Ministry of Health
Sri Lanka

National Guidelines

Guidelines on Management of Dengue Fever & Dengue Haemorrhagic Fever in Children and Adolescents

SRI LANKA COLLEGE OF PAEDIATRICIANS

May 2023

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In Collaboration with the
Sri Lanka College of Paediatricians

Revised Edition
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Developed by in collaboration with

National Dengue Control Unit

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Message from the Director General of Health Services, Ministry of Health, Sri Lanka

Among many communicable diseases prevalent in the Asian region, dengue continues to be a major health problem having continuous epidemics in many countries, where in Sri Lanka an increasing number of children and adolescent patients are being reported.

The revised *"Guidelines on the Management of Dengue Fever and Dengue Haemorrhagic Fever in Children and Adolescents"*, developed by the Sri Lanka College of Paediatricians in collaboration with the National Dengue Control Unit of the Ministry of Health, is expected to provide the necessary knowledge for improved patient management and fill any gaps regarding the above topic. I take this opportunity to thank all experts who were involved in developing this guideline.

I am sure this document will help in strengthening case management in both public and private settings in Sri Lanka and have a positive influence in reducing the number of severe cases and deaths due to dengue among children and adolescents in Sri Lanka.

Dr Asela Gunawardena
Director General of Health Services

Message from the Deputy Director General (Public Health Services) 1, Ministry of Health, Sri Lanka

Dengue has become a major public health issue in recent years, with high morbidity, and considerable mortality. It remains a major health problem among children and adolescents as well.

Nevertheless, Sri Lanka has made notable progress in reducing the case fatality rate as a result of improved clinical care and various intersectoral activities on dengue prevention and control. *"Guidelines on the management of Dengue Fever and Dengue Haemorrhagic Fever in Children and Adolescents"*, developed in 2010 have greatly contributed to this achievement. In the context of further strengthening and reshaping clinical management with the latest evidence, the Sri Lanka College of Paediatricians in collaboration with the National Dengue Control Unit of the Ministry of Health has revised the guidelines.

The latest *"Guidelines on the Management of Dengue Fever and Dengue Haemorrhagic Fever in Children and Adolescents"* is a complete guide which could be utilized at all levels of health care providers in both public and private settings in Sri Lanka to provide evidence-based treatment to children and adolescents with dengue fever, dengue haemorrhagic fever and expanded dengue syndrome.

I appreciate the immense contribution of all the stakeholders; the Sri Lanka College of Paediatricians and National Dengue Control Unit in this endeavour.

Dr S.M. Arnold
Deputy Director General (Public Health Services) 1

Message from the President, Sri Lanka College of Paediatricians

In recent years Sri Lanka has successfully reduced the incidence and mortality from dengue infection in children and adolescents. Improved early detection and a standardized treatment protocol with enhanced diagnostics at all medical care institutions will further reduce mortality.

The need to revise the national dengue management guidelines was a long-standing need, and the Sri Lanka College of Paediatricians was pleased to lead the revision. We considered this project a top priority, and I thank all our members who contributed.

These guidelines provide recommendations for all Paediatricians and healthcare professionals caring for children with dengue infection. This clinical framework is intended to provide a structure for the outpatient and in-patient management. The recommendations within this guide are based on existing principles of management of dengue infection and expert consensus opinion in the absence of high-quality evidence.

I hope that these guidelines will assist clinicians in saving the lives of children with dengue in this country.

Professor Guwani Liyanage
President, Sri Lanka College of Paediatricians

Message from the Director, National Dengue Control Unit

Dengue fever and Dengue haemorrhagic fever have made a significant impact on disease morbidity and mortality in the country in the recent past. The out-patient and in-ward departments of most hospitals in Sri Lanka are observing an increase in the number of child and adolescent patients with dengue over the recent years. The growing number of children infected with the dengue virus can have poor outcomes if early identification and proper medical care are overlooked.

"Guidelines on the management of Dengue fever and Dengue haemorrhagic fever in Children and Adolescents" developed in 2010 have clearly helped to reduce the mortality due to Dengue. With the purview of updating the guidelines to meet emerging issues in patient management, the Sri Lanka College of Paediatricians and the National Dengue Control Unit of the Ministry of Health have revised the guidelines to supersede the previous document published by the Epidemiology Unit, Ministry of Health in 2010.

The new guideline for the *"Management of Dengue fever and Dengue haemorrhagic fever in Children and Adolescents"* is developed based on the best available evidence, which refers to the clinical management of dengue infection among children and adolescents in Sri Lanka. Thirty per cent of the dengue caseload currently belongs to the age group below 19 years, and the majority of the caseload will be addressed by this guideline. These revised national guidelines on the management of dengue fever and dengue

haemorrhagic fever in children and adolescents are intended to reach all levels of health care services to reduce morbidity and mortality due to dengue illness.

I congratulate and thank the team of Paediatricians and members of the National Dengue Control Unit who contributed towards developing the updated guideline.

Dr Nalin Ariyarathne
Director, National Dengue Control Unit

Contents

1 Introduction

Many patients infected with the dengue virus remain asymptomatic (approximately 90%). Others after an incubation period of approximately 6 (3-14) days, develop a febrile illness which could turn out to be one of the following (Figure 1.1):

1. Undifferentiated febrile illness
2. Dengue Fever (DF)
3. Dengue Haemorrhagic Fever (DHF)
4. Expanded Dengue Syndrome

Differentiation between DF and DHF is difficult during the initial few days.

1.1 Undifferentiated fever

Those who have been infected with the dengue virus, especially for the first time (i.e., primary dengue infection), may develop a simple fever indistinguishable from other viral infections. Undifferentiated/asymptomatic individuals will still be transmitting the disease.

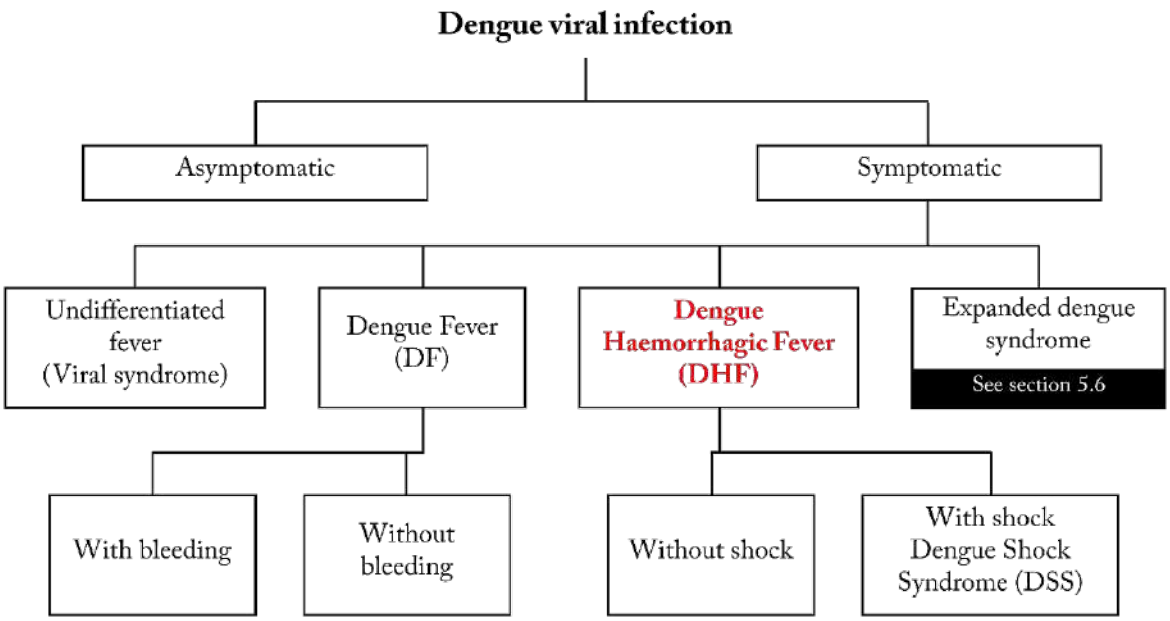


Figure 1.1 Classification of dengue viral infection.

