Protocol for Malaysian Hospitals. Putrajaya: MoH; 2019
2. World Health Organization. Handbook of Clinical Management of Dengue. Geneva: WHO; 2012

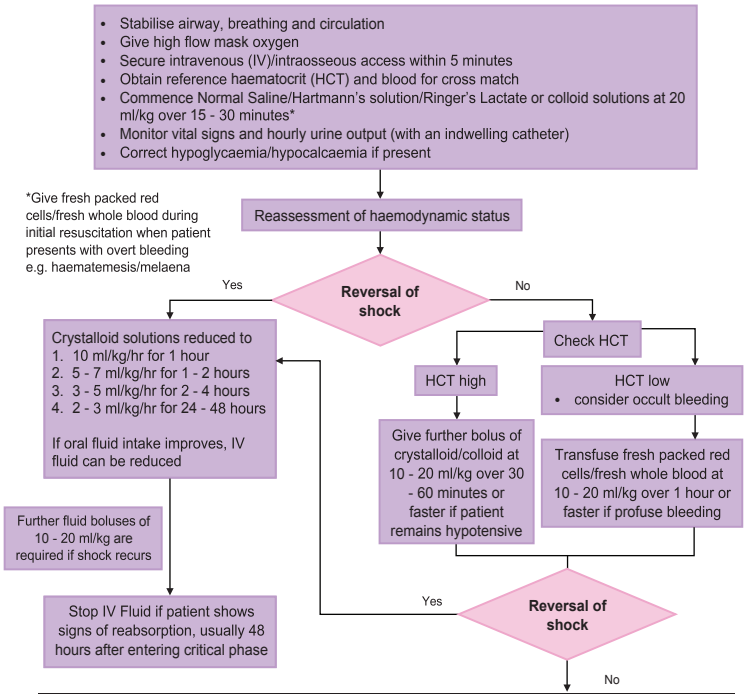
Algorithm 4. Fluid Management of Compensated Dengue Shock in Children



Modified:

1. Ministry of Health Malaysia. Paediatric Protocol for Malaysian Hospitals. Putrajaya: MoH; 2019
2. World Health Organization. Handbook of Clinical Management of Dengue. Geneva: WHO; 2012
3. Davis AL, Carcillo JA, Aneja RK et al. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. Crit Care Med. 2017;45(6):1061-1093.

Algorithm 5. Fluid Management of Decompensated Dengue Shock in Children



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 remains 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 ○ check coagulation profile
• septic shock (co-infection)
○ take blood culture and start IV antibiotics (refer to National Antibiotic Guidelines 2019) ○ consider inotropes/vasopressors (adrenaline or noradrenaline)
• cardiac dysfunction
○ perform echocardiogram if available ○ consider inotropes/vasopressors (adrenaline or dobutamine)
• correction of electrolyte imbalances and acidosis
• monitoring of intra-abdominal pressure (IAP) - control ascitic fluid drainage with great caution if IAP is elevated

Modified:

1. Ministry of Health Malaysia. Paediatric Protocol for Malaysian Hospitals. Putrajaya: MoH; 2019
2. World Health Organization. Handbook of Clinical Management of Dengue. Geneva: WHO; 2012
3. Davis AL, Carcillo JA, Aneja RK et al. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Paediatric and Neonatal Septic Shock. Crit Care Med. 2017;45(6):1061-1093.

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 a mosquito from the genus Aedes which has a biting preference for certain times of the day i.e. the morning and late afternoon. *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 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).[1, level III]

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

During the period 2000 - 2019, the annual number and the Senior Medical Lecturer & Public Health Physician Universiti Putra Malaysia, Selangor of dengue cases in Malaysia varied substantially, from the lowest value of 7,103 cases (30/100,000 population) in 2000 and reaching a peak of 120,836 cases (390/100,000 population) in 2015. After the peak, there was a 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% in dengue cases. Refer to **Figure 1**.

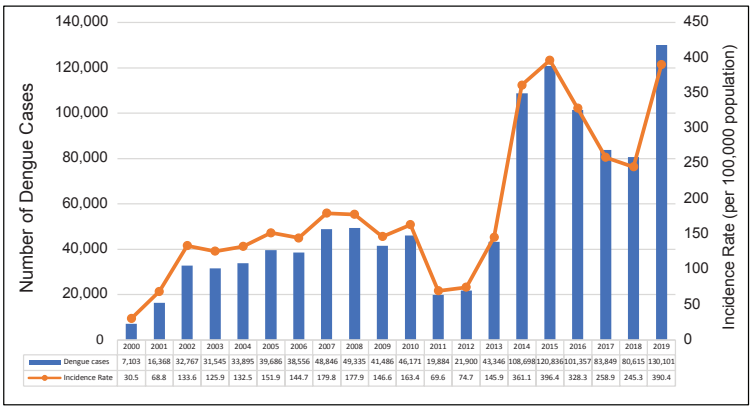
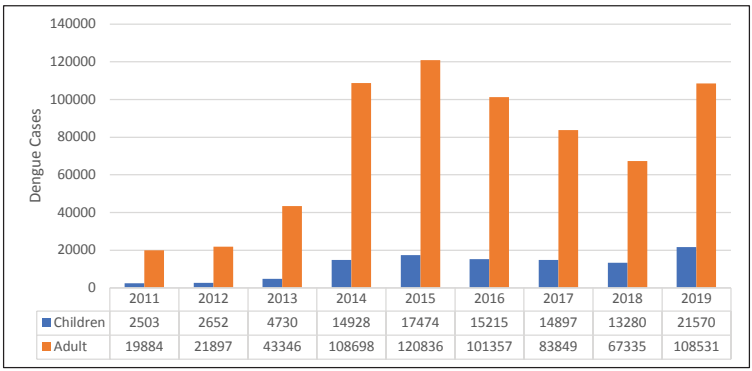


Figure 1. Annual number and incidence rate of dengue in Malaysia, 2000 - 2019

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 has been estimated by World Health Organization (WHO) that 500,000 people with severe dengue require hospitalisation each year, a large proportion of whom are children.[2 - 3, level III]

In the 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.[3, level III] In Malaysia, the annual percentage of cases among children has increased from 2014 to the current percentage of about 20% in 2019 (refer to **Figure 2**).



