National Guideline
for Clinical Management of
Dengue

VERSION 01

Vector Borne Disease Control Programme
Department of Public Health
Ministry of Health and Sports
The Republic of the Union of Myanmar
June, 2018

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Contents

Abbreviations

Ae.	*Aedes*
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
BP	Blood Pressure
°C	Degree Celsius
CBC	Complete blood count
CNS	Central nervous system
CPAP	Continuous positive airway pressure
CRF	Chronic renal failure
CRT	Capillary refill time
CT	Computed tomography
CVP	Central venous pressure
CVVH	Continuous veno-venous haemodialysis
DEN	Dengue
DEN-1	Dengue virus serotype 1
DEN-2	Dengue virus serotype 2
DEN-3	Dengue virus serotype 3
DEN-4	Dengue virus serotype 4
DF	Dengue fever
DHF	Dengue haemorrhagic fever
DIC	Disseminated intravascular coagulopathy
DSS	Dengue shock syndrome
ECG	Electrocardiogram
ED	Emergency department

ELISA	Enzyme-linked immunosorbent assay
FBC	Full blood count
FFP	Fresh frozen plasma
FWB	Fresh whole blood
G6PD	Glucose-6-phosphate dehydrogenase
GCS	Glasgow Coma Scale
GP	General practitioner
Hb	Haemoglobin
HCO3	Bicarbonate
Hct	Haematocrit
HI	Haemagglutination Inhibition
HIA	Haemagglutination inhibition Assay
HIV	Human immunodeficiency virus
HR	Heart rate
IBW	Ideal body weight
ICU	Intensive care unit
IgM	Immunoglobulin M
IgG	Immunoglobulin G
IHA	Indirect haemagglutination
INR	International normalized ratio
JVP	Jugular venous pressure
RNA	Ribonucleic acid
SEA	South-East Asia
VBDC	Vector Borne Diseases Control
WHO	World Health Organization

1. Introduction

Dengue is one of the most common vector-borne diseases in Southeast Asia and has been ranked as the most important mosquito-borne viral disease with epidemic potential in the world. Some 2.5 billion people – two fifths of the world's population in tropical and subtropical countries – are at risk. An estimated 390 million dengue infections occur worldwide annually (2017). A very large proportion (approximately 90%) of them are children aged less than five years, and about 2.5% of those affected die. The epidemiology of dengue in South-East Asia is undergoing a change in terms of the human host, place, the dengue virus and the bionomics of the vectors. Shift in affected age groups, sex differences and expansion from urban to rural areas are evident. The WHO's Global Strategy for Dengue Prevention and Control (2012-2020) highlighted reducing the dengue burden by at least 50 per cent in terms of mortality and at least 25 per cent in terms of morbidity by 2020 (WHO 2012) comparing to base year 2010.

Epidemics of dengue are increasing in frequency. During epidemics, infection rates among those who have not been previously exposed to the virus are often 40% to 50% but can also reach to 80% to 90%. Seasonal variation is observed. *Aedes (Stegomyia) aegypti* is the primary epidemic vector. Imported cases are common. Co-circulation of multiple serotypes/genotypes is evident. Dengue is primarily an urban disease but is now spreading to rural areas worldwide. The trend is now changing due to socio economic and man-made ecological changes, It has resulted in invasion of Ae. aegypti mosquitoes into the rural areas, which has tremendously increased the chances of spread of the disease to rural areas.

2. Dengue in Myanmar

Dengue endemicity of Myanmar in SEA Region is in category A. The first evidence of occurrence of Dengue Fever (DF) was reported during 1960 in Myanmar. It is a notifiable disease since 1964. The first Dengue Haemorrhagic Fever (DHF) outbreak occurred in Yangon in 1970 and spread to other States & Regions such as Bago, Mandalay and Mon since 1974. After 1974, dengue spread to most of the states and regions apart from Chin and Kayah States. In 2014, all states and regions were affected except Chin State. All States and Regions were affected in 2015.

During 1994, one of the most severe outbreaks of DF/DHF occurred in Yangon and other States/Regions where, 11,648 cases and 444 deaths occurred. In 2009, the country witnessed a total 22,398 cases and 181 deaths reported from all States/Regions except Chin State. In 2015 highest number of cases was recorded totaling to 42,913 cases and 140 deaths. A well-integrated prevention and control program to combat the dengue across all levels and across different sectors and among all stakeholders is essential to be in place.

This guideline includes new concepts, based on scientific evidence, on the management of Dengue Fever (DF) and Dengue Haemorrhagic Fever (DHF). It emphasizes the importance of prevention, early detection and treatment of shock and other complications and early referral, disease surveillance, vector management and control, emergency preparedness and outbreak response.

Other factors for increased risk of vector breeding

Urbanization

As per United Nations reports, 40% of the population in developing countries now lives in urban areas, which is projected to rise to 56% by 2030 largely due to rural–urban migration. Such migration from rural to urban areas is due to both “push” (seeking better earning avenues) and “pull” (seeking better amenities such as education, health care, etc.) factors. The failure of urban local governments to provide matching civic amenities and infrastructure to accommodate the influx generates unplanned settlements with inadequate potable water, poor sanitation including solid waste disposal, and poor public health infrastructure. All this raises the potential for Ae. aegypti breeding to a high level and makes the environment for transmission conducive.

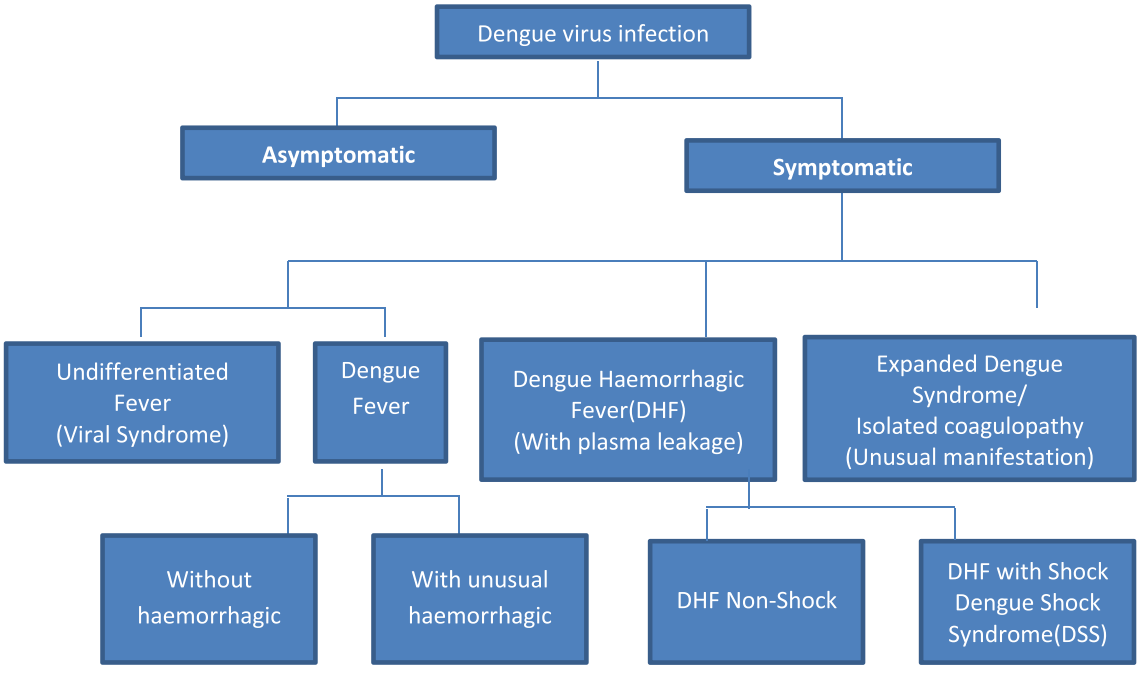
Increased travel

With expanding travel and an exponential increase in tourism and trade, there exists a high possibility of introduction of new DENV serotypes/genotypes through healthy viraemic persons, thus helping in the build-up of a high transmission potential.

3. Clinical Manifestations and Diagnosis and Management

Dengue virus infection may be asymptomatic or may cause undifferentiated febrile illness (viral syndrome), dengue fever (DF), or dengue haemorrhagic fever (DHF) including dengue shock syndrome (DSS). Infection with one dengue serotype gives lifelong immunity to that particular serotype, but there is only short-term cross-protection for the other serotypes. The clinical manifestation depends on the virus strain and host factors such as age, immune status, etc

Figure (1) Manifestation of dengue virus infection



Source: Comprehensive guideline for prevention and control of dengue and dengue haemorrhagic fever, WHO 2011

Case definitions

Undifferentiated fever

Those who have been infected with dengue virus, especially for the first time (i.e. primary dengue infection), may develop a simple fever indistinguishable from other viral infections.

