# Medical Officers Guidebook for Clinical Management of Dengue

## *Introduction*

Dengue is a major public health concerns globally, a common cause of illness seen in primary care settings in tropical and subtropical countries. It is endemic in more than 100 countries of Africa, America, Eastern Mediterranean, South-East Asia and Western Pacific. It is the most rapidly spreading mosquito-borne viral disease of mankind, with a 30-fold increase in global incidence over the last five decades. According to World Health Organization (WHO), about 50-100 million new dengue infections are estimated to occur annually in more than 100 endemic countries, with a steady increase in the number of countries reporting the disease.

Every year, during the period July - November, an upsurge in the cases of dengue/DHF has been observed in India. The disease has a seasonal pattern; the cases peak after the monsoons. It is transmitted by Aedes aegypti and Aedes albopictus.

Literature shows that case fatality in Dengue can be minimized by early treatment attention. Medical Officers play a pivotal role in the early recognition and management of dengue fever when patients progress through the different phases of illness.

## *Dengue virus*

The agent of dengue,i.e. dengue viruses, are categorized under the genus Flaviviridae. They are single stranded RNA virus. The dengue virus genome is composed of three structural protein genes encoding the nucleocapsid of core protein(C), a membrane associated protein (M), an envelope protein (E) and seven non-structural (NS) proteins — NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5. The functions for all the individual NS-proteins are not well characterized. However,NS1 protein has been shown to interact with the host immune system, and known to evoke T cell responses. In dengue virus infection, patients have measurable levels of NS1 protein in the blood, which are utilized as a diagnostic marker of the infection.There are four dengue virus serotypes which are designated as DENV-1, DENV-2, DENV-3 and DENV- 4. These serotypes can co-exist in the endemic areas because the immunity to one serotype does not afford protection from the infection by a heterotopous serotype. Although all four serotypes are antigenically similar, they are different enough to elicit cross- protection only for a few months after infection by any one of them. Infection with any one serotype confers lifelong immunity to that virus serotype. The ability of all DENV serotypes to utilize pre-existing heterotypic flavivirus antibody to enhance antigen antibody reaction, a unique feature of DENV, distinguishes it from all other flaviviruses and is considered to be the primary basis of DENV pathogenesis.Individual variations occur in antibody responses to the dengue virus. Secondary infections are associated with elevated risks of severe disease outcomes. Primary and secondary infections are distinguishable based on their antibody responses.

## *Understanding dengue fever*

Dengue viruses cause symptomatic infections or asymptomatic seroconversion. Patients with asymptomatic infection are viraemic and thus may be a source of infection. Symptomatic dengue infection is a systemic and dynamic disease. The incubation period lasts for 5 to 7 days and the onset of the illness is abrupt. It has a wide clinical spectrum, which includes both severe and non-severe clinical manifestations.

Common presenting symptoms include high-grade fever, headache, retro-orbital pain, myalgia, arthralgia, nausea, vomiting and rash. The symptoms usually last for 2-7 days. As the symptoms are relatively nonspecific in early stages, other differential diagnoses need to be considered in the first 72 hours. In patients with moderate-to-severe disease, the course of the illness follows three phases: febrile, critical and recovery.

The severity of the disease usually becomes apparent during defervescence, that is, during transition from the febrile to the afebrile phase. This often coincides with the onset of the critical phase, usually occurs on days 3 to 8 of illness. The critical phase is distinguished by the pathophysiological phenomenon of increased capillary permeability, which lasts approximately for 24 to 48 hours and is more common in secondary dengue infections. This phase is followed by the recovery phase. The key to achieve a good clinical outcome is to have an understanding of the different phases of the disease and be alert to the clinical problems that could arise during these phases.

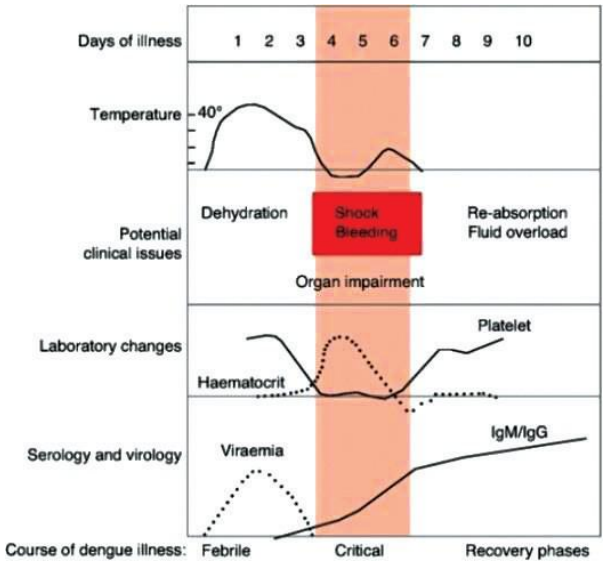



Figure 1: Course of Dengue illness

## Febrile phase of dengue

After the incubation period, the illness starts abruptly with high fever accompanied by non-specific symptoms such as facial flushing, skin erythema, generalised body aches and headache. This febrile or viraemia phase usually lasts for 2 to 7 days. It can be clinically difficult to distinguish dengue from other viral febrile illnesses in the early febrile phase.

In addition to a recent history of dengue within the family or neighborhood, **the three early clinical predictors of dengue at ≤72 hours of fever were nausea and/or vomiting, postural dizziness and lower total white cell count compared to patients with other febrile illnesses (OFI).** Symptoms such as headache, myalgia, arthralgia and retro-orbital pain that were frequently reported by patients with dengue fever were also observed in patients with OFI with no significant differences. Similarly, children with dengue were more likely to report anorexia, nausea and vomiting. They had a positive tourniquet test, lower total white cell counts, absolute neutrophil and monocyte counts and higher plasma ALT and AST than the children with OFI. Symptoms of upper respiratory tract infections such as injected pharynx and enlarged tonsils did not exclude dengue.

After 2 to 3 days of high fever, anorexia and nausea, most patients may have varying degrees of dehydration and lethargy. The quality of life decreases to approximately 40% to 50% at the onset of fever with experiences of somatic pain and discomfort and difficulties in cognition, sleep, mobility, self-care and anxiety or depression. Mild haemorrhagic manifestations such as petechiae and mucosal membrane bleeding (e.g., nose and gums) may be seen. Easy bruising and bleeding at venipuncture sites are present in some cases. Massive vaginal bleeding (in women of childbearing age) and gastrointestinal bleeding may occur during this phase, although this is not common. The liver may be enlarged and tender after a few days of fever. The earliest change in the full blood count is a progressive decrease in white blood cell count, which should alert the physician to a high probability of dengue. This leucopenia is most likely due to a virus-induced down-regulation of haematopoiesis.

## Critical phase

During the transition from febrile to afebrile phase, usually after day 3 or as late as day 7 of fever, patients without an increase in capillary permeability improve without going through the critical phase. Their appetites improve and they feel better. Patients with increased capillary permeability, however, experience worsening of symptoms with the subsidence of high fever. Defervescence usually occurs on days 3 to 8 of illness when temperature drops to 38°C or less and remains below this level. Patients may have warning signs, mostly as a result of plasma leakage. Warning signs usually precede the manifestations of shock and appear towards the end of the febrile phase, usually between days 3 and 7 of illness.

**Warning and danger signs and symptoms of dengue fever**

- Bleeding: epistaxis, scanty haemoptysis, haematemesis, gum bleeding, black coloured stools, excessive menstrual bleeding, dark-coloured urine or haematuria.
- Lethargy and/or restlessness, sudden behavioural changes.
- Convulsions.
- Difficulty in breathing or palpitation or breathlessness.
- Persistent vomiting >3 times a day.
- Severe abdominal pain
- Enlarged and/or tender liver
- Clinical fluid accumulation.
- Postural hypotension-dizziness.
- Pale, cold clammy hands and feet.
- Not able to drink and no urine output for 4-6 h/ urine output less than 0.5 ml/kg/h.
- Rising HCT (>45%)together with rapid fall in platelet count.
- Metabolic acidosis.
- Derangement of liver/ kidney function tests.
- Pleural effusion/ ascites/ gall bladder oedema on imaging.

*It is important to note* that the warning signs should not be randomly applied without making a clinical diagnosis of dengue.

In the full blood count picture, **progressive leucopenia followed by a rapid decrease in platelet count usually precedes plasma leakage. An increasing haematocrit (HCT) above the baseline is another early sign.** The period of clinically significant plasma leakage usually lasts 24-48 h. The degree of plasma leakage varies. A rising haematocrit precedes changes in blood pressure (BP) and pulse volume. The degree of haemoconcentration above the baseline haematocrit reflects the severity of plasma leakage; however, this can be masked by early intravenous fluid therapy. Usually pleural effusion and ascites are clinically detectable only after an intravenous fluid therapy unless the plasma leakage is significant, which is a case of patient in a state of shock. A right lateral decubitus chest radiograph, ultrasound detection of free fluid in the chest or abdomen or gall bladder wall oedema may precede clinical detection. In addition to the plasma leakage, haemorrhagic manifestations such as easy bruising and bleeding at venepuncture sites occur frequently. Shock occurs when a critical volume of plasma is lost through leakage; it is often preceded by warning signs. Some patients progress to the critical phase of plasma leakage and shock before defervescence. In these patients, a rising haematocrit and rapid onset of thrombocytopenia or the warning signs indicate the onset of plasma leakage. Most patients with dengue having warning signs recover from intravenous rehydration, although some will deteriorate to severe dengue.

### Recovery phase

As the patient survives the 24- to 48-hour critical phase, a gradual reabsorption of extravascular compartment fluid takes place in the following 48 to 72 hours. During this time, patient's general well-being improves, appetite returns, gastrointestinal symptoms abate, haemodynamic status stabilizes and diuresis ensues. Some patients may exhibit a confluent erythematous or petechial rash in small areas of normal skin described as **"isles of white in the sea of red"**. Some may experience generalised pruritus. Bradycardia and electrocardiographic changes are common during this stage. The hematocrit stabilizes or may become lower due to the dilutional effect of reabsorbed fluid. The white blood cell count usually starts to rise soon after defervescence but the recovery of the platelet count is typically later than that of the white blood cell count. Respiratory distress from massive pleural effusion and ascites, pulmonary oedema or congestive heart failure may occur during the critical and/or recovery phases if excessive intravenous fluids have been administered.

### Worsening hypovolemic shock

Worsening hypovolemic shock manifests as increasing tachycardia and peripheral vasoconstriction. Not only are the extremities cold and cyanosed but the limbs become mottled, cold and clammy. By this stage the breathing becomes more rapid and increases in depth, a compensation for the metabolic acidosis (Kussmaul's breathing). Finally, there is decompensation, both systolic and diastolic BPs decrease suddenly and dramatically, and the patient is said to have hypotensive or decompensated shock.

At this time the peripheral pulses disappear while the central pulse (femoral) will be weak. Hypotension develops when physiologic attempts to maintain systolic BP and perfusion are no longer effective.

