GOVERNMENT OF KERALA

Abstract

Health & Family Welfare Department - Kerala State Dengue Fever Treatment and Referral Guidelines 2023 - Orders issued

HEALTH & FAMILY WELFARE (F) DEPARTMENT

G.O.(Rt)No.1654/2023/H&FWD Dated,Thiruvananthapuram, 10-07-2023

Read:- Letter No.DHS/12469/2023-PH1 dated 30.06.2023 from the Director of Health Service

ORDER

Dengue ranks as the most important, rapidly emerged mosquito-borne viral disease in recent years and is endemic in all continents. In order to manage the dengue fever cases effectively and systematically, Government are pleased to issue "Kerala State Dengue Fever Treatment and Referral Guidelines, 2023" incorporating phases of symptomatic Dengue, Dengue in pregnancy, clinical course of Dengue Haemorrhagic Fever (DHF), clinical features of DF/DHF & DSS, case definitions and treatment, hospitalisation criteria, clinical management including circulation of fluids, protocol for Dengue fever risk stratification and referral, as annexed to this order.

(By order of the Governor)
A P M MOHAMMED HANISH
PRINCIPAL SECRETARY

To:
The State Mission Director - National Health Mission, Thiruvananthapuram.
The Director of Health Services, Thiruvananthapuram.
The Director of Medical Education, Thiruvananthapuram.
The Director, Public Health Lab, Thiruvananthapuram.
All District Medical Officers.
Principal Accountant General (A&E/Audit) Kerala,

G.O.(Rt)No.1654/2023/H&FWD

Thiruvananthapuram.
Information & Public Relations (Web & New Media) Department
Stock File/ Office Copy (to file F2/213/2023-HEALTH)

Forwarded /By order

Signed by
Vilasini K V
Date: 10-07-2023 14:25:00

Section Officer

DENGUE FEVER TREATMENT AND REFERRAL GUIDELINES – KERALA STATE 2023

EPIDEMIOLOGY

Dengue ranks as the most important, rapidly emerged mosquito-borne viral disease in recent years and is endemic in all continents. It has shown an increase due to various reasons – construction activities, lifestyle changes, deficient water management, improper water storage, stagnation of rain water in containers lying outside houses and practices leading to proliferation of vector breeding sites in urban, semi-urban and rural areas.

The epidemiology of dengue is an intricate phenomenon which depends upon a complex relationship between epidemiological factors, viz. host (man and mosquito), agent (virus) and the environment (abiotic and biotic factors). The complexity of relationship among these factors eventually determines the level of endemicity in an area. During inter-epidemic periods, the transmission of dengue remains low due to extremes of temperature with low relative humidity, but during monsoons the environment becomes suitable for vectors. Temperatures in the range of 25 C ± 5 C, relative humidity around 80% and innumerable small water collections result in high vector density.

DENGUE VIRUS

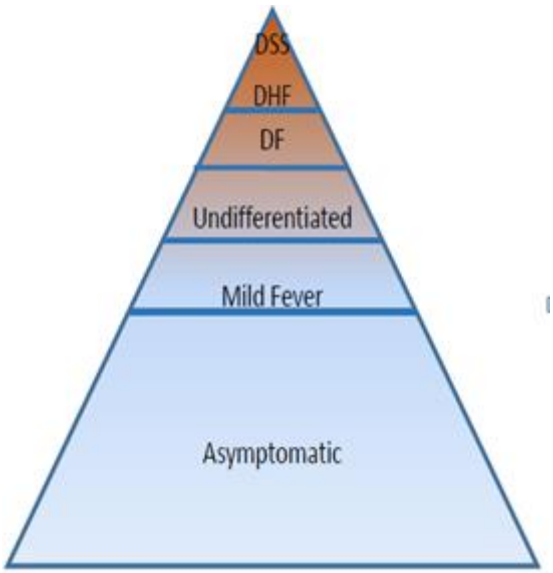
The agent of dengue, i.e. dengue viruses, are categorized under the genus Flavivirus. These viruses contain single stranded RNA and are small in size (50nm). There are four dengue virus serotypes which are designated as DENV-1, DENV-2, DENV-3 and DENV-4. Serotype DENV-5 which is sylvatic has not been detected in Kerala.These serotypes may be in circulation either singly, or more than one can be in circulation in any area at the sametime. Although all four serotypes are antigenically similar, they are different enough to elicit crossprotection only for a few months after infection by any one of them [Heterotypic immunity].Recent studies shows that heterotypic immunity might persist from months to upto two years. Infection with any one serotype confer lifelong immunity to the virus serotype [Homotypic immunity].

MOLECULAR EPIDEMIOLOGY

The four dengue virus serotypes [DENV-1–4], form a phylogenetic group and differ in nucleotide sequence from each other. These are closely related to one another rather than to other flaviviruses and form an antigenic complex of
their own. The four dengue virus serotypes can co-circulate in the endemic areas because the immunity to one serotype does not afford protection from the infection by a heterotopous serotype. 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. The ability of all DENV serotypes to utilize pre-existing heterotypic flavivirus antibody to enhance infection [Antibody dependent enhancement ADE] is a unique feature of DENV which distinguishes it from all other flaviviruses and is considered to be the primary basis of DENV pathogenesis.

CLINICAL MANIFESTATIONS

An estimated 40%–80% of DENV infections are asymptomatic. Symptomatic dengue most commonly presents as a mild to moderate, nonspecific, acute febrile illness; ≤5% of all dengue patients develop severe, life-threatening disease. Early clinical findings are nonspecific but require a high index of suspicion; recognizing early signs of shock and promptly initiating intensive supportive therapy can reduce risk for death among patients with severe dengue by ≥20-fold.



- Infection with one of the four dengue viruses will induce long-lived immunity for that specific virus.
- Because there are four dengue viruses, people can be infected with DENV multiple times in their life.
- Approximately 1 in 20 patients with dengue virus disease progress to develop severe, life-threatening disease called severe dengue.
    - The second infection with DENV is a risk factor for severe dengue.
- Early clinical findings are nonspecific but require a high index of suspicion because recognizing early signs of shock and promptly initiating intensive supportive therapy can reduce risk of death among patients with severe dengue to <0.5%.

Phases of Symptomatic Dengue

- **Febrile Phase**
- Symptomatic dengue begins abruptly after an incubation period of 5–7 days (range 3–10 days) and has a 3-phase clinical course: febrile, critical, and convalescent. Fever typically lasts 2–7 days and can be biphasic. Other signs and symptoms include severe headache; retro-orbital pain; bone, joint, and muscle pain; macular or maculopapular rash; and minor hemorrhagic manifestations, including ecchymosis, epistaxis, bleeding gums, hematuria, petechiae, purpura, or a positive tourniquet test result. Some patients have an injected oropharynx and facial erythema in the first 24–48 hours after onset. Warning signs of progression to severe dengue occur in the late febrile phase around the time of defervescence (i.e., temperature <100.4°F [38°C]) and can include severe abdominal pain, difficulty breathing, extravascular fluid accumulation, progressive increase in hematocrit (hemoconcentration), postural hypotension, lethargy or restlessness, liver enlargement, mucosal bleeding, and persistent vomiting.