1.2 Case Definitions of DF and DHF

1.2.1 Dengue Fever (DF)

Clinical criteria that define DF include 2-7 days of illness with high fever, headache, retro-orbital pain, myalgia, arthralgia/ bone pain, rash and haemorrhagic manifestations e.g.: positive tourniquet test or petechiae, with no evidence of plasma leakage.

1.2.2 Dengue Haemorrhagic Fever (DHF)

In the first few days of illness in DHF patients' signs and symptoms are similar to that of DF. However, in DHF the patients will develop features of plasma leakage. The case definition of DHF includes:

1. High fever or recent history of acute fever
2. Haemorrhagic manifestations
3. Thrombocytopenia of $\leq 100 \times 10^9$/L
4. Objective evidence of plasma leakage

In patients with definite evidence of plasma leakage, the presence of haemorrhagic manifestations including a positive tourniquet test is not essential for diagnosing DHF. However, the term **"DHF"** is retained because these patients may develop overt or concealed bleeding during the course of the illness.

Rarely there are instances where patients would start leaking before their platelet count drops below 100×10^9/L.

2 Natural Course of the Illness

Dengue infection is a dynamic disease. Its clinical course changes as the disease progresses and consists of three stereotypic phases.

- Febrile phase
- Critical phase
- Convalescent phase

2.1 Febrile phase (common to both DF & DHF)

Dengue fever and dengue haemorrhagic fever are two different clinical conditions from the beginning. They look very similar in the first few days. Following are some features observed in the febrile phase.

- High fever 2-7 days.
- Facial flushing, skin erythema, headache, retro-orbital pain, myalgia, arthralgia, nausea, and vomiting.
- Haemorrhagic manifestations include petechiae, purpura, gum or nasal bleeding, gastrointestinal bleeding, haematuria, menorrhagia, and positive tourniquet test.

- Total white cell count could be high or normal initially, and in the majority, the counts drop towards the latter part of the febrile phase to levels below 5×10^9/L.
- Platelet count is normal initially and will come down to $<100\times10^9$/L in about half of DF and almost all of DHF patients.
- Tender hepatomegaly favours a diagnosis of DHF.

It is often difficult to differentiate DF from DHF in the febrile phase of the illness. Therefore, suspected DF and DHF patients should be closely followed up in order to identify the DHF patients going into plasma leakage phase to ensure correct fluid management during the critical phase.

3 Diagnosis & Outpatient Management

3.1 Suspecting dengue infection in a child with acute onset of fever

The following features would suggest dengue infection.

- Headache & retro-orbital pain
- Nausea or vomiting
- Arthralgia & myalgia
- Flushed appearance of the skin
- Rash (diffuse, erythematous, macular)
- Positive tourniquet test* (negative test does not exclude the possibility of dengue)
- Leucopenia (WBC $<5\times10^9$/L)
- Platelet count $< 150\times10^9$/L

**tourniquet test is done by measuring the blood pressure using a cuff of appropriate size for each patient (the width is to cover 2/3 of the upper arm). Raise the pressure to midway between systolic and diastolic blood pressure for 5 minutes. Release the pressure and wait for one minute before reading the result. A positive test is considered when there are ≥ 10 petechiae per square inch.*

Some patients may present with respiratory symptoms such as cough, rhinitis or injected pharynx and gastrointestinal symptoms

such as abdominal pain, diarrhoea or vomiting with or without the classical clinical presentation described above.

3.1.1 Dengue NS1 Antigen test

- This is useful for early diagnosis of dengue infection.
- When available it should be performed in the first few days of the illness. Its positivity is highest in the first 3 days of fever.
- The test is likely to be positive more in the primary than the secondary dengue infections.
- **Negative NS1 test does not exclude dengue infection.**

3.2 Criteria for admission

Medical officers are expected to use **clinical judgment** regarding admission. However, it is essential to admit the following patients:

- All patients with a platelet count of $\leq 150 \times 10^9$/L
- Increase in HCT >10%
- All patients with any of the following **warning signs** mentioned in Box 3.1

Consider early admission in the categories of patients stated in Box 3.2.

Box 3.1 Warning signs of dengue

Warning signs

- Persistent vomiting
- Lethargy, restlessness, and drowsiness
- Mucosal bleeding
- No urine output for 6 hours
- Severe abdominal pain
- Cold extremities and features of shock
- Clinical fluid accumulation: pleural effusion, ascites
- Tender hepatomegaly

Box 3.2 Categories of patients needing early admission

Patients needing early admission

- Infants
- Obese patients
- Patients with major co-morbidities / medical problems (such as diabetes, nephrotic syndrome, chronic renal failure, haemolytic diseases, poorly controlled asthma)
- Adverse social circumstances

3.3 Management of children who do not need admission

- Ensure adequate oral fluid intake (maintenance fluid). This should consist of oral rehydration fluid, king coconut water, other fruit juices, kanji or soup rather than plain water. Exclude red and brown drinks.
- Adequate physical rest (keep at home)
- Tepid sponging for fever
- Paracetamol (Do not exceed 60mg/kg/24hrs). Warn that the fever may not fully settle with paracetamol and advise not to take in excess.
- Anti-emetics and H2 receptor blockers if necessary.
- **All NSAIDs in any form and steroids** should not be prescribed.
- **First FBC** should be done on completion 48 hours from the onset of fever/illness. If the platelet count is above 200×10^9/L, it should be repeated daily. If the platelet count is below 200×10^9/L, it should be repeated twice a day. However, the clinician could decide the frequency of FBC based on clinical judgment.
- The patient needs admission if the platelet count drops below 150×10^9/L.
- **Advise** parents to **return immediately** for review if any of the following occur:
    - Clinical deterioration with settling of fever
    - Inability to tolerate oral fluid
    - Severe abdominal pain/ vomiting
    - Cold and clammy extremities

- Bleeding manifestations including inter-menstrual bleeding or menorrhagia
- Not passing urine for more than 6 hours
- Behaviour changes: confusion, restlessness, lethargy, irritability

4 In-ward Management of DF/DHF

4.1 Management of patients still in the febrile phase

- It is recommended to keep a cannula in situ.
- Ensure adequate fluid intake.

  Oral fluids are recommended if oral intake is good. If the patient is vomiting or dehydrated and not taking adequate oral fluid, consider intravenous (IV) fluids. Total fluid requirement (oral + IV) will depend on the degree of dehydration. The rate of infusion has to be reduced soon after the correction of dehydration.