	2011	2012	2013	2014	2015	2016	2017	2018	2019
Children	2503	2652	4730	14928	17474	15215	14897	13280	21570
Adult	19884	21897	43346	108698	120836	101357	83849	67335	108531

Figure 2. Annual dengue cases among children and adults in Malaysia

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

1.2 Classification

Dengue classification has undergone major changes since 2009. The previous 1997 classification of DF and dengue hemorrhagic fever (DHF) drew much 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.[4, level II-2; 5, level III] Malaysia has 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 causes problems in dengue but increased vascular permeability leading to plasma leakage can tip an in individual over to a severe form of dengue. Refer to **Figure 3**.

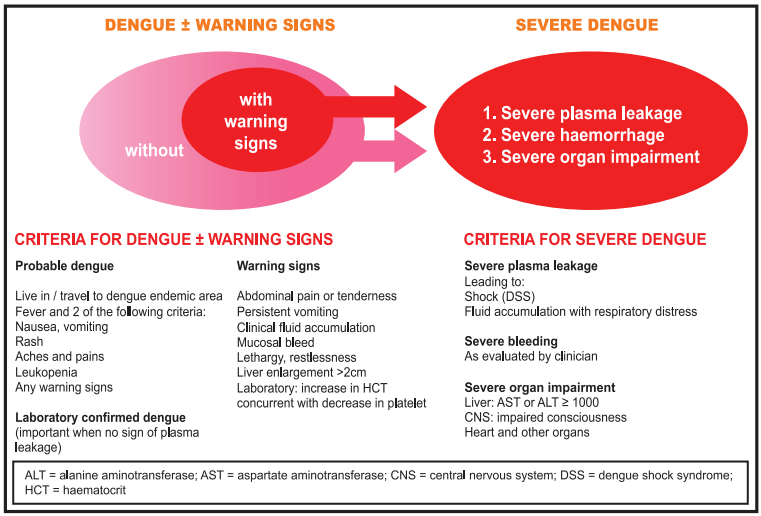


Figure 3. Dengue classification and severity

Adapted: World Health Organization. Handbook of Clinical Management of Dengue. Geneva: WHO; 2012

1.3 Severity

Dengue infection may be asymptomatic or present with a broad range of clinical manifestations from [mild febrile illness (known as DF) to life-threatening shock syndrome]. Numerous viral, host and vector factors are thought to impact the 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-circulate are at risk for primary/secondary infections with any DENV.[6 - 8, level III]

Dengue infection in children is often difficult to differentiate from OFI hence often delaying appropriate management in a timely manner. Children generally present with non-specific clinical features of OFI.[6, 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 between the ages of 3 to 8 months in South East Asia. Infants with primary infection may develop severe dengue when the mothers have prior DENV immunity.[9, level III]

2. CLINICAL MANIFESTATIONS AND PATHOPHYSIOLOGY

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

Dengue illness begins abruptly after an incubation period of 4 - 10 days following the mosquito bite. 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.[10, 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 38ºC. 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.[10, level III]

Warning signs of dengue

- Abdominal pain - abdominal tenderness and continuous pain (not intermittent)[11, level III]
- Persistent vomiting - ≥2 episodes of vomiting that amounts to fatigue or requires intravenous (IV) fluids[12, level II-3]
- Mucosal bleed - bleeding from nose, gums, conjunctiva, vagina, gastrointestinal/ respiratory/urinary tract[11, level III]
- Lethargy, restlessness[10, level III]
- Liver enlargement >2 cm[10, level III]
- Clinical fluid accumulation - pleural effusion and ascites[11, 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 10^3 cells/mm[10 - 11, level III]

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

Significant critical phase usually lasts 24 - 48 hours, mostly worse 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. The HCT level is closely associated with loss of plasma volume and the higher the level of haemoconcentration, the greater the severity of the disease.[13, 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.[3, level III] 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.[10, level III] 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 1. Haemodynamic Assessment: Continuum of Haemodynamic Changes

Parameters	Normal Circulation	Compensated shock*	Decompensated / Hypotensive shock
Consciousness level	Clear and alert	Clear and alert	Change of mental state (restless, drowsy)
Extremities	Warm and pink extremities	Cold extremities	Cold, clammy extremities
Capillary refill time (CRT)	Brisk (<2 sec)	Prolonged (>2 sec)	Very prolonged, mottled skin
Peripheral pulse volume	Good volume peripheral pulses	Weak & thready peripheral pulses	Feeble or absent peripheral pulses
Heart rate	Normal heart rate for age	Tachycardia	Severe tachycardia with bradycardia in late shock
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

Modified: World Health Organization. Handbook for Clinical Management of Dengue. Geneva: WHO; 2012

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.[10, 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".[10, level III]

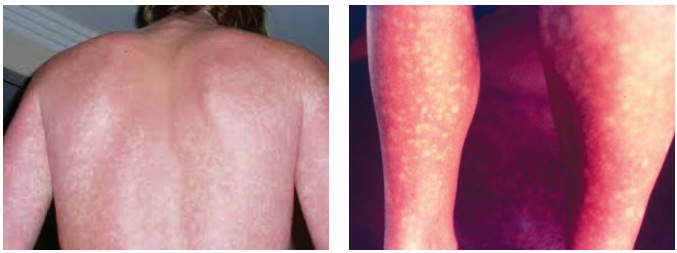


Figure 4. Isles of White in the Sea of Red

- 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.[10, level III; 14] 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.[10, level III]

The clinical course of dengue illness is shown in **Figure 5**.

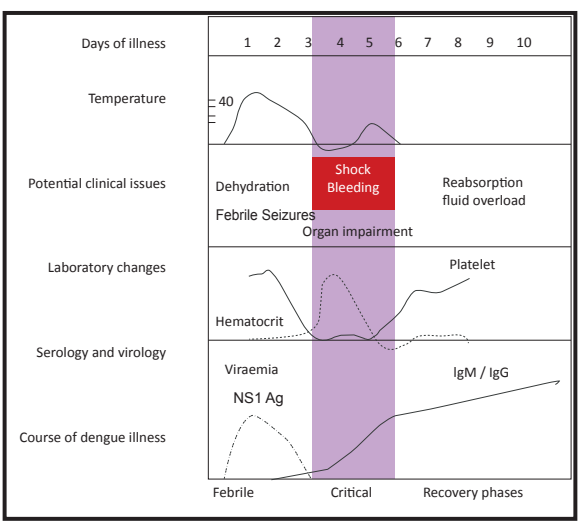


Figure 5. The Course of Dengue Illness

Adapted: World Health Organization. Handbook for Clinical Management of Dengue. Geneva: WHO; 2012