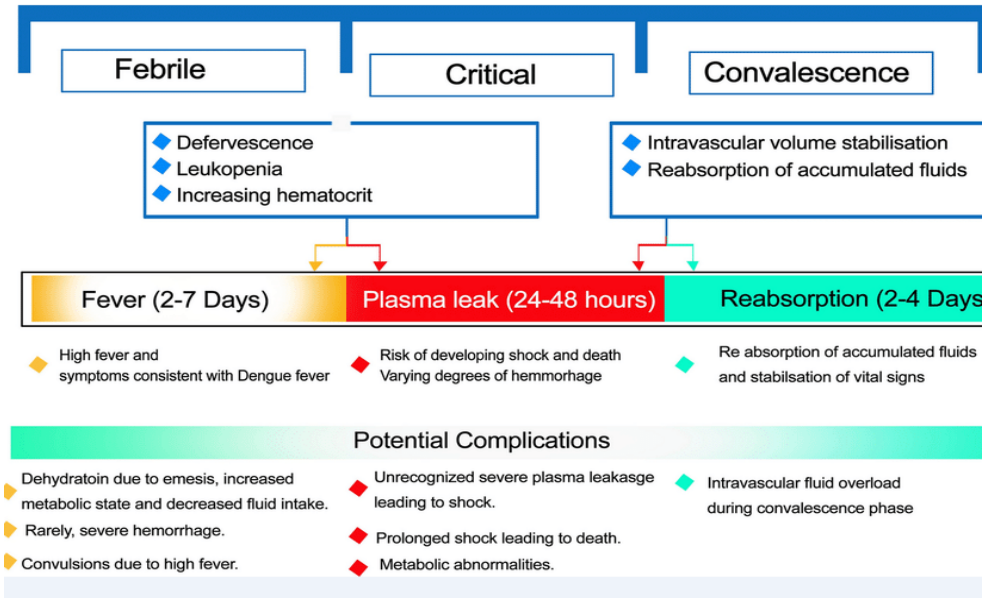
- **Critical Phase**
- The critical phase of dengue begins at defervescence and typically lasts 24–48 hours. Most patients improve clinically during this phase, but those with substantial plasma leak (resulting from marked increase in vascular permeability) progress to severe dengue. Patients with substantial plasma leak can develop ascites or pleural effusions, hemoconcentration, and

hypoproteinemia. Physiologic compensatory mechanisms narrow the pulse pressure as diastolic blood pressure increases, initially maintaining adequate circulation; patients might appear well despite early signs of shock.

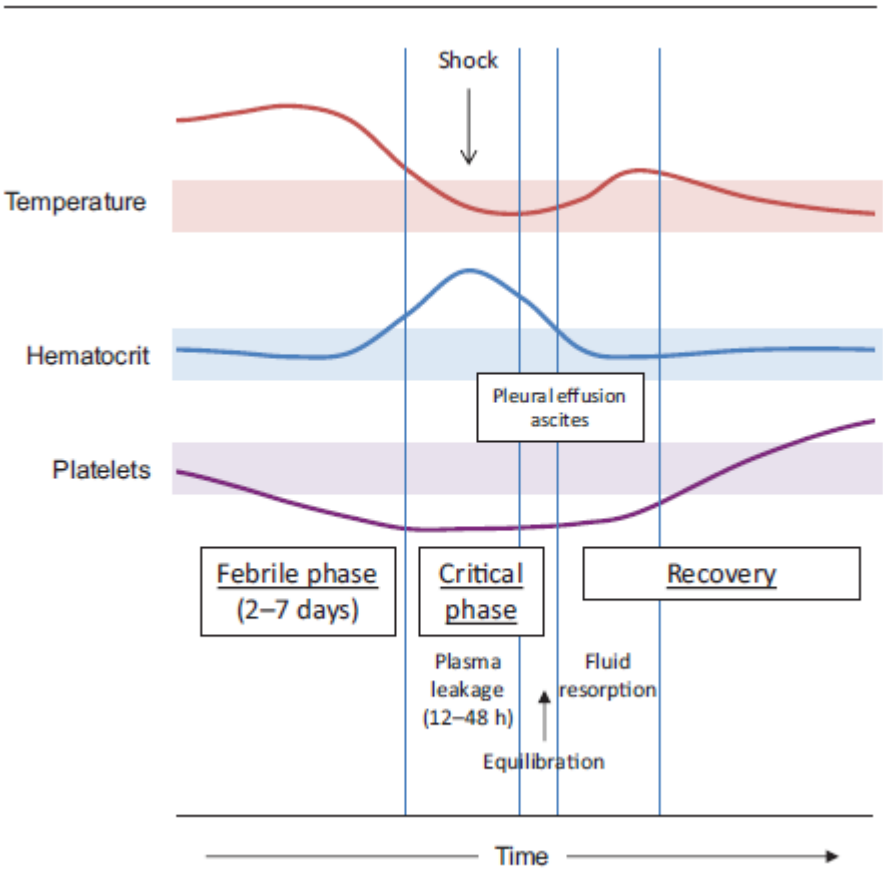
- Once hypotension develops, however, systolic blood pressure rapidly declines, and irreversible shock and death can ensue despite resuscitation efforts. Especially in cases of prolonged shock, patients can develop severe hemorrhagic manifestations, including hematemesis, melena, or menorrhagia. Uncommon manifestations during this phase include encephalitis, hepatitis, myocarditis, and pancreatitis. Laboratory findings commonly include elevated aspartate aminotransferase and alanine aminotransferase, hyponatremia, leukopenia, lymphopenia, thrombocytopenia, and a normal erythrocyte sedimentation rate.

- **Convalescent Phase**
- As plasma leakage subsides, patients enter the convalescent phase and well-being improves; extravasated intravenous fluids and abdominal and pleural effusions are reabsorbed, hemodynamic status stabilizes (although bradycardia could manifest), and diuresis ensues. The patient's hematocrit stabilizes (or falls because of the dilutional effect of the reabsorbed fluid), and the white cell count usually starts to rise, after which the platelet count recovers. The convalescent phase rash might desquamate and be pruritic.

Phases of infection in Dengue Hemorrhagic fever



CLINICAL COURSE OF DENGUE HAEMORRHAGIC FEVER [DHF]



Dengue in Pregnancy

Data are limited on health outcomes of dengue in pregnancy and effects of maternal infection on the developing fetus. Perinatal transmission can occur, and peripartum maternal infection can increase the likelihood of symptomatic infection in the newborn. Signs and symptoms in perinatally infected neonates typically present during the first week of life and include ascites or pleural effusions, fever, hemorrhagic manifestations, hypotension, and thrombocytopenia. Placental transfer of maternal IgG against DENV from a previous maternal infection might increase risk for severe dengue among infants infected at 6–12 months of age when the protective effect of antibodies wanes.

CLINICAL CRITERIA FOR DF/DHF AND 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, haemorrhagic 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, ecchymoses or purpura
3. Bleeding from mucosa, gastrointestinal tract, injection sites or other sites

Plus

c). Thrombocytopenia (<100 000 cells 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 and sex $\geq$ 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 ($\leq$ 20% mm Hg) or hypotension for age, cold and clammy skin and restlessness.

EXPANDED DENGUE SYNDROME

System	Unusual or atypical manifestations
CNS involvement	Encephalopathy, encephalitis, febrile seizures, I/C bleed
G. I. involvement	Acute Hepatitis / fulminant hepatic failure, cholecystitis, cholangitis acute pancreatitis
Renal involvement	Acute renal failure, hemolytic uremic syndrome, acute tubular necrosis
Cardiac involvement	Cardiac arrhythmia, cardiomyopathy, myocarditis, pericardial effusion
Respiratory	Pulmonary oedema, ARDS, pulmonary hemorrhage. pleural effusion
Eye	Conjunctival bleed, macular hemorrhage,visual impairment, Optic neuritis

Tourniquet test: The tourniquet test is performed by inflating a blood pressure cuff to a midpoint between the systolic and diastolic pressure and maintain for five minutes. The test is considered positive when 10 or more petechiae per one 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 (DSS) and may be false negative in obesity.

CASE DEFINITION

Probable DF/DHF:

A case compatible with clinical description of dengue Fever during outbreak:

OR

Non-ELISA based NS1 antigen/ IgM positive.