  When IV fluids are needed during the **febrile phase**, use **5% dextrose in 0.9 % NaCl.**
- Adequate physical rest.
- Do not exceed 60mg/kg/24hrs of paracetamol.
- **Avoid all NSAIDS and steroids.**

4.1.1 Monitoring during the febrile phase

- Use the **monitoring chart I** (febrile phase) when the platelet count is below 150×10^9/L or when warning signs are present – (Annexure III)
    - Temperature
    - Vital parameters - pulse, blood pressure (both systolic and diastolic), respiratory rate, capillary refill time and urine output 4 hourly (may need more frequent monitoring depending on the clinical situation)
    - Intake and output (maintain a urine output above 0.75ml/kg/hr)
    - FBC twice daily
    - Inward PCV or Hct twice daily, more frequently when clinically indicated

4.2 Critical/ Leaking phase

Key points

- The critical phase is heralded by the onset of plasma leakage.
- Platelet count dropping below 100×10^9/L is the most useful and the earliest indicator that the patient is probably entering the critical phase.
- Plasma leakage is the main cause of shock. Prolonged shock leads to bleeding, multi-organ failure and death.

Key points- contd.

- Rapid drop in temperature may occur as the patient enters the critical phase (In DF and other viral infections as fever subsides the patient's general condition improves, but in DHF it may get worse). During the early phase of plasma leakage, many patients continue to have a fever with a lower intensity.
- The rate of leaking is highly variable from patient to patient.
- The leak usually starts slowly, increases gradually, reaching a peak usually around 24 hours then slows down and ceases altogether at the end the of leakage phase (usually within 48 hours from the onset). But sometimes it may last less than 48 hours or may extend even beyond 48 hours.
- Identifying the beginning and the end of the critical phase is a key factor in guiding fluid therapy in DHF.
- It is important to monitor patients hourly.
- If the patient presents in shock, the patient may have been in critical phase for a significant period of time, probably up to 24 hrs. Therefore, there is a possibility that some patients will have approximately another 24 hours remaining in the critical phase.
- If a patient is already dehydrated during the latter part of the febrile phase (due to vomiting, diarrhoea or lack of adequate fluid intake) and hydration is not corrected he or she might go into shock before 24 hours. In this instance the remaining duration of the critical phase may be more than 24 hours.
- However, until the very last stage of shock, a patient appears conscious and alert. If the patient is not closely monitored early shock could be missed.

4.2.1 Early detection of the critical phase (plasma leakage)

- Platelet count reaching towards 100×10^9/L should alert the clinician that the patient may be in or entering the critical phase of DHF.

  A patient with a platelet count below 100×10^9/L may be in one of the following three categories:
  - DF
  - DHF febrile phase
  - DHF critical phase

- A **progressively rising haematocrit** (Hct) towards 20% from the baseline suggests that the patient may have entered the critical phase. Patients who have received IV fluids (sometimes even with excessive oral fluids) or bleeding may not show a rise in Hct.

  The 20% rise in Hct is calculated by taking into consideration the baseline haematocrit. For example, if the initial Hct is 35%, an increase up to 42% indicates a 20% increase. When the baseline Hct is not known, it is safe to assume that the baseline is around 35% and may be slightly lower in young children and infants, and higher in older children. The infants may have a lower Hct due to physiological and iron deficiency anaemia.

- **Objective evidence of fluid leak**

  Limited ultrasound scan (Chest and abdomen) to detect peri cholecystic collection of fluid or ascites and pleural effusion.

- When in doubt, the following **biochemical parameters*** would suggest that the patient is in the critical phase:
    - Serum albumin of <3.5g/dl
    - Serum cholesterol of <100mg/dl (non-fasting)

**Not routinely recommended due to the costs involved, but useful when there is doubt. Since the baseline values may vary, a significant drop during the illness is suggestive of plasma leak*

4.2.2 Monitoring during the critical phase

The total duration of leaking is highly variable from patient to patient, and it is of paramount importance to monitor frequently and very carefully during this phase.

Hence, it is important to maintain monitoring charts. Please refer to the following annexures.

- **Annexure IV**: Monitoring chart II for patients during the critical phase
- **Annexure V**: Monitoring chart III for patients during shock

Monitoring should include total fluid administered (Oral+ IV) and the following clinical parameters:

- Pulse- Rate and Volume*
- Blood pressure (BP) and pulse pressure* (the aim is to maintain a pulse pressure close to 30mmHg during the entire critical phase)
- Capillary refill time (CRFT)*
- Warmth/coldness of peripheries*

- Respiratory rate*
- Evidence of overt bleeding and quantification
- Regular inward PCV measurements** (6 hourly) in non-shock patients and more regularly in patients who develop shock are essential.

**Vital signs should be monitored hourly when the patient is stable during the critical phase. However, the frequency of monitoring should be increased to every 15 minutes when the patient is leaking rapidly or while in shock until haemodynamic stability is achieved.*

***When making decisions trend of PCV is important rather than a single value. (Please note that there is a difference in venous Hct and capillary PCV. Thus, try to adhere to either venous or capillary whenever possible.)*

***If venous PCV is performed make sure that strict sterile techniques are used.*

- Fluid input and urine output should be calculated using either the actual weight, the ideal weight for height or the adjusted body weight of the child in the following manner.
  - If the **actual weight is less than the ideal weight** use the **actual weight.**
  - If the actual weight is **a little more than the ideal weight** for the height, use the **ideal weight**
  - If there is a **marked discrepancy between the ideal weight and the actual weight** (≥2SD weight for height or BMI) then in such instances, it is best to use the **adjusted body weight (Figure 4.1)**

Calculation of the adjusted body weight

$$\text{Adjusted body weight} = 0.4\left(\text{Actual body weight} - \text{Ideal body weight}\right) + \text{Ideal body weight}$$

Figure 4.1 Calculation of the adjusted body weight

- Indications for catheterization:
  - All high-risk patients during critical phase
  - Patient with shock
  - Patient with complications

Clinical decisions should be taken based on the combination of parameters but not a single parameter.

Golden rules in the management of the critical phase

- Early detection of beginning and recognizing the end of plasma leakage
- Meticulous monitoring
- Matching the fluid administration to the fluid leak
- Anticipation, early detection and treatment of concealed bleeding and other complications

4.3 Fluid management in the critical phase

4.3.1 Calculation of the fluid quota for the critical phase

- Fluid quota is **only a guide** for the management of dengue patients during the critical period of DHF.
- Patients managed using fluid within this safe quota, are less likely to develop fluid overload.
- The amount of fluid recommended during the entire critical phase (irrespective of its length) should be **Maintenance + 5% of weight (50ml/kg)**. Weight should be calculated as given in section **4.2.2**
- All patients will not need the full quota of M+ 5% fluid, and many may need less than this, as the rate, peak and duration of leaking are variable from patient to patient. Some patients may need fluid above the calculated fluid quota to maintain vital parameters.

Examples of calculation of fluid quota

Calculation of maintenance fluid

100ml/kg for the first 10 kg

+ 50 ml/kg for the next 10 kg

+ 20 ml/kg for balance weight

Calculation of the Deficit:

5% body weight = 50ml x body weight (kg)

E.g., 1

A 7-year-old boy with a weight of 22 kg. The ideal body weight is 24 kg. Use actual body weight for calculations.