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:[10, 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 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).[15, level III]

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

Table 2. Differential Diagnosis for Dengue in Children

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

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

3.2 Laboratory Diagnosis

Since the clinical symptoms for dengue viral infection in children are so diverse, accurate clinical diagnosis is challenging. Virus detection and serological conversion had been the main targets for diagnosis for many years. Now, point-of-care diagnostic tests like dengue combo rapid test can be used in conjunction with assessment of clinical presentation to arrive at the diagnosis. Difficulty in diagnosis is further confounded by appearance of different biomarkers at different phases of dengue and their persistence also depends on whether it is primary or secondary dengue (refer to **Figure 6**). Therefore, if the first test done to confirm the diagnosis of dengue is negative but there is still **clinical suspicion of dengue**, the diagnostic test needs to be repeated. The choice of test depends on the timeline from onset of symptoms to presentation (refer to **Algorithm 1).**

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%).[16 - 17, level III]

Dengue rapid test is a good tool for detection of DENV IgM in acute dengue infection (AUC=0.91).[18, level II-2]

Combination of NS1 Ag with an IgM/IgG rapid test in acute dengue infection results in an increased sensitivity to:[19, 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 6**, **Table 3** and **Table 4** on appropriate test to be done during different phases of dengue infection.

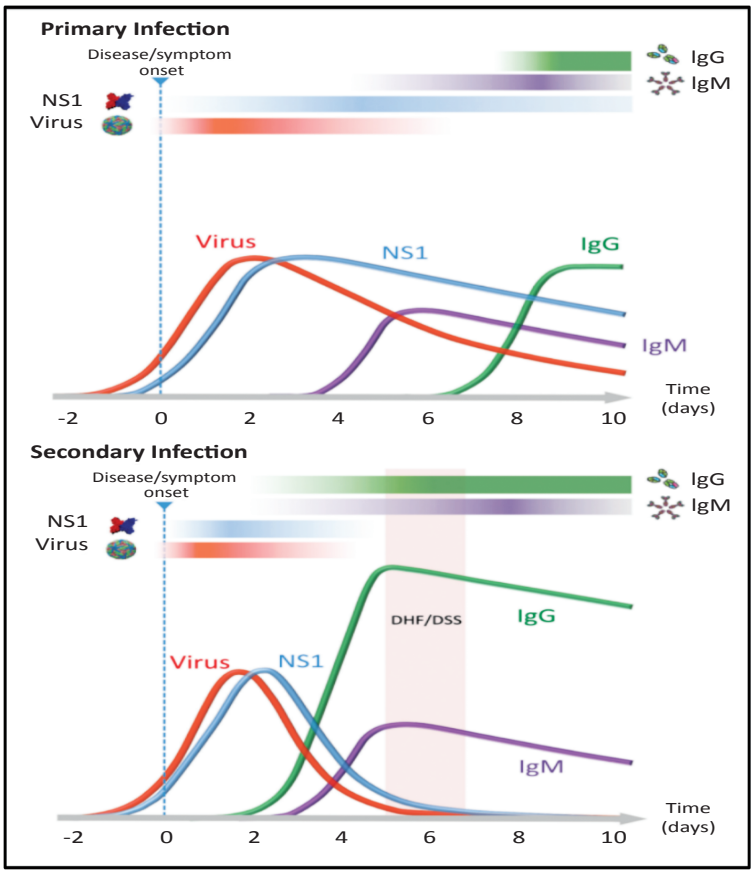


Figure 6. Timeline of dengue biomarker appearance in patients experiencing primary and secondary infection

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.[20, level III]

Table 3. Dengue Diagnostics and Sample Characteristics

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

Adapted: World Health Organization. Handbook for Clinical Management of Dengue. Geneva: WHO; 2012

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

Laboratory diagnosis	Method	Interpretation
Confirmed dengue infection	Virus isolation	Virus isolated
	Genome detection	Positive RT-qPCR
	Antigen detection	Positive NS1 Ag
	IgM	From negative IgM to positive IgM in paired sera
	IgG	From negative IgG to positive IgG in paired sera
Probable dengue infection	IgM	Positive IgM
	IgG	Positive IgG

Adapted: World Health Organization. Handbook for Clinical Management of Dengue. Geneva: WHO; 2012

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.[10, 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.[21]

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.[22]

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. WHO listed seven warning signs in 2009 guidelines. However, recent study shows that the signs listed below are significantly associated with severe dengue:[23, level II-2]

- 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,[23, level II-2] obesity[23 - 24, level II-2]
- epidemiology: secondary infection by DENV, infection by DENV-2[23, level II-2]
- clinical signs: pulse pressure <20 mmHg, systolic BP <90 mmHg [23, level II-2]
- laboratory parameters: WBC >5,000 /µL, haemoglobin (Hb) <9 g/dL,[23, level II-2] prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT), low fibrinogen level[25, level III]
- imaging: gallbladder wall thickening >5 mm[23, level II-2] presence of pleural effusion, ascites and/or gallbladder wall thickening[25, level III]

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 physical examination should be performed to arrive at the correct diagnosis. For paramedics who attend the child before a doctor, use the Checklist for Initial Assessment Dengue in Children for Paramedics to avoid missing the 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.[10, level III]
- Perform tepid sponging if the patient still has a high fever.[10, 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.[10, 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: [10, 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.
- advise caregivers to 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 **Algorithm 2** and **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.[26, 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: [10, 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.[27, 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. [28, 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*.[29]

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:[30 - 31, level III]
- 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 and decreasing base excess

Dynamic prediction model that incorporates signs, symptoms and daily laboratory measurements improves DSS prediction (AUC=0.70).[32, level II-3] 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.[33, level III]

Frequency of monitoring of clinical and laboratory parameters will depend on severity and phase of illness (refer to **Table 5**).[3, level III] 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

Parameters for Monitoring	Frequency of monitoring		
	Febrile phase	Critical phase	Recovery phase
Clinical			
• General well-being • Appetite/oral intake • Vomiting/diarrhoea • Warning signs	Daily or more frequently towards late febrile phase	At least twice a day and more frequently as indicated	Daily or more frequently as indicated
Haemodynamic status • Skin **C**olour (pink/ cyanosis) • **C**apillary refill time • Extremities (**T**emperature - cold/warm) • Pulse **V**olume • Pulse **R**ate • Blood pressure • Pulse pressure Respiratory status • Respiratory rate • Oxygen saturation (pulse oximeter /SpO_2) Neurological status • Consciousness level • Restlessness • Seizures	4 - 6 hourly depending on clinical status	2 - 4 hourly depending on clinical status **In shock:** Every 15 - 30 minutes until stable, then 1 - 2 hourly	4 - 6 hourly