Confirmed case

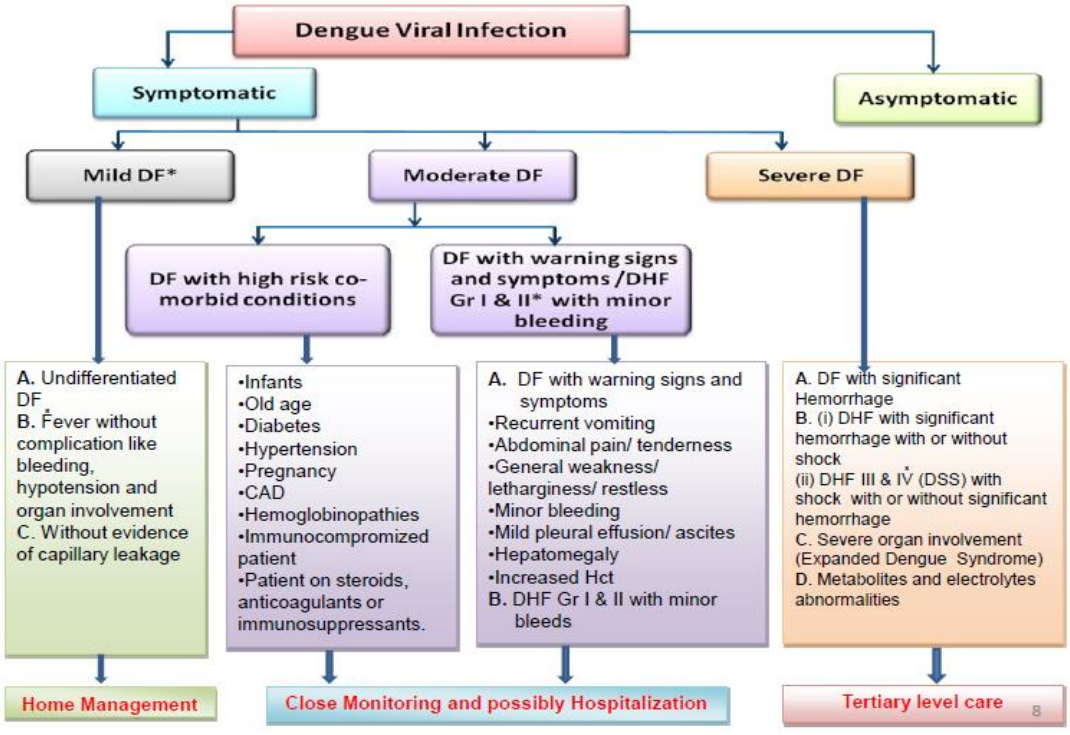
A case compatible with the clinical description of dengue fever with at least one of the following

- Isolation of the dengue virus (Virus culture +VE) from serum, plasma, leucocytes.
- Demonstration of IgM antibody titre by ELISA positive in single serum sample.
- Demonstration of dengue virus antigen in serum sample by NS1-ELISA.
- IgG seroconversion in paired sera after 2 weeks with Four fold increase of IgG titre.
- Detection of viral nucleic acid by polymerase chain reaction (PCR).

WARNING SIGNS TO IDENTIFY DENGUE PATIENTS AT RISK OF PROGRESSION TO SEVERE DISEASE

- Abdominal pain: progressive until it is continuous or sustained and intense, and at the end of the febrile stage.
- Sensory disorder: irritability, drowsiness, and lethargy.
- Mucosal bleeding: gingivorrhagia, epistaxis, vaginal bleeding not associated with menstruation or more menstrual bleeding than usual, and hematuria.
- Fluid accumulation: clinical, on imaging, or both, at the end of the febrile stage.
- Hepatomegaly: more than 2 cm below the costal margin and abrupt onset.
- Vomiting: persistent (three or more episodes in one hour or four episodes in six hours)
- Progressive increase in hematocrit: on at least two consecutive measurements during patient monitoring

DENGUE CASE CLASSIFICATION



***Close monitoring:** Hct, Plt, Hb, fluid intake/output, HR, RR, BP, and Consciousness

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.
DHFI: Above criteria plus positive tourniquet test and evidence of plasma leakage. Thrombocytopenia with platelet count less than 100000/ cu.mm and Hct rise more than 20% over baseline.

DHFII: Above plus some evidence of spontaneous bleeding in skin or other organs (black tarry stool, epistaxis, gum bleeds) and abdominal pain. Thrombocytopenia with platelet count less than 100000/ cu.mm and Hct rise more than 20% over baseline.

DHFIII (DSS): Above plus circulatory failure (weak rapid pulse, narrow pulse pressure < 20 mm Hg, Hypotension, cold clammy skin, restlessness). Thrombocytopenia with platelet count less than 100000/ cu.mm and Hct rise more than 20% over baseline.

DHFIV (DSS): Profound shock with undetectable blood pressure or pulse. Thrombocytopenia with platelet count less than 100000/ cu.mm and Hct rise more than 20% over baseline.

CRITERIA FOR HOSPITALISATION

- Dengue with warning signs
- Dengue with criteria of severe disease.
- Oral intolerance.
- Difficulty breathing.
- Narrowing pulse pressure [≤ 20 mm of Hg].
- Arterial hypotension .
- Acute renal failure.
- Prolonged capillary refill time [> 2 sec].
- Pregnancy .
- Coagulopathy.

CLINICAL PHASE WISE MANAGEMENT OF DENGUE FEVER

Febrile Phase

- **Paracetamol** 10mg/kg q 6^{th} hourly. Avoid NSAIDS, steroids, antibiotics.
- Encourage plenty of isotonic **oral fluids** especially fluids like ORS, milk, salted kanji water, coconut water etc., which would ensure hydration with proper

electrolyte balance. Plain water should be given with caution as it can lead to hyponatremia and may contribute to leakage of fluid into interstitial space.

IV fluids

As far as possible avoid IV fluids in this stage and advocate oral feeds. Only 1/3rd of the fluid administered will remain in the intravascular compartment rest will go to the interstitial compartment and resorption will occur only during the resorptive phase. Fluids administered in the febrile phase will not prevent shock in the critical phase but paradoxically may make treatment more difficult due to the presence of more fluid in the interstitium even before the onset of the leaky phase. If **IV fluids** are indicated due to vomiting or any other Gastrointestinal contraindication then administer only isotonic IV fluids DNS or Plasmalyte @ **1.5ml/kg/hour** ensuring adequate urine output (>1ml/kg/hr) **and** normal vitals.

- Educate regarding warning signs especially on the importance of monitoring urine output.

CRITICAL PHASE

Usually critical phase is marked by defervescence with leucocyte count at its nadir with rapidly falling platelet count. Excessive fatiguability despite defervescence may herald critical phase.Remember patient may be still febrile in this phase. Lecupenia is not mandatory. In fact only 20% of dengue death patients have leucopenia. Leucocytosis may be indicative of occult bleed or coinfection **.**

STEP 1 : Categorise as DF or DHF

Every patient presenting in this stage needs to be *categorised as Dengue fever (DF) or Dengue haemorrhagic fever (DHF).* Usually it's the DHF cases that may progresses to shock, bleeding etc. Dengue fever cases are unlikely to develop severe capillary leak but can manifest with Expanded Dengue syndrome (EDS). More than 50% of EDS result from undetected shock leading to organ failure.

How to identify DHF?

Classically DHF is defined as evidence of **haemorrhage** (spontaneous or positive tourniquet test) and **capillary leak** in a patient with **fever** and platelet count less than **1 lakh.** All the 4 criteria may not be present in the early stage so any patient

with evidence of bleed or capillary leak should be considered as having DHF and closely followed up.

Evidence of capillary leak includes

- Increase in hematocrit by more than 20%.
- Ascites or pleural effusion by Chest X-ray , USS or clinical examination.
- Gall bladder edema
- Serum albumin less than 3.5gm/dl.
- Intense persistent abdominal pain has a positive predictive value of 90% in diagnosing capillary leakage and 82% in diagnosing shock.

Hepatomegaly may precede the development of plasma leakage. S. Albumin is especially useful in cases of anemia, haemorrhage, early IV fluids and absence of a baseline hematocrit. A low ESR < 10mm/hr may help in differentiatingsDengue shock from septic shock.

Step 2 : Look for warning signs or signs of severe dengue

Warning signs

- Intense abdominal pain (PPV 90% for plasma leak and 82% for shock). Often precedes shock by 24 hours. The epigastric pain is refered pain due to sudden accumulation of fluid in perirenal and pararenal spaces

- Vomiting > 3 times in an hour or 4 times in 6 hour.
- Clinical fluid accumulation as ascites or pleural effusion without respiratory distress or hemodynamic compromise.
- Mucosal bleeding
- Irritability or lethargy : Both are believed to occur due to cerebral hypoperfusion.
- Hepatomegaly more than 2 cm due to hepatic congestion, haemorrhage, fatty metamorphosis,pushing down of liver by pleural effusion
- Progressive rise in hematocrit in at least 2 occasions.

Severe Dengue

- Shock or respiratory distress due to plasma leakage
- Clinically significant bleed as considered by the attending physician.
- Severe organ involvement- Hepatitis, myocarditis, Encephalitis.