One key clinical sign of this deterioration is a change in mental state as brain perfusion declines. The patient becomes restless, confused and extremely lethargic. Seizures may occur and agitation may alternate with lethargy. On the other hand, children and young adults have been known to have a clear mental status even in profound shock. Adults have been known to be able to work until the stage of profound shock is reached.

The failure of infants and children to recognize, focus or make eye contact with parents may be an early ominous sign of cortical hypo perfusion, as is the failure to respond to painful stimuli such as venepuncture. Parents may be the first to recognize these signs, but they may be unable to describe them, other than to say something is wrong. Listen to parents! Hypotension is a late finding and signals an imminent total cardiorespiratory collapse.

### Prolonged hypotensive shock

Prolonged hypotensive shock and hypoxia lead to severe metabolic acidosis, multiple organ failure and an extremely difficult clinical situation. It may take a few hours for patients to progress from warning signs to compensated shock and another few hours for compensated shock to progress to hypotensive shock, but only minutes for hypotensive shock to progress to cardiorespiratory collapse and cardiac arrest.

Hypotension is associated with prolonged shock which is often complicated by major bleeding. Patients with severe dengue have varying degrees of coagulation abnormalities, but these are usually not sufficient to cause major bleeding. When major bleeding does occur, it is almost always associated with profound shock since this, in combination with thrombocytopenia, hypoxia and acidosis, can lead to multiple organ failure and advanced disseminated intravascular coagulation.

Massive bleeding may occur without prolonged shock in instances when acetylsalicylic acid(aspirin), ibuprofen, or corticosteroids have been taken. Bleeding may occur in patients with previous peptic or duodenal ulcers. Acute liver and renal failure and encephalopathy may be present in severe shock; these have been described even in the absence of severe plasma leakage or shock. Cardiomyopathy and encephalitis

have also been reported in a few dengue case series. However, most deaths from dengue occur in patients with profound and prolonged shock resulting from plasma leakage and complicated by bleeding and/or fluid overload.

**Table 1**

**Medical complications seen in the febrile, critical and recovery phases of dengue.**

| Phase | Complication |
|---|---|
| Febrile phase | Dehydration: High fever may cause neurological disturbances and febrile seizures in young children |
| Critical phase | Shock from plasma leakage: Severe haemorrhage and organ impairment |
| Recovery phase | Hypervolemia (only if intravenous fluid therapy has been excessive and/or has extended into this period) and acute pulmonary oedema |

**The various risk factors associated with severe disease of dengue are listed as below :**

- Infants.
- Young children.
- Pregnant women.
- Diabetes mellitus.
- Hypertension.
- Haemolytic conditions.
- Older persons.
- Obese patients

## *Clinical EVALUATION*

Clinical evaluation of the patients involves four steps-

1. History taking,
2. Clinical examination,
3. Investigations and
4. Diagnosis and assessment of disease phase and severity.

### Step 1 : A patient's history should include-Ask

- Date of onset of fever (date is preferable to the number of days of fever)
- Other symptoms and severity
- Ask the 3 three golden questions:
  - Oral fluid intake-quantity and types of fluids
  - Urine output-quantify in terms of frequency and estimated volume and time of most recent voiding
  - Types of activities performed during this illness (e.g., can the patient go to school, work, market, etc?)

These questions, though not specific to dengue, give a good indication of patient's hydration status and how well the patient copes with his illness.

- Other fluid losses-such as vomiting or diarrhoea
- Presence of warning signs, particularly after the first 72 hr of fever
- Family or neighbor having dengue or travel to dengue-endemic areas
- Medications (including non-prescription or traditional medicine) in use
- List of medications and the time they were last taken
- Risk factors

### Step 2 : Clinical examination - Assess :

- Mental state
- Hydration status
- Peripheral perfusion done by holding the patient's hand, assessing the colour, capillary refill time, temperature of the extremities, pulse volume and pulse rate (CCTVR)
- Haemodynamic status
- Tachypnoea/acidotic breathing/pleural effusion
- Abdominal tenderness/hepatomegaly/ ascites
- Rash and bleeding manifestations
- Tourniquet test (repeat if previously negative or if there is no bleeding manifestation)

### Step 3 : Investigation

For confirmation of dengue infection, Government of India (GoI) recommends use of **ELISA–based antigen detection test (NS1)** for diagnosing the cases from the first day of fever onwards and antibody detection test **IgM capture ELISA (MAC-ELISA)** for diagnosing the cases after the fifth day of onset of disease.

**(NS1 for samples collected from day-1 to day-5 and IgM after day-5)**

Directorate of National Vector Borne Disease Control Programme (NVBDCP), GoI has identified a network of laboratories (sentinel surveillance hospitals and apex referral laboratories) for surveillance of dengue fever cases across the country. These laboratories are also meant to augment the diagnostic facilities in all endemic areas. They are linked with Apex Referral Laboratories (ARLs) with advanced diagnostic facilities for backup support and serotyping of dengue samples. For details, please refer to NVBDCP website www.nvbdcp.gov.in.

- If facilities are available, a full blood count (FBC) should be done at the first visit to establish the baseline haematocrit. However, a normal FBC during the first 72 hours of illness does not exclude dengue infection. The haematocrit in the early febrile phase can be used as the patient's own baseline. This should be repeated after the 3rd day of illness and in those with warning signs and with risk factors for severe disease.
- In the absence of the patient's baseline haematocrit, age-specific population haematocrit levels can be used as a surrogate during the critical phase. In the absence of a baseline HCT level, a HCT value of >40% in female adults and children aged <12 years and >46% in male adults should raise the suspicion of plasma leakage
- Leucopenia usually precedes the onset of the critical phase and has been associated with severe disease. A rapid decrease in platelet count, concomitant with a rising haematocrit compared to the baseline, is suggestive of progress in the plasma leakage/critical phase of the disease. These changes are usually preceded by leucopenia ($\leq$5000 cells/mm$^3$).
- **A decreasing white blood cell and platelet count makes the diagnosis of dengue very likely.**

- Additional tests such as liver function test, glucose, serum electrolytes, urea and creatinine, bicarbonate or lactate, cardiac enzymes, electrocardiogram (ECG) and urine-specific gravity should be considered in patients with co-morbidities or in patients with clinically severe disease as indicated.Aspartate aminotransferase (AST) levels were higher compared to the levels of alanine aminotransferase (ALT). The degree of rise of AST and ALT was significantly more in DHF and DSS, as compared to DF

**Interpretation of Haematocrit**

Haemodynamic state should be the principal driver of IV fluid therapy. Haematocrit level should only be a guide.

Interpretation of rising or persistently high haematocrit

| Haematocrit | | Vitals | | Interpretation | Action |
|---|---|---|---|---|---|
| A rising or persistently high haematocrit | + | Unstable vital signs | = | Active plasma leakage | Need for further fluid replacement |
| A rising or persistently high haematocrit | + | Stable haemodynamic status | = | Does not require extra intravenous fluid | Continue to monitor closely. HCT should start to fall within next 24 hours as plasma leakage stops. |

Interpretation of a decrease in haematocrit

| Haematocrit | | Vitals | | Interpretation | Action |
|---|---|---|---|---|---|
| A decrease in haematocrit | + | Unstable vital signs | = | Major haemorrhage | Need for urgent transfusion |
| A decrease in haematocrit | + | Stable haemodynamic status | = | Haemodilution and/ or reabsorption of extravasated fluids | IV fluids should be reduced in step-wise manner or discontinued immediately to avoid pulmonary oedema |

## Step 4 : Diagnosis, assessment of disease phase and severity

Based on the evaluation of history, physical examination and/or FBC and haematocrit, one could clinically determine the diagnosis of dengue, the phase patient is in, the presence or absence of warning signs, the hydration and haemodynamic state of the patient and whether the patient requires admission.

Dengue viral infected person may be asymptomatic or symptomatic and clinical manifestations vary from undifferentiated fever to florid haemorrhage and shock.

The clinical presentations depend on various factors such as age, immune status of the host, the virus strain and primary or secondary infection. Infection with one dengue serotype gives lifelong immunity to that particular serotype.

### Undifferentiated dengue Fever (UDF)

In primary dengue infection patient may develop mild to moderate fever and it is often difficult to distinguish from other viral infections. Maculopapular rash may or may not appear during fever or defervescence. The symptoms of DF may not be very distinguished and signs of bleeding or capillary leakage may be absent.

The rash associated with measles and rubella has a particular distribution from the head to the trunk and extremities, but in dengue the rash usually first appears on the trunk and later extends to the face and extremities.

Figure 2

*DENGUE patient with MACULOPAPULAR rash*

*Finger impression on skin of a DENGUE patient*

*ROUNDED stetho impression on skin of a DENGUE patient*

## Severe dengue Fever

Majority of the dengue virus infected persons are asymptomatic but symptomatic patients may present with undifferentiated fever, non-severe and severe manifestation. Some patients with dengue virus infection present with severe manifestations like shock, plasma leakage, bleeding and organ involvement.

DHF has been divided into four grades based on **i > thrombocyte count, ii > haematocrit, iii > evidence of capillary leakage, iv > bleeding and v > hypotension.**

Non severe cases may be DF and DHF grade I and II without significant bleeding. Severe dengue may be DHF III and IV with or without significant bleeding. DHF grade I and II may be severe when they present with significant bleeding or with metabolic and electrolyte abnormalities. Sometimes DF may present with life threatening significant bleeding without evidence of capillary leakage or haemoconcentration. Some Dengue Fever patients may also present with multiple organ involvement without bleeding and shock. In some patient there may be unusual atypical presentation also.

It is also reported in various literatures that high morbidity and mortality in DF/DHF is due to involvement of the following organs during illness:

- Hepatic
- Renal
- Cardiac
- Pulmonary
- CNS

**Grading of DF/ DHF**

**DF:** Fever of 2-7 days with two or more of following- Headache, Retro orbital pain, Myalgia, Arthralgia with or without leukopenia, thrombocytopenia and no evidence of plasma leakage.

**DHF I:** Above criteria plus positive tourniquet test and evidence of plasma leakage. Thrombocytopenia with platelet count less than 1,00,000/cu.mm and Hct rise more than 20% over baseline or Fall in Hematocrit by 20% after Fluid replacement.

**DHF II:** Above plus some evidence of spontaneous bleeding in skin or other organs (black tarry stool, epistaxis, gum bleeds) and abdominal pain.

**DHF III (DSS):** Above plus circulatory failure (weak rapid pulse, narrow pulse pressure < 20 mm Hg, Hypotension, cold clammy skin, restlessness).

**DHF IV (DSS):** Profound shock with undetectable blood pressure or pulse.

## Expanded dengue Syndrome (EDS)

Mild or Severe organ involvement may be found in DF/DHF. Unusual manifestations of DF/DHF are commonly associated with co-morbidities and with various other co-infections.