Dengue Fever (DF)

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

Dengue Haemorrhagic Fever (DHF)

In the first few days DHF patients will have sign and symptoms similar to that of DF.

However in DHF, (usually beyond day 3) will develop features of plasma leakage.

The following criteria are necessary for the case definition of DHF

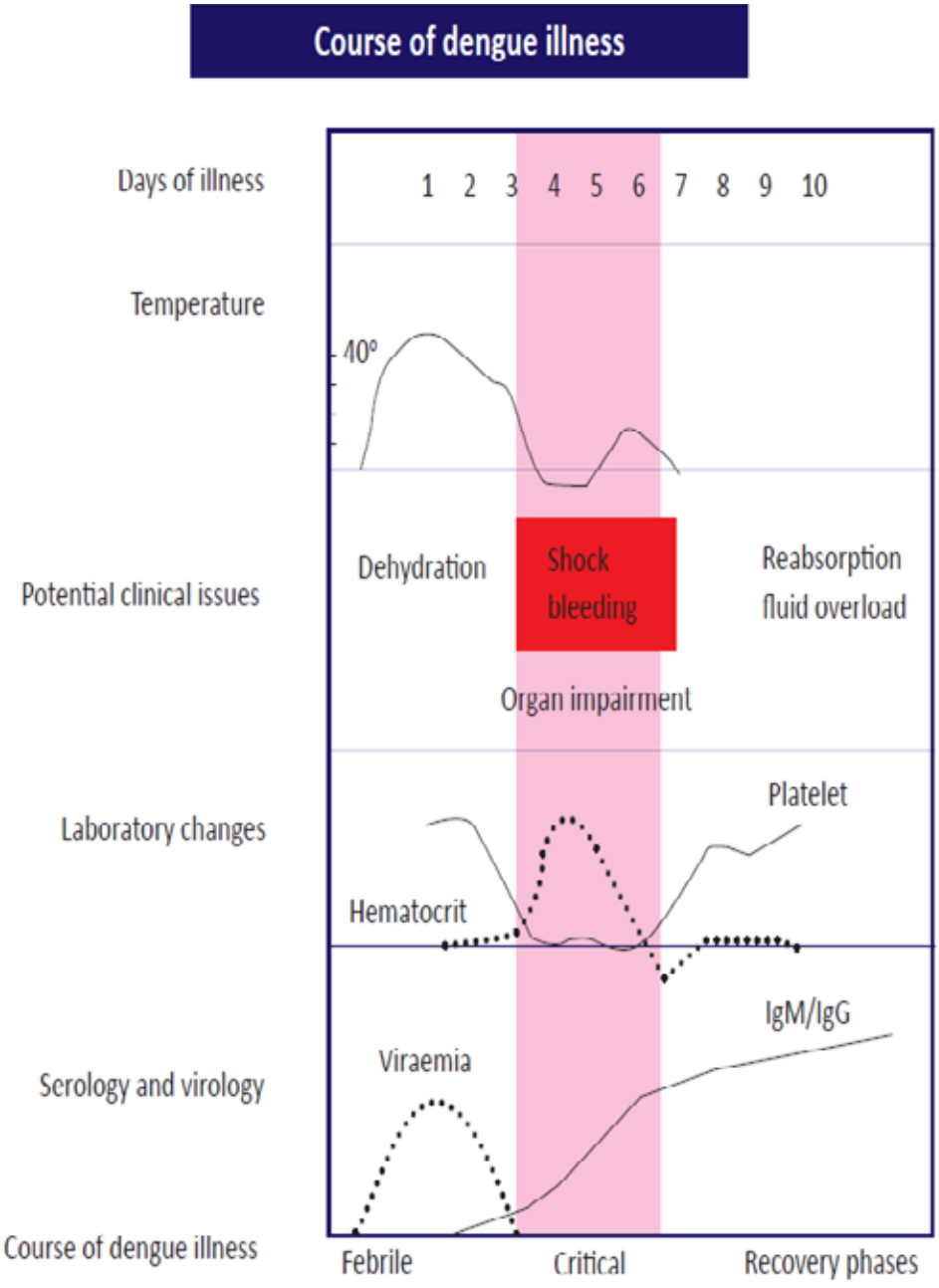
1. High fever or recent history of acute fever
2. Haemorrhagic manifestations* (at least a positive tourniquet test)
3. Thrombocytopenia of ≤100,000 cell/mm3
4. Objective evidence of plasma leakage

** In patients who have definite evidence of plasma leakage, presence of haemorrhagic manifestations is not essential for the diagnosis of DHF.*
However the term "DHF" is retained because these patients may develop overt or concealed bleeding during the course of illness.

Expended Dengue Syndrome (EDS)

DHF with unusual manifestations such as neurological, hepatic, renal and other isolated organ involvement. These could be explained as 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. The underlying causes depend on the timing of these manifestations in relation to the viremia, plasma leakage or convalescence.

Figure (2) below shows the course of dengue illness with different parameters



Source : Dengue guideline for diagnosis, treatment, prevention and control, WHO 2009

Table (1) WHO classification of dengue infections(DF) and grading and severity of Dengue Haemorrhagic Fever(DHF)

DF/DHF	Grade	Sign and Symptoms	Laboratory
DF		Fever with two of the following: • Headache. • Retro-orbital pain. • Myalgia. • Arthtralgia/bone pain. • Rash. • Haemorrhagic manifestations. Hess* test + > 70% • **No evidence of plasma leakage**	• Leucopenia (wbc ≤5000 Cells/mm3). • Thrombocytopenia (Platelet Count <150 000 cells/mm3). • Rising haematocrit (5% – 10%) from base line • No evidence of plasma loss.
DHF	**I**	Fever and haemorrhagic manifestation Hess test + > 90% **evidence of plasma leakage**	• Thrombocytopenia <100 000 cells/mm^3 majority of cases < 50,000cells/cu.mm^3 • Hct rise ≥20% from base line (due to plasma leakage)
DHF	**II**	As in **Grade I plus** spontaneous bleeding.	• Thrombocytopenia <100 000 cells/mm^3 • Hct rise ≥20%.
DSS (Compensated Shock)	**III**	As in **Grade I or II plus** circulatory failure (weak pulse, narrow pulse pressure (≤20 mmHg), 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%.
Expended 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.	

Source: http://www.who.int/csr/resources/publications/dengue/Denguepublication/en/

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 If the baseline 36%, 20% rise = 36x20/100=7, therefore 36+7=43 %

(Not 36+20=56)

Investigation

Complete Blood Count(CBC) and hematocrit (Hct)-

- Recommendation for CBC
  - all febrile patients at the first visit to get the baseline Hct, WBC and Platelets
  - 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 sign 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 (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 Haemagglutination Inhibition (Hi) titre of 1280 or greater	One of the following - PCR (+ve) - Virus culture (+ve) - IgM seroconversation in paired sera - IgG seroconversation in paired sera or fourfold IgG titre increase in paired sera

Adapted from Dengue and Control (DENCO) study

Additional test should be considered as indicated according to the patient's clinical status

- Blood glucose
- Serum electrolytes, calcium, urea, creatine, bicarbonate
- Coagulation profile
- Liver function test

