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Dengue Virus Infection

Standard Operating Procedure (SOP)



Union of Myanmar Special region - 1
Pediatric (SOP)

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VIII. INFECTIONS AND INFESTATIONS

Dengue Virus Infection

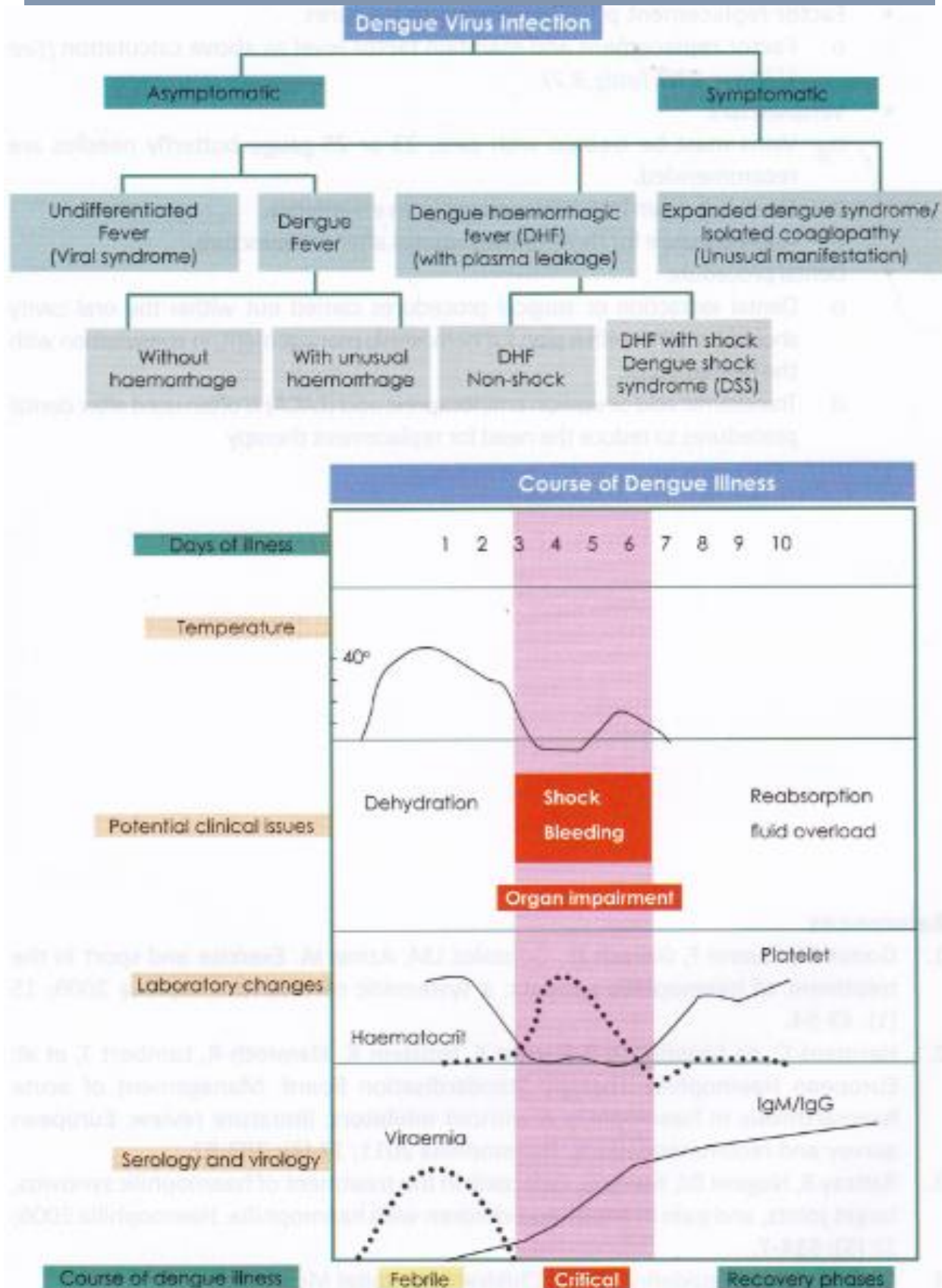


Table 8.1 WHO classification of dengue infection and grading of severity of DHF

DF/DHF	Grade	Signs and symptoms	Laboratory
DF		Fever with two of the following: • Headache • Retro-orbital pain • Myalgia • Arthralgia/bone pain • Rash • Haemorrhagic manifestations • Hess test*+(>70%) • No evidence of plasma leakage	• Leucopenia (WBC <5,000 cells/mm³) • Thrombocytopenia (Platelet count <150,000 cells/mm³) • Rising haematocrit (5% - 10%) from baseline • No evidence of plasma loss
DHF	I	Fever and haemorrhagic manifestation • Hess test + (>90%) • Evidence of plasma leakage	• Thrombocytopenia <100,000 cells/mm³; Hct rise 220% majority of cases <50,000 cells/mm³ • Hct rise 220% from baseline (due to plasma leakage)
DHF	II	As in Grade I plus spontaneous bleeding	• Thrombocytopenia <100,000 cells/mm³ • Hct rise >20%
DSS (Compensated Shock)	III	As in Grade I or II plus circulatory failure (weak pulse, narrow pulse pressure (<20 mm Hg). hypotension, restlessness)	• Thrombocytopenia <100,000 cells/mm³ • Hct rise ≥20%
DSS (Hypotensive Shock)	IV	As in Grade III plus profound shock with undetectable BP and pulse	• Thrombocytopenia <100,000 cells/mm³ • Hct rise ≥20%
Expanded Dengue Syndrome		• Complications of severe profound shock or associated with underlying host conditions/ diseases or coinfections. • Central nervous system (CNS) manifestations including convulsions, spasticity, changes in consciousness and transient paresis have been observed.	