Parameters for Monitoring	Frequency of monitoring		
	Febrile phase	**Critical phase**	**Recovery phase**
• Signs of bleeding • Abdominal tenderness, hepatomegaly • Ascites, pleural effusion	Daily or more frequently towards late febrile phase	At least twice a day and more frequently as indicated	Daily or more frequently as indicated
• Urine output	8-hourly	2 - 4 hourly **In shock**: Hourly	4 - 6 hourly
Laboratory			
• FBC	Daily or more frequently if indicated	4 - 12 hourly depending on clinical status **In shock:** Repeat before and after each attempt of fluid resuscitation and as indicated	Daily
• Blood Urea Serum Electrolytes (BUSE)/Creatinine • Liver Function Test (LFT) (including aspartate transaminase (AST)/alanine transaminase (ALT) • Blood sugar	As indicated	At least once or more frequently as indicated	As indicated
• Arterial Blood Gas (ABG)/Venous Blood Gas (VBG) • Lactate • Coagulation profile	As indicated	As indicated **In shock:** Monitor ABG/VBG and lactate closely	As indicated

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.[10, level III] 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 patients in shock should have their blood sample taken and cross-matched 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:[10, 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.[34, level III; 35, level I] These fluids should not contain glucose.[10, level III] Isotonic crystalloid solutions should be used for maintenance therapy.[10, level III; 36, level I] Early intervention with colloidal solutions is not indicated.[35, 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.[37, level I]

In the case of persistent shock despite resuscitation with crystalloid solutions, colloid solutions can be considered.[14] Clinicians should use colloid solutions based on their personal experience, familiarity with particular products, local availability and costs involved.

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 on children with dengue, minor advantages in initial recovery were shown with HES while significantly more allergic adverse reactions were associated with dextran.[35, 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.[38, level I]

Recommendation 5
- 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.

5.2.2 Treatment of warning signs

In children with dengue presenting with warning signs or signs of dehydration (refer to **Appendix 8**), judicious volume replacement with IV fluid therapy from this early stage may modify the course and severity of disease. Refer to **Algorithm 3**.

5.2.3 Treatment of compensated shock

Treatment plan for patients with compensated shock is as follows (refer to **Algorithm 4**):[10, level III] Obtain a reference HCT before starting IV fluid therapy.

- Secure IV/intraosseous (IO) access within five minutes.
- Start IV fluid resuscitation with isotonic crystalloid solutions at 10 - 20 ml/kg 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 colloid solution at 10 - 20 ml/kg over an hour 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 colloid solution may need to be repeated if shock recurs.

Children with compensated shock should be closely monitored in hospitals with paediatricians and managed by senior staffs.

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:[10, level III]

- Secure IV access within five minutes.
- Initiate IV fluid resuscitation with crystalloid solution at 20 ml/kg as a bolus over 15 - 30 minutes for quick shock reversal.
- Colloid solution 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.[35, level I]
- 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 staffs.

Refer to **Algorithm 5**.

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 staffs in hospitals with paediatricians.
  - Those with prolonged and/or 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:[10, 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.[10, level III]
- In local setting, children with shock should at least 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.[10, 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.[10, 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.[10, 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.[10, level III]

In addition, patients with severe dengue should be monitored for: [10, 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.[10, 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.[10, 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 6. Range of Haematocrit in Different Age Groups

Age	HCT (%)
Cord blood	45 - 65
2 weeks	42 - 66
3 months	31 - 41
6 months - 6 years	33 - 42
7 - 12 years	34 - 40
Adult male	42 - 52
Adult female	37 - 47

Source: Ministry of Health Malaysia. Paediatric Protocol for Malaysian Hospitals. Putrajaya: MoH; 2019

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.[10, level III]

Hyperglycaemia:[10, 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.[10, level III; 36, level I] This maintenance fluid should be included as part of fluid therapy according to the **Algorithm 2**, **3** and **4**.

Table 7. Holliday-Segar calculator

Weight	Total fluids	Infusion rate
First 10 kgs	100 ml/kg	4 ml/kg/hour
Subsequent 10 kgs	50 ml/kg	2 ml/kg/hour
All additional kg	20 ml/kg	1 ml/kg/hour

Source: Ministry of Health Malaysia. Paediatric Protocol for Malaysian Hospitals. Putrajaya: MoH; 2019

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.[10, 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)[39, 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.[10, 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.[10, 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.[10, 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%.[40 - 42, level III] A wide-spectrum of neurological manifestations have been described including encephalopathy, encephalitis, immune-mediated syndromes and muscular dysfunctions.[42 - 43, level III]

Acute encephalopathy is the most common neurological complication with prevalence at 0.5 - 5.1%.[40, 42, 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.[42, 44, 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.[42, level III]

Immune-mediated neurological syndromes associated with dengue infection have been described in paediatric populations. Acute transverse myelitis, acute disseminated encephalomyelitis and Guillain-Barre Syndrome usually follow their natural course. Standard management as per the disorder is recommended.[42, 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 ranging from 38.7% to 87%. Prevalence is generally higher in the more severe category of dengue infection (dengue with

warning signs and severe dengue).[45 - 46, level III] 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.[47 - 48, level III] Acute liver failure is rare (range 1.1% - 5.8%).[47 - 49, level III]

AST level is usually higher than ALT level in contrast to other causes of viral hepatitis.[50, level III] 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.[46, 49, level III]

- 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 including acetaminophen
  - close monitoring of neurological parameters
  - management of hepatic encephalopathy

There is no evidence to support the routine use of N-Acetyl cysteine 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.[51, level III]

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.[52, level II-2]

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.[10, level III]

5.2.14 Blood transfusion

Blood transfusion is only indicated in patients with:[10, level III]

- 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:[10, level III]

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
   - dose of platelet and fresh frozen plasma transfusion is 10 - 15 ml/kg

- There is no evidence to support the practice of transfusing platelet and fresh frozen plasma for severe bleeding in dengue.[10, level III]
  - 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.[10, level III]

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.[10, level III]

6. SPECIAL GROUPS

6.1 Neonates

Neonates can acquire DENV through vertical transmission or at the time of delivery. They may be asymptomatic and the clinical manifestations vary from mild to severe illness.[10, level III]

Symptomatic and supportive treatment under close observation is the mainstay of treatment in neonates with dengue infection.[10, 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.