Early stages of shock are characterised by narrow pulse pressure as in dengue there is no circulation of lipopolysaccharides to cause a hot phase. *Wide pulse pressure shock may occur if there is coinfection with bacteria, hepatic failure or neurogenic shock due to CNS involvement*

Step 3 Investigations to be sent in critical phase

- CBC with PCV and ESR
- Blood grouping cross matching
- PT INR
- RFT
- LFT
- S. Albumin
- Blood glucose
- Serum calcium
- Cardiac enzymes – Trop T or Trop I, if myocarditis is suspected.
- Blood gas analysis
- Urine analysis
- Urine myoglobin in case of severe myalgia with acute kidney injury
- USG and echo
- In case of persisting fever into critical phase Serum Ferritin,LDH, CRP must be sent.

Step 4 Treatment

Dengue with warning signs

Start with 6ml/kg/hour with a target urine output of 1ml/kg/hour. Escalate or deescalate fluid rate according to urine output every hour(WHO recommends 10ml/kg/hour in children but in most children it may be highly deleterious in the

later shock stage as it will accumulate in the interstitium compromising respiration and fluid and nutrient delivery to organs subsequently]. Hence always aim to administer the minimum required fluid with the aim of matching rate of fluid administration with rate of leak. Oral fluids taken should also be included in the fluid intake..

Monitor vitals hourly and hematocrit 4 hourly.

*In case of children, if more than **three 10ml/kg/hour** boluses without improvement or rising hematocrit it should be considered as severe dengue and managed accordingly*.

Treatment of Shock

Consider the patient in shock if

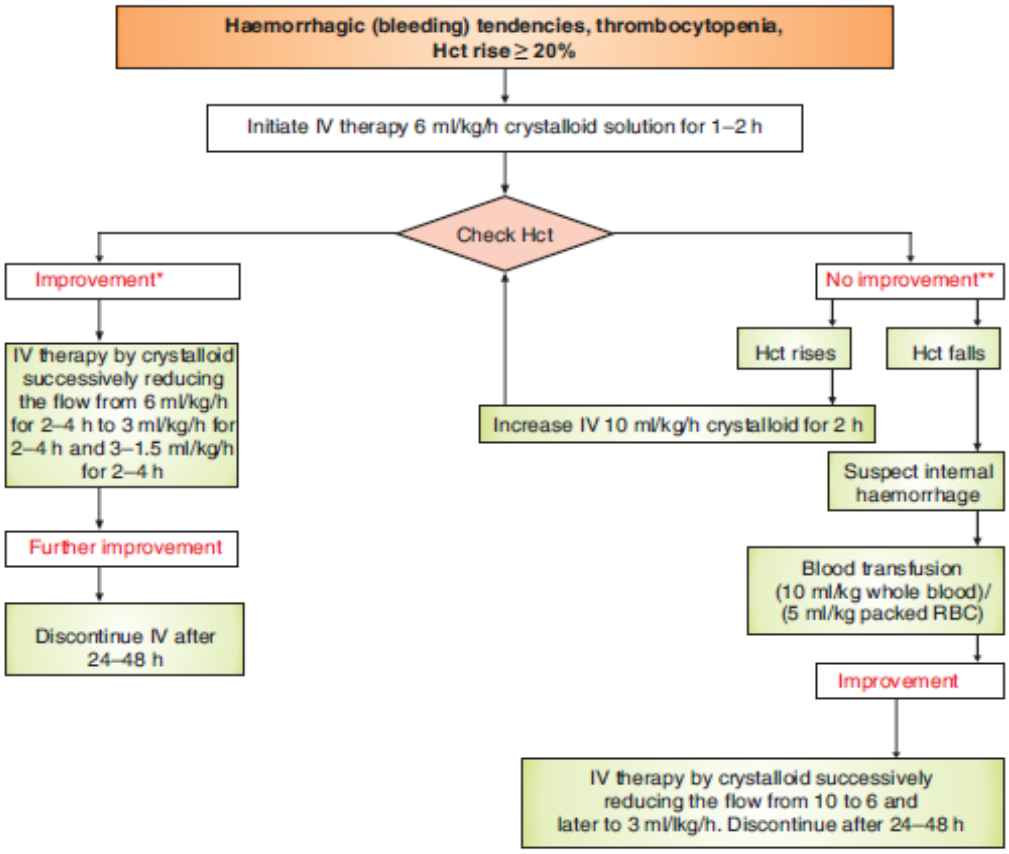
- Pulse pressure is less than 20mm Hg or
- Rapid, low volume pulse with any 2 of the following (CFT >2seconds, cold clammy skin, mottling)
- MAP less than 70mm of Hg in adults and those above 10 years of age, MAP less than 50 in 1-6month, <55mm in 6-12 months, < 60mm in 6-8 yrs, < 65mm in 8- 10 yrs is considered hypotension.

Fluids

General considerations

- Use ideal body weight for calculating fluid requirements in obese patients.
- For patients in shock limit fluid administration to 24 to 48 hours. For those without shock 60 to 72 hours fluid may be needed.
- Fluid intake calculations must include oral and IV.
- Intake output chart must be maintained hourly
- Try to limit fluids to maintainance + 5%.
- Rate of fluid administration should match the rate of fluid leak.

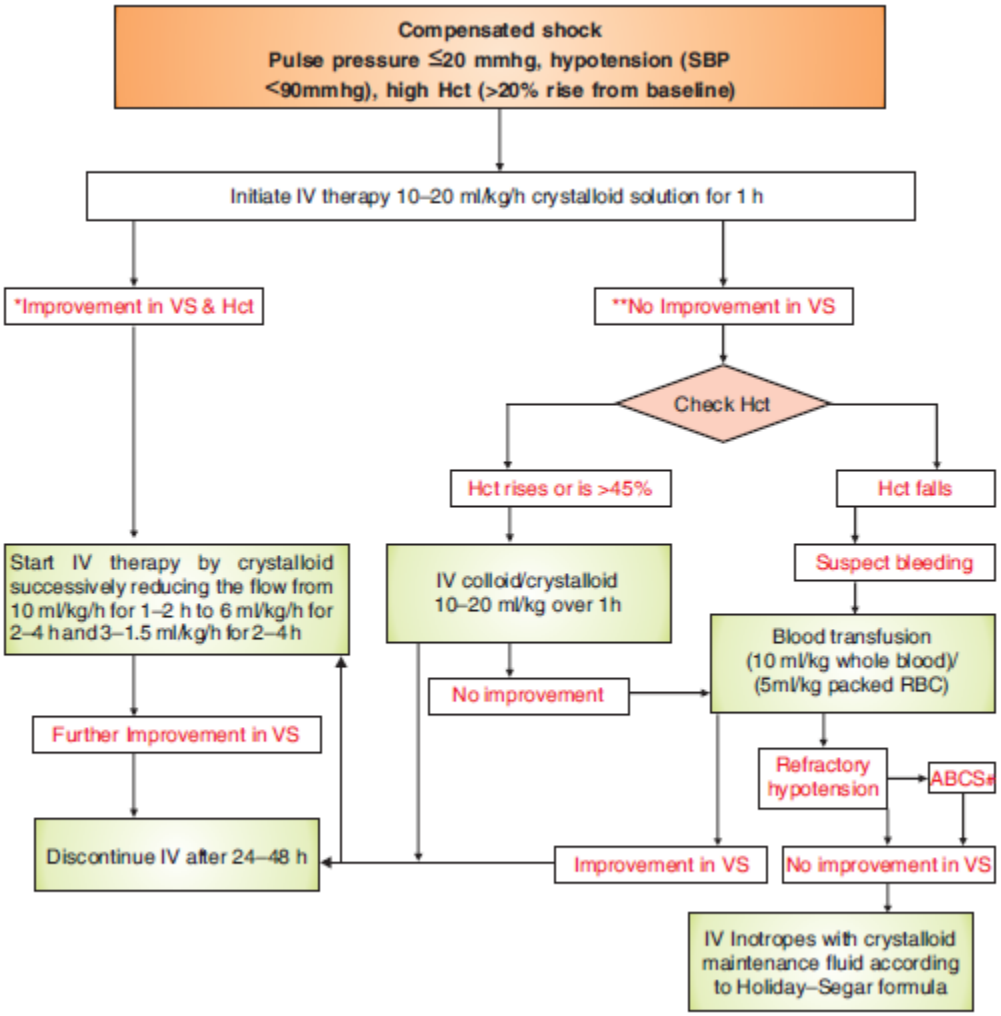
VOLUME REPLACEMENT ALGORITHM FOR PATIENTS WITH DHF 1 &2



Notes:
*Improvement: Hct falls, pulse rate and blood pressure stable, urine output rises
**No Improvement: Hct or pulse rate rises, pulse pressure falls below 20 mmHg, urine output falls

* Fluid administration must be tailored to individual patient. Always monitor urine output closely.Target urine output 0.5 to 1ml per kg per hour. once urine output target attained, rapidly decrease rate of fluid administration.