Maintenance: 100 x 10 + 50 x 10 + 20 x 2	=	1540 ml
Deficit: 5%= 50 x 22	=	1100 ml
Total fluid quota = 1540 ml + 1100 ml	=	2640 ml

E.g., 2

An 8-year-old boy with a body weight of 48 kg. His BMI is more than 2SD. His height is 145 cm. The ideal body weight for his height is 37 kg.

In this situation, consider adjusted body weight for fluid calculations.

Adjusted BW = 0.4 x (actual BW- ideal BW) + Ideal BW

= 0.4 x (48 – 37) + 37

4.3.2 Guide to the rate of fluid administration: In a patient presenting without SHOCK

- All patients entering the critical phase need IV 0.9% NaCl + 5% dextrose or Hartmann's solution + 5% dextrose through IV cannula (largest possible size for the age) in addition to oral fluid. The initial fluid requirement (oral + IV) is 1.5 ml/kg/hr. Those who can drink well may be given IV fluids as 0.5ml/kg/hr to 'keep vein open' and the balance as oral.
- When "dextrose saline" is not available, such a solution could be made by adding 50ml of 50% dextrose to 450ml of normal saline.
- Calculate the total fluid quota for the patient (M+ 5%) at the beginning of the critical phase.
- Subsequent rate of infusion will depend on the rate of leak judged by pulse rate, BP, pulse pressure, CRFT, PCV/Hct and UOP. Keep in mind that the rate of leaking will vary from patient to patient, and even in the same patient from time to time. (Figure 4.2)
- Calculate the UOP in ml/kg/hr, at each void. In a patient who is stable, **hourly urine output is the best guide to deciding the rate of fluid infusion**. A urine output of **0.75 -1 ml/ kg/hour** is sufficient to maintain renal functions during the critical period. **UOP above 1 ml/kg/hour indicates that the fluid rate is too high. UOP less than 0.75ml/kg/hr suggests an inadequate fluid rate**.
- Consider **early catheterisation** if monitoring urine output is difficult. Catheterisation is **essential in high-risk categories**.

- If a higher rate of maintenance fluid is needed to maintain the clinical parameters, consider Dextran 40.

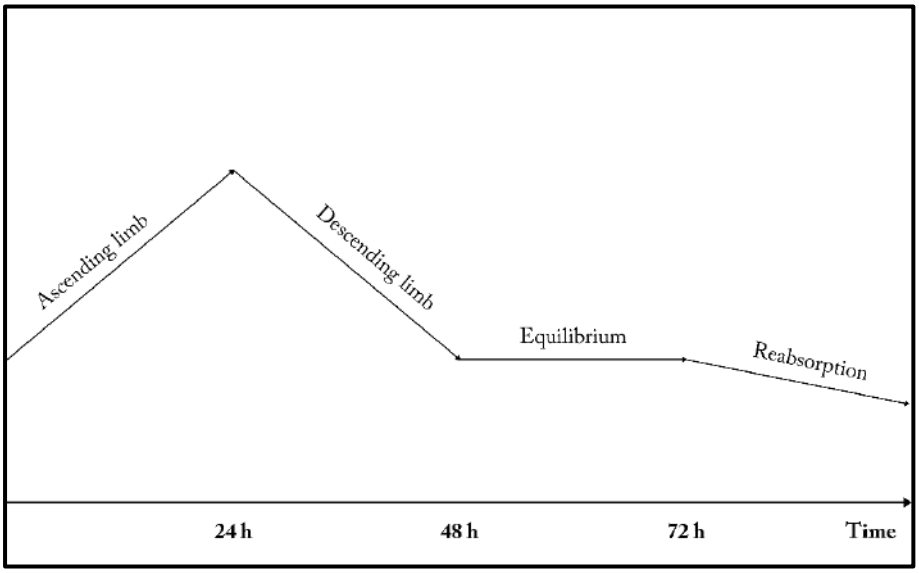


Figure 4.2 Natural course of DHF: The fluid rate should be adjusted according to the rate of leaking.

Figure 4.2 is a schematic diagram describing the pattern of leaking and the fluid requirement in a patient with classic dengue haemorrhagic fever. The leaking will start gradually and comes to a peak and then starts slowing down. However, this pattern may not be seen in all patients. Individual patient's fluid rate will depend on the rate of leaking as determined by the clinical parameters.

- It is also worth noting that although it is possible to manage some patients with less than M + 5% volume of fluid, it should always be done only by maintaining a urine output of 0.75 -1 ml/kg/hour and adequate pulse pressure throughout the critical phase with frequent monitoring.

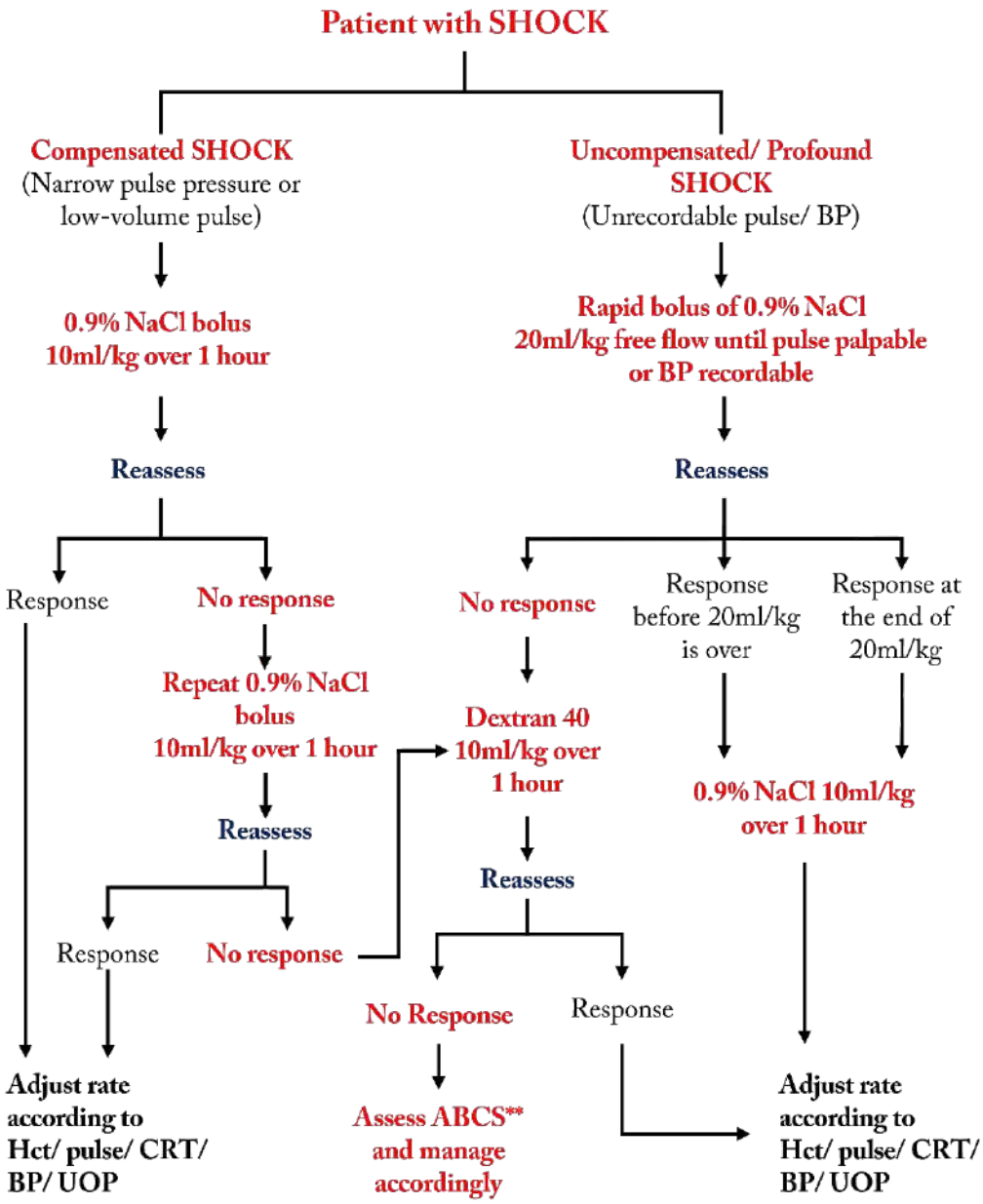
4.3.3 Guide to the rate of fluid administration: In a patient presenting WITH SHOCK