Hess Test

Positive→>10 petechiae/in square inch at maximum site of petechiae

If 20 or more petechiae- Definitely positive

Negative→<10 petechiae/in square inch at maximum site of petechiae

Example calculation of 20% rise in Hct from baseline

e.g. base line 36%, 20% rise= $36 \times 20 / 100 = 7$, therefore $36 + 7 = 43\%$ (Not $36 + 20 = 56\%$)

Investigations

Complete blood count (CBC) and hematocrit (Hct)-

- Recommendations for CBC:
 - All febrile patients at the first visit to get the baseline HCT, WBC and PLT
 - All patients with warning signs
 - All patients with fever >3 days
 - All patients with circulatory disturbance/shock (these patients should undergo a glucose check)

Results of CBC: if leucopenia and/or thrombocytopenia is present, those with warning signs should be sent for immediate medical consultation

If CBC is not available in township level, check Hb then multiply by 3 to estimate Hct

Laboratory Test to Confirm the Diagnosis

Table 8.2 Interpretation of dengue diagnostic tests

Highly suggestive	Confirmed
One of the following • IgM (+ve) in a single serum sample • IgG (+ve) in a single serum sample with a Haemagglutination Inhibition (HI) titre of 1280 or greater	One of the following • PCR (+ve) • Virus culture (+ve) • IgM seroconversion in paired sera • IgG seroconversion in paired sera or fourfold IgG titre increase in paired sera

- Additional test should be considered as indicated according to the patient's clinical status
 - Blood glucose
 - Serum electrolytes, calcium, urea, creatinine, bicarbonate
 - Coagulation profile
 - Liver function test

Warning signs

Clinical Warning Signs (*Required strict observation and medical intervention)

Significant abdominal pain

- Severe enough to be patient's chief complaint
- Could be mistaken as surgical condition

- Is associated with increased vascular permeability and/or shock in the defervescence phase
- Tense abdomen due to ascites + liver congestion can cause abdominal pain>Consider fluid overload instead

Persistent vomiting

- Three or more times per day and patient is not able to tolerate oral fluid
- Important sign of plasma leakage

Lethargy

- Patient is confined to bed for most of the day.
- Patient sleeps most of the time.
- Patient is uninterested in food or television.
- Patient is too weak to walk to toilet.

Restlessness

- Sign of severe shock +cerebral hypoperfusion

Mucosal bleeding

- warning of more severe manifestations

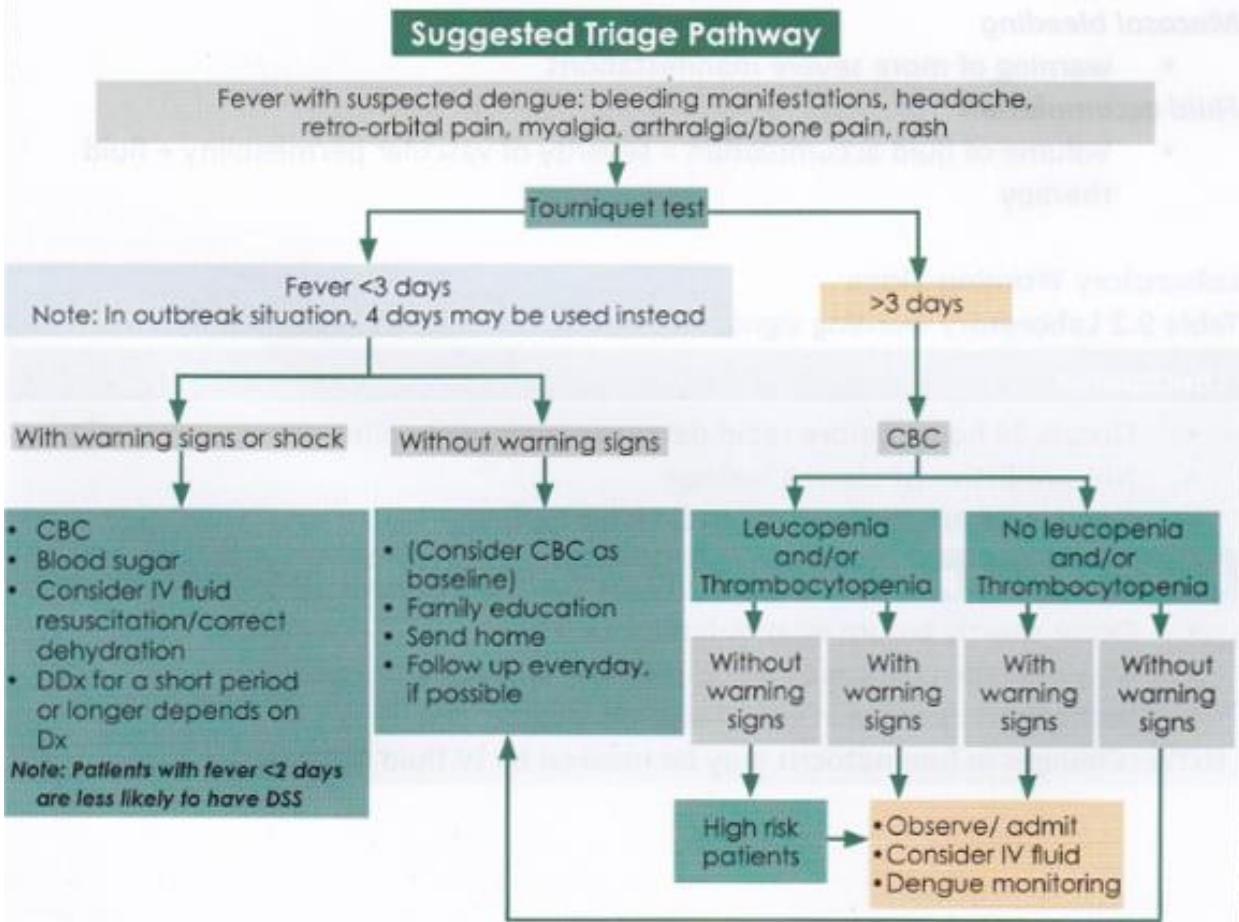
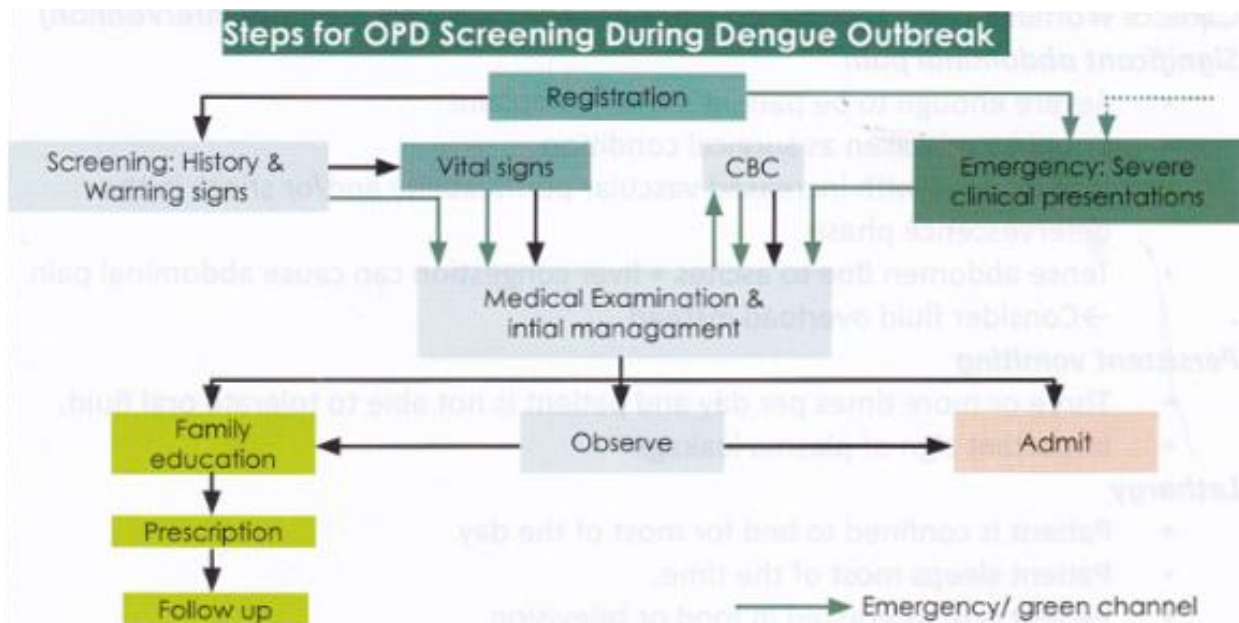
Fluid accumulation