VOLUME REPLACEMENT ALGORITHM FOR DHF GRADE III

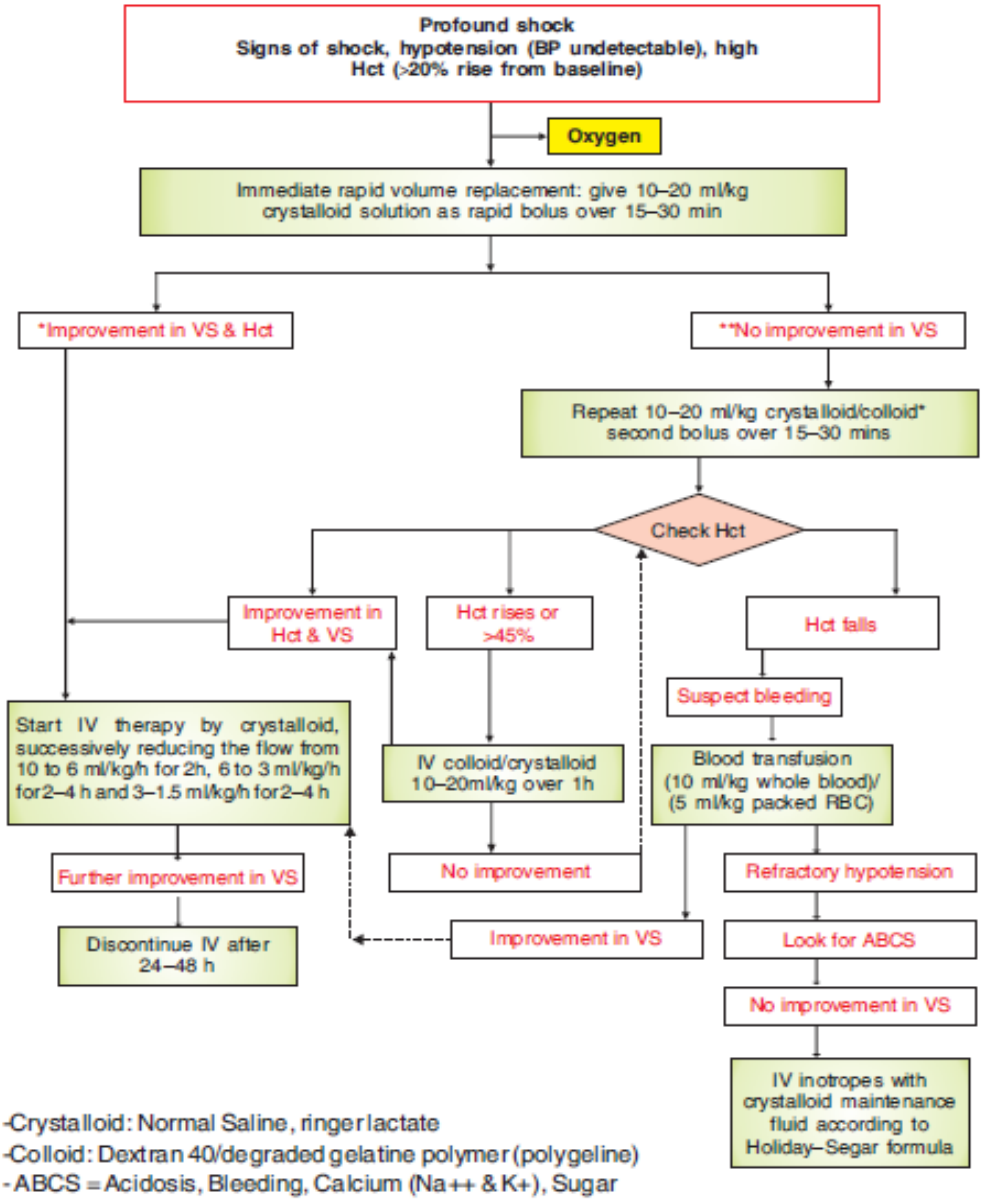


Crystalloid: Normal Saline, ringer lactate
Colloid: Dextran 40/degraded gelatine polymer (polygeline)
ABCS = Acidosis, Bleeding, Calcium (Na++ & K+), Sugar

Notes:
*Improvement: Hct falls, pulse rate and blood pressure stable, urine output rises
**No improvement: Hct or pulse rate rises, pulse pressure falls below 20 mmHg, urine output falls

- Unstable vital signs: urine output falls, signs of shock
- In cases of acidosis, hyperosmolar or Ringer's lactate solution should not be used
- Serial platelet and Hct determinations: drop in platelets and rise in Hct are essential for early diagnosis of DHF
- Cases of DHF should be observed every hour for vital signs and urine output

VOLUME REPLACEMENT ALGORITHM FOR DHF IV



*Fluid administration should be tailored to individual patient needs. Fluid boluses over one hour are often preferred over rapid push pull administration of fluid as it can precipitate bleeding.

Treatment of Dengue shock

- Start with 20ml/kg / hour if absent pulse or 10ml/kg/hour of Normal saline (adult 500ml/hour) if pulse present with hypotension. (WHO recommends 20ml/kg in 15 to 30 mts). *Pushing in fluids by push pull method in children with absent pulse was observed to lead to increased risk of immediate massive haemorrhage and more capillary leak due to increase in shear pressure on the capillary endothelium*.
- **Monitor vitals every 15 minutes**. Once the pulse appears decrease rate to 10ml/kg /hour. Measure hematocrit 2 to 4 hourly and also before and after colloid and blood transfusion.
- If the patient does not improve continue 10 – 20 ml/kg / hour monitoring every 15 minutes to decide on decrease in rate.
- If after 60ml/kg of crystalloid if patient remains in shock consider colloid. If patient is already puffy then colloid may be given after 2 boluses.

Dextran 40 is preferred over hexa startch as colloid. Give in a dose of 10ml/kg/hour. Limit to 30ml/kg/day. Dextran 10ml/kg can decrease PCV by 10 points, if PCV fall is more than that consider occult bleed.

- If no improvement a second dose of colloid may be given. 20% albumin can also be considered.
- Look for ABCD if shock continues
    - A – Acidosis. Give bicarbonate 1 ml/kg as acidosis favours bleeding
    - B – Blood. Whole blood 10ml/kg or packed cell 5ml/kg is used. Reconstituted blood can also be used.
      Indications for blood transfusion.
        - Clinically severe bleed > 6-8ml/kg of IBW or 300ml in adults.
        - Worsening acidosis.
        - Unstable vitals with normal or low PCV.
        - Rise in PCV of less than 20 % with persistent shock .
        - Refractory shock inspite of 60ml/kg of fluids.

It is mandatory to check PCV before and after transfusion. If PCV does not rise after transfusion should consider as continuing bleed and blood transfusion repeated if *vitals remain unstable*

Rate of blood transfusion depends on vitals if in shock give over 1 hour otherwise 3 – 5ml/kg/hr

- C – Calcium. If hypocalcemia present give calcium gluconate 1ml/kg slow IV after equal dilution with D5 alternatively calcium infusion at a dose of 0.1 -0.2 ml/kg/hr can also be given.
- D – Dextrose-check for hypoglycemia and if present correct it.

- **Platelets** : There is no role for prophylactic platelet transfusion . May consider if less than 10,000/mm3 or if active massive bleed is continuing in spite of coagulopathy correction . A ratio of PRC : FFP : platelet of 2:1:1 may be considered in massive bleed. For surgery platelet count of >50,000cells/mm3 and for neurosurgery and eye surgery a count of more than 1 lakh is needed.