Clinical manifestations observed in EDS are as follows:

**Table 2**

| System | Unusual or atypical manifestations |
|---|---|
| CNS involvement | Encephalopathy, encephalitis, febrile seizures, intra-cranial bleed |
| G. l. involvement | Acute Hepatitis/ fulminant hepatic failure, cholecystitis, cholangitis acute pancreatitis |
| Renal involvement | Acute renal failure, haemolytic uremic syndrome, acute tubular necrosis |
| Cardiac involvement | Cardiac arrhythmia, cardiomyopathy, myocarditis, pericardial effusion |
| Respiratory | Pulmonary oedema, ARDS, pulmonary haemorrhage, pleural effusion |
| Eye | Conjunctival bleed, macular haemorrhage, visual impairment, optic neuritis |

## Clinical Criteria for DF/ DHF/ DSS

**Clinical Features of DF :**

An acute febrile illness of 2-7 days duration with two or more of the following manifestations:

Headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations.

**Dengue Haemorrhagic Fever (DHF) :**

a) A case with clinical criteria of dengue fever;

**plus**

b) Haemorrhagic tendencies evidenced by one or more of the following
   1. Positive tourniquet test
   2. Petechiae, echymoses or purpura
   3. Bleeding from mucosa, gastrointestinal tract, injection sites or other sites;

**plus**

c) Thrombocytopenia (<100 000 per cumm)

**plus**

d) Evidence of plasma leakage due to increased vascular permeability, manifested by one or more of the following
   1. A rise in average haematocrit for age & sex ≥ 20%
   2. A more than 20% drop in haematocrit following volume replacement treatment compared to baseline
   3. Signs of plasma leakage (pleural effusion, ascites, hypoproteinemia)

**Dengue Shock Syndrome (DSS) :**

All the above criteria for DHF with evidence of circulatory failure manifested by rapid and weak pulse and narrow pulse pressure (≤ 20% mm Hg) or hypotension for age, cold and clammy skin and restlessness.

**Differential Diagnosis of DF/ DHF**

- **Conditions that mimic the febrile phase of dengue infection**

**Flu-like syndromes**

Influenza, measles, chikungunya, infectious mononucleosis, 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**

Meningoencephalitis

Febrile seizures

- **Conditions that mimic the critical phase of dengue infection**

**Infectious**

Acute gastroenteritis, malaria, leptospirosis, typhoid fever, typhus, viral hepatitis, Acute HIV-seroconversion illness, bacterial sepsis, septic shock

**Malignancies**

Acute leukaemia and other malignancies

**Other clinical pictures**

Acute abdomen

- Acute appendicitis
- Acute cholecystitis
- Perforated viscus

Diabetic ketoacidosis

Kawasaki syndrome

Lactic acidosis

Leukopenia, thrombocytopenia and bleeding

Platelet disorders

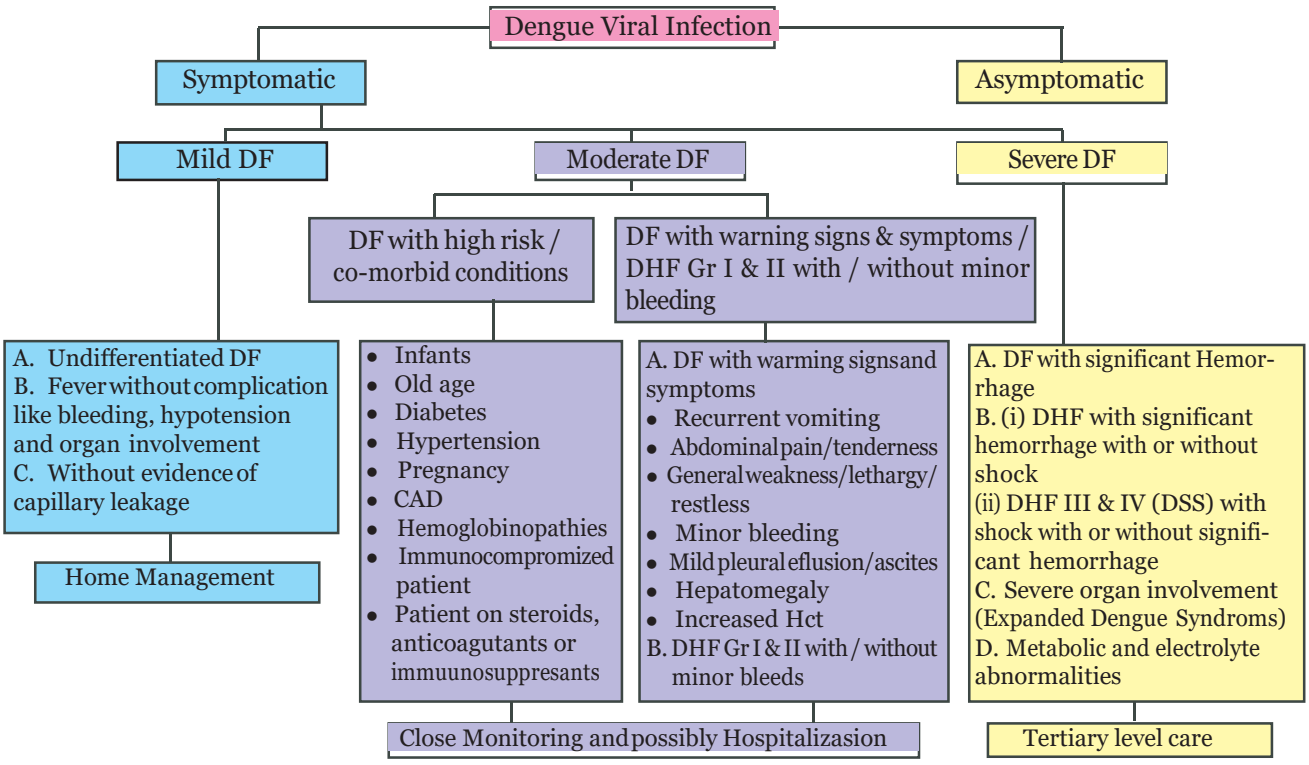
Renal failure

Respiratory distress (Kussmaul's breathing)

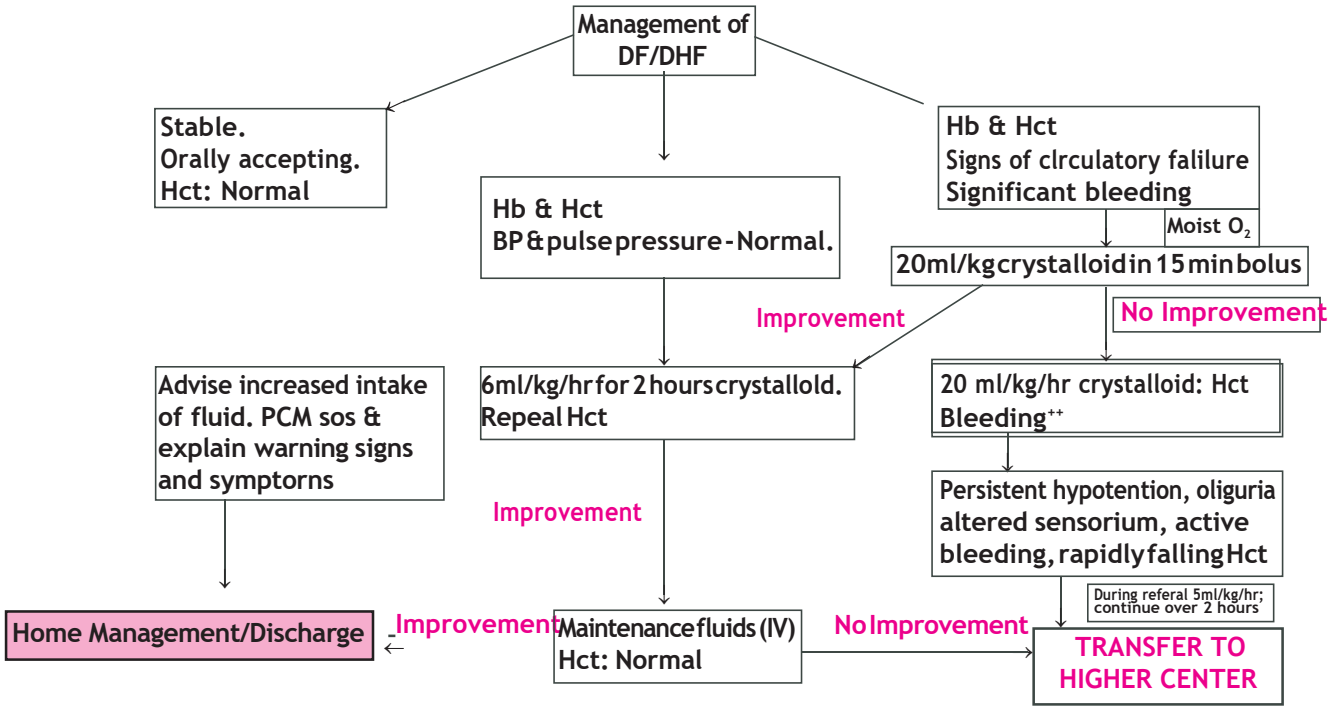
Systemic lupus erythematosus

## *CLINICAL MANAGEMENT*

**Dengue case classification**



## MANAGEMENT OF DENGUE CASES AT PRIMARY HEALTH CARE LEVEL AND REFERRAL




### General Management of Dengue Fever (DF)

i. Management of dengue fever is symptomatic and supportive

ii. Bed rest is advisable during the acute phase.

iii. Use cold/tepid sponging to keep temperature below 38.5° C.

**iv.** Antipyretics may be used to lower the body temperature. Aspirin/NSAIDs like ibuprofen, etc should be avoided since it may cause gastritis, vomiting, acidosis, platelet dysfunction and severe bleeding. **Do not even use combination of paracetamol plus above mentioned drugs.**

Paracetamol is preferable in the doses given below :

| | |
|---|---|
| 1-2 years: 60 -125 mg/dose | 3-6 years: 125 mg/dose |
| 7-12 years: 250 mg/dose | Adult : 500 mg/dose |

v. Encourage oral intake to replace fluid loss from fever and vomiting. Small amounts of oral fluids should be given frequently for those with nausea and anorexia. The choice of fluids should be based on the local culture: coconut water, rice water or barley water. Oral rehydration solution or soup and fruit juices may be given to prevent electrolyte imbalance and are preferable to plain water. Commercial carbonated drinks (cold drinks)/ drinks that exceed the isotonic level (5% sugar) should be avoided. They may exacerbate hyperglycaemia related to physiological stress from dengue and diabetes mellitus. Sufficient oral fluid intake should result in a urinary frequency of at least 4 to 6 times per day. A record of oral fluid and urine output could be maintained and reviewed daily in the ambulatory setting.

vi. Patients should be monitored for 24 to 48 hours after they become afebrile for development of complications.

[Note: In children the dose of paracetamol is calculated as per 10-15 mg/Kg body weight per dose. Paracetamol dose can be repeated at intervals of 6 hrs depending upon fever and body ache.]