Clinical presentation of dengue in infants is similar to older children.[10, 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.[10, 53, 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.[10, level III]

Compared to those with acute undifferentiated febrile illness, infants with dengue infection are more likely to have:[53, 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.[10, level III]
  - Any increment of ≥20% from baseline HCT is considered haemoconcentration. Refer to **Table 6** on **Range of Haematocrit in Different Age Groups**.

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.[10, level III]

Infants with dengue infection should be referred for in-hospital management.[10, level III]

Recommendation 8
- Dengue infection in infant should be managed in a 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 stages of thalassemia. It may also occur in other haemoglobinopathies and glucose-6-phosphate dehydrogenase (G6PD) deficiency.[54, level III]

- Haemoconcentration during plasma leakage may be missed in anaemic patients with dengue due to low baseline HCT level.[54, 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.[10, 54, level III]

7. DISCHARGE

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

Table 7. Discharge Criteria

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

Adapted:

1. World Health Organization. Handbook for Clinical Management of Dengue. Geneva: WHO; 2012
2. Ministry of Health, Malaysia. Clinical Practice Guidelines Management of Dengue in Children. Putrajaya: MoH; 2004

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.[55, 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 of younger children. Analysis on long-term safety was not available then.[56, 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 subjects compared with control in seronegative 2 to 16 years old participants. The vaccine prevented hospitalisation 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 VCD and severe VCD subjects respectively. Thus, the vaccine was protective in those who had exposure to dengue before vaccination.[57, 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:[3, 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 vaporisers
- household fixtures e.g. window and door screens and air-conditioning

Although no evidence could be found to support the efficacy of repellent in reducing dengue incidence,[58, level III] experts advocate the use of repellent.

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:

i. availability of CPG to healthcare providers (hardcopies and softcopies)
ii. conferences and updates on management of dengue in children including those who involved in professional bodies
iii. Clinical Audit on Dengue Mortality
iv. public awareness activities e.g. COMBI (Communication for Behavioural Impact)

Limiting factors in the CPG implementation include:

i. limited awareness and knowledge in management of dengue in children among healthcare providers
ii. variation in treatment practice and preferences among healthcare providers
iii. insufficient resources especially trained personnel, diagnostic kits and infrastructure
iv. 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. Dengue and severe dengue. (Available at: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue)
2. Bhatt S, Gething PW, Brady OJ et al. The global distribution and burden of dengue. Nature. 2013;496(7446):504-7.
3. World Health Organization. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control: New Edition. Geneva: WHO; 2009.
4. Alexander N, Balmaseda A, Coelho IC et al. Multicentre prospective study on dengue classification in four South-east Asian and three Latin American countries. Trop Med Int Health. 2011;16(8):936-48.
5. Manock SR, Jacobsen KH, de Bravo NB et al. Etiology of acute undifferentiated febrile illness in the Amazon basin of Ecuador. Am J Trop Med Hyg. 2009;81(1):146-51.
6. Wahala WM, Silva AM. The human antibody response to dengue virus infection. Viruses. 2011;3(12):2374-95.
7. Rothman AL. Immunity to dengue virus: a tale of original antigenic sin and tropical cytokine storms. Nat Rev Immunol. 2011;11(8):532-43.
8. Halstead SB. Dengue. Lancet. 2007;370(9599):1644-52.
9. Capeding RZ, Brion JD, Caponpon MM et al. The incidence, characteristics, and presentation of dengue virus infections during infancy. Am J Trop Med Hyg. 2010;82(2):330-6.
10. Lucy CSL, Guadalupe GM, Martinéz E et al. Handbook for clinical management of dengue: World Health Organization; 2012.
11. Narvaez F, Gutierrez G, Pérez MA et al. Evaluation of the traditional and revised WHO classifications of Dengue disease severity. PLoS Negl Trop Dis. 2011;5(11):e1397.
12. Sreenivasan P, S G, K S. Development of a Prognostic Prediction Model to Determine Severe Dengue in Children. Indian J Pediatr. 2018;85(6):433-9.
13. Kittigul L, Pitakarnjanakul P, Sujirarat D et al. The differences of clinical manifestations and laboratory findings in children and adults with dengue virus infection. J Clin Virol. 2007;39(2):76-81.
14. Ministry of Health Malaysia. Management of Dengue Fever in Children. Putrajaya: MoH; 2004.
15. Cavailler P, Tarantola A, Leo YS et al. Early diagnosis of dengue disease severity in a resource-limited Asian country. BMC Infect Dis. 2016;16(1):512.
16. Shan X, Wang X, Yuan Q et al. Evaluation of the diagnostic accuracy of nonstructural protein 1 Ag-based tests for dengue virus in Asian population: a meta-analysis. BMC Infect Dis. 2015;15:360.
17. Zhang H, Li W, Wang J et al. NS1-based tests with diagnostic utility for confirming dengue infection: a meta-analysis. Int J Infect Dis. 2014;26:57-66.
18. Blacksell SD, Doust JA, Newton PN et al. A systematic review and meta-analysis of the diagnostic accuracy of rapid immunochromatographic assays for the detection of dengue virus IgM antibodies during acute infection. Trans R Soc Trop Med Hyg. 2006;100(8):775-84.
19. Fry SR, Meyer M, Semple MG et al. The diagnostic sensitivity of dengue rapid test assays is significantly enhanced by using a combined antigen and antibody testing approach. PLoS Negl Trop Dis. 2011;5(6):e1199.
20. Muller DA, Depelsenaire AC, Young PR. Clinical and Laboratory Diagnosis of Dengue Virus Infection. J Infect Dis. 2017;215(suppl_2):S89-s95.
21. Ministry of Health Malaysia. Management of Dengue Infection in Adults (Third Edition). Putrajaya: MoH; 2015.
22. Ministry of Health Malaysia. Case Definitions for Infectious Diseases in Malaysia: Third Edition. Putrajaya: MoH; 2017.