Warning Signs

Clinical Warning Sign *(*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

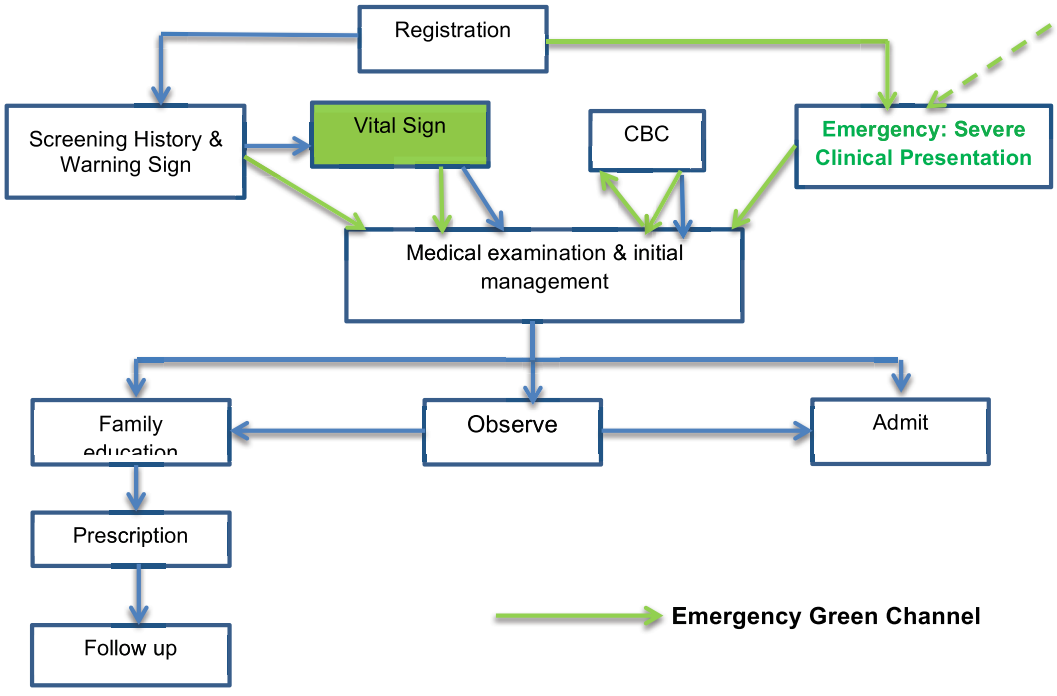
- Volume of fluid accumulation = severity of vascular permeability + fluid therapy

Laboratory warning signs

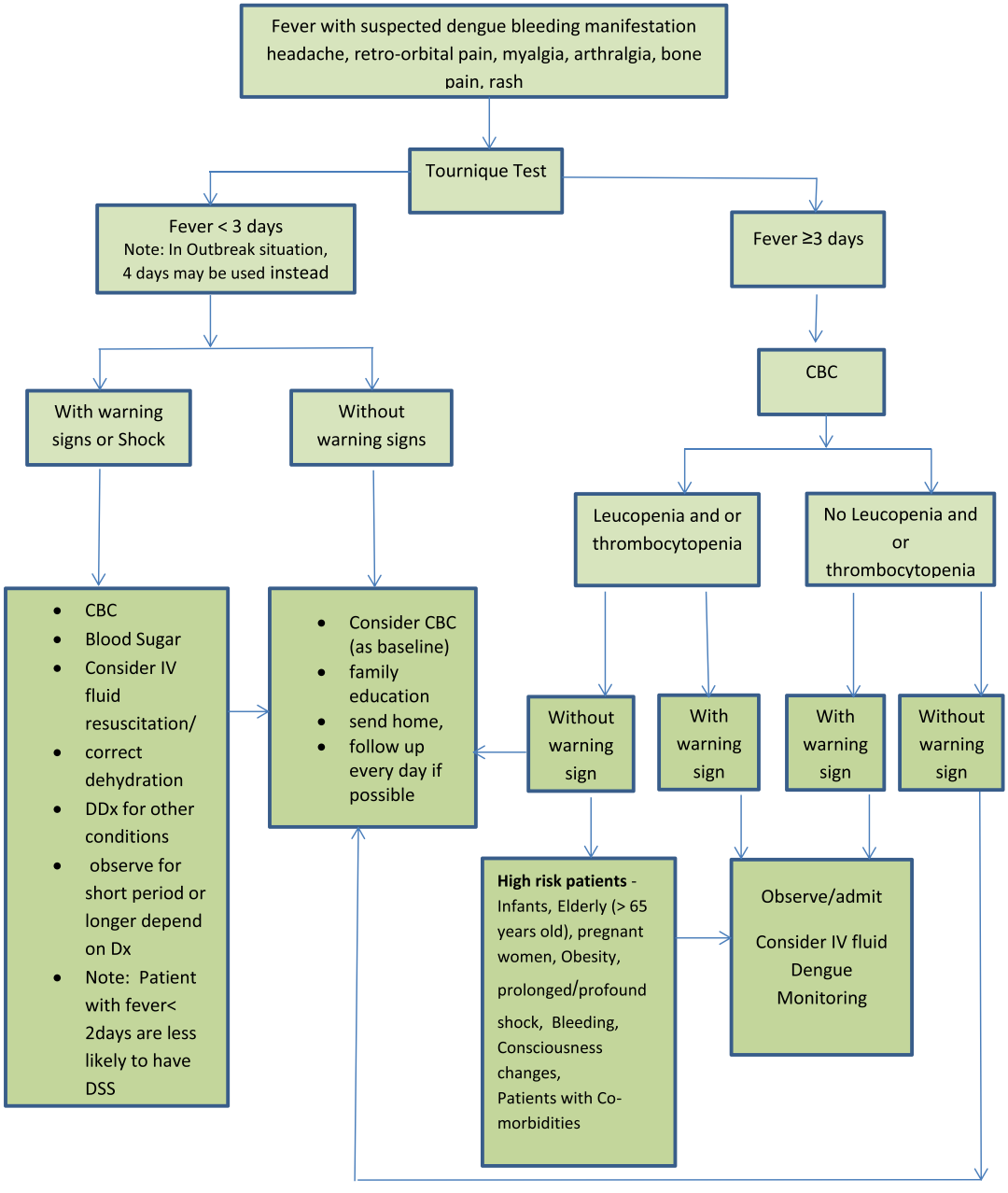
Table (3) Laboratory warning Signs

Leucopenia
- Occur 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 : Change in haematocrit may be masked by IV fluid therapy***

Algorithm 1 Steps for OPD Screening During Dengue Outbreak



Algorithm 2 - Suggested triage pathway



Stepwise approach to the Management of dengue patients

Step I. Overall assessment

History:

The history should include:

- Date of onset of fever/illness;
- Quantity of oral intake;
- Assessment for warning signs;
- Gastrointestinal disorders (nausea, vomiting, diarrhoea, gastritis)
- Change in mental state: restlessness, drowsiness, lethargy, lipothymia, dizziness, seizure and vertigo
- urine output (frequency in last 24 hours, volume and time of last voiding);
- Relatives with dengue or within the neighbourhood, ot 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 areas (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), whether there are warning signs, the 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/cu.mm^3

Hess test positive (or petechiae) + WBC ≤ 5,000 cells/cu.mm.

Rapid Diagnostic Test of Dengue Infections* : helps in differentiating Dengue from Other Acute Febrile Illness but does not guide clinicians for IV fluid management. It cannot replace CBC.

- **NS1Ag** is recommended in febrile phase when there is viremia. The sensitivity ranges from 40 - 70%. The highest percentage of positive test is on the first 2 days of fever. On day 4 of fever the percentage of positive test may be reduced to 30-40%.
- **IgM/ IgG** is recommended from day 5 onwards. The sensitivity is 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 recomended between day 4 onwards, the overall sensitivity may increase to >90%.

(***Those 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

Depending on the clinical manifestations and other circumstances, patient should be classified as
(Group A) – Patients who may be treated at home
(Group B) – Patients who require in-hospital management
(Group C) – Patients who require emergency treatment

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 sign
- 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 electrolyte and sugar to replace losses from fever and vomiting.

Antipyretic: 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 stool 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 hemolytic diseases)
- Those living far from a health facility without reliable means of transport

Action plan for DHF patients with warning signs (*during critical phase, non-shock patient*)

- Obtain a reference Hct before IV fluid therapy
- **IV Fluid**
  - ***Type*** **-** isotonic solution (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 critical phase
  - Urine output 4-6 hourly (to maintain once per every 4-6 hour ie, 0.5 – 1 ml/kg/hr)
  - Hct – before and after fluid replacement then 6-12 hourly
  - Blood glucose and other organ function as indicated
- After first hour of initial fluid replacement, adjust the rate may be either of the following rate