**Advice in patient's card**

**What should be done?**

- Adequate bed rest
- Adequate fluid intake : at least 5 glasses of other fluids (with electrolytes) in addition to normal daily intake of plain water e.g. milk, fruit juice (caution with diabetic patient), oral rehydration solution (ORS) or barley/rice water/coconut water

  Note: Plain water alone may cause electrolyte imbalance
- Take paracetamol (as per doctors' advice; not more than 3 to 4 times in 24 hours in children)
- Tepid sponging
- Look for mosquito breeding places in and around the home and eliminate them

**What should be avoided?**

- Do not take acetylsalicylic acid (aspirin), mefenamic acid, ibuprofen or other NSAIDs or steroids. If you are already taking these medications please consult your doctor
- Do not take combination of paracetamol with above mentioned drugs
- Antibiotics are not necessary

**If any of following is observed, the patient should be immediately taken to the nearest hospital; *these are warning signs for DENGUE:***

- Bleeding :
  - red spots or patches on the skin
  - bleeding from nose or gums
  - vomiting blood
  - black-coloured stools
  - heavy menstruation/vaginal bleeding
- Frequent vomiting or not able to drink
- Severe abdominal pain
- Drowsiness, mental confusion or seizures
- Pale, cold or clammy hands and feet
- Difficulty in breathing
- Dizziness
- No urination for 4–6 hours

## Management of DHF Grade I and II

Any person who has dengue fever with thrombocytopenia, high haemoconcentration and presents with abdominal pain, black tarry stools, epistaxis, bleeding from the gums etc.needs to be hospitalized. All these patients should be observed for signs of shock. The critical period for development of shock is during transition from febrile to afebrile phase of illness, which usually occurs after third day of illness. Rise of haemoconcentration indicates plasma leakage and loss of volume for which proper fluid management plays an important role. Despite the treatment, if the patient develops fall in BP, decrease in urine output or other features of shock, the management for Grade III/ IV DHF-DSS should be instituted.

Oral rehydration should be given along with antipyretics like Paracetamol, sponging, etc. as described above. The algorithm for fluid replacement therapy in case of DHF Grade I and II is given in Chart 1

## Management of Shock (DHF Grade III/IV)

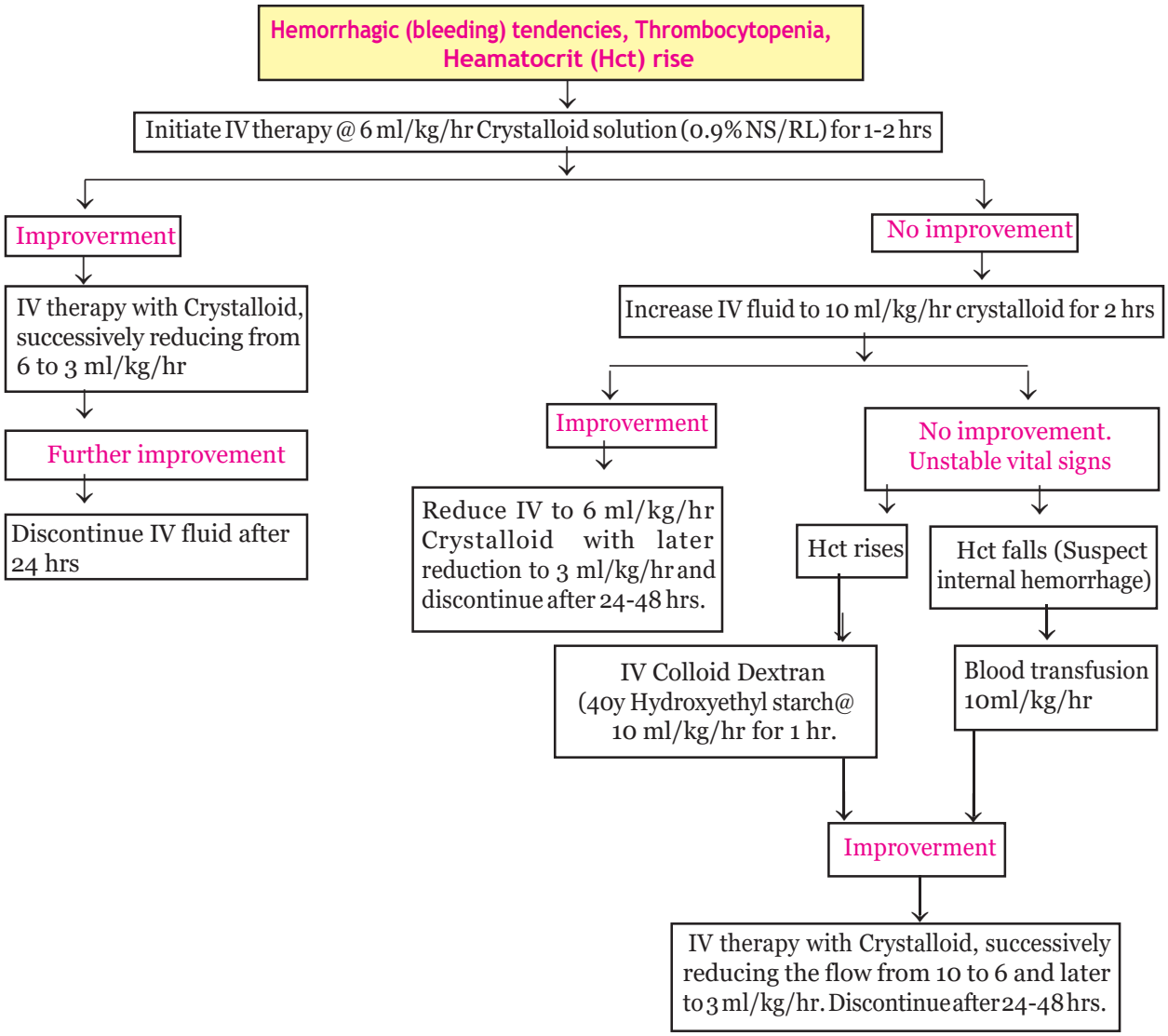
Immediately after hospitalization, the haematocrit, platelet count and vital signs should be examined to assess the patient's condition and intravenous fluid therapy should be started. The patient requires regular and continuous monitoring. If the patient has already received about 1000 ml of intravenous fluid, it should be changed to colloidal solution preferably Dextran 40 or if haematocrit further decreases fresh whole blood transfusion 10-20ml/kg/dose should be given.

However, in case of persistent shock even after initial fluid replacement and resuscitation with plasma or plasma expanders, the haematocrit continues to decline, internal bleeding should be suspected. It may be difficult to recognize and estimate the degree of internal blood loss in the presence of haemoconcentration. It is thus recommended to give whole blood in small volumes of 10ml/kg/hour for all patients in shock as a precaution.

Oxygen should be given to all patients in shock.

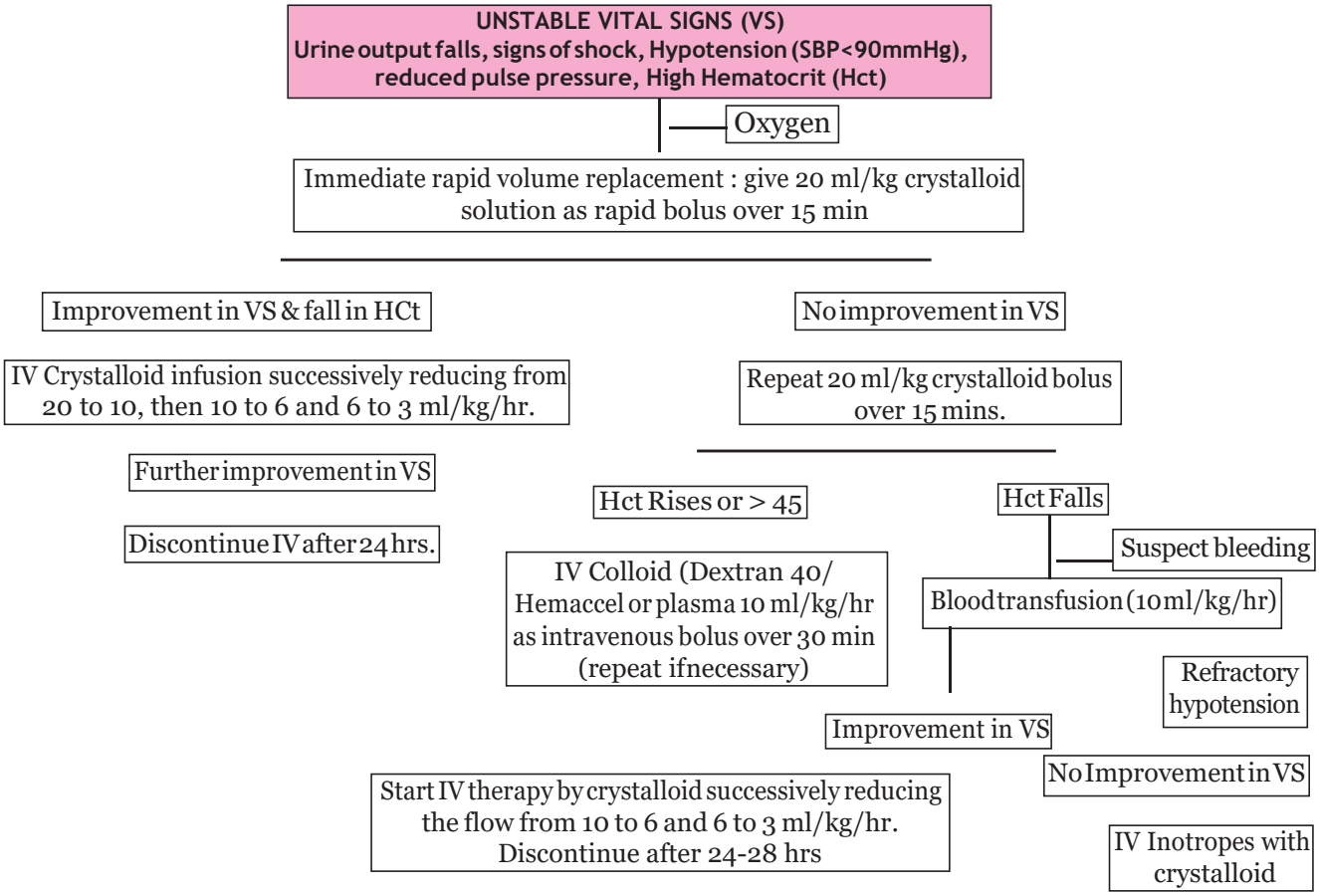
Treatment algorithm for patients with DHF Grades III and IV is given in Chart 2.