- The following clinical features are observed in shock;

Clinical features of SHOCK

- Sweating
- Dizziness
- Abdominal pain
- Restlessness
- Altered conscious level
- Cold extremities
- Prolonged capillary refill time >2 sec
- Unexplained tachycardia
- Low volume pulse
- Narrowing pulse pressure <20 mmHg or hypotension

- In general, shock occurs at the peak of leaking, around 24 hours from the onset. It can be assumed that the remaining time period of leaking is another 24 hours. However, it could be more or less than 24 hours and fluid administration should be guided by the clinical parameters. The maximum amount of fluid that could be used in this instance is M+5%.
- The algorithm for the management of dengue shock is shown in figure 4.3.



All patients in shock: call for help, give oxygen, keep flat/ head low position

** A: Acidosis, B: Bleeding, C: Calcium & electrolytes, S: Sugar

Figure 4.3 Algorithm for the management of shock in dengue haemorrhagic fever

4.3.4 Indications for colloids (Dextran 40)

- During rapid leaking, 0.9% saline may leak out of the intravascular compartment within 1-2 hours of administration. Even fluids like fresh frozen plasma (FFP) will readily leak. Dextran 40 will remain longer.

- The following are the indications for colloids;
    - During the management of shock, after administering a total of 20 ml/ kg of crystalloids if the vital signs are unstable
    - During the management of shock in a patient who has already received a significant amount of fluid and is at risk of fluid overload.
    - When the amount of fluid received over a period appears to be in the direction of exceeding M + 5% deficit

Key points in colloid administration

- Dextran 40 is recommended **only during the critical phase**.
- It should only be given at a rate of **10ml/Kg /hour** over a maximum period of one hour.
- Dextran may sometimes interfere with grouping and cross-matching of blood. It is advisable to preserve a sample of blood for grouping and cross-matching before administering Dextran.
- PCV should be measured before and after administering Dextran 40. Expected PCV drop is 8-10 from the pre-infusion value. If the drop is more than 10, suspect concealed bleeding.
- One could use up to 3 boluses of Dextran 40 (each as 10ml/kg/hour) during a 24-hour period (6 doses within 48 hours).

5 Complications of Dengue

Complications of dengue are usually uncommon with proper fluid management, monitoring and timely interventions. The following are some of the complications that can occur.

1. Prolonged shock
2. Fluid overload
3. ABCS (acidosis, bleeding, hypocalcaemia/ electrolyte imbalance, hypoglycaemia)
4. Secondary bacterial infection
5. Death

Following high-risk patients are more likely to develop complications:

1. Infants
2. Obese patients
3. Underlying diseases
4. Expanded Dengue Syndrome
5. Pregnancy

5.1 Prolonged shock

- Delayed diagnosis/ delayed resuscitation and late presentation are the common reasons for prolonged shock.
- Shock lasting > 4 hours (prolonged shock) will lead to organ failure and the prognosis of such a patient is poor.
- Organ failure, especially liver and kidney should be avoided at all costs. Survival is poor in multiorgan failure.

5.2 Fluid overload

5.2.1 Causes of fluid overload

- Not paying attention to the already used and the remaining fluid quota during the management of the leaking phase.
- Continuing IV fluids beyond the critical phase unnecessarily.
- Not using colloid and blood when indicated.
- Not adjusting the fluid to match the rate of leaking.
- Over-administration of fluids without correcting associated complications such as acidosis, bleeding and hypocalcaemia (ABCS, see section 5.3)
- Use of hypotonic fluids.

5.2.2 Features of fluid overload

- Early signs and symptoms include cough, puffy eyelids, distended abdomen (ascites), tachypnoea, and dyspnoea.

- Late signs and symptoms include moderate to severe respiratory distress, wheezing (an early sign of interstitial pulmonary oedema), tachycardia, gallop rhythm and lung crepitations. Restlessness/agitation and confusion are signs of hypoxia and impending respiratory failure.

5.2.3 Management of fluid overload

- Assessment of the intravascular volume status of the child is crucial when managing fluid overload. The intravascular compartment may be depleted despite the patient being fluid overloaded, especially during the critical phase.
- A patient with fluid overload can be in any of the following scenarios.

1. **Fluid overload with depleted intravascular volume status**

   Giving furosemide alone at this stage is dangerous. Furosemide can be administered only after restoring the intravascular volume by giving a bolus of Dextran 40. The patient should be on continuous monitoring during this period for 1-2 hours.

2. **Fluid overload with good intravascular volume status**

   Furosemide alone may be given. However, close monitoring is still essential.

- DHF patients are **very sensitive to furosemide**. So the dose should be **smaller than the usual dose (0.1 mg/kg as a bolus)**. This can be repeated if necessary.

5.3 ABCS

- Consider ABCS when there is no improvement despite adequate fluid therapy.

A: **A**cidosis
B: **B**leeding
C: **C**alcium and electrolytes
S: **S**ugar

5.3.1 Acidosis

- Acidosis is not uncommon in profound shock, and prolonged acidosis makes patients more prone to DIC which contributes to massive bleeding.
- Metabolic acidosis in DHF is mainly due to inadequate tissue perfusion and should improve with adequate fluid resuscitation. Giving NaHCO3 without fluid resuscitation can lead to intracellular acidosis.
- If the patient remains unstable and pH remains below 7.25 or HCO_3 is less than 15 mmol/L after 2 crystalloid boluses and one colloid bolus, $NaHCO_3$ can be considered.
- When facilities are not available for a blood gas analysis, one may use empirical $NaHCO_3$ 1ml/kg slow bolus (max 50ml) diluted in an equal volume of normal saline.

5.3.2 Bleeding

- Bleeding in dengue can be concealed or overt and may contribute to shock. It should be treated with **packed red cells**, and **not with other blood products** eg. platelets/ FFP
- Concealed bleeding should be suspected when,
  - Hct drops without clinical improvement.
  - Severe metabolic acidosis and end-organ dysfunction (liver or renal) despite adequate fluid replacement.
  - Minimal increment of Hct in a child with shock
  - Exaggerated drop of Hct after a 10ml/kg bolus of dextran (>10)
- Use of Packed Red Cells (PRC)
  - Use **PRC at 5ml/kg over one hour** and repeat only if needed.
  - 5ml/kg of PRC will increase Hct by 5 points. (E.g.: 30→35)
  - Even if bleeding is likely, and **if Hct is >45%**, do not give blood without bringing down the HCT first by giving dextran.