23. Wakimoto MD, Camacho LA, Guaraldo L et al. Dengue in children: a systematic review of clinical and laboratory factors associated with severity. Expert Rev Anti Infect Ther. 2015;13(12):1441-56.
24. Zulkipli MS, Dahlui M, Jamil N et al. The association between obesity and dengue severity among pediatric patients: A systematic review and meta-analysis. PLoS Negl Trop Dis. 2018;12(2):e0006263.
25. Lovera D, Araya S, Mesquita MJ et al. Prospective applicability study of the new dengue classification system for clinical management in children. Pediatr Infect Dis J. 2014;33(9):933-5.
26. American Academy of Pediatrics. Red Book: 2018 Report of the Committee on Infectious Disease (31st Edition). Itasca, IL: AAP; 2018.
27. Pothapregada S, Kamalakannan B, Thulasingam M et al. Is Reactive Dengue NS1Antigen Test a Warning Call for Hospital Admissions? J Clin Diagn Res. 2016;10(4):Sc04-7.
28. Mishra S, Ramanathan R, Agarwalla SK. Clinical Profile of Dengue Fever in Children: A Study from Southern Odisha, India. Scientifica. 2016;2016:6391594.
29. Ministry of Health Malaysia. Garispanduan Rujukan dan Perpindahan Pesakit di Antara Hospital-hospital Kementerian Kesihatan. Putrajaya: MoH; 2009.
30. Hassan N, Mukhopadhyay S, Bhattacharjee P et al. Bed side prognostic markers for dengue fever: serum lactate, base excess and central peripheral temperature gradient. International Journal of Contemporary Pediatrics. 2017;4(6):2041-5.
31. Pongpan S, Patumanond J, Wisitwong A et al. Validation of dengue infection severity score. Risk Manag Healthc Policy. 2014;7:45-9.
32. Lam PK, Ngoc TV, Thu Thuy TT et al. The value of daily platelet counts for predicting dengue shock syndrome: Results from a prospective observational study of 2301 Vietnamese children with dengue. PLoS Negl Trop Dis. 2017;11(4):e0005498.
33. Phakhounthong K, Chaovalit P, Jittamala P et al. Predicting the severity of dengue fever in children on admission based on clinical features and laboratory indicators: application of classification tree analysis. BMC Pediatr. 2018;18(1):109.
34. Hung NT. Fluid management for dengue in children. Paediatr Int Child Health. 2012;32 Suppl 1(s1):39-42.
35. Wills BA, Nguyen MD, Ha TL et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. N Engl J Med. 2005;353(9):877-89.
36. Feld LG, Neuspiel DR, Foster BA et al. Clinical Practice Guideline: Maintenance Intravenous Fluids in Children. Pediatrics. 2018;142(6).
37. Perel P. Colloids versus crystalloids for fluid resuscitation in Dengue fever patients - a review (unpublished). 2012.
38. Li L, Li Y, Xu X et al. Safety evaluation on low-molecular-weight hydroxyethyl starch for volume expansion therapy in pediatric patients: a meta-analysis of randomized controlled trials. Crit Care. 2015;19(1):79.
39. Ministry of Health Malaysia. Malaysian Paediatric Protocol for Malaysian Hospitals (Fourth Edition). Putrajaya: MoH; 2019.
40. Shokeen P, Yadav S, Verma CR et al. Neurological complications in Dengue fever. International Journal of Contemporary Pediatrics. 2018;Volume 5(3).
41. Kamel MG, Nam NT, Han NHB et al. Post-dengue acute disseminated encephalomyelitis: A case report and meta-analysis. PLoS Negl Trop Dis. 2017;11(6):e0005715.
42. Carod-Artal FJ, Wichmann O, Farrar J et al. Neurological complications of dengue virus infection. Lancet Neurol. 2013;12(9):906-19.
43. Li GH, Ning ZJ, Liu YM et al. Neurological Manifestations of Dengue Infection. Frontiers in cellular and infection microbiology. 2017;7:449.
44. Witayathawornwong P. Dengue haemorrhagic fever with encephalopathy/fatality at Petchabun Hospital: a three-year prospective study (1999-2002). Dengue Bulletin. 2004; 28:77-86.

45. Srivastava G, Chhavi N, Goel A. Validation of Serum Aminotransferases Levels to Define Severe Dengue Fever in Children. Pediatr Gastroenterol Hepatol Nutr. 2018;21(4):289-96.
46. Martínez Vega R, Phumratanaprapin W, Phonrat B et al. Differences in Liver Impairment Between Adults and Children with Dengue Infection. Am J Trop Med Hyg. 2016;94(5):1073-9.
47. Mohan N Goyal D, Karkra S et al. Profile of Dengue hepatitis in children from India and its correlation with WHO Dengue case classification. Asian Pac J Trop. 2017;7:327-31.
48. Roy A, Sarkar D, Chakraborty S et al. Profile of hepatic involvement by dengue virus in dengue infected children. North American journal of medical sciences. 2013;5(8):480-5.
49. Laoprasopwattana K, Jundee P, Pruekprasert P et al. Outcome of Severe Dengue Viral Infection-caused Acute Liver Failure in Thai Children. Journal of tropical pediatrics. 2016;62(3):200-5.
50. Chongsrisawat V, Hutagalung Y, Poovorawan Y. Liver function test results and outcomes in children with acute liver failure due to dengue infection. Southeast Asian J Trop Med Public Health. 2009;40(1):47-53.
51. Kirawittaya T, Yoon IK, Wichit S et al. Evaluation of Cardiac Involvement in Children with Dengue by Serial Echocardiographic Studies. PLoS Negl Trop Dis. 2015;9(7):e0003943.
52. Andries AC, Duong V, Cappelle J et al. Proteinuria during dengue fever in children. Int J Infect Dis. 2017;55:38-44.
53. Chau TN, Anders KL, Lien le B et al. Clinical and virological features of Dengue in Vietnamese infants. PLoS Negl Trop Dis. 2010;4(4):e657.
54. Chuansumrit A, Tangnararatchakit K, Sirachainan N et al. Dengue infection in hematologic-oncologic pediatric patients: aggravation of anemia and bleeding risk. Southeast Asian J Trop Med Public Health. 2012;43(2):311-22.
55. Capeding MR, Tran NH, Hadinegoro SR et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. Lancet. 2014;384(9951):1358-65.
56. Hadinegoro SR, Arredondo-García JL, Capeding MR et al. Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease. N Engl J Med. 2015;373(13):1195-206.
57. Sridhar S, Luedtke A, Langevin E et al. Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. N Engl J Med. 2018;379(4):327-40.
58. Roza S, Ku Nurhasni KAR, Balqis AB et al. Integrated Vector Management for Aedes Control. Health Technology Assessment. Malaysia: Malaysian Health Technology Assessment Section (MaHTAS); 2019. 147 p.