**Chart 1: Management of DHF Grade I and II**




**Improvement : Hematocrit falls, pulse rate and blood pressure stable, urine output rises**
**No Improvement : Hematocrit or pulse rate rises, pulse pressure falls below 20 mm/Hg. Urine output falls**
**Unstable Vital signs : Urine output falls, signs of shock**

## Chart 2 : Management of Shock (DHF Grade III / IV)




## Chart 3 : Management of compensated shock in children

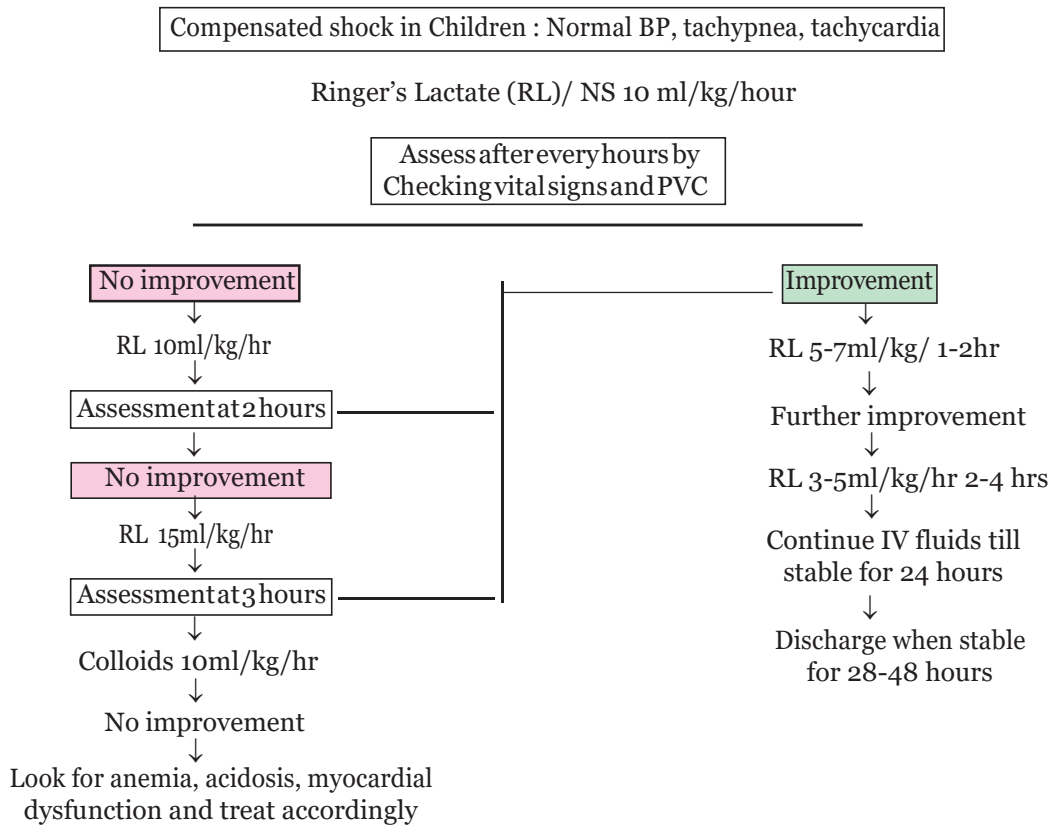
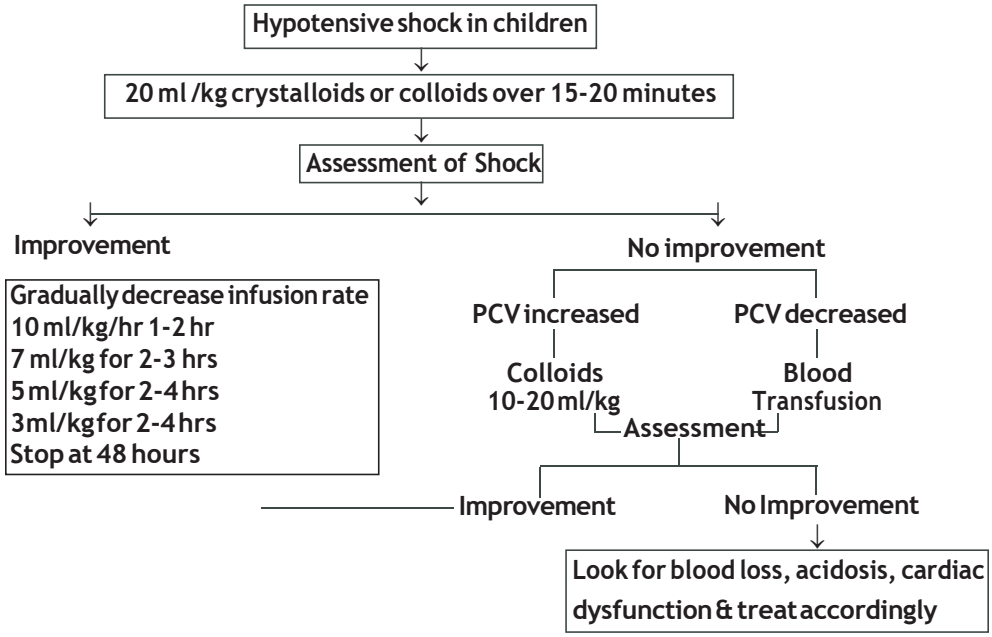


**Chart 4 : Management of hypotensive shock in children**




| When to start and stop intravenous fluid therapy |
|---|
| ***Febrile phase*** |
| **Limit** IV fluids. |
| Early IV therapy may lead to fluid overload especially with non-isotonic IV fluid |
| ***Critical phase*** |
| IV fluids are usually required for 24–48 hours |
| NOTE: For patients who present with shock, IV therapy should be <48 hours |
| ***Recovery phase*** |
| IV fluids should be stopped so that extravasated fluids can be reabsorbed |

**Choice of intravenous fluids for resuscitation**

Replacement of plasma lost because of increased vascular permeability is a mainstay of severe dengue management, particularly during the critical stage. Two main types of volume expander are used to replace lost fluid in the management of dengue fever: crystalloids and colloids. Crystalloids are aqueous solutions of mineral salts or other water-soluble molecules, whereas colloids contain larger insoluble molecules such as gelatin, dextrans or starches.

There is no clear advantage of the use of colloids over crystalloids in terms of the overall outcome. However, colloids may be the preferred choice if the blood pressure has to be restored quickly. Colloids have been shown to restore the cardiac index and reduce the level of haematocrit faster than crystalloids in patients with intractable shock and pulse pressure less than 10 mm Hg.One of the greatest concerns regarding colloid use is the impact on coagulation.

**Crystalloids**

Normal plasma chloride ranges from 95 to 105 mmol/L. Saline 0.9% is a suitable option for initial fluid resuscitation, but repeated large volumes of 0.9% saline may lead to hyperchloremic acidosis. Hyperchloraemic acidosis may aggravate or be confused with lactic acidosis from prolonged shock. Monitoring the chloride and lactate levels will help to identify this problem. When serum chloride level exceeds the normal range, it is advisable to change to other alternatives such as Ringer's Lactate.

**Ringer's Lactate**

Ringer's Lactate has lower sodium (131 mmol/L) and chloride (115 mmol/L) contents and an osmolality of 273 mOsm/L. It may not be suitable for resuscitation of patients with severe hyponatremia. However, it is a suitable solution after 0.9% Saline has been given and the serum chloride level has exceeded the normal range. **Ringer's Lactate should preferably be avoided in liver failure and in patients taking metformin where lactate metabolism may be impaired.**

**Colloids**

The types of colloids are gelatin-based, dextran-based and starch-based solutions. One of the biggest concerns regarding their use is their impact on coagulation. Theoretically, dextrans bind to von Willebrand factor/Factor VIII complex and impair coagulation the most. However, this was not observed to have clinical significance in fluid resuscitation in dengue shock. Of all the colloids, gelatin has the least effect on coagulation but the highest risk of allergic reactions. Allergic reactions such as fever, chills and rigors have also been observed in Dextran 70. Dextran 40 can potentially cause an osmotic renal injury in hypovolaemic patients.

**What type of intravenous fluid therapy should we use ?**

- Use isotonic solutions (normal saline, Ringer's lactate)
- Colloids are preferred if the blood pressure has to be restored urgently

**When are colloids given?**

- Hypotensive shock
- Repeated shock – 2nd or 3rd shock and onwards
- After >20 to 30 ml/kg of crystalloids
- If Hct does not decrease after crystalloid administration in shock state

  DOSE: Limited to 30 to 50 ml/kg/day

**What intravenous fluids should not be used?**

- Hypotonic solution, e.g. 0.45% saline, even during the febrile phase.
- Dextrose solutions should be limited to avoid hyperglycaemia, but may be used in hypoglycaemia with close blood glucose monitoring
- Albumin solutions

**HOW MUCH & HOW FAST to run intravenous fluid?**

- Give the minimum IVF required to maintain good perfusion and urine output of about 0.5 ml/kg/hr.
- Volume based on ideal body weight if overweight.
- Titrate to haemodynamic state and age

What does **"titrate IVF rate to haemodynamic state"** mean?

Reassess haemodynamic responses immediately after every IV bolus.

AFTER correction of shock:

Reduce IV infusion rate in step-wise manner whenever:

- Haemodynamic state is stable
- Rate of plasma leakage decreases towards end of critical phase indicated by:
  - Improving haemodynamic signs
  - Increasing urine output
  - Adequate oral fluid intake
  - Haematocrit decreases below baseline value in a stable patient

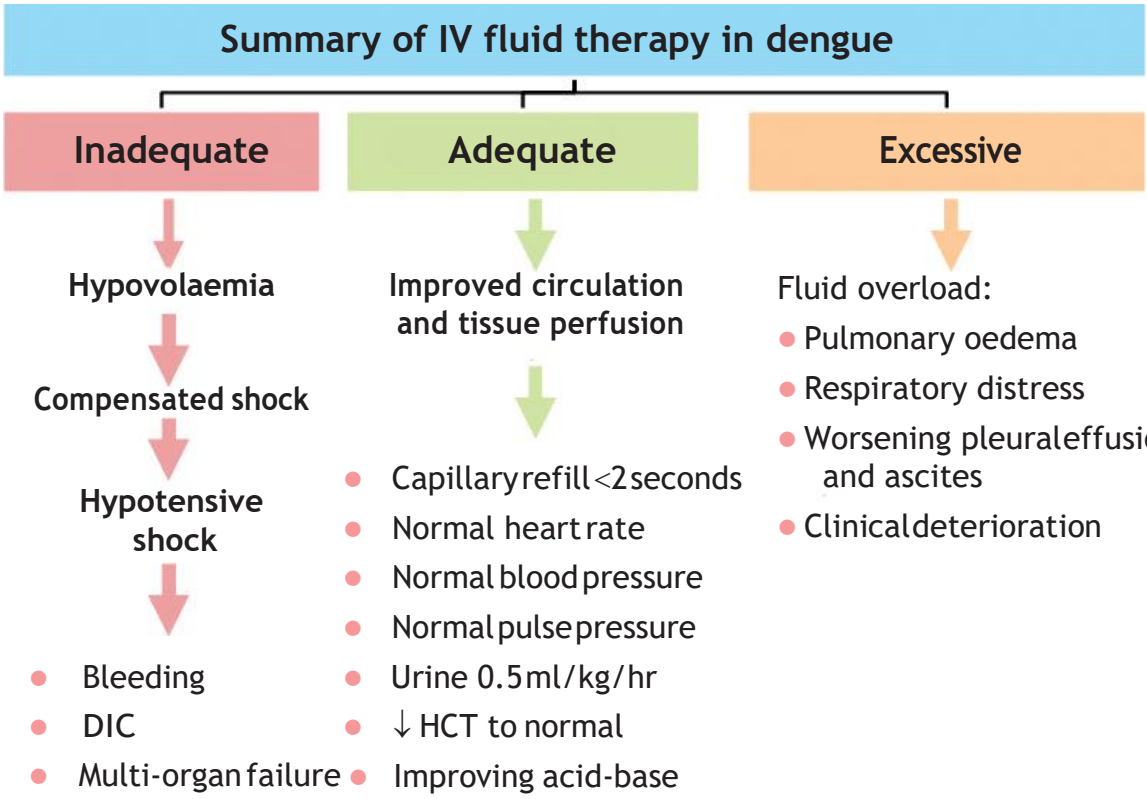



Table 3: Ideal body weight (IBW) for overweight/obese adults can be estimated based on the following formula

| Female | Male |
|---|---|
| 45.5 kg + 0.91(height – 152.4cm) or<br>45.5 kg + 2.3 kg for each inch over 5 ft | 50.0 kg + 0.91(height – 152.4 cm) or<br>50 kg + 2.3 kg for each inch over 5 ft |

**Calculation of fluid**

Required amount of fluid should be calculated on the basis of body weight and charted on a 1-3 hourly basis, or even more frequently in the case of shock. For obese and overweight patients calculation of fluid should be done on the basis of ideal body weight. The regimen of the flow of fluid and the time of infusion are dependent on the severity of DHF. The schedule given below is recommended as a guideline. It is calculated for dehydration of about 5% deficit (plus maintenance).