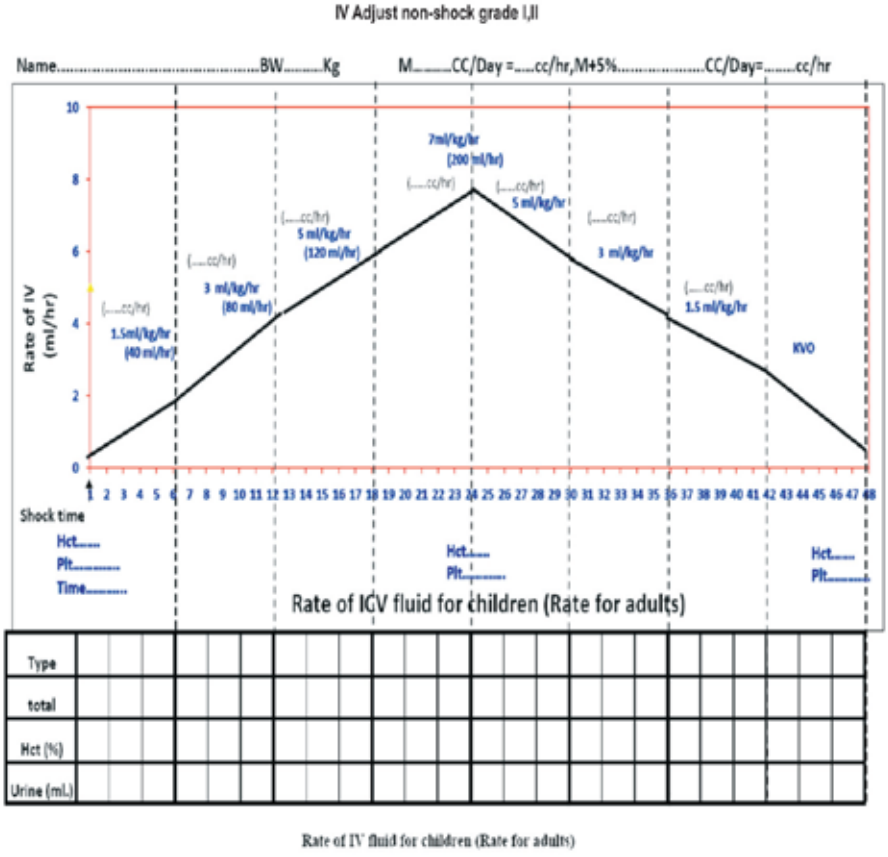
- 1.5 ml/kg/hr
- 2-3 ml/kg/hr
- 3-5 ml/kg/hr
- 5-7 ml/kg/hr

- 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 (For rewrite and define clinically deteriorate)

Note

- *5 ml/kg/hr = maintenance + 5% deficit*
- *7 ml/kg/hr = maintenance + 7%deficit*
- *Platelet count falls below 100,000 to 50,000/cumm → Hct up to 10% rise from baseline*
- *Platelet count falls below 50,000/cumm → 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 0.5 ml/kg/hr*

Figure (3) Rate of infusion in non-shock cases



Rate of IV fluid for children (Rate for adults)

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

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

- 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 DHF patients with warning signs
- Adjust fluid (oral + IV) – same as above as in DHF patients with warning signs

For infant dengue – Use isotonic fluid during critical phase except in infants <6 months in whom ½ Strength Saline is to be used

Note for infant

- *Basal Hct may be lower than the Hct of older children eg, 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 (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	50-75	
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 IBM >50 kg, 1.5 – 2 ml/kg can be used for quick calculation of hourly maintenance fluid regimen. For adults with IBW ≤ 50Kg, 2-3ml/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 below

Table (5) - Haemodynamic assessment: continuum of haemodynamic changes

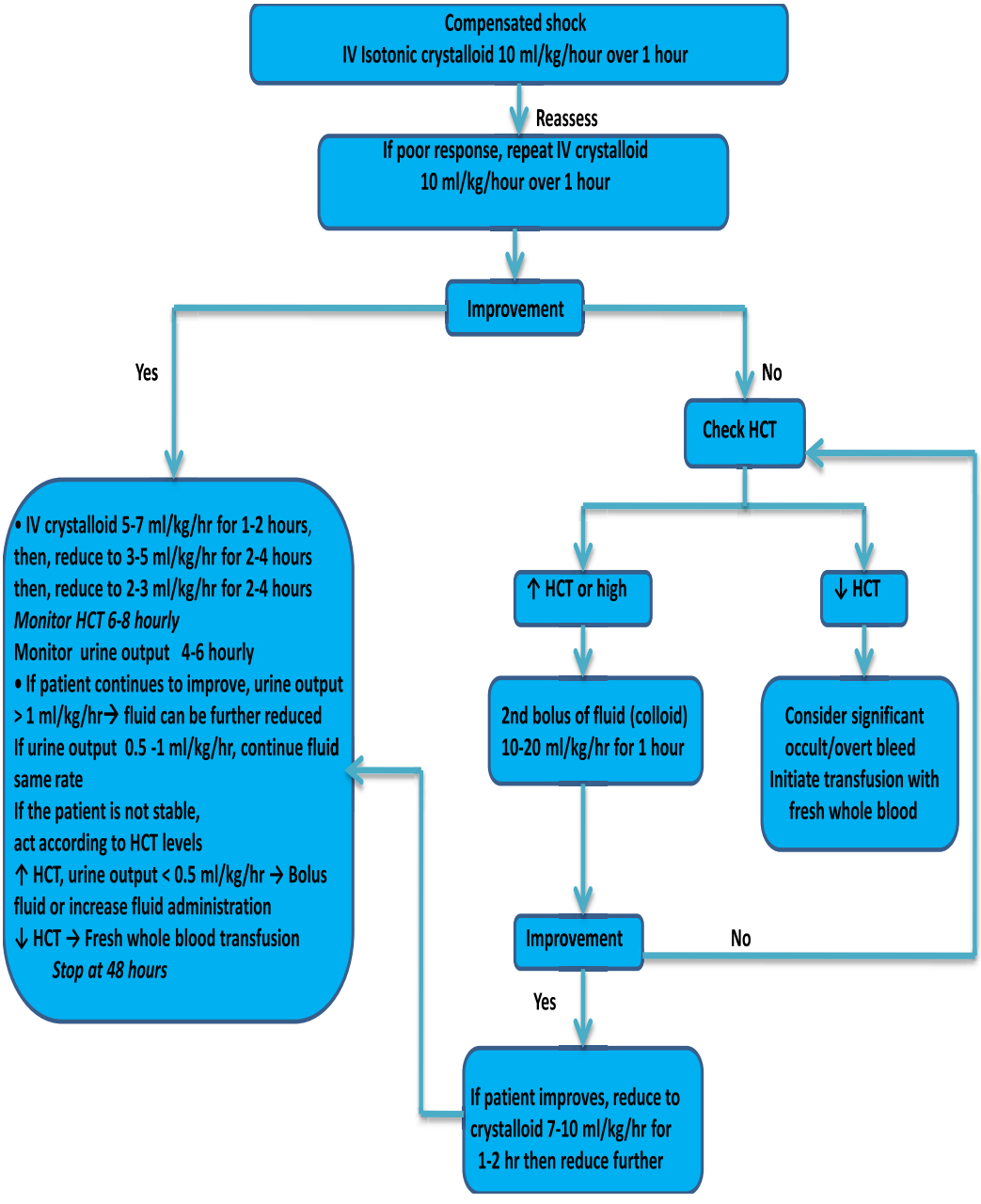
Parameter	Stable circulation	Compensated Shock	Hypotensive Shock
Conscious level	Clear and lucid	Clear and lucid (Shock can be missed if you do not touch the patient	Change of mental state (restless, combative)
Capillary refill time	Brisk(<1 sec)	Prolong (> 2sec)	Very Prolonged mottled skin
Peripheral 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 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 mmHg 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+ (age in years x 2) mmHg