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.
9. pyrexia*.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 (compensated)
- Quiet tachypnoea (tachypnoea without increased effort)
- Cold extremities and delayed capillary refill time (CRT) of >2 seconds
- Weak volume peripheral pulses
- Normal oxygen saturation (SpO_2: 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 (pCO_2) and low bicarbonate level)
- May remain conscious and alert

Worsening hypovolaemic shock (decompensated)
- 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

APPENDIX 4

CHECKLIST FOR PARAMEDICS ON INITIAL ASSESSMENT OF DENGUE IN CHILDREN

Name: Age:
Identification Card No.: Date/Time:

		Yes	No
1.	**Presence of fever**		
	If NO, any history of taking fever medicine e.g. paracetamol		
2.	**Living in dengue area**	✔	
3.	**Clinical criteria:**		
	• Rash		
	• Nausea/vomiting		
	• Aches/pains		
	• Low white cell count		
4.	**Warning signs:**		
	• Persistent abdominal pain		
	• Persistent vomiting - ≥2 episodes of vomiting/24 hours		
	• Red spot (petechiae) on the skin, bleeding from nose or gums, vomiting blood, black-coloured stool, heavy menses, blood in urine		
	• Lethargy or poor feeding		
	• Respiratory distress		
	• Laboratory: haematocrit (HCT) above 40% and platelet count <100 x 10^3/μL		
5.	**Special population:**		
	• Infant (age <12 months old)		
	• Co-morbidities - any medical illness		
6.	**Haemodynamic status CCTVR**		
	• Skin **C**olour - cyanosis		
	• **C**apillary refill time - >2 seconds		
	• Extremities - **T**emperature (cold)		
	• Pulse **V**olume - weak		
	• Pulse **R**ate - abnormal		

Diagnosis/management	Health clinic	Emergency Dept., Hospital
• Probable dengue (1+2+3)	Refer doctor	Non-critical zone
• Probable dengue with warning signs (1+2+3+4)	Refer doctor for assessment pre-admission	Semi-critical zone
• Probable dengue in special population (1+2+3+5)	Refer doctor for assessment pre-admission	Semi-critical zone
• Any criteria that include 4	Refer doctor for assessment pre-admission	Semi-critical zone
• Any criteria that include 6	Refer doctor immediately for resuscitation	Critical zone

HOME CARE ADVICE FOR CHILDREN WITH DENGUE

WHAT SHOULD BE DONE?

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

Age group	Per drink
<5 years old	100 - 120 ml
5 - 10 years old	160 - 180 ml
>10 years old	200 - 220 ml

  - 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:

- lack of energy 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

Patient's name: Identification Card No. / Passport No:
Address : Date of onset of fever :
Result of Dengue Combo Test: (Date:) Date of notification :

Date	Day of fever	Last dose paracetamol	Temp. (°C)	BP (mmHg)	PR (min)	Hb (g/dL)	HCT (%)	WBC ($x10^3/\mu L$)	Platelet ($x10^3/\mu L$)	Attending Clinic/ Tel. No	Next Appointment

HOSPITAL DENGUE MONITORING CHART

(24-Hours Clinical, Laboratory and Fluid Monitoring) Date: _____(1 page per calendar day)

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.*

Time*	00:	01:	02:	03:	04:	05:	06:	07:	08:	09:	10:	11:	12:	13:	14:	15:	16:	17:	18:	19:	20:	21:	22:	23:
Shock**																								
Temperature																								
Blood pressure																								
Pulse rate																								
Respiratory rate																								
Haematocrit																								
Haemoglobin																								
Platelet count																								
Lactate																								
Glucose																								
Urea/ Creatine																								
Crystalloid type, ml/hr																								
Colloid type, ml/hr																								
Blood product type, ml/hr																								
Oral intake (ml)																								
Cumulative input																								
Urine (ml)																								
Inotrope/ Others																								
Remarks																								

APPENDIX 7

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

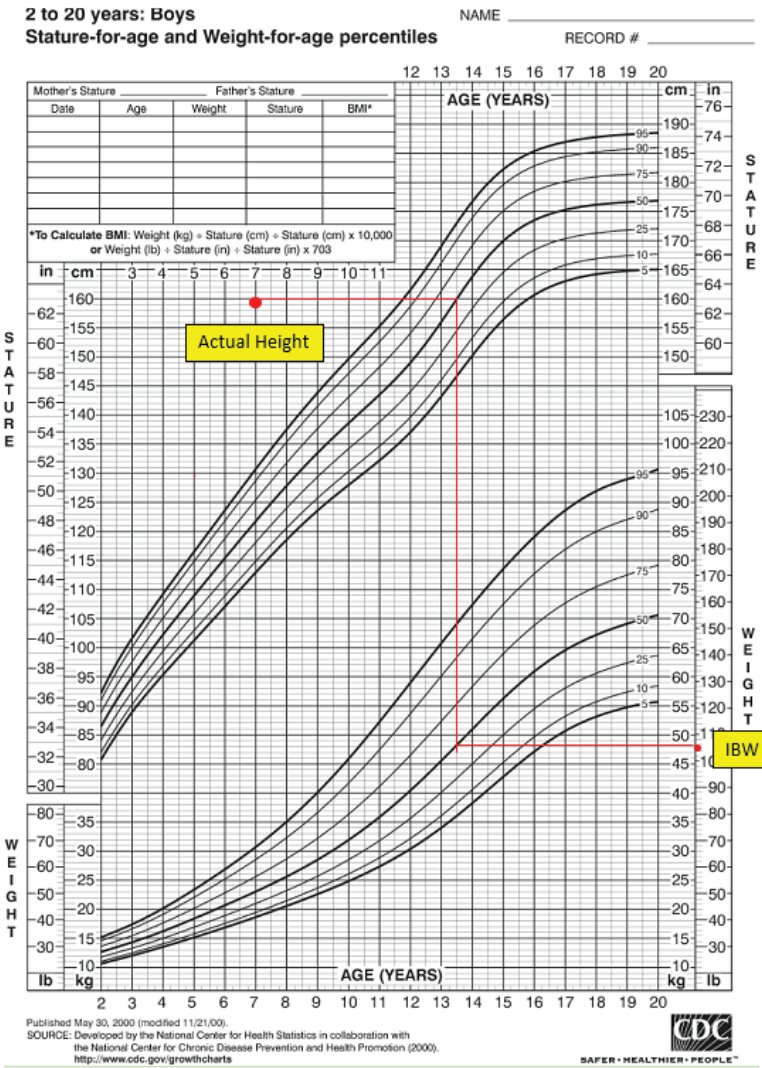
Refer to the growth chart below for method of plotting.