**Table 4:**

The maintenance fluid should be calculated using the Holliday-Segar formula as follows:

| Body weight in kg | Maintenance volume for 24 hours |
|---|---|
| <10kg | 100ml/kg |
| 10-20 | 1000+50 ml / kg body weight exceeding 10 kg |
| More than 20 kg | 1500+20 ml / kg body weight exceeding 20 kg |

For intravenous fluid therapy of patients with DHF, following regimens of fluid are suggested: 1.5/ml/kg/hr, 3ml/kg/hr; 6ml/kg/hr; 10ml/kg/hr, and 20ml/kg/hr. For ready reference, the calculated fluid requirements, based on body weight and rate of flow of fluid volume for the five regimens are given in Table 5.

| Bodyweight (in kgs) | Volume of fluid to be given in 24 hrs (Maintenance + 5% deficit) |
|---|---|
| 5 | 500+250=750 |
| 10 | 1000+500=1500 |
| 15 | 1250+750=2000 |
| 20 | 1500+1000=2500 |
| 25 | 1600+1250=2850 |
| 30 | 1700+1500=3200 |

| Bodyweight (in kgs) | Volume of fluid to be given in 24 hrs (Maintenance + 5% deficit) |
|---|---|
| 35 | 1800+1750=3550 |
| 40 | 1900+2000=3900 |
| 45 | 2000+2250=4250 |
| 50 | 2100+2500=4600 |
| 55 | 2200+2750=4950 |
| 60 | 2300+3000=5300 |

| Bodyweight (in kgs) | Rate of fluid (ml/hours) | | | | |
|---|---|---|---|---|---|
| | Regimen 1 1.5ml/kg R-1 | Regimen 2 3ml/kg R-2 | Regimen 3 6ml/kg R-3 | Regimen 4 10ml/kg R-4 | Regimen 5 20ml/kg R-5 |
| 5 | 8 | 15 | 30 | 50 | 100 |
| 10 | 15 | 30 | 60 | 100 | 200 |
| 15 | 23 | 45 | 90 | 150 | 300 |
| 20 | 30 | 60 | 120 | 200 | 400 |
| 25 | 38 | 75 | 150 | 250 | 500 |
| 30 | 45 | 90 | 180 | 300 | 600 |
| 35 | 53 | 105 | 210 | 350 | 700 |
| 40 | 60 | 120 | 240 | 400 | 800 |
| 45 | 68 | 135 | 270 | 450 | 900 |
| 50 | 75 | 150 | 300 | 500 | 1000 |
| 55 | 83 | 165 | 330 | 550 | 1100 |
| 60 | 90 | 180 | 360 | 600 | 1200 |

### Remember !!!

- The fluid volumes mentioned are approximate.
- The fluid replacement should be just sufficient to maintain effective circulation during the period of plasma leakage.
- The recommended intravenous fluids are Normal saline, Ringers Lactate or 5% DNS.
- One should keep a watch for urine output, liver size and signs of pulmonary oedema. Hypervolemia is a common complication.
- Normally intravenous fluids are not required beyond 36 to 48 hrs.
- Normally change should not be drastic. Do not jump from R-3 to R-5 since this can overload the patient with fluid. Similarly, reduce the volume of fluid from R-5 to R-4, from R-4 to R-3, and from R-3 to R-2 in a stepwise manner.
- Remember that ONE ML is equal to 15 DROPS. In case of micro drip system, one ml is equal to 60 drops. (If needed, adjust fluid speed in drops according to equipment used).
- It is advised to start with one bottle of 500 ml initially, and order more as and when required. The decision about the speed of IV fluid should be reviewed every 1-3 hours. The frequency of monitoring should be determined on the basis of the condition of the patient.

### Management of severe bleeding

In case of severe bleeding, patient should be admitted in the hospital and investigated to look for the cause and site of bleeding and immediate attempt should be made to stop the bleeding. Internal bleeding like GI bleeding may be sometime severe and difficult to locate.

Patients may also have severe epistaxis and haemoptysis and may present with profound shock. Urgent blood transfusion is life saving in this condition. However, if blood is not available shock may be managed with proper IV fluid or plasma expander. If the patient has thrombocytopenia with active bleeding, it should be treated with blood transfusion and then if required platelet transfusion. In case of massive haemorrhage blood should be tested to rule out coagulopathy by testing for prothrombin time (PT) and APTT. Patients of severe bleeding may have liver dysfunction and in such case, liver function test should also be performed. In rare circumstances, intracranial bleed may also occur in some patients who have severe thrombocytopenia and abnormality in coagulation profile.

**Indications for platelet transfusion**

- Platelet transfusion is not the mainstay of treatment in patients with DF. In general, there is no need to give prophylactic platelets even if at platelet count <40 000/mm$^3$.
- Prophylactic platelet transfusion may be given at levels of <10 000/mm$^3$ in the absence of bleeding manifestations.
- Haemorrhage with or without thrombocytopenia.
- Prolonged shock with coagulopathy and abnormal coagulogram.
- In case of systemic bleeding, platelet transfusion may be needed in addition to red cell transfusion. Whole fresh blood transfusion doesn't have any role in managing thrombocytopenia.

**Indications for blood transfusion**

- Loss of blood (overt blood)—10% or more of total blood volume
- Refractory shock despite adequate fluid administration, and declining Hct
- Replacement volume should be 10 ml/kg body weight at a time and coagulogram should be done
- If fluid overload is present, packed cell transfusion is to be given.

**Use of whole blood/ fresh frozen plasma/ cryoprecipitate in coagulopathy**

Use of whole blood/ fresh frozen plasma/cryoprecipitate is to be done in coagulopathy with bleeding as per advice of the treating physician and the patient's condition.

## *Management of DF/ DHF with co-morbid illness*

### *DENGUE viral hepatitis:*

Some patient may have impairment of liver function test due to dengue viral infection. In some DF patients the AST/ALT level may be very high and PT may be prolonged. Hepatic involvement is commonly associated with pre-existing conditions like chronic viral hepatitis, cirrhosis of liver and haepatomegaly due to some other cause. Patient may also develop hepatic encephalopathy due to acute liver failure.

Liver involvement also sometimes associates with DF in pregnancy. Low albumin due to chronic liver disease may be associated with severe DHF and bleeding. GI bleeding is common in this condition and patient may go to severe DSS. These patients should be managed carefully with hepatic failure regimen with appropriate fluid and blood transfusion. If PT is prolonged, intravenous vitamin K1 may be initiated in such conditions.

### *DENGUE myocarditis:*

Dengue infection may rarely cause acute myocarditis which also may contribute for the development of DSS. Cardiac complications may be seen in presence of CAD, hypertension, diabetic and valvular heart disease. Management of shock with IV fluid in such cases is sometime difficult due to myocardial dysfunction. Patient may develop pulmonary oedema due to improper fluid management. Some CAD patient may be already taking Aspirin and other anti-platelet agent which may also contribute for severe bleeding unless these are stopped during dengue infection. Cardiac ischemia or electrolyte disturbances should be frequently reassessed. Patient may develop congestive or biventricular failure and therefore should be treated properly for better morbidity and mortality outcome.

### *DF in Hypertension:*

Hypotension is a late sign of shock. However, a BP reading that is considered normal for age may, in reality, be low for patients with uncontrolled hypertension. Similarly, what is considered as "mild" hypotension may in fact be profound.

ß-blockers, a common anti-hypertensive medication, cause bradycardia and may block the tachycardic response in shock. The heart rate should not be used as an assessment of perfusion in patients on ß-blockers. Anti-hypertensive agents such as calcium channel blockers may cause tachycardia.Tachycardia in these patients may not indicate hypovolemia. Knowing the baseline heart rate before the dengue illness is helpful in the haemodynamic assessment.

### *DF in Diabetes:*

Sometimes diabetic patients may present with severe complication in DF when target organs are involved like diabetic retinopathy, neuropathy, nephropathy,vasculopathy, cardiomyopathy and hypertension. Due to dengue infection in diabetes the blood sugar may become uncontrolled which may sometimes require insulin therapy for better management.

Hypoglycaemia may occur in those patients taking oral hypoglycaemic agents (e.g.long-acting sulphonylurea), but who had poor oral intake. Hypoglycaemia could be aggravated by severe hepatitis from dengue. Gastrointestinal absorption of oral hypoglycaemic agents is unreliable because of vomiting and diarrhoea during the dengue illness. Some hypoglycaemic agents such as metformin may aggravate lactic acidosis, particularly in dengue shock. These agents should be avoided or discontinued during dengue shock and also in those with severe hepatitis.

### *Renal involvement in DF:*

Acute Tubular Necrosis (ATN) may develop during DHF and may complicate to acute kidney injury (AKI) if fluid therapy is not initiated in time. Renal function may be reversible, if shock is corrected within a short span of time. If the shock persists for long time patient may develop renal complications. Urine output monitoring in dengue infection is very important to assess renal involvement. Microscopic/macroscopic haematuria should be examined in DHF patients. Other investigations like blood urea,creatinine, electrolytes, GFR, ABG should be performed in patients with severe dengue/DHF. Fluid intake should be closely monitored in case of AKI to avoid fluid overload and pulmonary oedema. Dengue patient may develop severe DHF in presence of diabetic nephropathy, hypertensive nephropathy, connective tissue disorders (SLE) and other pre-existing chronic diseases.

### *CNS involvement in DF :*

Altered sensorium may develop in dengue patient due to various conditions like shock (DSS), electrolyte imbalance (due to persistent vomiting), fluid overload (dilutional hyponatremia or other electrolyte imbalance), hypoglycemia, hepatic encephalopathy and also due to involvement of CNS by dengue virus. Acute encephalopathy or encephalitis may be seen in some patients with severe dengue. Sometimes it may be difficult to clinically exclude cerebral Malaria and enteric encephalopathy which may also appear during same period (epidemic). Dengue serology (IgM) in CSF may help to confirm dengue encephalopathy or encephalitis.