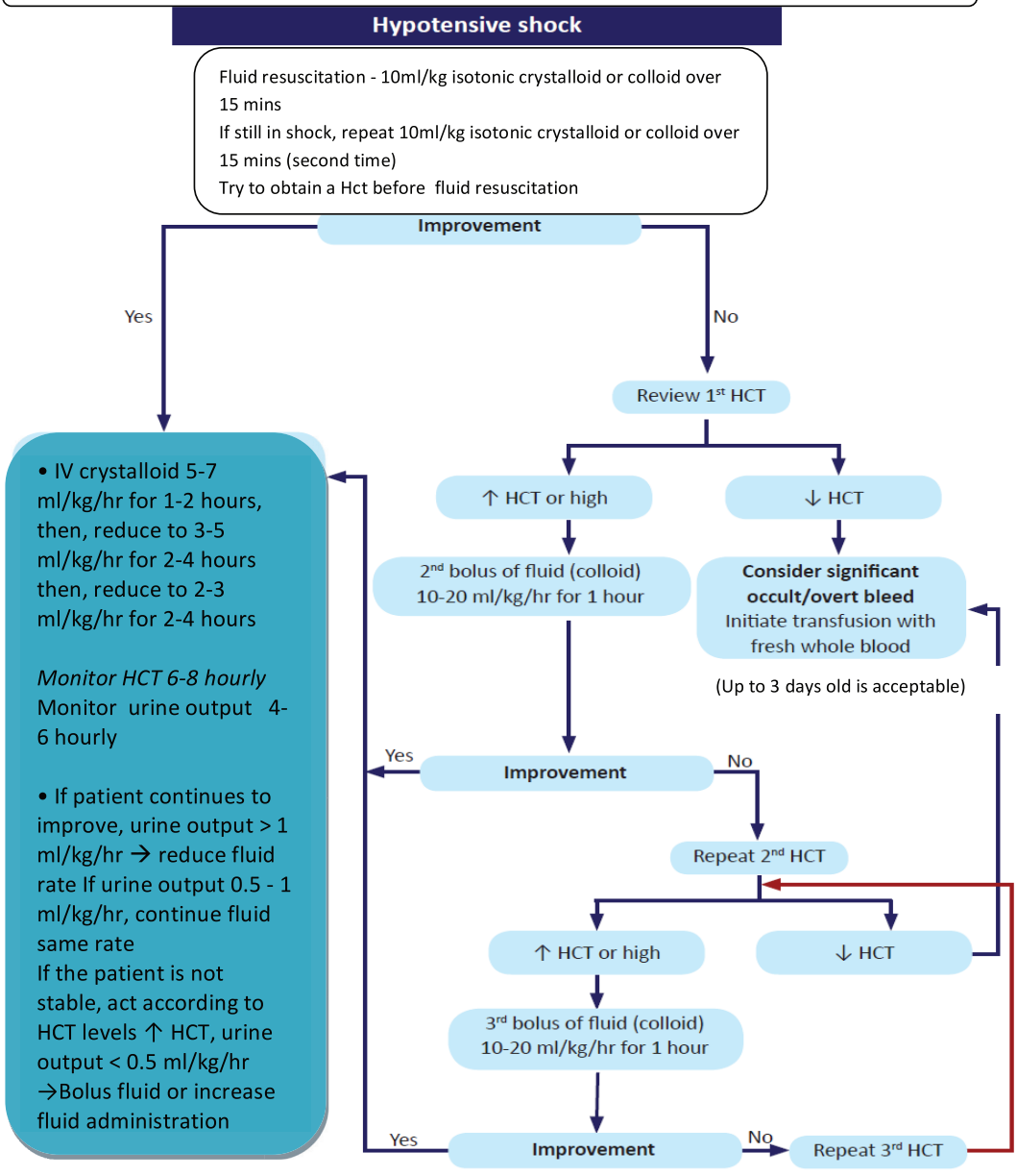
Narrow pulse pressure, 20 mmHg alone is seen in many normal children.Therefore other criterion + pulse pressure 20 mmHg must be fullfilled for diagnosis of compensated shock

Algorithm 4 for fluid management in Compensated shock(DSS grade III)



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

Algorithm 5 for fluid management in hypotensive shock (DSS grade IV)

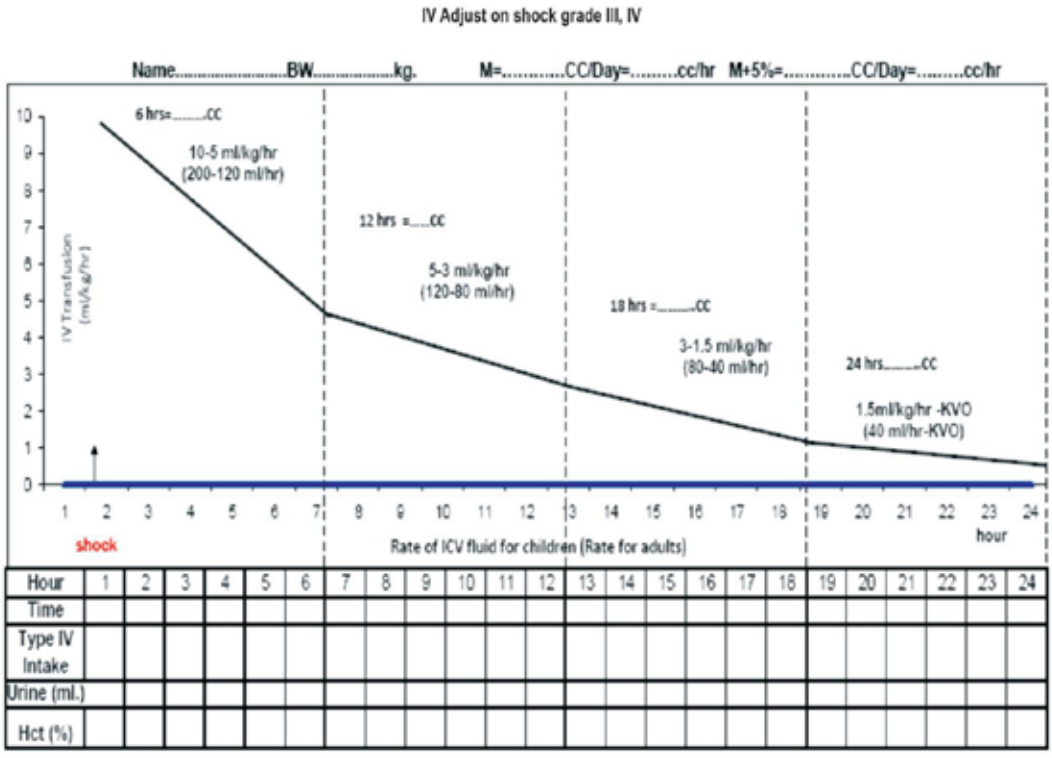


Source: Kalayanarooj S. and Nimmannitya S. In: Guidelines for Dengue and Dengue Haemorrhagic Fever Management. Bangkok.Medical Publisher, Bangkok 2003

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 cnnot have adequate oral fluid intake or ie vomiting*
    - *When HCT continues to rise 10-20% despite oral rehydration*
    - *Shock*
- ***Recovery Phase:***
    - *Generally no IV fluid*

Figure (4) Rate of infusion in DSS case



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 pulse pressure, tachycardia, metabolic acidosis, poor urine output) indicate 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 thrombocytopaenia***, 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-steroid anti-inflammatory agents
- Have preexisting 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 to gether with unstable haemodynamic status, regardless of the haematocrit level
- A decrease in haematocrit after fluid resuscitation together with unstable haemodynamic status, regardless of the haematocrit level
- 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 + 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 indictor of major bleed*

Action plan for the treatment of haemorrhagic complications

- Give 5 to 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 practices 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 cell are (up to 3 days old is acceptable)*

Respiratory distress in severe dengue

May be due to

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

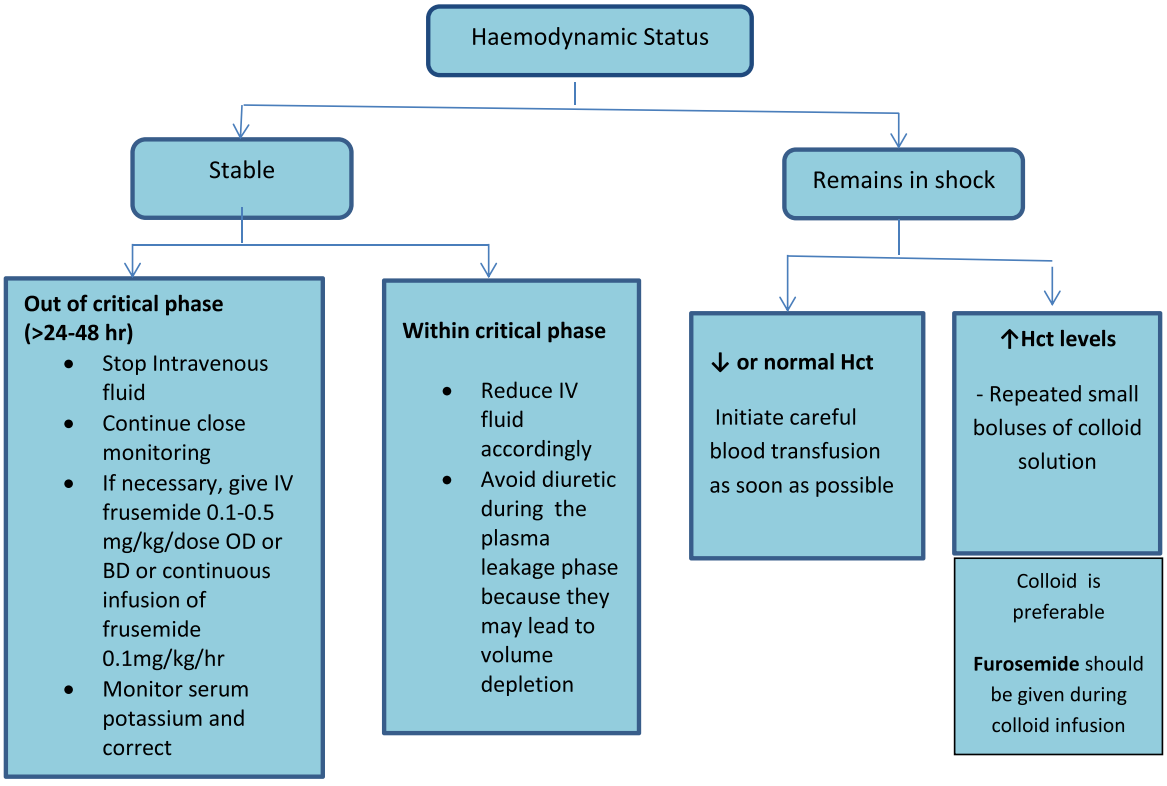
Fluid overload

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

Action plan for 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 patient's haemodynamic status.