Volume of fluid accumulation = severity of vascular permeability + fluid therapy

Laboratory Warning signs

Table 8.3 Laboratory warning signs

Leucopenia
• Occurs 24 hours before rapid decrease in platelet count • Not predictive of plasma leakage • Good indicator that patient could have dengue
Rapid decrease in platelet count + rising trend in haematocrit
• Occur shortly before or at defervescence • May precede changes in blood pressure and pulse pressure • Indicate an increase in vascular permeability
NOTE: Changes in haematocrit may be masked by IV fluid therapy



STEPWISE APPROACH TO THE MANAGEMENT OF DENGUE PATIENTS

Step I

Overall assessment

History

The history should include:

- Date of onset of fever or illness
- Quantity of oral intake
- Assessment for warning signs
- Gastrointestinal disorders (nausea, vomiting, diarrhea, gastritis)
- Change in mental state: restlessness, drowsiness, lethargy, lipothymia, dizziness, seizures, and vertigo
- Urine output (frequency in last 24 hours, volume, and time of last voiding)
- Relatives with dengue or within the neighborhood, or recent travel to dengue endemic areas (14 previous days) other patient characteristics: e.g. infant (29 days to 6 months), obese, asthmatic, has diabetes or hypertension, others
- Travelling to malaria endemic area (consider malaria)

Physical examination

The physical examination should include

- Assessment of mental state
- Assessment of hydration status
- Assessment of haemodynamic status
- Checking for tachypnoea/acidotic breathing/pleural effusion
- Checking for abdominal tenderness/hepatomegaly/ascites
- Examination for rash and bleeding manifestations
- Tourniquet test (repeat if previously negative or if there is no bleeding manifestation)

Step II. Diagnosis, assessment of disease phase and severity

To determine the phase (febrile, critical or recovery), warning signs (WSs) hydration and haemodynamic status of the patient, and whether the patient requires admission

Febrile phase, usually 4 to day 7 of illness

- May have WSs
- Normal WBC
- Platelet count $>100,000$ cells/mm³

Hess test positive (or petechiae) + WBC $<5,000$ cells/mm³

Rapid Diagnostic Test of Dengue Infections*: helps in differentiating dengue from other AFI but does not guide clinicians for IV fluid management. It cannot replace CBC.

- **NS₁Ag**: The highest percentage of positive test is on the first 2 days of fever (Sensitivity ranges-40-70%). On day 4 of fever the percentage of positive test may be reduced to 30-40%.
- **IgM/IgG** is recommended from day 5 onwards
(Sensitivity – 60-80% on day of shock or defervescence and reached 100% one day after shock/defervescence)
- Duo test (**NS₁Ag + IgM/IgG**) is more expensive and is recommended between day 4 onwards, the overall sensitivity may increase to >90%
(*These tests are not recommended as compulsory tests)

Step III. Management

Disease notification and early detection of shock is crucial

Management decisions, Depending on the clinical manifestations and other circumstances

Management Decisions

Group A-Patients who may be treated at home

- Are able to tolerate adequate volumes of oral fluids
- Pass urine at least once every six hours
- Do not have any of the warning signs
- Do not have any of co-existing conditions

Those with stable haematocrit can be sent home after being advised ***to return to the hospital immediately if they develop any of the warning signs*** and to adhere to the following action plan

Fluids: Encourage oral intake of oral rehydration solution (ORS), fruit juice and other fluids containing electrolytes and sugar to replace losses from fever and vomiting

Antipyretics: paracetamol for high fever if the patient is uncomfortable. The interval of paracetamol dosing should not be less than six hours

Instruct the care-givers that the patient should be brought to hospital immediately if any of the following occur

- No clinical improvement
- Deterioration around the time of defervescence
- Severe abdominal pain
- Persistent vomiting
- Cold and clammy extremities
- Lethargy or irritability/restlessness
- Bleeding (e.g. black stools or coffee-ground vomiting)
- Not passing urine for more than 4-6 hours

Group B-Patients who require in-hospital management

- Patients with warning signs
- Those with co-existing conditions that may make dengue or its management more complicated (infancy, obesity, diabetes mellitus, renal failure, chronic haemolytic diseases)
- Those living far from a health facility without reliable means of transport

Action plan for dengue patients with warning signs

(during critical phase, NON-SHOCK PATIENT)