## *Management of DF with co-infections*

### *TB:*

Patients may develop breathlessness and massive haemoptysis in PulmonaryTuberculosis. These patients may also develop moderate to massive pleural effusion and ARDS. If patient has DF in presence of TB and is on ATD, then should be closely monitored for further development of respiratory/pulmonary complications to prevent morbidity and mortality.

### *HIV:*

Dengue may cause severe complications like DHF, DSS, significant bleeding and organ involvement among HIV and AIDS patients. Outcome of DF is poor amongst severely immune compromised patients those who have opportunistic infection and very low CD4 count. Multi-organ involvement may be common in DF and responsible for high mortality. Management of DF with HIV and AIDS should be undertaken with HIV specialist consultation.

### *Malaria:*

Malaria is also a common co-infection in dengue as it is prevalent across India and transmission also coincides during the same period/season. Malaria should be excluded in the beginning without loss of much time as it has its specific management.Antimalarial treatment should be started as soon as possible to prevent complication and give better outcome during co-infection.

### *CHIKUNGUNYA:*

It is also reported that in some geographical areas both the infections are prevalent at the same time. Acute complications are sometimes severe in DF in presence of Chikungunya. In case of predominant joint involvement in a DF patient, Chikungunya should be investigated and proper management to be carried out accordingly.

### *Enteric Fever:*

Water borne diseases like Typhoid fever and gastroenteritis are also common during monsoon season when dengue infection is also reported in large number. In the initial phase DF patient may be more complicated with Typhoid if antibiotic treatment is started late. In highly suspected cases blood culture for Typhoid fever should be sent to confirm the diagnosis as Widal test may not be positive before 2 weeks of fever.

## *Management of DENGUE in pregnancy*

DF infection in pregnancy carries the risk of more bleeding, foetal complications, low birth weight and premature birth. Risk of vertical transmission also increases during pregnancy. Severe bleeding may complicate delivery and/or surgical procedures performed on pregnant patients with dengue during the critical phase, i.e. the period coinciding with marked thrombocytopenia with or without coagulopathy and vasculopathy.Pleural effusion, ascites, hypotension are commonly associated with DF in pregnancy. Involvement of lungs and liver is also common in pregnancy. Patients may have respiratory symptom due to massive pleural effusion and high SGOT/SGPT due to liver involvement.Complications of DF depend on the different stages of pregnancy like early, late, peri-partum and post partum periods.

However, it is to be kept in mind that

- The lower BP and tachycardia of normal pregnancy could be misinterpreted as hypotensive shock.
- The lower baseline haematocrit after the second trimester of pregnancy should be noted. Establishing the baseline haematocrit during the first 2–3 days of fever is essential for early recognition of plasma leakage.
- Clinical signs of plasma leakage such as pleural effusion and ascites could be difficult to elicit in the presence of a gravid uterus.

Management of dengue infection in pregnancy should be taken seriously to reduce morbidity and mortality in mother as well as foetus.

Pregnancy is a state of hyper dynamic circulation and fluid replacement should be carefully done to prevent pulmonary oedema. Regular BP monitoring should be performed during DF in pregnancy. Fulminant hepatic failure, ARDS and acute renal failure in pregnancy may be associated with dengue infection. There is no difference in fluid therapy compared with the non-pregnant state. However it is important to note that the growing gravid uterus may result in narrower tolerance of fluid accumulation in the peritoneal and pleural cavity

The presence of wounds or trauma during the critical phase of dengue with marked thrombocytopenia, coagulopathy and vasculopathy creates a substantial risk of severe haemorrhage. If severe haemorrhage occurs, replacement with transfusion of fresh whole blood/fresh packed red cells should be promptly instituted. Frequent platelet count and coagulation profile testing should be performed during DF in pregnancy.

Delivery should take place in a hospital where blood/blood components and a team of skilled obstetricians and a neonatologist are available. Prophylactic platelet transfusion is not recommended unless obstetrically indicated.

**Post-delivery- (** *Keep in mind***)**

- Newborns with mothers who had dengue just before or at delivery, should be closely monitored in hospital after birth in view of the risk of vertical transmission. Severe foetal or neonatal dengue illness and death may occur when there is insufficient time for the production of protective maternal antibodies.
- Vertical dengue infection transmission from pregnant women to their foetus has been reported in different studies from 1.6 -64%. Clinical manifestations of vertically infected neonates vary from mild illness such as fever with petechial rash, thrombocytopenia and hepatomegaly, to severe illness with pleural effusion, gastric bleeding, circulatory failure and massive intracerebral haemorrhage.
- Clinicians should be aware that presentation of either maternal or neonatal disease may be atypical and confound diagnosis. Congenital infection could eventually be suspected on clinical grounds and then confirmed in the laboratory.

**Inevitable delivery during critical phase -** *what to do?*

- If delivery is inevitable, bleeding should be anticipated and closely monitored.
- Blood and blood products should be cross-matched and saved in preparation for delivery.
- Trauma or injury should be kept to the minimum if possible.
- It is essential to check for complete removal of the placenta after delivery.

- Transfusion of platelet concentrates should be initiated during or at delivery but not too far ahead of delivery, as the platelet count is sustained by platelet transfusion for only a few hours during the critical phase.
- Fresh whole blood/fresh packed red cell transfusion should be administered as soon as possible if significant bleeding occurs. If blood loss can be quantified, it should be replaced immediately. Do not wait for blood loss to exceed 500 ml before replacement, as in postpartum haemorrhage. Do not wait for the haematocrit to decrease to low levels.
- Ergotamine and or oxytocin infusion as per standard obstetrical practice should be commenced to contract the uterus after delivery to prevent postpartum haemorrhage.

## *Management of DENGUE in infants*

Dengue virus can cause a spectrum of outcomes in infants, ranging from asymptomatic infection to mild or clinically significant severe disease similar to older children and adults. Compared to older children upper respiratory tract symptoms (cough, nasal congestion, runny nose, dyspnoea), gastrointestinal symptoms (vomiting, diarrhoea), and febrile convulsions are more common in infants with dengue. The burden of severe dengue lies predominantly in infants 4—9 months of age.

The degree of increase above the baseline haematocrit often reflects the severity of plasma leakage. However, rise of haematocrit may not be sometimes detectable because the normal value of haematocrit in infants 2-12 months of age is relatively low and may be even lower in iron deficiency anaemia. Thrombocytopenia and leukopenia are often observed in this phase. Liver involvement is found more frequently in infants compared to children. Progression of infants with dengue is the same as that of children and adults during the recovery phase.

### Management of dengue among infants without warning signs

Oral rehydration should be encouraged with oral rehydration solution (OHS), fruit juice and other fluids containing electrolytes and sugar, together with breast feeding or formula feeding. Parents or caregivers should be instructed about fever control with antipyretics and tepid sponging. They should be advised to bring the infant back to the nearest hospital immediately if the infant has any of the warning signs.

### Management of dengue among infants with warning signs

When the infant has dengue with warning signs intravenous fluid therapy is indicated. In the early stage, judicious volume replacement by intravenous fluid therapy may modify the course and severity of the illness. Initially isotonic crystalloid solutions such as Ringer's Lactate (RL), Ringer's Acetate (RA), or 0.9% saline solution should be used. The capillary leak resolves spontaneously after 24-48 hours in most of the patients.

### Management of infants with severe dengue: Treatment of shock

Volume replacement in infants with dengue shock is very challenging and it should be done promptly during the period of defervescence. Each and every case should be critically analyzed separately.

### Management of neonatal dengue

After delivery, the new born may go into shock which may be confused with septic shock or birth trauma. In this case, history of febrile illness during pregnancy is important which may help to diagnose Dengue Shock Syndrome among neonates and infants. Close observation, symptomatic and supportive treatment are the mainstay of management.

## *SUGGESTED Admission & Discharge criteria*

| **Admission criteria** | |
|---|---|
| **Warning signs** | Persistent high grade fever (38.5°C and above) Any of the warning signs including sudden drop of temperature |
| **Signs and symptoms related to hypotension (possible plasma leakage)** | Dehydrated patient, unable to tolerate oral fluids<br>Dizziness or postural hypotension<br>Profuse perspiration, fainting, prostration during defervescence<br>Hypotension or cold extremities Difficulty in breathing/shortness of breath (deep sighing breaths) |
| **Bleeding**<br>**Organ impairment** | Spontaneous bleeding, independent of the platelet count<br>Renal, hepatic, neurological or cardiac<br>– enlarged, tender liver, although not yet in shock<br>– chest pain or respiratory distress, cyanosis |
| **Findings through further Investigations** | Rising haematocrit<br>Pleural effusion, ascites or asymptomatic gall-bladder thickening |
| **Co-existing conditions** | Pregnancy, Co-morbid conditions, such as diabetes mellitus, hypertension, peptic ulcer, haemolytic anemias and others. Overweight or obese (rapid venous access difficult in emergency). Infancy or old age |
| **Social circumstances** | Living alone; Living far from health facility; Without reliable means of transport |

| **Discharge criteria** | The admitted patients who have recovered from acute dengue infection with visible clinical improvement having no fever for at least 24 - 48 hours, normal blood pressure, no respiratory distress from pleural effusion or ascites, improvement in clinical status (general well-being, return of appetite, adequate urine output, no respiratory distress), persistent platelet count >50,000/cu.mm may be discharged from hospital. |
|---|---|

**N.B. This is suggestive only & MO should judge on case to case basis and decide.**

**Nursing advice in admitted patient**

**High-grade fever:** Record & note temperature 6 hourly & as asked. Tepid sponging/paracetamol. Encourage intake of plenty of oral fluids.

**Abdominal pain:** Severe abdominal pain may be a sign of severe complication, so remain vigilant and inform the treating doctor.

**Bleeding :** Estimate and record the amount of blood loss, monitor vitals and inform the doctor.

**Plasma leakage:** Monitor vitals, Hct and input/output. Encourage oral intake if possible and start IV fluid as per instructions. Strictly follow type of fluid & fluid rate.

**Shock/impending shock :** Monitor vitals, input/output, Hct and sensorium. Start IV fluids/inotropes as per instructions.

**Decreased urine output :** First rule out catheter blockade by palpating the bladder. Flush the catheter if blocked. Continue monitoring vitals, input/output and inform the doctor.

**Respiratory distress :** Check oxygen saturation and administer oxygen via face mask or nasal catheter if SpO2 <90%. Look for cardiac involvement and inform the doctor.

**Convulsions/encephalopathy :** Pay attention to maintenance of airway, breathing and circulation (ABC). Be ready with resuscitation set for emergency intubation and mechanical ventilation.

**Fluid overload:** It may develop during recovery phase of the illness due to fluid shifts. Closely observe for pedal oedema, neck vein engorgement and respiratory distress. Continue strict input/output monitoring during the recovery phase.