Figure (5) Management of fluid overload



Note: *Sodium bicarbonate for metabolic acidosis is not recommended pH ≥ 7.15*

*Gelofusin can be used if dextran 40 or colliod 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 (Prothrombin Time(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% NaCL as maintenance (fluid restriction - 2/3 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 to 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 normocarbia (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 hour
- 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 closeer monitoring and probably accorded special treatment of a higher tier of hospital care :

- Infants < 1 year
- Obese patients
- Pregnant women
- 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 importants information : clinical conditions with progression, time of shock, serries of Hct, platelet count, viatl 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 acompanied.
- Specialist or more experience doctors should be notify 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.

4. Management of Dengue Infection in Adults

Clinical course of Dengue infection in adult

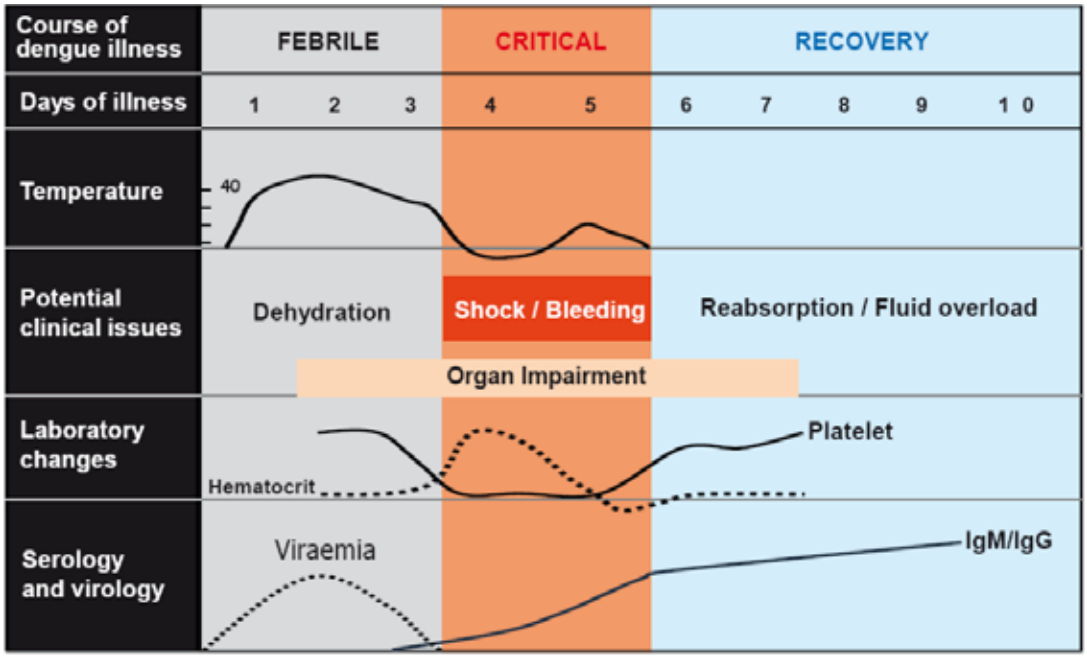
Dengue virus is transmitted via the bite of Aedes mosquitoes in particular *A. aegypti & A. albopictus.*

The virus is present in blood in early acute phase only, generally for 1-5 days. The incubation period is 4-7 days (range 3-14). Dengue infection is a dynamic disease.

Common manifestations

3 phases

1. Febrile phase	Dehydration, high fever may cause neurological disturbance
2. Critical phase	Shock from plasma leakage, severe haemorrhage, organ impairment
3. Recovery phase	Hypervolemia (only if intravenous fluid therapy has been excessive and/or has extended into this period)



Other important manifestations:

- Acute abdomen - due to hepatitis, acalculous cholecystitis and shock, and occasionally misdiagnosed as acute appendicitis.
- Hepatitis and liver failure

- Neurological manifestation - (<1%) mainly encephalitis or encephalopathy. Rare manifestations include myelitis and Guillain Barré Syndrome.
- Haemophagocytic syndrome - unusual progressive cytopenia and multi-organ complications

Criteria for Dengue

Diagnosis of Dengue fever and Dengue haemorrhagic fever

Dengue fever

Probable diagnosis:

Acute febrile illness with two or more of the following:

- Headache
- Retro-orbital pain
- Myalgia
- Arthralgia/bone pain
- Rash
- Haemorrhagic manifestations
- Leucopenia (WBC ≤5,000 cells/mm^3)
- Thrombocytopenia (platelet count <150,000 cells/mm^3)
- Rising haematocrit (5 - 10%)

And at least one of following:

- Supportive serology on single serum sample: titre ≥1,280 with haemagglutination inhibition test, comparable IgG titre with enzyme-linked immunosorbent assay, or positive in IgM antibody test
- Occurrence at the same location and time as confirmed cases of Dengue fever

Confirmed diagnosis:

Probable case with at least one of the following:

- Isolation of dengue virus from serum, CSF or autopsy samples
- Fourfold or greater increase in serum IgG (by haemagglutination inhibition test) or increase in IgM antibody specific to dengue virus
- Detection of dengue virus or antigen in tissue, serum or cerebrospinal fluid by immunohistochemistry, immunofluorescence or enzyme-linked immunosorbent assay
- Detection of Dengue virus genomic sequences by reverse transcription-polymerase chain reaction

Dengue haemorrhagic fever

All of following:

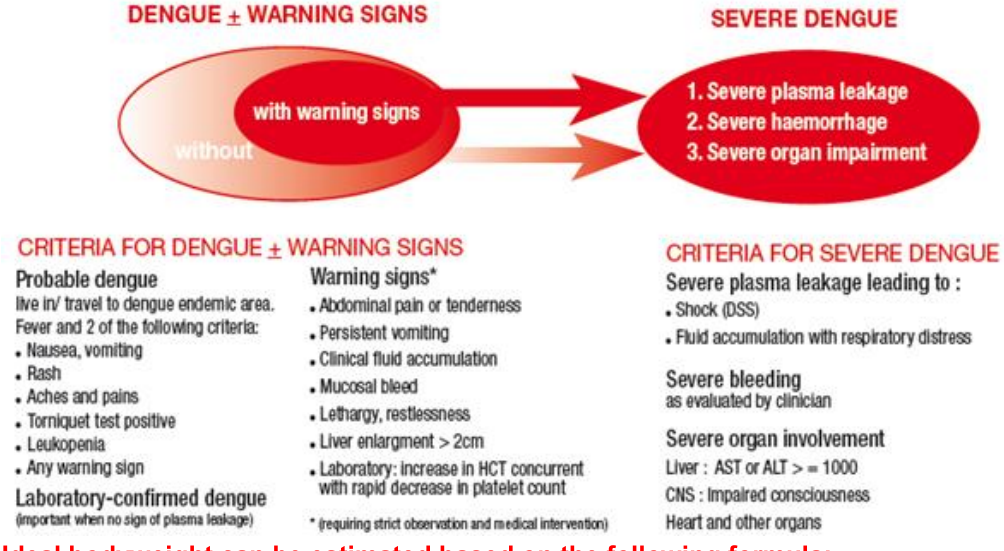
- Acute onset of fever of two to seven days duration
- Haemorrhagic manifestations, shown by any of the following: positive tourniquet test, petechiae, ecchymoses or purpura, or bleeding from mucosa, gastrointestinal tract, injection sites, or other locations
- Platelet count ≤100,000 cells/mm^3
- Objective evidence of plasma leakage due to increased vascular permeability shown by any of the following:
  - Rising haematocrit/ haemoconcentration ≥20% from baseline or decrease in convalescence, or
  - Evidence of plasma leakage such as pleural effusion, ascites or hypoproteinaemia/ hypoalbuminaemia