- **Coagulopathy** : Priority is for fluid and blood transfusion but if bleeding continues correction of coagulopathy is warranted. Check fibrinogen level if less than 100mg/dl give Cryoprecipitate @ 0.15 U /kg or 2 units per 10 kg.
- If the patient clinically improves decrease rate to 6 ml/kg/hr – 3ml/kg/hr – 1.5 ml/kg /hr monitoring urine output and ensuring urine output of 1ml/kg /hr**.**

Treatment of fluid overload with shock

In a patient with massive capillary leakage resulting in gross ascites/pleural effusion etc, further crystalloid administration to correct shock will result in excessive pleural effusion/ascites leading to respiratory distress. In such situations instead of crystalloids, colloids like Dextran 40 or 20% human albumin should be administered.

- IV Dextran 40,10ml/kg over 1 hour. Usually BP is restored in 10 -30 minutes . Then administer inj Furosemide 0.25mg/kg. Alternatively furosemide infusion can also be started but this leads to slower resolution of respiratory distress but better hemodynamic stability. Subsequently adjust fluid rate to obtain a urine out put of 0.5- 1ml/kg/hour. Monitor every 15minutes as patient can go into shock due to excessive diuresis. In case of severe fluid overload Dextran may be repeated with repeat Furosemide at 30 to 60 minutes interval, but subsequent dose of furosemide should be half of the initial dose if the first

dose resulted in high urine output and double the dose of furosemide if the 1st dose did not result in diuresis.

- If there is no urine output check the intravascular status . Higher doses (double dose)of furosemide may be tried.If the IVC is full it may indicate acute kidney injury and need for early initiation of RRT.
- Peritoneal dialysis catheter insertion will remove ascitic fluid leading to decrease in **intra abdominal pressure** which in turn will increase venous return to heart and improve renal perfusion often reversing renal failure.
- Other alternative RRT like CVVH can be opted for depending on availability and expertise.
- If above management fails pleural and ascitic fluid tapping may be done after informed consent of risk of bleeding to decrease respiratory distress and control of intra abdominal hypertension.

Ancillary treatment

- **HLH [secondary Hemophagocytic lymphohistiocytosis]** : If fever is persisting into critical phase and counts are decreasing think of infection associated HLH and screen for the same by measuring serum ferritin, triglycerides, fibrinogen . Ferritin more than 10,000 is highly sensitive and specific in diagnosing infection associated HLH. Treatment with IVIG + steroids +/- plasmapharesis may be considered.
- **Infections** Persisting hypoalbuminemia after 48 hours with fever and shock may indicate secondary infection leading to septic shock. Procalcitonin estimation, blood culture and escalation of antibiotic must be done if needed. Screen for co-infections like leptospirosis, scrub etc also.
- **Hepatic Injury** : If SGOT/ SGPT more than 1000 IU/ L consider
  - NAC [N-acetyl cysteine] 150mg /kg over 1 hour followed by 100mg /kg as infusion in D5 over 24 hours and continue it till PT INR less than 1.5.
  - Oral rifaximine 30mg/kg/day for gut sterilisation
  - Avoid hypoglycaemia
  - Measure phosphorous if low supplement phosphorous .
  - Treat hypokalemia if present

- Avoid constipation- lactulose may be given to ensure 2 – 3 semi solid stools / day.
- Inj. Vitamin K 0.3 to 0.5 mg/kg stat.
- If GI bleed present aspirate GI content .
- Inj pantoprazole 1mg/kg IV OD
- Recombinant factor VII in case of massive bleed associated with hepatic failure.
- **Renal Injury** - Grade according to RIFLE criteria
    - Avoid nephrotoxic drugs
    - Adjust dose of drugs being received as needed
    - Early initiation of RRT in situations where improvement in intravascular fluid status is unaccompanied by improvement in urine output.
- **Myocardial injury**

  May manifest with rhythm abnormalities, ST - T changes, poor ejection fraction and elevated cardiac enzymes.
    - Fluid management in patients with myocarditis and acute kidney injury should be guided by IVC volume status.
    - Symptomatic treatment of rhythm abnormalities
    - Maintain normal electrolytes including calcium, magnesium, potassium and phosphorous.

- **Hyperglycemia**

  If 2 values of blood glucose are above 180mg/dl titrate insulin infusion to achieve a target of blood glucose of 100 – 150mg/dl
- **Encephalitis**

  Death usually occurs due to massive brain edema leading to herniation. Patient may present with brain stem involvement during any phase of Dengue. A significant proportion of children with Dengue encephalitis present without warning signs.
    - Treat seizure or add prophylactic fosphenytoin
    - Give 3% normal saline 5ml per kg over 1 hour. Target serum sodium level of 145 to 150 meq per litre.

- Use isotonic fluids for resuscitation. Too much fluid may exacerbate ICP hence use judiciously.
- Intubate if GCS less than 8 or rapidly decreasing by more than 3 points. Take all precautions to prevent peri intubation surge in ICP. Hyperventilate, sedate with lorazepam 0.1mg/kg and fentanyl 1mcg/kg. Give Lidocaine 1mg/kg to prevent ICP surge due to gagging. Paralyse with vecuronium 0.1mg/kg and intubate.
- Post intubation keep a higher rate targeting a Pco2 of 30 - 35mm in the first 12 to 24 hours. This would also help to maintain pH during shock so that inotropes can act better.
- Monitor urine output and pupillary reactions closely. Increase in urine output is usually indicative of central Diabetes insipidus. Measure urine and serum sodium and osmalality and confirm the diagnosis. DI if present should be treated by replacing the urine output with Isolyte P and IV vasopressin added to titrate urine output to 2- 3 ml/kg/hour.
- Polyuria can also be due to cerebral salt wasting hence check urinary sodium and use a fluid with sodium content similar to urine to replace urinary loss.
- Consider steroids in refractory cases.

- **Resorption phase**

Charecterised by improvement in general well being, increase in serum albumin and stabilisation of vitals with fall in PCV and increased urine output. Stop IV fluid completely. Monitor intravascular fluid status. If fluid status good with normal vitals and increasing respiratory rate rule out pneumonia and consider resorption pulmonary edema.

- If not spontaneously diuressing consider Furosemide infusion @ 0.1 – 1mg/kg/hour.
- Hypokalemia may be present which needs treatment.

Oral potassium chloride 2 meq/kg /day to be added if potassium less than 3 .5meq/L with no ECG changes. If potassium less than 2.8 meq per litre or

with ECG changes give IV correction @ 0.3meq/kg/hr for 3 hours ensure that the peripheral concentration of potassium is ideally not more than 80 meq/litre.

CALCULATION OF FLUIDS

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).
The maintenance fluid should be calculated using the Holiday and Segar formula as follows

Body weight in kg	Maintenance volume for 24 hours
<10 kg	100 ml / 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 a child weighing 40 kgs, the maintenance is: 1500 + (20x20) = 1900 ml. Amount of fluid to be given in 24 hrs is calculated by adding maintenance + 5% dehydration which is equivalent to 50 ml/kg. This should be given in 24 hrs to maintain just adequate intravascular volume and circulation. Therefore for a child weighing 40 kg the fluid required will be 1900 + (40 x 50)=3900 ml in 24 hrs. For intravenous fluid therapy of patients with DHF, four regimens of flow 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 bodyweight and rate of flow of fluid volume for the Five regimens are given in Table 1.

Choice of intravenous fluids for resuscitation

There is no clear advantage to 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.

Crystalloids

Normal plasma chloride ranges from 95 to 105 mmol/L 0.9% Saline 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 probably 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, gelatine 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.

Table 1. Requirement of fluid based on bodyweight

Bodyweight (In kgs)	Volume of fluid to be given in 24 hrs Maintenance + 5% deficit	Rate of fluid (ml/hours)				
		Regimen 1 1.5ml/kg	Regimen 2 3ml/kg	Regimen 3 6ml/kg	Regimen 4 10ml/kg	Regimen 5 20ml/kg
5	500+250=750	8	15	30	50	100
10	1000+500=1500	15	30	60	100	200
15	1250+750=2000	23	45	90	150	300
20	1500+1000=2500	30	60	120	200	400
25	1600+1250=2850	38	75	150	250	500
30	1700+1500=3200	45	90	180	300	600
35	1800+1750=3550	53	105	210	350	700
40	1900+2000=3900	60	120	240	400	800
45	2000+2250=4250	68	135	270	450	900
50	2100+2500=4600	75	150	300	500	1000
55	2200+2750=4950	83	165	330	550	1100
60	2300+3000=5300	90	180	360	600	1200

Note:

- 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. Hypervolumea 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 R3, and from R-3 to R-1 in a stepwise manner.