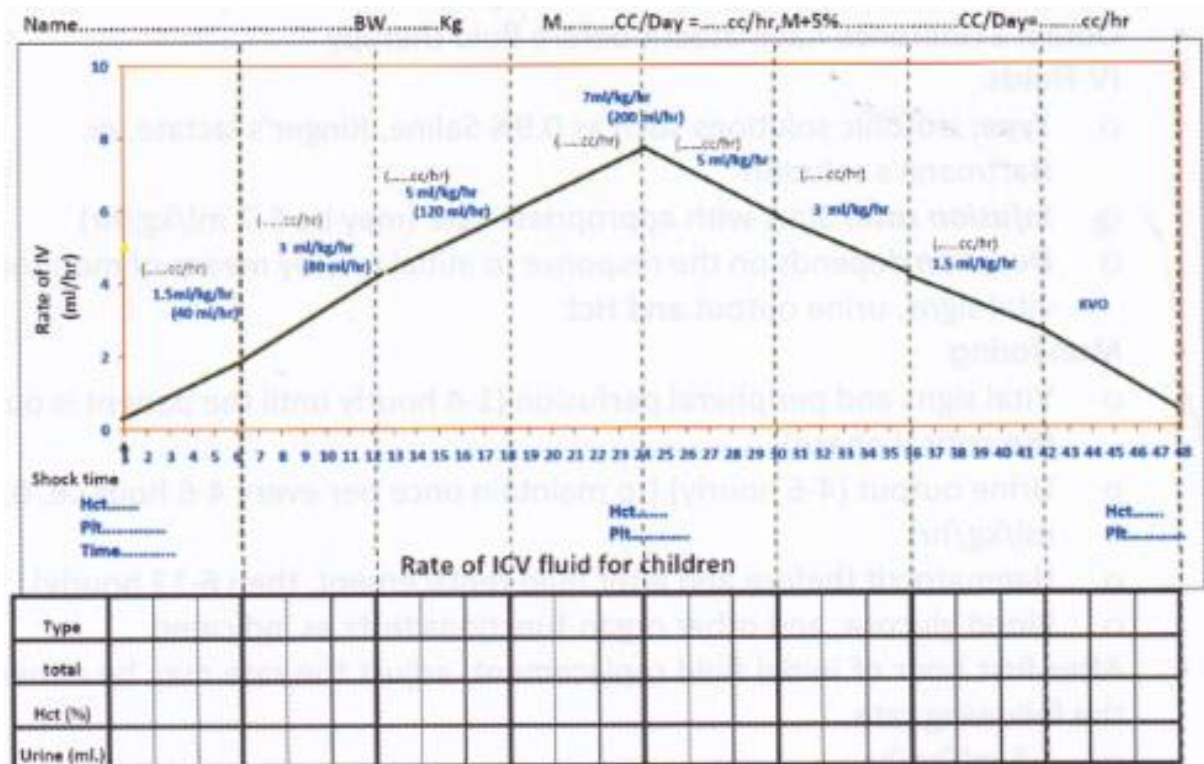
- Obtain a reference haematocrit before fluid therapy
- IV Fluids:
 - **Type:** Isotonic solutions such as 0.9% Saline, Ringer's lactate, or Hartmann's solution
 - **Infusion rate:** Start with appropriate rate (may be 5-7 ml/kg/hr)
 - **Duration** depends on the response to initial rate by means of monitoring vital signs, urine output and Hct
- Monitoring
 - Vital signs and peripheral perfusion (1-4 hourly until the patient is out of the critical phase)
 - Urine output (4-6 hourly) (to maintain once per every 4-6 hour i.e. 0.5-1ml/kg/hr)
 - Haematocrit (before and after fluid replacement, then 6-12 hourly)
 - Blood glucose, and other organ-functions tests as indicated
- After first hour of initial fluid replacement, adjust the rate may be either of the following rate
 - 1.5 ml/kg/hr
 - 2-3 ml/kg/hr
 - 3-5 ml/kg/hr
 - 5-7 ml/kg/hr
- If clinical condition stable, urine output 0.5-1 ml/kg/hr for 4 hours and stable or minimally rise Hct → same fluid rate (*Note: Not changed after every hour*)
- If clinically deteriorate, urine output <0.5 ml/kg/hr and rapid rise in Hct from baseline → step up fluid rate
- If clinically stable, urine output >1 ml/kg/hr for 4 hours and stable Hct → step down fluid rate
- If patient goes into shock → algorithm for shock

Note

- 5 ml/kg/hr = maintenance + 5% deficit
- 7 ml/kg/hr = maintenance + 7% deficit
- Platelet count falls below 100,000 to 50,000/mm³ → Hct up to 10% rise from baseline
- Platelet count falls below 50,000/mm³ → Hct >10 - 20% rise from baseline

- IV fluid usually last for 24-48 hours
- IV fluid rate should be adjusted to maintain good perfusion and urine output of at least 0.5 ml/kg/hr

IV Adjust non-shock grade l.n



Rate of iy fuld for children (Rate for aduits)

Action plan for DHF patient with co-existing conditions without warning signs

(NON-SHOCK PATIENT)

- Encourage oral fluid
- If oral intake is not adequate for maintenance fluid, add IV fluid to reach maintenance level in critical phase (oral + IV= maintenance)
- Monitoring-Same as above as in dengue with warning signs
- Adjust fluid (oral + IV)-Same as above as in dengue with warning signs

For infant dengue - Use isotonic fluid during critical phase except in infants <6 months in whom % Strength Saline is to be used

Note for infant

- Basal Hct may be lower than the Hct of older children e.g. 30%
- Therefore, Hct level 36% may be 20% rise from basal level and consider as hemoconcentration
- Critical phase will last shorter than that of older children (may be 12 hours)

- More difficult to diagnose
- Investigate-FBC, Hct, NS1, IgG& IgM + LFT, ABCS

For obese patient - Use ideal body weight

Table 8.4 Hourly maintenance fluid regimen for overweight or obese patients

Estimated ideal body weight or IBW (kg)	Normal maintenance fluid (ml/hour) based on Holliday-Segar formula	Fluid regimen based on 2-3 ml/kg/hour (ml/hour)	Fluid regimen based on 1.5-2 ml/kg/hour (ml/hour)
5	10	10-15	
10	20	20-30	
15	30	30-45	
20	60	40-60	
25	65	50-57	
30	70	60-90	
35	75	70-105	
40	80	80-120	
50	90	100-150	
60	100		90-120
70	110		105-140
80	120		120-150

Notes

For adults with IBW>50 kg, 1.5-2 ml/kg can be used for quick calculation of hourly maintenance fluid regimen. For adults with IBW ≤50 kg, 2-3 ml/kg can be used for quick calculation of hourly maintenance fluid regimen