Dengue shock syndrome

Criteria for dengue haemorrhagic fever as above with signs of shock including:

- Tachycardia, cool extremities, delayed capillary refill, weak pulse, lethargy or restlessness, which may be a sign of reduced brain perfusion
- Pulse pressure ≤20 mmHg with increased diastolic pressure, e.g. 100/80 mmHg
- Hypotension by age, defined as 80 to 90 mmHg for adults

Warning Signs



Ideal bodyweight can be estimated based on the following formula:

- Female: 45.5 kg + 0.91(height -152.4) cm
- Male: 50.0 kg + 0.91(height -152.4) cm

WHO Dengue classification

Grade I

In the presence of haemoconcentration, fever and non-specific constitutional symptoms, a positive tourniquet test is the only haemorrhagic manifestation

Grade II

Spontaneous bleeding in addition to the manifestation of Grade I

Grade III *

Circulatory failure, pulse pressure less than 20 mmHg but systolic pressure is still normal

Grade IV *

Profound shock, hypotension or unrecordable blood pressure

* Grades III and IV are classified as Dengue Shock Syndrome (DSS)

Laboratory investigations

Disease monitoring lab test

- Full Blood Count (FBC)
- Leucopaenia followed by progressive thrombocytopaenia and rising HCT are suggestive of DHF
- Liver Function Test
- Elevated liver enzymes AST > ALT

Diagnostic tests

- Dengue Serology Test – Dengue IgM is usually positive after day 5-7 of illness
- Non-Structural Protein-1 (NS1 Antigen) – NS1 Ag is a new diagnostic tool that may be useful in the early phase of Dengue infection
- Combination of NS1 Ag + IgG/IgM in the same kit (Duo/Combo) (Sensitivity of up to 90%)

Interpretation of dengue diagnostic tests [adapted from Dengue and Control (DENCO) study]

Highly suggestive	Confirmed
One of the following • IgM (+ve) in a single serum sample • IgG (+ve) in a single serum sample with a 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

Management

Stepwise approach to the management of Dengue

Step I. Overall assessment

1.1 History, including information on symptoms, past medical and family history

1.2 Physical examination, including full physical and mental assessment

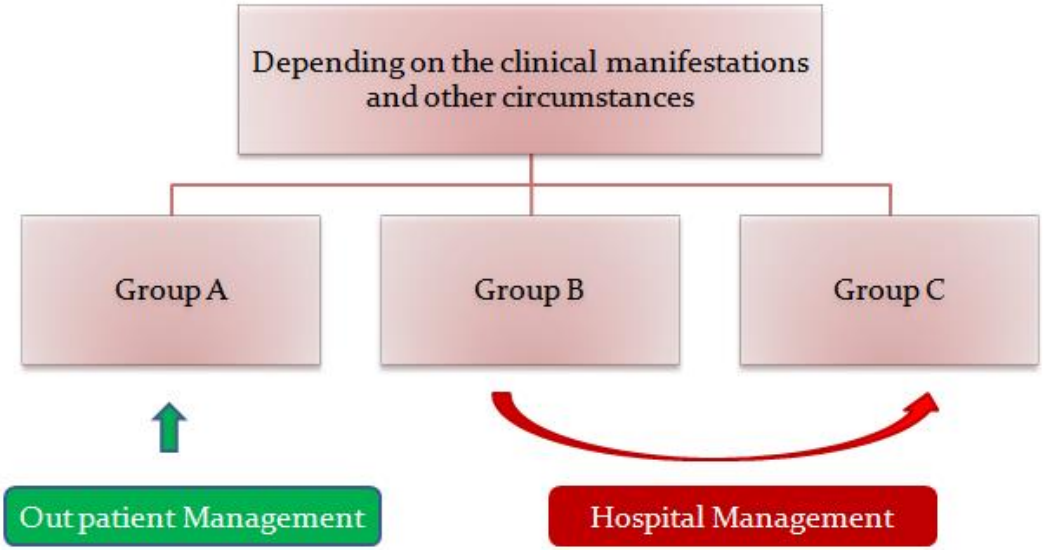
1.3 Investigation, including routine laboratory and dengue-specific laboratory

Step II. Diagnosis, assessment of disease phase and severity

Step III. Management

III.1 Disease notification

III.2 Management decisions



Out-patient management (Group A)

- Encourage oral intake of ORS, fruit juice and other fluids
- Give paracetamol for high fever
- Monitor daily by health care provider

Referral from primary care providers to hospital (Group B & C)

Symptoms

Warning signs

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation (pleural effusion, ascites)
- Mucosal bleed
- Restlessness or lethargy
- Liver enlargement > 2 cm
- Laboratory: Increase in HCT concurrent with rapid decrease in platelet
- Bleeding manifestations
- Inability to tolerate oral fluids
- Reduced urine output
- Seizure

Signs

- Dehydration
- Shock
- Bleeding
- Any organ failure

Special Situations

- Patients with co-morbidity e.g. diabetes, hypertension, ischaemic heart disease, coagulopathies, morbid obesity, renal failure, chronic liver disease, COPD, haemoglobinopathy
- Elderly (>65 years old)
- Pregnancy
- Social factors that limit follow-up e.g. living far from health facility, no transport, patient living alone

Laboratory Criteria

- Rising HCT accompanied by reducing platelet count

In-hospital management

Fluid management

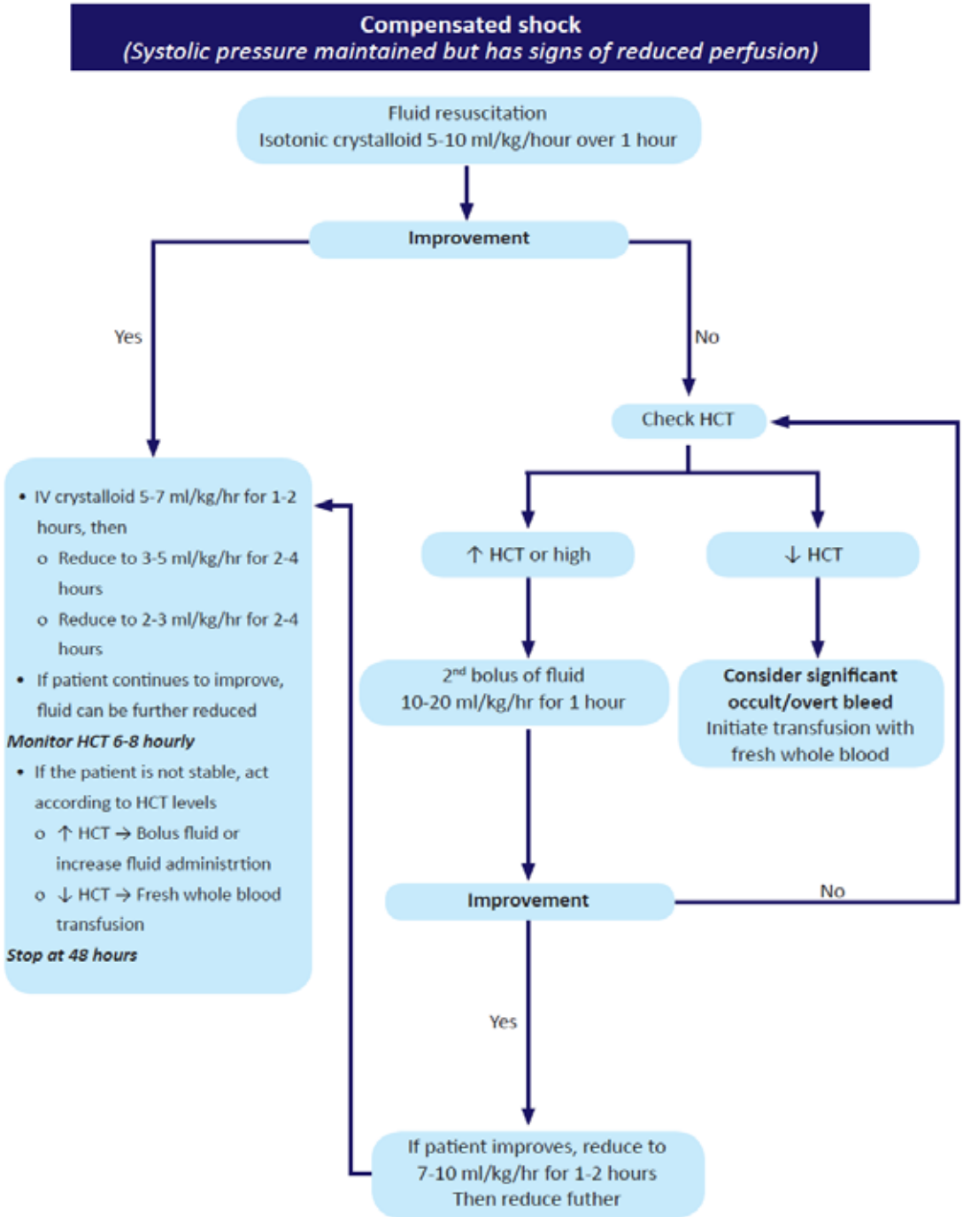
Non-shock patients (DHF Grade I & II)