- Remember that ONEML 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

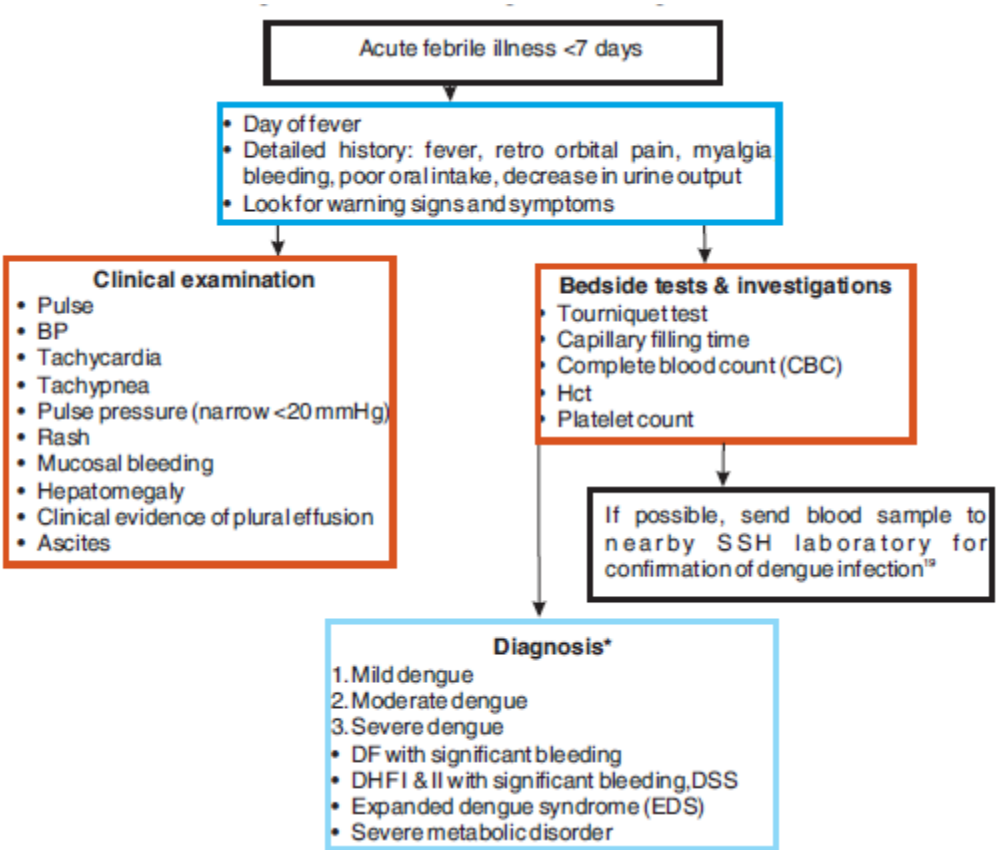
required. The decision about the speed of IV fluid should be reviewed every 1-3 hours. The frequency of monitoring should be determined on the basis of the condition of the patient.

PROTOCOL FOR DENGUE FEVER RISK STRATIFICATION AND REFERRAL

Multiple studies have shown that case fatality rate[CFR] in dengue during outbreak years is high due to ineffective utilization of available resources. Majority of severe dengue deaths happens in tertiary care centres. Despite state of art infrastructure, critical care support and protocolized management, death in severe dengue still occurs. These deaths are because of inadequacies in risk stratification and allocation of resources resulting due to the sheer number of patients getting referred to tertiary care centers. The huge number of referrals during outbreaks stretches the available resources to the maximum and there is an improper allocation of resources.

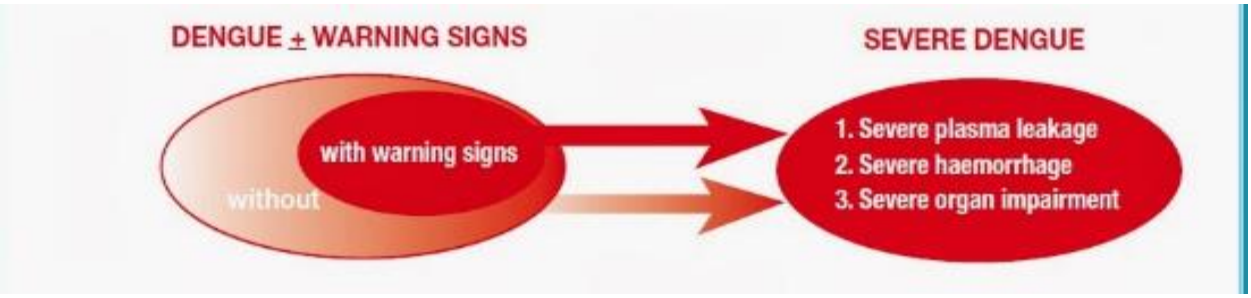
The hallmark of DHF is capillary leakage and for effective utilization of resources, it has to be ensured that only patients with evidence of capillary leakage or expanded dengue syndrome [myocarditis/ARDS/encephalitis] reach tertiary care centres. Referral based on degree of thrombocytopenia alone will lead to unnecessary crowding in tertiary care centres which might comprise the intensive monitoring required for patients with DHF and DSS.

Diagnosis of Dengue Cases


Acute febrile illness <7 days
• Day of fever
• Detailed history: fever, retro orbital pain, myalgia bleeding, poor oral intake, decrease in urine output
• Look for warning signs and symptoms
Clinical examination
• Pulse
• BP
• Tachycardia
• Tachypnea
• Pulse pressure (narrow <20 mmHg)
• Rash
• Mucosal bleeding
• Hepatomegaly
• Clinical evidence of plural effusion
• Ascites
Bedside tests & investigations
• Tourniquet test
• Capillary filling time
• Complete blood count (CBC)
• Hct
• Platelet count
If possible, send blood sample to nearby SSH laboratory for confirmation of dengue infection[19]
Diagnosis*
1. Mild dengue
2. Moderate dengue
3. Severe dengue
• DF with significant bleeding
• DHF I & II with significant bleeding, DSS
• Expanded dengue syndrome (EDS)
• Severe metabolic disorder

Classification of Dengue Severity

Dengue without warning signs (DNWS)	Dengue with warning signs (DWWS)	Severe dengue (SD)
Person who lives or has traveled to areas with dengue transmission in the last 14 days and presents fever, usually of 2 to 7 days duration, and at least 2 of the following criteria: 1. Nausea / vomiting 2. Exanthema 3. Headache / retro-orbital pain 4. Myalgia / arthralgia 5. Petechiae or tourniquet test (+) 6. Leukopenia	Every dengue case that, near and preferably at defervescence, presents one or more of the following signs: 1. Intense abdominal pain or tenderness 2. Persistent vomiting 3. Fluid accumulation 4. Mucosal bleed 5. Lethargy/restlessness 6. Postural hypotension (lipothymia) 7. Liver enlargement >2 cm 8. Progressive increase in hematocrit	Every dengue case that has one or more of the following manifestations: 1. Shock or respiratory distress due to severe plasma leakage. 2. Severe bleeding: based on evaluation by the attending physician 3. Severe organ involvement (liver impairment, myocarditis, etc.)
	Requires strict monitoring and immediate medical intervention	
First level Ambulatory management	**Admit to hospital or dengue units**	**Hospitalize in ICU**



INTERVENTION GROUPS

	Group A	Group B1	Group B2	Group C
Severity classification	Dengue without warning signs (DNWS)	Dengue without warning signs (DNWS)	Dengue with warning signs (DWWS)	Severe dengue (SD)
Group criteria	Tolerate sufficient volumes of oral fluids Urinate at least once every 6 hours No associated diseases or conditions, or social risk	Presence of associated diseases or conditions: • Pregnancy • ≤ 1 years old • ≥ 65 years old • Morbid obesity • Hypertension • Diabetes mellitus • Asthma • Renal damage • Hemolytic diseases • Chronic hepatomegaly • Peptic ulcer disease or gastritis of any etiology • Being treated with anticoagulants • Other or, Presence of social risk: • The patient lives alone or far from where they can receive medical care • Does not have transportation • Lives in extreme poverty	Every dengue case that, near and preferably at defervescence, presents one or more of the following signs: 1. Intense abdominal pain or tenderness 2. Persistent vomiting 3. Fluid accumulation 4. Mucosal bleed 5. Lethargy/restlessness 6. Postural hypotension (lipothymia) 7. Liver enlargement >2 cm 8. Progressive increase in hematocrit	Every dengue case that has one or more of the following manifestations: • Shock or respiratory distress due to severe plasma leakage. • Severe bleeding: based on evaluation by the attending physician • Severe organ involvement (liver impairment, myocarditis, etc.)
Management level of care	First level. At-home treatment	Possible referral to hospital or dengue units. Requires observation and treatment of their associated infection or condition.	Hospital or dengue units. Requires IV fluid administration.	Intensive Care Unit. Requires emergency treatment