Group C - Patients who Require Emergency Treatment for Severe Dengue

- Fluid resuscitation will depend on whether the patient is having
 - Compensated shock
 - OR
 - Hypotensive shock
- The differences of the two clinical conditions are shown in Table 9.5

Table 8.5 Haemodynamic assessment: continuum of haemodynamic changes

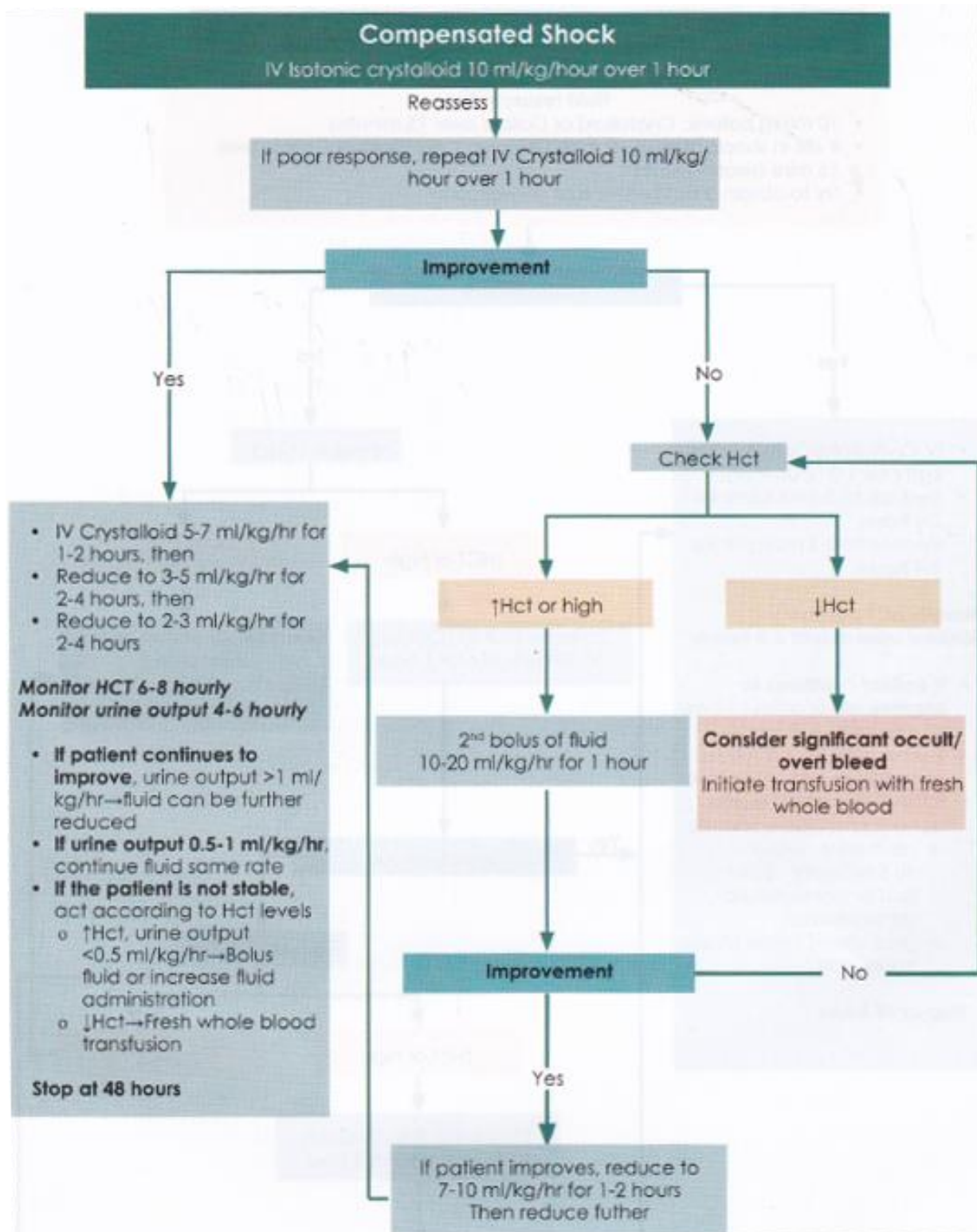
Parameters	Stable circulation	Compensated shock	Hypotensive shock
Conscious level	Clear and lucid	Clear and lucid (shock can be missed if you do not touch the patient)	Change of mental state (restless, combative)
Capillary refill time	Brisk (<1 Sec)	Prolong (>2 Sec)	Very prolonged mottled skin
Peripheral pulse volume	Good volume	Weak and thready	Feeble or absent
Heart rate	Normal for age	Tachycardia	Severe tachycardia with bradycardia in late shock
Blood pressure	Normal for age Normal pulse pressure for age	Normal systolic pressure but rising diastolic pressure Narrowing pulse pressure Postural hypotension	Narrow pulse pressure (<20 mmHg) Hypotension (See definition below) Unrecordable blood pressure
Respiratory rate	Normal for age	Tachypnoea	Metabolic acidosis hyperpnoea/Kussmaul's breathing

Definition of Hypotension

- Systolic blood pressure of <90mmHg or mean arterial pressure < 70 mm Hg in adults
- Systolic blood pressure decrease of >40 mmHg or < 2 SD below normal for age
- In children up to 10 years of age, the 5th centile for systolic blood pressure can be determined by the formula $70 + (\text{age in years} \times 2)$ mmHg