Note:

- Even with bleeding, the Hct drop may take time (4-5 hours). When the patient does not show improvement, it is important to repeat Hct frequently.
- Haemoglobin level may remain normal despite significant blood loss.

5.3.3 Hypocalcaemia

- Hypocalcaemia is common in DHF.
- When a When a dengue patient has a convulsion, one reason could be hypocalcaemia.
- Serum calcium level should be measured in complicated dengue patients.
- When to give calcium?
    - Give empirical calcium if the patient is having complications and deteriorating or not showing expected improvement with fluid.
    - Dose 1ml/kg (maximum 10 ml) of 10% calcium gluconate diluted in an equal volume of 0.9% saline as a slow IV bolus over 15-20min (look for bradycardia).
    - Can be repeated every 6 hours if the patient is not improving.

5.3.4 Hypoglycaemia

- **Prevention of hypoglycaemia**: As hypoglycaemia is common in DHF, one should try to prevent it by using 0.9% NaCl with 5% dextrose as maintenance fluid.
- **Treatment of hypoglycaemia**: If the capillary blood sugar is less than 70 mg/dL administer 10% dextrose, 2 ml/kg followed by 0.9% NaCl with 5% dextrose infusion.

5.3.4 Hyponatraemia

- Hyponatraemia may occur due to the inadvertent use of hyponatraemic fluids.
- When a dengue patient has a convulsion, it could be due to hyponatraemia.
- Prevention of hyponatraemia:
  - Use 0.9% NaCl as intravenous fluids.
  - Do not use hyponatraemic IV fluids (e.g. 0.45% NaCl).
  - Use ORS, fruit juices and kind coconut water as oral fluids.
  - Do not use water alone as oral fluids.
- Management of hyponatraemia:
  - If symptomatic:

    3% NaCl 3-5ml/kg as a slow IV bolus over 20 minutes through a larger vein
  - If asymptomatic,

    Fluid restriction itself should correct hyponatraemia. Repeat electrolytes regularly.

5.4 Encephalopathy

Encephalopathy in DHF is mainly due to hepatic encephalopathy. The basic principle of management is maintaining adequate Cerebral Perfusion Pressure (CPP) by maintaining Mean Arterial Pressure (MAP) and reducing Intra Cranial Pressure (ICP).

$$\mathbf{CPP = MAP - ICP}$$

The following are recommended in the management.

- Adequate oxygenation (intubation may be needed for those with respiratory failure or low GCS)
- Fluid management
    - Aim for a normovolaemic state.
    - Switch to colloids early.
- Maintain MAP
    - Adequate fluids as above.
    - Inotropes and Vasopressors
- Reduce ICP
    - Keep head in midline position.
    - Elevate the head end of the bed to 30- 45 degrees.
    - Avoid neck flexion.
    - 3% NaCl 3-5 ml/kg slow boluses.
    - Controlled hyperventilation (maintain $PaCO_2$ between 30 to 35 mmHg)
    - Maintain blood sugar level > 70 mg/dL.
    - Maintain sodium and potassium at normal levels.
- Use IV phenobarbitone to reduce cerebral metabolism and to control seizures.
- When liver enzymes are markedly elevated, suspect hepatic encephalopathy.
    - Look for concealed bleeding and transfuse PRC accordingly.
    - Start liver failure regimen.

5.5 Haemophagocytic lymphohistiocytosis (HLH)

- HLH is a rare multisystem disorder in children which is known to occur following dengue infections.
- HLH in DHF is treatable if identified early. Mortality is very high with delayed diagnosis.
- HLH should be suspected when the patient is having ongoing fever with multisystem involvement.
- Bone marrow biopsy is necessary for the diagnosis.
- Early diagnosis & treatment with steroids (dexamethasone/ methylprednisolone) will completely cure the disease.
- When in doubt better to discuss with haematologist and paediatric oncologist.

5.6 Expanded Dengue Syndrome

- There have been some reports of 'unusual dengue' where the patients had developed clinical manifestations which are different to what is usually expected in DF or DHF.
- These include encephalopathy and other neurological manifestations, and organ failure such as hepatic, renal, cardiac and other isolated organ involvement. These could be explained as complications of profound shock or associations of underlying comorbidities or co-infections.
- It is important to note that expanded dengue syndrome is a rare entity, and patients should not be categorized into this group without detailed and careful evaluation.

5.7 Causes of death in dengue

The **main causes** of death are,

- prolonged shock
- fluid overload
- massive bleeding
- unusual manifestations e.g., encephalopathy
- dual infection/ secondary sepsis

5.6 Adjunct therapy

5.6.1 Platelet transfusion

Indications for platelet transfusion

- Prophylactic platelet transfusion is **NOT** recommended.
- Thrombocytopaenia is unlikely to produce spontaneous significant bleeding in DHF/DSS. Even with a very low platelet count, do not give platelets unless there is significant bleeding.

5.6.2 Tranexamic acid

- Tranexamic acid is an anti-fibrinolytic agent that preserves and stabilizes fibrin's matrix structure and thereby helps to control bleeding.
- It can be recommended to control menstrual bleeding and gastrointestinal bleeding in dengue.
- Haematuria is a contraindication for its use.
- However, there are no control studies on its use in dengue.

5.6.3 Norethisterone

- This can be administered to control menstrual bleeding along with tranexamic acid.

5.6.4 Recombinant factor VII

- Recombinant factor VII is not routinely indicated.
- The need should be discussed with a consultant haematologist.

5.6.5 Inotropic support

- **NOT INDICATED** in the management of uncomplicated DHF.

5.6.6 Steroids/ IV immunoglobulin

- Use of steroids (hydrocortisone, dexamethasone and methylprednisolone) and/or intravenous immunoglobulin is **NOT** recommended.

5.6.7 Fresh frozen plasma transfusion (FFP)

- Transfusion of FFP is **NOT** recommended.

6 Convalescent (Recovery) phase

The convalescent phase usually lasts 2-5 days for both DF and DHF. In DHF, the convalescent phase starts at the end of the critical phase and the extravasated fluid will be reabsorbed during this period.

6.1 Features of convalescent phase

- Improved general well-being with the following;
  - **A**: Improved **A**ppetite
  - **B**: **B**radycardia
  - **C**: **C**onvalescent rash (typically appears as white patches on a red background) and itching
  - **D**: **D**iuresis
- The definitive indicator that the patient has entered the convalescent phase is the progressive rise of platelets.

6.2 Complications during convalescence

- Fluid overload (Management discussed in 5.1)
- Nosocomial infections e.g., pneumonia, urinary tract infection, thrombophlebitis, sepsis.

6.3 Discharge from the hospital

- The following criteria should be fulfilled before discharge from the hospital.
    - No fever for at least 36-48 hours without the usage of antipyretic drugs.
    - At least two days have lapsed after recovery from shock.
    - Good general condition with improving appetite.
    - No distress from pleural effusions or ascites.
    - Platelet count is progressively rising, and preferably above 50 x 10^9/L.
    - Liver enzymes are improving.
    - No other complications.