CRITERIA FOR HOSPITALISATION OF DENGUE PATIENTS

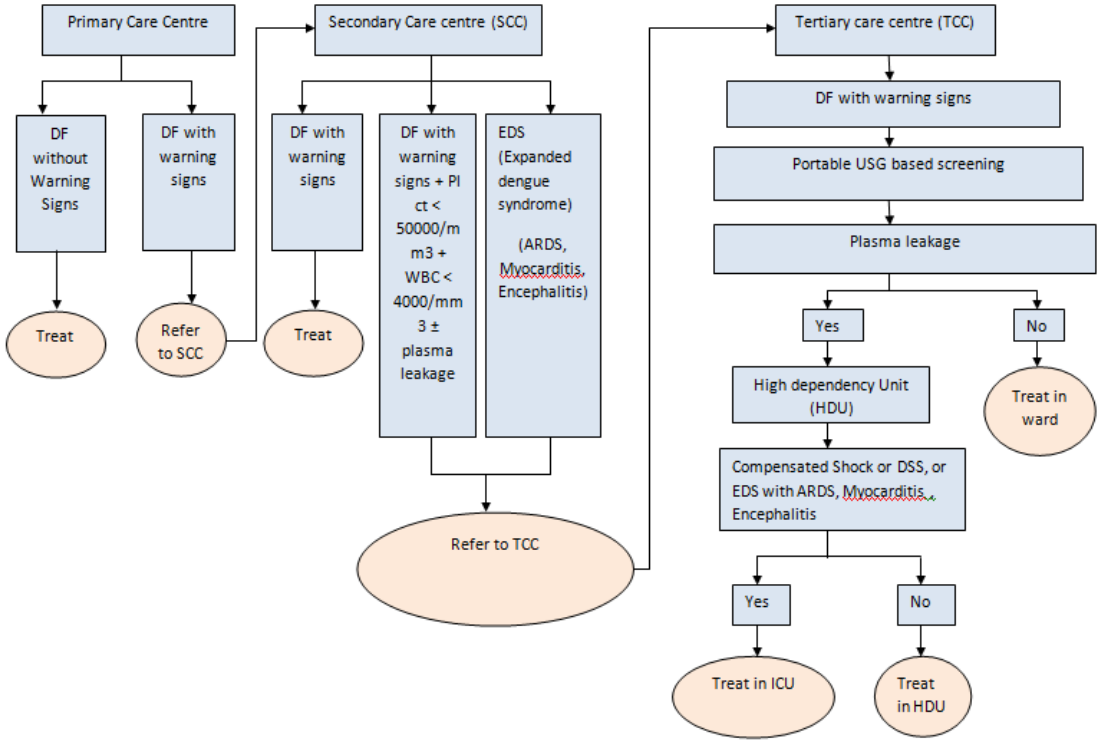
The following hospitalization criteria are based on a systematic review and meta-analysis conducted in 2019. A total of 217 studies were identified that included 237,191 patients with a dengue diagnosis in whom the relationship between different potential prognostic factors and progression to severe disease was evaluated.

Criteria for the hospitalization of dengue patients
Patients with dengue and any of the following symptoms should be hospitalized: • Dengue with warning signs • Severe dengue • Intolerance to oral administration of fluids • Respiratory distress • Narrowed pulse pressure • Prolonged capillary perfusion (more than 2 seconds) • Hypotension • Acute renal failure • Pregnancy • Coagulopathy
Additional considerations: Other factors that may determine the need to hospitalize dengue patients include the presence of comorbidities, very young and very old age, social and/or environmental conditions. The decision to admit patients with these conditions should be individualized.

CRITERIA FOR DISCHARGE OF DENGUE PATIENTS

Criteria for discharge of dengue patients	
Clinical criteria	• Absence of fever for 48 hours without administration of antipyretics • Improvement of clinical status (general well-being, good appetite, normal hemodynamic status, normal or increased diuresis, no respiratory distress or evidence of bleeding)
Laboratory criteria	• Increasing trend for platelet count • Stable hematocrit, without intravenous fluids

RISK STRATIFICATION BASED REFERRAL PROTOCOL FOR DENGUE IN KERALA



- *All patients with warning signs, leucopenia and thrombocytopenia should ideally be screened using USG abdomen to look for early evidence of capillary leakage like Gall bladder wall edema.*

If USG is not available for early detection of capillary leakage, the following surrogate markers of capillary leak may be used.

1. Increase in hematocrit by more than 20% from baseline.
2. Ascites or pleural effusion by Chest X-ray or clinical examination.
3. Serum albumin less than 3.5gm/dl.
4. Intense persistent abdominal pain has a positive predictive value of 90% in diagnosing capillary leakage and 82% in diagnosing shock.
5. *Hepatomegaly may precede the development of plasma leakage*.

- *Those with evidence of plasma leakage should be shifted to a high dependency area, earmarked in the ward where protocolised fluid management algorithm should be strictly implemented.*
- *For this stratification, nurses and all doctors should be trained to maintain mandatory patient monitoring charts[Annexure]*.
- *During large dengue outbreaks, medical /nursing students can also be trained to maintain patient monitoring charts*.
- Those patients with compensated shock with MODS, Dengue shock syndrome and expanded dengue syndrome in the form of myocarditis, ARDS or encephalitis should be shifted to Intensive care units.
- All doctors and nurses should be trained with regard to optimization of ABCSF [acidosis, bleeding, hypocalcemia, hypoglycemia and fluid status] in severe dengue.

References

1. National Guidelines for Clinical Management of Dengue Fever-Government of India 2015.
2. Guidelines for the Clinical Diagnosis and Treatment of Dengue, Chikungunya and Zika-PAHO 2022
3. Dengue Treatment Protocol SAT PICU 2019.
4. Clinical practice guidelines for Dengue/ Dengue Hemorrhagic fever management for Asian economic community – Thailand.
5. National guidelines for the management of Dengue fever and Dengue Haemorrhagic fever in children and adolescents. December 2010.Ministry of health Srilanka.
6. Handbook for clinical management of Dengue. WHO 2012.

ANNEXURES

Top sheet for Monitoring of Dengue/ Suspected Dengue Cases									
..... **Hospital**					Patient Regn. No.-				
Name		Age (y/m)		Sex	M/ F/ O	Ward		Bed no.	
Parameters on admission: Admission date - ...../...../2020									
Fever for	..... days	Co-morbidity		Bleeding.	Y / N	Shock	Y / N	Tourniquet Test	Pos / Neg

Lab test for Dengue: NS1 ELISA/ IgM ELISA Result – Positive/ Negative	Date of sample:	Date of test: .....

Body weight (kg)		Height (cm)		Ideal body wt, if obese (kg)		**Urine output: minm target** for 24 hrs (body wt x 12)	..... ml

Day-1 : Date-										**Sig. of BIC/ MO/SR**	
	6 am	10 am	4 pm	10 pm			10 am	4 pm	10 pm	M	
Pulse						Temp.				E	
BP						RR				**Sig. of SN**	
Urine (ml)					Total (ml)		Morn.	Eve.	Any other imp. finding	M	
Ur. scanty	Y / N	Y / N	Y / N	Y / N	.....	Pain abd.				E	
	Morning sample		Evening sample			L. motion				N	
PCV (Hct)						Vomiting				**SrIC:**	
Platelet						Bleeding				**SrIC:**	

Dengue ICU Monitoring Chart

Date											Name			age		wt		
TIME																		
PR																		
RR																		
CFT																		
BP																		
SpO2																		
Liver																		
GCS/ pupils																		
IVF																		
ml																		
ml/kg																		
mcg/kg/mt																		
mcg/kg/mt																		
mcg/kg/mt																		