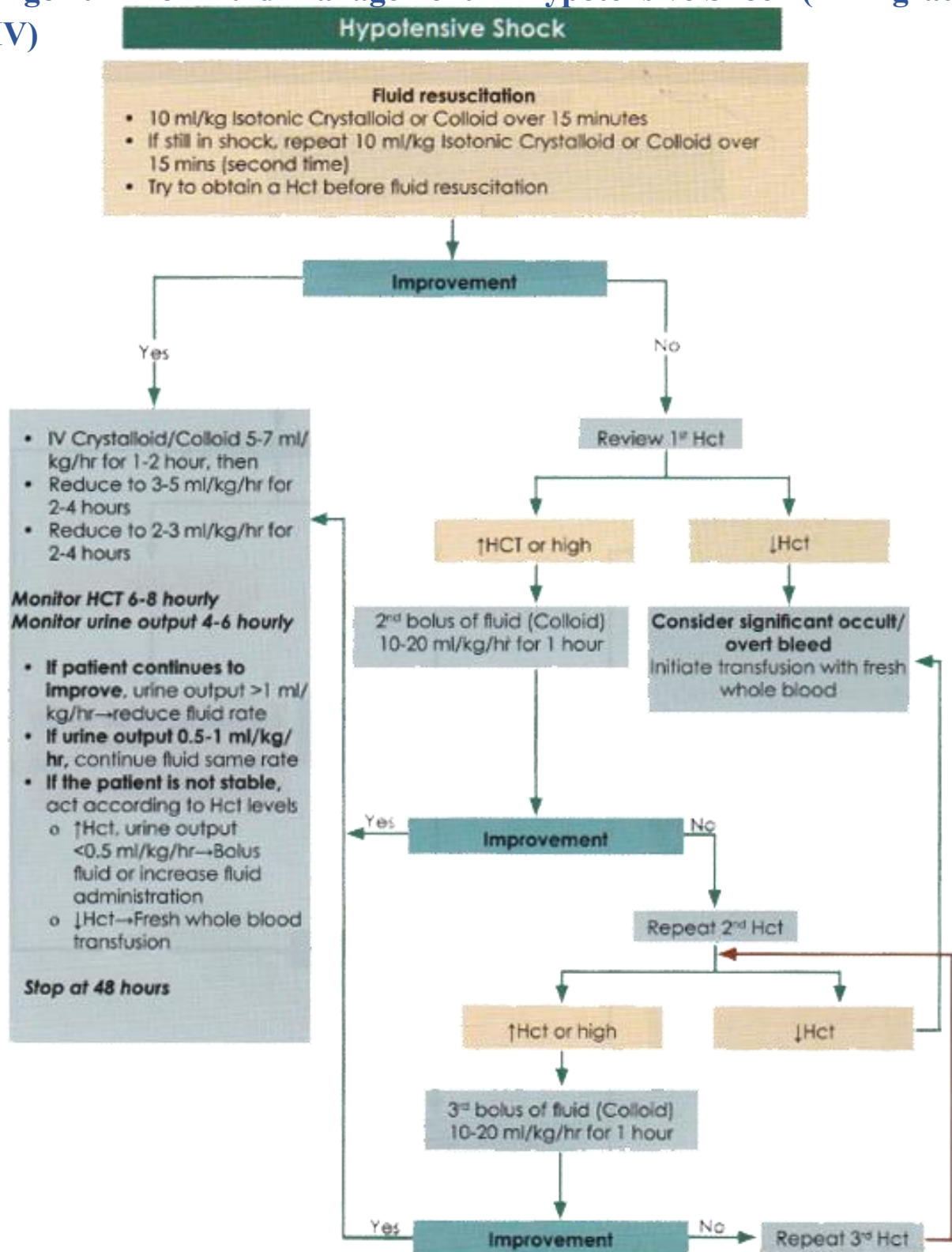
Narrow pulse pressure, 20 mmHg alone is seen in many normal children. Therefore other criterion + pulse pressure <20 mmHg must be fulfilled for diagnosis of compensated shock

Algorithm for Fluid Management in Compensated shock (DHF grade III)



Source: Kalayanaroojs. and Nimmannitya s. in: Guidelines for Dengue and Dengue Haemorrhagic Fever Management. Bangkok. Medical Publisher, Bangkok 2003

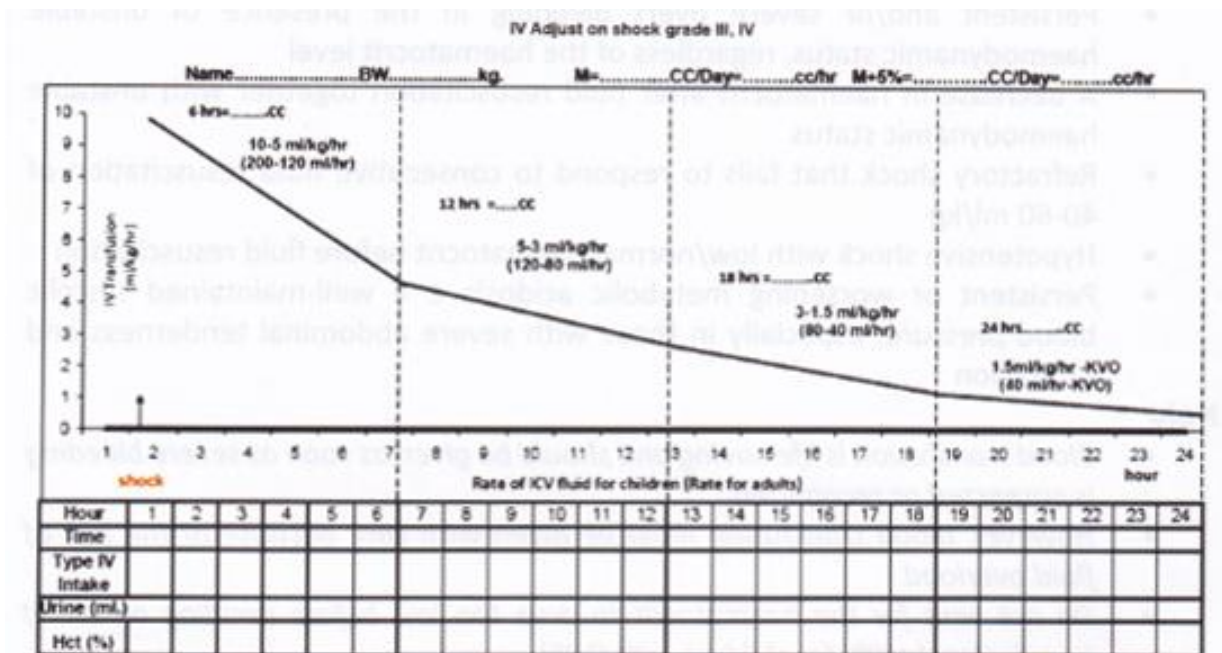
Algorithm for Fluid Management in Hypotensive Shock (DHF grade IV)



Source: Kalayanarooj S. and Nimmannitya S. In: Guidelines for Dengue and Dengue Haemorrhagic Fever Management, Bangkok. Medical Publisher, Bangkok 2003

Note

- Maximum limit of colloid
 - Isotonic colloid (e.g. Gelofusin) = 50 ml/kg/day
 - Hypertonic colloid (e.g. dextran 40) = 30 ml/kg/day
- Indication for IV fluid
 - Febrile phase: only in cases with severe vomiting and moderate to severe dehydration
 - Critical phase
 - When the patient cannot have adequate oral fluid intake or is vomiting
 - When HCT continues to rise 10-20% despite oral rehydration
 - Shock
- Recovery phase: generally no IV fluid



Source: Kalayanarooj S. and Nimmannitya S. In: *Guidelines for Dengue and Dengue Haemorrhagic Fever Management*. Bangkok, Medical Publisher, Bangkok 2003

Treatment of Haemorrhagic Complications

A decrease in haematocrit together with unstable vital signs (particularly narrowing of the pulse pressure, tachycardia, metabolic acidosis, poor urine output) indicates major haemorrhage and the need for urgent blood transfusion.