7 Laboratory Diagnosis

Laboratory diagnosis of dengue is achieved by isolation of the virus, detection of antigen, detection of the genome or by detection of antibodies. Dengue virus can be isolated from a blood sample collected during the first 4 -5 days of illness. Virus isolation and typing are mainly used in research and surveillance.

Detection of the genome by PCR from blood can be performed during the acute phase of the illness and used in routine diagnosis as well as in research and surveillance. However, the cost of the assay and its availability limit its use in clinical practice. Dengue serotypes can be identified from virus isolation and detection of the genome by PCR.

Detection of NS-1 antigen from blood (by ELISA or by immunochromatography) is a useful method which can be performed during the first few days of fever. The highest positivity is observed within the first 3 days. The sensitivity of these tests varies and ranges between 60% to 90%. Therefore, a negative test result will not exclude dengue illness and treating the patient on clinical grounds is important.

Detection of Dengue IgM and IgG are performed on blood samples collected preferably after the 5th day of illness. The range of tests available for the detection of antibodies includes ELISA, immunochromatography and haemagglutination inhibition assay with varying sensitivity and specificity. Detection of IgM antibodies or demonstration of a four-fold rise in IgG antibodies (seroconversion) confirm the diagnosis of dengue.

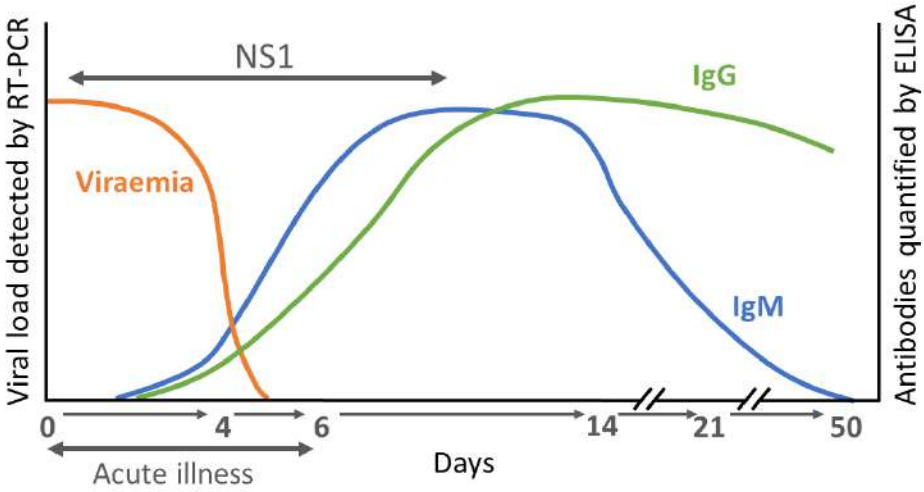


Figure 7.1 **Dengue virus, antigen and antibody response used in the diagnosis** (Reproduced from Guzman et al.)

8 Transferring a patient to another institution

Facilities in some peripheral hospitals may not be adequate to manage a patient with DHF. Furthermore, a patient in prolonged shock may need intensive care facilities. Hence, these patients may be transferred to an institution with such facilities after stabilising.

If the patient has signs of shock, resuscitate the patient as per the algorithm in figure 4.3 before transfer. Correct hypoglycaemia and continue IV fluids and oxygen during the transfer. Ensure that the receiving paediatrician is kept informed.

Proper resuscitation before transferring is important. A medical officer and a nurse familiar with the patient should accompany the patient. Adequate information regarding the patient should be provided in the transfer form and this should include daily fluid balance, investigation results and treatment given. It is important to send copies of the temperature and monitoring charts as well.

9 Management of Dengue during infancy

DHF has been documented in primary infection among infants whose mother was infected during pregnancy. Vertical transmission has been reported leading to neonatal DF or DHF.

Infants who develop primary dengue infection may have a simple fever indistinguishable from other viral infections. It may have a wide range of clinical presentations. Maculopapular rashes (blanching erythema) may accompany the fever or may appear during defervescence. Upper respiratory and gastrointestinal symptoms are common. They may also present with febrile convulsions.

Splenomegaly has been observed in young infants (especially under six months) clinically or by ultrasound scan. Infants have less respiratory reserves, therefore would not tolerate large effusions or pulmonary oedema. They are more susceptible to liver impairment and electrolyte imbalance leading to hyponatremia.

DHF in infancy may not have leucopenia. Often total WBC is > 10 x 10^9/L. Infants can have physiological or iron deficiency anaemia and therefore their baseline Hct could be lower than older children. Liver enzymes are elevated early in the disease. Electrolyte abnormalities including hyponatraemia are also common. They are more prone to develop hypoglycaemia, so regular monitoring of blood sugar is important.

Key points in managing Dengue in infancy

- Infants may have a shorter duration of plasma leakage (lasts for < 24 hours - may be as short as 6 to 12 hours) and usually respond quickly to fluid resuscitation. Optimal fluid management from the entry into the critical phase is vital. Infants should be evaluated frequently for oral fluid intake (i.e., breastfeeding) and urine output (hence the early need for catheterization).
- 0.9% saline + 5% dextrose should be used as the crystalloid in all infants.
- Dextran 40 should be considered early when high rates of crystalloids are required.
- Discontinue IV fluids soon after the leaking phase as the risk of fluid overload is high.
- Continuing on-demand breastfeeding is recommended.

10 Management of Dengue in obese children

Obesity is a high-risk category in DHF. Obese children are more prone to go into shock and fluid overload. Therefore, careful fluid management is vital. The following are recommended to prevent both shock and overload.

- Calculate fluid for the **adjusted body weight.**
- Calculate UOP for the **adjusted body weight**.
- Catheterize early.
- Consider colloid early if high rates of crystalloids are needed or poor response to crystalloids.
- Consider blood transfusion early when indicated.
- Empirical calcium gluconate to prevent hypocalcemia
- **Consider expert opinion early if the patient is not improving.**

Calculation of the adjusted body weight

$$\text{Adjusted body weight} = 0.4\left(\text{Actual body weight} - \text{Ideal body weight}\right) + \text{Ideal body weight}$$

Figure 10.1 Calculation of the adjusted body weight

Annexures

Annexure I:

Ideal body weight for height: Boys

(Ideal weight taken as the weight for height on the 50th centile)

Height (cm)	Ideal Body Weight (kg)	Height (cm)	Ideal Body Weight (kg)
100	15.50	138	31.50
101	15.75	139	32.33
102	16.00	140	33.00
103	16.33	141	34.00
104	16.66	142	35.00
105	17.00	143	35.50
106	17.33	144	36.33
107	17.66	145	37.00
108	18.00	146	38.00
109	18.50	147	39.00
110	18.75	148	39.66
111	19.00	149	40.50
112	19.50	150	41.33
113	20.00	151	42.00
114	20.25	152	42.66
115	20.50	153	43.33
116	21.00	154	44.00
117	21.33	155	45.00
118	21.66	156	45.50
119	22.00	157	46.33

Height (cm)	Ideal Body Weight (kg)	Height (cm)	Ideal Body Weight (kg)
120	22.50	158	47.00
121	22.75	159	47.75
122	23.33	160	48.50
123	23.50	161	49.00
124	24.00	162	49.75
125	24.50	163	50.50
126	25.00	164	51.00
127	25.33	165	52.00
128	25.66	166	53.00
129	26.00	167	53.75
130	26.66	168	54.50
131	27.33	169	55.25
132	27.66	170	56.33
133	28.33	171	58.00
134	28.66	172	58.75
135	29.50	173	60.00
136	30.00	174	62.00
137	30.66	175	64.00