Source:

1. Phillips S, Edlbeck A, Kirby M et al. Ideal body weight in children. Nutr Clin Pract. 2007;22(2):240-5.
2. Kang K, Absher R, Farrington E et al. Evaluation of Different Methods Used to Calculate Ideal Body Weight in the Pediatric Population. J Pediatr Pharmacol Ther. 2019;24(5):421-430.

APPENDIX 7

GROWTH CHART



APPENDIX 8

SIGNS OF DEHYDRATION

Assess:			
Look at child's general condition	Well, alert	Restless or irritable	Lethargic or unconscious
Look for sunken eyes	No sunken eyes	Sunken eyes	Sunken eyes
Offer the child fluid	Drinks normally	Drinks eagerly, thirsty	Not able to drink or drinks poorly
Pinch skin of abdomen	Skin goes back immediately	Skin goes back slowly	Skin goes back very slowly (>2 seconds)
Classify	**Mild Dehydration** <5% Dehydrated* *IMCI: No signs of Dehydration*	≥2 above signs: **Moderate Dehydration** 5 - 10% Dehydrated *IMCI: Some signs of Dehydration*	≥2 above signs: **Severe Dehydration** >10% Dehydrated
Treat	**Plan A** Give fluid and food to treat diarrhoea at home	**Plan B** Give fluid and food for some dehydration	**Plan C** Give fluid for severe dehydration. Provide food as soon as child tolerates.

**% 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

APPENDIX 9

CHARACTERISTICS OF COMMON CRYSTALLOID/COLLOIDS SOLUTIONS AVAILABLE IN MALAYSIA

CRYSTALLOID SOLUTIONS

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

COLLOIDAL SOLUTIONS

Content	Human plasma	Succinylated gelatin 4% (e.g. Gelafundin/Infusol)	Hydroxyethyl starch 6% (HES) (e.g. Voluven)	Albumin 5%
Sodium (mmol/L)	136 - 145	154	154	130 - 160
Chloride (mmol/L)	98 - 106	120	154	130 - 160
Osmolarity (mosmol/L)	291	308	308	309
Serious adverse effects	NA	• Anaphylactoid reaction of various severity including shock	• Anaphylactoid reaction of various severity including shock • Acute kidney injury	• Anaphylactoid reaction of various severity including shock

Source: Product insert of the respective solution

LIST OF ABBREVIATIONS

µL	microlitre
ABG	arterial blood gas
AKI	acute kidney injury
ALT	alanine transaminase
APTT	activated partial thromboplastin time
AST	aspartate transaminase
BP	blood pressure
BUSE	blood urea serum electrolytes
CART	Classification and Regression Tree
COMBI	Communication for Behavioural Impact
CPG	clinical practice guidelines
CRT	capillary refill time
CSF	cerebrospinal fluid
CVVH	continuous veno-venous haemodialysis
DENV	dengue virus
DF	dengue fever
DHF	dengue haemorrhagic fever
DSS	dengue shock syndrome
ECG	electrocardiogramme
EDTA	ethylenediamine tetraacetic acid
ELISA	enzyme-linked immunosorbent assay
FBC	full blood count
g	gramme
GCS	Glasgow Coma Scale
G6PD	glucose-6-phosphate dehydrogenase
Hb	haemoglobin
HCT	haematocrit
HDU	high dependency unit
HES	hydroxyethyl starch
HI	Haemagglutination Inhibition
HIV	Human Immunodeficiency Virus
hr	hour
IAP	intra-abdominal pressure
IBW	ideal body weight
ICU	intensive care unit
IgG	immunoglobulin G
IgM	immunoglobulin M
IMR	Institute of Medical Research
IO	intraosseous
IR	incidence rate
IV	intravenous
kg	kilogramme
L	litre
LFT	liver function test
MKA	*Makmal Kesihatan Awam*
MKAK	*Makmal Kesihatan Awam Kebangsaan*
ml	millilitre

mmol	milimoles
mosmol	miliosmole
NA	not applicable
NAC	N-acetyl cysteine
NPHL	National Public Health Laboratory
PHL	Public Health Laboratory
NS	normal saline
NS1 Ag	non-structural protein 1 antigen
NSAIDs	non-steroidal anti-inflammatory drugs
OFI	other febrile illness
ORS	oral rehydration salts
pCO_2	partial pressure of carbon dioxide
PICC	peripheral inserted central catheter
PR	pulse rate
PT	prothrombin time
RCT(s)	randomised controlled trial(s)
RN	registered number
RRT	renal replacement therapy
RT-PCR	reverse transcriptase-polymerase chain reaction
SpO_2	oxygen saturation
TCM	traditional and complementary medicines
VBG	venous blood gas
VCD	virologically-confirmed dengue
WBC	white blood count
WHO	World Health Organization

ACKNOWLEDGEMENT

The members of CPG DG would like to express their gratitude and appreciation to the following for their contributions:

- Panel of external reviewers who reviewed the draft technically
- Technical Advisory Committee of CPG for their valuable input and feedback
- Health Technology Assessment and Clinical Practice Guidelines Council for approval of the CPG
- Dr. Izzuna Mudla Mohamed Ghazali on review of draft CPG as new Head of MaHTAS
- Dr. Chong Chin Eu on development of the CPG
- Matron Wong Wai Chee on retrieval of evidence
- All those who have contributed directly or indirectly to the development of the CPG

DISCLOSURE STATEMENT

The panel members of both Development Group and Review Committee had completed disclosure forms. None hold shares in pharmaceutical firms or act as consultants to such firms. Details are available upon request from the CPG Secretariat.

SOURCE OF FUNDING

The development of the CPG on Management of Dengue in Children (Second Edition) was supported financially in its entirety by the MoH.

MALAYSIAN HEALTH TECHNOLOGY
ASSESSMENT SECTION
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
62590 Putrajaya, Malaysia

e ISBN 978-967-19299-1-9