Minor mucosal bleeding may occur in any patient with dengue but, if the patient remains stable with fluid resuscitation/replacement, no treatment is necessary. The bleeding usually improves rapidly during the recovery phase.

In patients with **profound thrombocytopenia**, ensure strict bed rest and protect from trauma to reduce the risk of bleeding. Do not give intramuscular injections to avoid haematoma. It should be noted that prophylactic platelet transfusions for severe thrombocytopenia in otherwise haemodynamically stable patients have not been shown to be effective and are not necessary.

Major bleeding occurs usually from the gastrointestinal tract. Internal bleeding may not become apparent for many hours until the first black stool is passed.

Patients at risk of major bleeding are those who

- Have prolonged/refractory shock
- Have hypotensive shock and renal or liver failure and/or severe and persistent metabolic acidosis
- Are given non-steroidal anti-inflammatory agents
- Have pre-existing peptic ulcer disease
- Are on anticoagulant therapy
- Have any form of trauma, including intramuscular injection

Severe bleeding can be recognized by:

- Persistent and/or severe overt bleeding in the presence of unstable haemodynamic status, regardless of the haematocrit level
- A decrease in haematocrit after fluid resuscitation together with unstable haemodynamic status
- Refractory shock that fails to respond to consecutive fluid resuscitation of 40-60 ml/kg
- Hypotensive shock with low/normal haematocrit before fluid resuscitation
- Persistent or worsening metabolic acidosis $\pm$ a well-maintained systolic blood pressure, especially in those with severe abdominal tenderness and distension

Note

- Blood transfusion is life-saving and should be given as soon as severe bleeding is suspected or recognized
- However, blood transfusion must be given with care because of the risk of fluid overload
- Do not wait for the haematocrit to drop too low before deciding on blood transfusion. (<40% for children with DHF)
- It is stressed that haematocrit levels alone should not be used for clinical decision making.
- Falling Hct together with unstable haemodynamic status should be considered as an indicator of major bleed

Action Plan for the Treatment of Haemorrhagic Complications

- Give 5-10 ml/kg of fresh-packed red cells or 10-20 ml/kg of fresh whole blood at an appropriate rate
- Observe the clinical response (A good clinical response includes improving haemodynamic status and acid-base balance.)
- Consider repeating the blood transfusion if there is further blood loss or no appropriate rise in haematocrit after blood transfusion.
- There is little evidence to support the practice of transfusing platelet concentrates and/or fresh frozen plasma for severe bleeding.

- It is being practiced when massive bleeding cannot be managed with just fresh whole blood/fresh packed cells (but it may exacerbate the fluid overload)

NB

- It is important that fresh whole blood or fresh red cells are given (Up to 3 days old blood is acceptable)

Respiratory Distress in Severe Dengue

May be due to

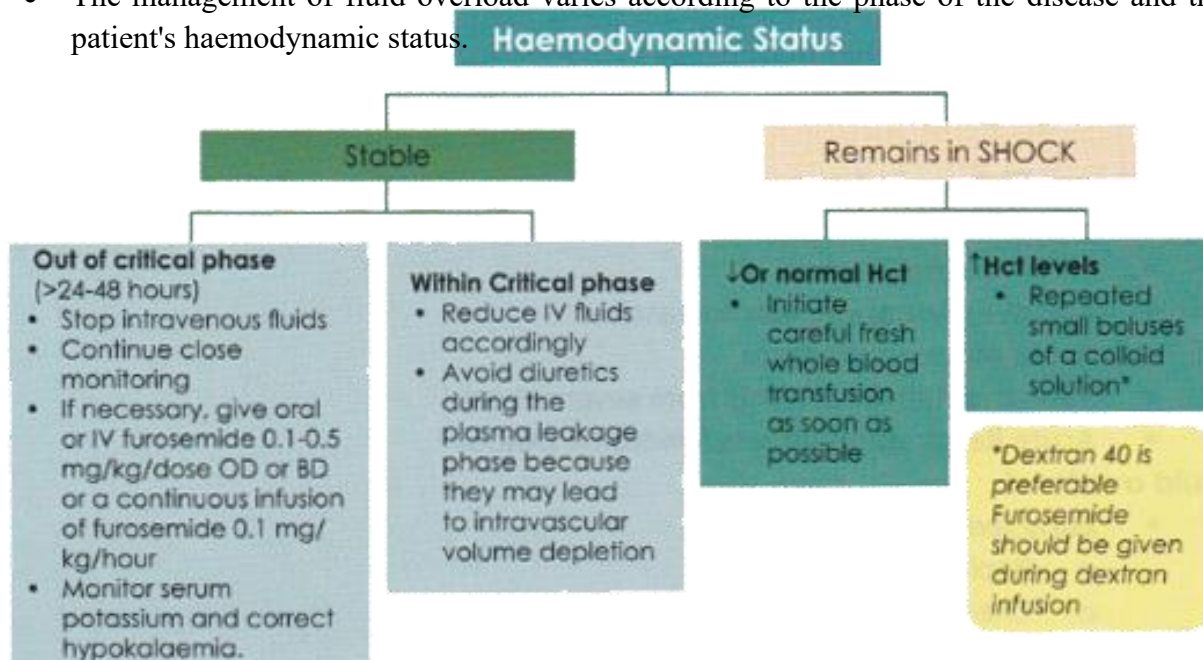
- Fluid overload
- Massive pleural effusion and ascites
- Acute pulmonary edema
- Severe metabolic acidosis from severe shock
- Acute Respiratory Distress Syndrome (ARDS)

Fluid overload

- Early features
 - Rapid breathing
 - Chest wall indrawing
 - Wheezing (rather than crepitations)
 - Large pleural effusions
 - Tense ascites
 - Increased jugular venous pressure (JVP)
- Late features
 - Pulmonary edema (cough with pink or frothy sputum ± crepitations, cyanosis)
 - Irreversible shock (heart failure, often in combination with ongoing hypovolaemia)

Action plan for the treatment of fluid overload is as follows

- Oxygen therapy should be given immediately
- The management of fluid overload varies according to the phase of the disease and the patient's haemodynamic status.