Annexure II:

Ideal body weight for height: Girls

(Ideal weight taken as the weight for height on the 50th centile)

Height (cm)	Ideal Body Weight (kg)	Height (cm)	Ideal Body Weight (kg)
90	13.00	127	25.25
91	13.25	128	26.00
92	13.50	129	26.33
93	13.66	130	27.00
94	13.75	131	27.66
95	14.00	132	28.33
96	14.25	133	29.00
97	14.75	134	29.66
98	15.00	135	30.50
99	15.25	136	31.50
100	15.50	137	32.00
101	16.oo	138	32.75
102	16.25	139	33.5
103	16.50	140	34.50
104	17.00	141	35.00
105	17.25	142	36.00
106	17.50	143	36.50
107	17.75	144	37.00
108	18.00	145	37.75
109	18.33	146	38.50

Height (cm)	Ideal Body Weight (kg)	Height (cm)	Ideal Body Weight (kg)
110	18.66	147	39.00
111	19.00	148	39.75
112	19.50	149	40.50
113	19.75	150	41.00
114	20.00	151	41.50
115	20.33	152	42.00
116	20.66	153	42.50
117	21.00	154	43.66
118	21.50	155	44.00
119	21.75	156	45.00
120	22.25	157	45.66
121	22.50	158	46.75
122	23.00	159	47.75
123	23.33	160	49.00
124	23.75	161	50.00
125	24.25	162	52.50
126	24.66	163	56.00

Annexure III

Monitoring Chart I: Monitoring during the febrile phase
(patients to be monitored 4 hourly)

Name of the patient .....BHT.....

Date time	HCT	Input (ml) Oral/ IV	HR /min	BP mmHg	Pulse Pressure	CRFT <2s/ >2s	Extremity Warm /Cold	RR	UOP /day Void/ catheter	UOP ml/kg/hr	Platelet Count 10^3	Treatment /Remarks

Annexure IV

Monitoring chart II: Management of DHF patients during the critical phase

(Patient to be monitored hourly)

Name of the patient ……BHT……Date and time of admission ……ward -……

Weight - ……	Height - ……	Ideal body weight - ……	M- ……	M+ 5% = ……ml

Critical Phase Commencing date and time -……End date and time ……

Fluid ml/Kg/ hr																								
10																								
9																								
8																								
7																								
6																								
5																								
4																								
3																								
2																								
1.5																								
1																								
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
used % / amount of fluid quota																								
HCT																								
HR																								
BP																								
Pulse Pressure																								
RR																								
CRFT																								
Extremities warm/cold																								
UOP void/catheter																								
UOP ml/Kg/hr																								
Platelet count																								

Annexure IV

Monitoring chart II: Management of DHF patients during the critical phase

(Patient to be monitored hourly)

Page 2

Fluid ml/Kg/ hr																								
10																								
9																								
8																								
7																								
6																								
5																								
4																								
3																								
2																								
1.5																								
1																								
	25..	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
used % of fluid quota																								
HCT																								
HR																								
BP																								
Pulse Pressure																								
RR																								
CRFT																								
Extremities warm/cold																								
UOP void/catheter																								
UOP ml/Kg/hr																								
Platelet count																								

Annexure V

Monitoring chart III: Management of DHF patients during the peak of leaking and during shock

(Patient to be monitored every 15 minutes)

Fluid Boluses Given

Normal Saline:.....

Starch: .....Maximum 5 per 24h / 10 per 48h

Dextran.....Maximum 3 per 24h / 06 per 48h

Other fluid: PRC/WB.....

Fluid ml/Kg/ hr																								
10																								
9																								
8																								
7																								
6																								
5																								
4																								
3																								
2																								
1																								
time																								
HCT																								
HR																								
BP																								
Pulse Pressure																								
RR																								
CRFT																								
Extremities warm/cold																								
UOP ml/Kg/hr																								
Platelet count																								

Annexure VI:

Dengue Vacccine

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Dengue was named one of the top ten threats to global health in 2019 and there have been many efforts to develop a safe and effective dengue vaccine [1]. The ideal dengue vaccine should induce long-lasting immunity to all four-dengue virus (DENV) serotypes so that severe disease would not occur at a later date due to waning of immunity. Dengvaxia (CYD-DTV) was the first dengue vaccine to be registered in 2015 in Mexico and was subsequently approved by the FDA in 2019 [2]. This was a recombinant vaccine where the envelope and PrM proteins of the DENV were incorporated into a yellow fever virus backbone [3]. Unfortunately, this vaccine showed poor efficacy for DENV2 serotype and was more likely to cause severe disease in dengue seronegative vaccinees [3]. Although the exact reasons occurrence of more severe disease in seronegative individuals was not clear, it was attributed to waning of DENV specific antibodies leading to severe disease by antibody dependent enhancement [3]. In addition, as this vaccine did not contain NS1 of the DENV, failure to induce adequate levels of NS1-specific antibody and T cell responses by this vaccine was also thought to contribute to its suboptimum performance [4]. Due to the safety signals of this vaccine, this vaccine was recommended to be given only to DENV seropositive individuals by the WHO [5].

Subsequent vaccine developers having learnt lessons from the suboptimum immune responses generated by CYD-TDV (Dengvaxia), have developed vaccines either using the DENV as a backbone or developing a live attenuated vaccine, which incorporates all four DENV serotypes. TAK-003 (QDENGA) developed by Takeda, having finished its phase 3 trials in many Asian and Latin American countries, has now been approved by the European Medicines Agency and registered in Indonesia. This vaccine, which is a live attenuated vaccine, has DENV2 as its backbone and incorporates the envelope and PrM proteins of the three other DENV serotypes [6]. It was shown to induce immune responses to all four DENV serotypes and showed an overall efficacy of 80.2% against virologically confirmed dengue with an efficacy rate of 83.6% against hospitalizations [6]. However, this vaccine did not induce equal efficacy against all four DENV serotypes. For instance, in baseline DENV seronegatives, the efficacy for DENV2 was 91.9%, for DENV1 was 43.5%, while and no efficacy against DENV3 (-23.4%) [6]. Unpublished data on the manufacturer's website states that the vaccine efficacy at 4.5 years was 84% against hospitalization without any safety signals [7]. As there was a lower number of dengue infections during the years 2020 and 2021 in the countries where this vaccine underwent trials, due to the COVID-19 pandemic, it would be important to see any potential safety signals during dengue outbreaks, especially due to DENV3.

Lastly, NIH TV003 developed by NIH USA is currently undergoing phase 3 trials in several countries in Asia and Latin America. This live attenuated vaccine was shown to induce high levels of neutralizing antibodies and controlled human challenge models showed that the

vaccine completely protected against infection [8, 9]. There was no viramiae observed in the vaccinees who were later challenged with the DENVs. It would be important to see the effectiveness of this vaccine in phase 3 clinical trials.

In summary, due to the presence of four DENV serotypes, and potential of enhancing disease for different serotypes in the presence of sub-neutralising levels of antibodies, an ideal vaccine should induce durable, long lasting immunity to all four DENV serotypes. Due to the safety signals.

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