**Practices to be kept in mind**

**In summary,** *training in the clinical management of dengue is essential if the clinician is to be able to navigate the patient through the three phases of the illness.*
*Training is needed, first, to understand the disease course and second, to be alert to the physiological problems.*
*Intravenous fluid therapy is life-saving in dengue shock. However, there is a "narrow therapeutic index". In other words, fluids have to be given timely, at the appropriate volume, rate, of the appropriate type (crystalloids, colloid and/or blood) and for the appropriate duration. Therein lies the challenge to physicians for the important practice of fluid titration through frequent and meticulous assessment. Progression of the disease through the critical phase should be tracked in hours of plasma leakage.*
*Recognizing the cues to discontinue intravenous fluid therapy is just as important as knowing when to start it. Given time and haemodynamic stability, other issues such as thrombocytopenia, coagulopathy and raised liver enzymes will recover spontaneously or with supportive care.*

**Annexure 1:**

**Tourniquet test:**

The tourniquet test is part of the new WHO case definition for dengue. The test is a marker of capillary fragility and it can be used as a triage tool to differentiate patients with acute gastroenteritis, for example, from those with dengue.

How to do a Tourniquet Test

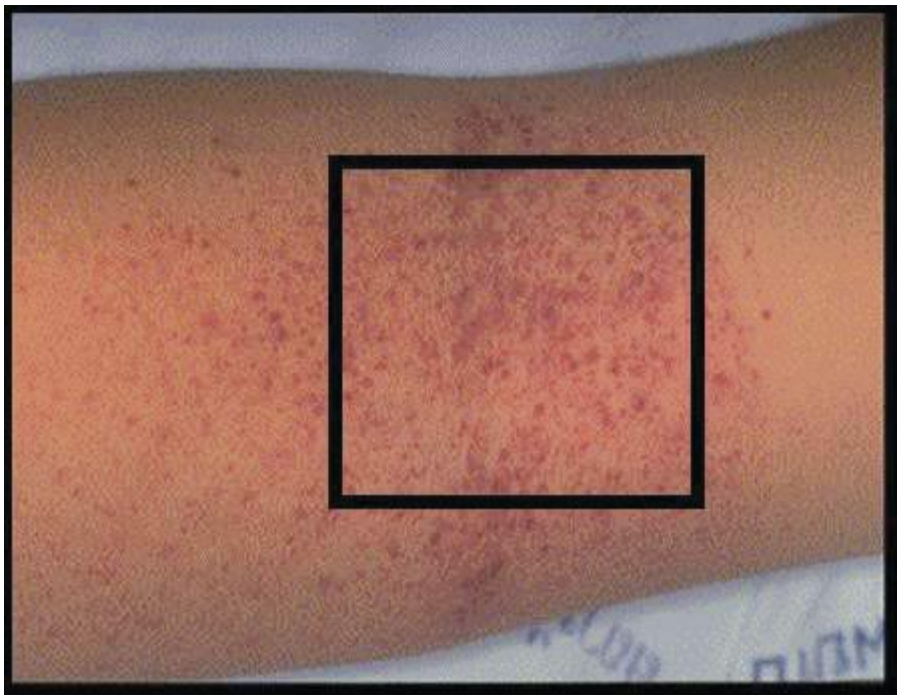
1. Take the patient's blood pressure and record it, for example, 100/70.

2. Inflate the cuff to a point midway between SBP and DBP and maintain for 5 minutes. (100 + 70) ÷ 2 = 85 mm Hg

3. Reduce and wait 2 minutes.

4. Count petechiae below antecubital fossa.

**A positive test is 10 or more petechiae per square inch.** The test is considered positive when 10 or more petechiae per square inch area over forearm are observed. In DHF, the test usually gives a definite positive test with 20 petechiae or more. The test may be negative or only mildly positive during the phase of profound shock.



## Annexure 2 : PLATELET PRODUCTS

### 1. Random donor platelets (RDP).

The platelets are prepared from whole blood. Depending upon the method of preparation, they can be classified as PRP platelets or buffy coat reduced platelets. Either of these platelet products have a volume of 40—50 ml, platelet content of $4.5x10^{10}$ per pack and shelf life of 5 days. These whole-blood derived platelet concentrates are expected to raise the platelet count by 5—7 thousand in adults and 20 thousand in paediatric patients.

### 2. Buffy coat pooled platelets (BCPP).

Pooled buffy coat platelet concentrates are derived from four donations of whole blood (obtained from the buffy coat of ABO identical donors re-suspended in plasma or additive solutions). BCPP has a volume of 160—200 ml, with platelet content ranging from 2.5 to $4.4x10^{11}$ per product.

### 3. Single donor apheresis (SDP).

These are collected by a variety of apheresis systems using different protocols. A single donation procedure may yield one to three therapeutic doses and the donation may be split between two or three bags, depending on counts. SDP are leukocyte reduced; however, in some apheresis systems, filtration may be required for leucocyte depletion. For SDP collection, donors are tested for platelet count, transfusion transmitted infection ('TTT) markers and blood group before collection. The average volume for SDP is 200—300 ml, yield or platelet content is $3x10^{11}$ per bag and is thus equal to 5—6RDP. Thus, it also often regarded as the jumbo pack. SDPs are expected to increase a patient's platelet count by 30—50 000/ul. BCPP serves as an alternative choice of SDP in case of emergency.

a. Compatibility testing is not required for platelet concentrates. Platelet concentrates from donors of the identical ABO group are given and the patient can have the components of choice and should be used as far as is possible. However, administrations of ABO non-identical platelet transfusions are also an acceptable transfusion practice; in particular, when platelet concentrates are in short supply.

b. Similarly, RhD-negative platelet concentrates should be given, where possible, to RhD-negative patients, particularly to women who have not reached menopause. If RhD-positive platelets are transfused to an RhD-negative woman of child bearing potential, it is recommended that anti-D should be given. A dose of 300 IU of anti-D should be sufficient to cover six SDP or 30 RDP RhD-positive platelets within a 6-week period.

c. Platelets with WBC counts of $<8.3x10^5$ in RDP and $<5x10^6$ in SDP or BCPP are regarded as leuco-reduced platelets. Leuco-reduced platelets offer the advantage of decreased CMV transmission, febrile non-haemolytic transfusion reaction and all immunization. Irradiated platelet or blood products are used for patients at risk of TA-GVHD.

d. The standard dose for adults is 5—6 units of random donor platelets or one unit of apheresis platelets or one unit of BCPP, equivalent to $3x1\ 0^{11}$ platelets. For neonates/infants, the dose of the platelets should be 10—15ml/kg of body weight.

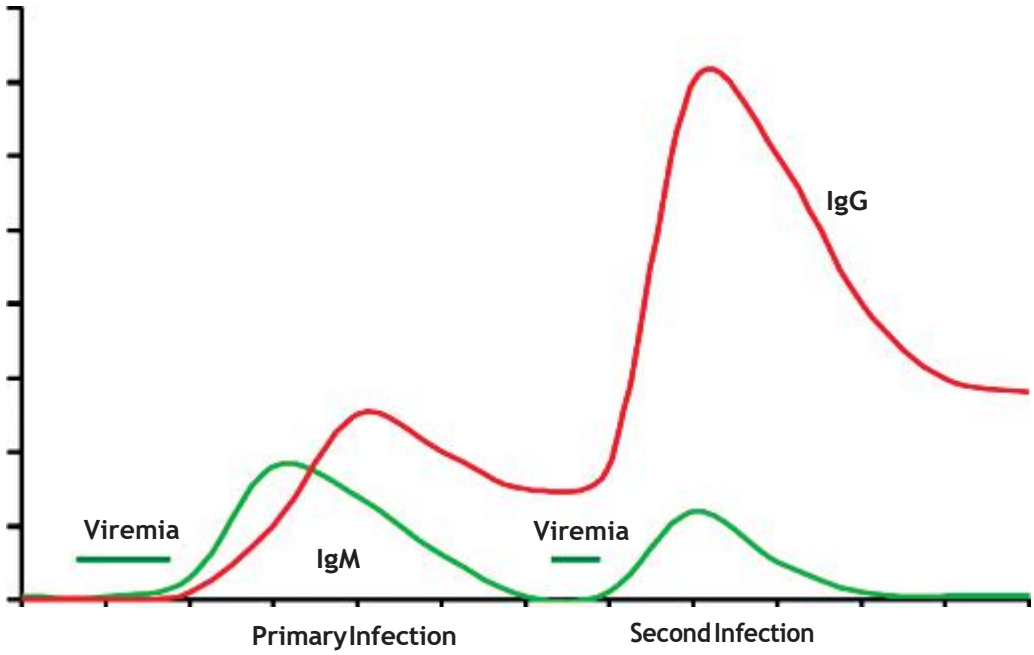
**Annexure 3**

**RDTs**

*A number of commercial RDT kits for anti-dengue IgM/IgG antibodies and NS1 antigen are commercially available, which give the results within 15 to 25 minutes. However, the accuracy of most of these tests is not known since they have not yet been properly validated. Some of the RDTs have been independently evaluated. The results showed a high rate of false positives compared to standard tests, while some others have agreed closely with standard tests. The sensitivity and specificity of some RDTs are also found to vary from batch to batch.*

*According to WHO guidelines, these kits should not be used in clinical settings to guide management of DF/DHF cases. Use of RDT is not recommended also under the disease control programme.*

**Interpretation for Primary and secondary infection**




**IgG + immunoglobulin G; IgM= immunoglobulin M**

*In a primary infection (i.e. when an individual is infected for the first time with a flavivirus), viraemia develops from 1–2 days before the onset of fever until 4–5 days after. Accordingly, anti-dengue IgM specific antibodies can be detected 3-6 days after fever onset. On average, IgM is detected in 50% of cases by days 3–5 after the onset of illness, this figure increasing to 95–98% for days 6-10. Thereafter low levels of IgM are detectable around one to three months after fever. In addition, the primary infection is characterized by slowly increasing but low levels of dengue-specific IgG, becoming elevated at days 9-10. Low IgG levels persist for decades, an indication of a past dengue infection.*

*A totally different picture is observed during a secondary infection, with a rapid and higher increase of anti-dengue specific IgG antibodies and slower and lower levels of IgM. High IgG levels remain for 30–40 days. A short-lasting but higher viremia level characterizes the secondary infection compared to the primary infection. Primary infections are characterized by high levels of IgM and low levels of IgG, while low levels of IgM with high levels of IgG characterize secondary infections.*

## References:


1. National Guidelines for Clinical Management of Dengue Fever. NVBDCP. GoI. 2014

2. Handbook for clinical management of dengue. ISBN 978 92 4 150471 3 (NLM classification: WC 528) © World Health Organization 2012

3. Lum L, Ng C, Khoo E. Managing dengue fever in primary care: A practical approach. Malaysian Family Physician/: the Official Journal of the Academy of Family Physicians of Malaysia. 2014;9(2):2-10.

4. MODULE 8A: IV Fluid Principles. Dengue Clinical Management. WHO Western Pacific Region

5. Clinical Assessment. Tourniquet Test handout. https://www.cdc.gov/dengue/training/cme/ccm/page73112.html

6. Hung NT. Fluid management for dengue in children. Paediatrics and International Child Health. 2012;32(s1):39-42.