Note: Sodium bicarbonate for metabolic acidosis is not recommended for PH >7.15 *Gelofusin can be used if Dextran 40 is not available

Severe Organ impairment

Dengue encephalopathy - Dengue patient with impaired consciousness and stable cardiovascular signs

Hepatic injury - Plasma transaminase activity exceeding 400 U/L most striking abnormality

Hepatic dysfunction:

- Coagulopathy (PT >20 sec)
- Hypoglycaemia
- Hypoalbuminaemia in acute fulminant liver failure only
- Increasing bilirubin

Action plan → treated as hepatic encephalopathy

- Secure and maintain airway in unconscious child
- High flow oxygen if SpO₂ <90% in child with encephalopathy
- Obtain venous access preferably central access
- Treat coagulopathy with IV vit K 2-10 mg if INR >1.5
- Avoid the use of blood products unless actively bleeding, requiring invasive procedures or severe coagulopathy (PT >60 sec)
- Treat with FFP, cryoprecipitate and plasma if required
 - IV fluid infusion
 - 10% dextrose to maintain blood glucose 4-6 mmol/l
 - 0.9% NS as maintenance (fluid restriction % maintenance to all parents)
- Enteral feeding-Nasogastric tube or orogastric tube (avoided in coagulopathy)
- Institute regular neuro-observations (every 15 mins)
- Consider lactulose to prevent hepatic encephalopathy (1-2 years-5 to 10 ml 8 hourly, 3-5 years-10-15 ml 8 hourly)
- Intubation and ventilatory support if available
 - Indications
 - Grade 2 encephalopathy
 - Raised intracranial pressure
 - Rapidly deteriorating course
 - Respiratory failure
 - Cardiovascular collapse
 - Oral intubation is preferred, with a cuffed ETT, due to risk of bleeding and aspiration
 - Management following intubation
 - Aim to oxygenate (PaO₂ >10 kPa) and maintain normocarbida (PaCO₂ 4.5-5.3)
- Consider mannitol if raised ICP suspected
- Central venous access if vasoactive agents or high concentration dextrose infusions are required
- Noradrenaline is the vasoactive agent of choice
- Consider IV hydrocortisone 1-2 mg/kg 6 hourly if adrenal insufficiency suspected

Discharge Criteria (All of the following conditions must be present)

Clinical

- No fever for 48 hours
- Improvement in clinical status (general well-being, appetite, haemodynamic status, urine output, no respiratory distress)

Laboratory

- Increasing trend of platelet count
- Stable haematocrit without intravenous fluids

Referral and Transportation :

More severe/complicated cases should be managed in hospitals where almost all laboratory investigations, equipment, medicines and blood bank facilities are available. The following patients should be referred for closer monitoring and probably accorded special treatment of a higher tier of hospital care:

- Infants <1 year
- Obese patients
- Prolonged/ profound shock
- Significant bleeding, hemolysis (hemoglobinuria)
- Repeated shock 1-2 times during treatment
- Patients who seem not response to conventional treatment
- Patients who continue to have rising Hct and no colloid is available
- Patients with co-morbidity condition
- Patients with early signs and symptoms of fluid overload
- Patients with organ(s) involvement
- Patient with neurological manifestations such as change of consciousness, semi-coma, coma, convulsion

Referral procedures

- Discussion and counselling with families
- Prior contact with the referral hospital; communicating with doctors and nurses responsible.
- Stabilizing patients before transfer.
- Ensure that the referral letter must contain important information : clinical conditions with progression, time of shock, series of Hct, platelet count, vital signs, type and amount of IV fluid, urine output and other important laboratory (LFT, BUN, Creatinine, blood sugar, blood gas, electrolyte, if available).
- Recommend IV fluid at a slower rate 5 ml/kg/hr to prevent fluid overload during transportation

- At least a nurse who knows the clinical course, laboratory and treatment of patients should be accompanied.
- Specialist or more experience doctors should be notified before transfer.

Common causes of death in dengue:

- Prolonged shock with multiple organs failure
- Massive bleeding
- Fluid overload

Most of dengue patients who died had 2-3 of the above conditions and delayed or misdiagnosed of DHF/DSS in the early stage is commonly found.

Outbreak preparedness for clinical management

There has been increasing incidence of dengue outbreaks in many countries globally, The following elements are recommended for the preparedness of dengue clinical management:

- Personnel to be recruited, trained and assigned appropriate duties:
 - Doctors
 - Nurses
 - Healthcare workers
 - Back-office personnel
- Clinical Practice Guidelines (CPG) [The above personnel should undergo a brief training in the use of this CPG]
- Medicines and solutions:
 - Paracetamol
 - Oral rehydration solution
 - IV fluid
- Crystalloid: 0.9% and 5%D/NSS, 5%DAR, 5%DLR
- Colloid --hyper-oncotic (plasma expander): 10% Dextran-40 in NSS, gelofusine
 - 20% or 50% glucose
 - Vitamin K1
 - Calcium gluconate
 - KCI solution
 - Sodium bicarbonate
- Equipment and Supplies:
 - IV fluids and vascular access, including scalp vein, medicut, cotton, gauze 70% alcohol
 - Oxygen and delivery system
 - Sphygmomanometer with 3 different cuffs size
 - Automate CBC machine (Coulter Counter)
 - Micro-centrifuge (for Hct determination)
 - Microscope (for platelet count estimation)
 - Glucometer (for blood sugar level)
- Laboratory support:

- Basic
 - Complete blood count (CBC): Hct, white blood count (WBC), platelet count, differential count
- More complicated cases
 - Blood sugar
 - Liver function test
 - Renal function test (BUN, Creatinine)
 - Electrolyte, Calcium
 - Blood gas analysis
 - Coagulogram: partial thromboplastin time (PTT), prothrombin time (PT), thrombin time (TT)
 - Chest x-ray
 - Ultrasonography
- Blood Bank:
 - Fresh whole blood, packed red cell, platelet concentrate