- Encourage adequate oral fluid intake.
- IV fluid is indicated in patients who are vomiting or unable to tolerate oral fluids.
- Crystalloid is the fluid of choice for non shock patients.
- Start with 5-7 ml/kg/hr for 1-2 hours, then reduce to 3-5 ml/kg/hr for 2-4 hrs and then reduce to 2-3 ml/kg/hr or less according to the clinical response.

Dengue Shock Syndrome (DSS) (DHF Grade III & IV)

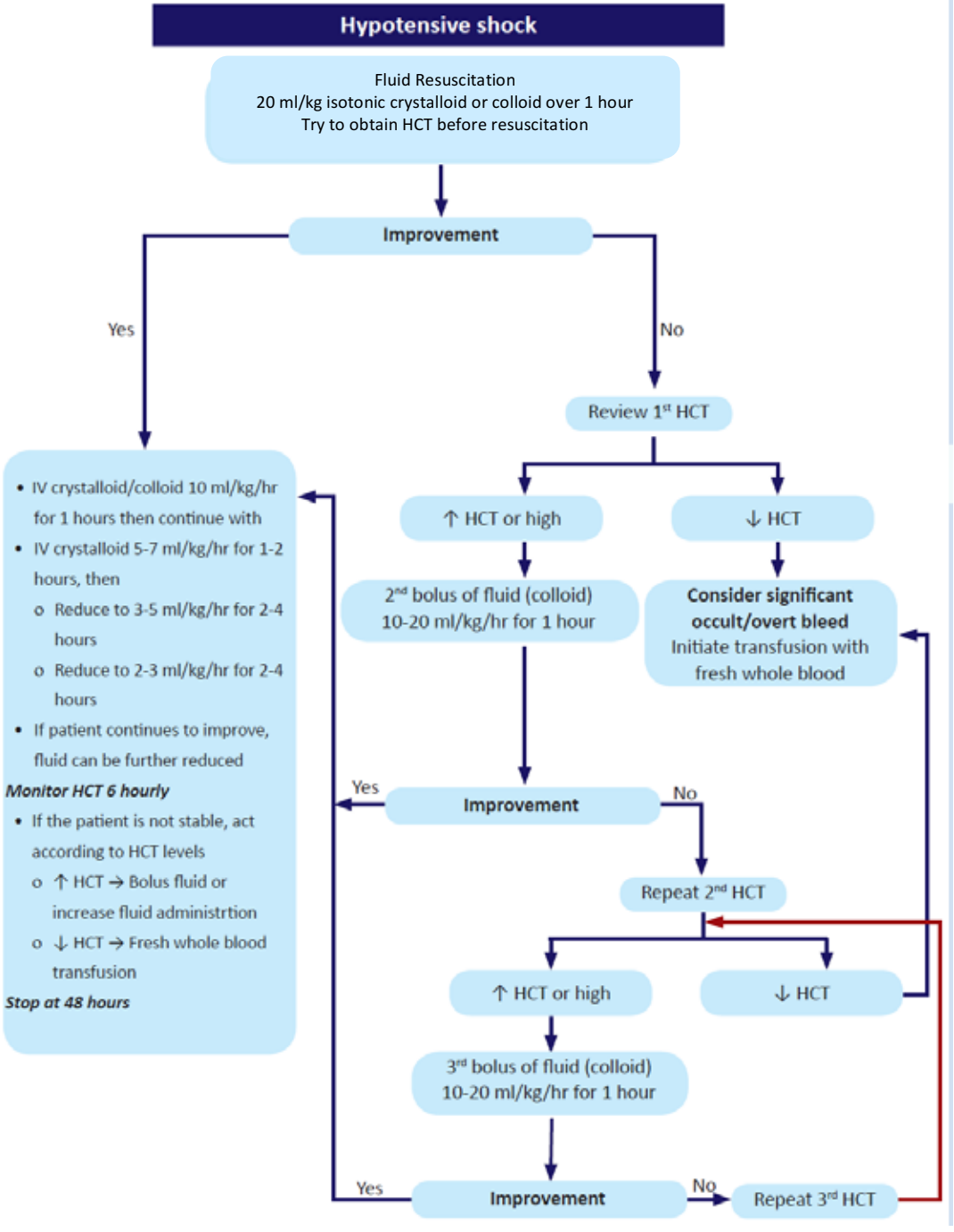
- Dengue shock syndrome is a medical emergency.
- All patients with dengue shock should be managed in high dependency / intensive care units. Fluid resuscitation must be initiated promptly.
- For initial resuscitation,
    - Crystalloids are the fluid of choice in patients with DSS.
    - Colloids may be preferred as the fluid of choice in patients with severe shock.

Algorithm (6) for fluid management in Compensatede shock in adult dengue



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

Algorithm (7) for fluid management in Hypotensive shock in adult dengue



- Clinical parameters must be monitored every 15-30 minutes during shock
- Improvement in the following parameters indicates adequate fluid resuscitation:

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

Clinical parameters

- Improvement of general well being/mental state
- Warm peripheries
- Capillary refill time <2sec
- BP stable
- Improving pulse pressure
- Less tachycardiac
- Increase in urine output
- Less tachypnoiec

Laboratory parameters

- Decrease in HCT
- Improvement in metabolic acidosis
    - In cases with persistent shock despite a decline in haematocrit after initial fluid replacement and resuscitation with plasma or plasma expanders, internal bleeding should be suspected. Blood transfusions may then be indicated.
    - Other possible causes of persistent shock include sepsis and cardiogenic shock (due to myocarditis or ischaemic heart disease).

Indications for referral to Intensive Care:

- Recurrent or persistent shock
- Requirement for respiratory support (non-invasive and invasive ventilation)
- Significant bleeding
- Encephalopathy or encephalitis

Management of DHF/DSS

Blood transfusion

- Patients with mild bleeding such as from the gums or per vagina, epistaxis and petechiae do not require blood transfusion.
- Blood transfusion with whole blood or packed cell (preferably less than 1 week) ± blood component is indicated in significant bleeding.
- Give 5–10 ml/kg of fresh-packed red cells or 10–20 ml/kg of fresh whole blood at an appropriate rate. (One unit of whole blood or packed cell in adults)

- In the presence of disseminated intravascular coagulation (DIC) - treat according to the haematology guideline.
- Platelet prophylaxis may be considered in adult dengue with underlying hypertension, heart disease, or those with anticoagulant or antiplatelet aggregation therapy and have marked thrombocytopenia <10,000 cells/cumm.

Discharge criteria

The following should be taken into consideration before discharging a patient.

- Absence of fever for 24 hours without the use of antipyretics, and a return of appetite
- Visible improvement in clinical picture
- Stable haematocrit
- Three days after recovery from shock
- Platelet count greater than 50,000/mm^3 and rising
- No respiratory distress
- Resolved bleeding episodes
- Resolution/recovery of organ dysfunction

Management of DHF in special situations

Dengue in Pregnancy

- Admission on the second day of fever and close follow up with FBC daily is indicated
- Gestation and the phase of Dengue should be considered in management plan
- Multi-disciplinary team consisting of obstetricians, physician, anaesthetist and paediatrician should be involved in the management
- All fever of more than 24 hours without a definite cause should be admitted to hospital. If admitted to the obstetric ward, urgent referral to physician needed. Need to explain family members about course of DHF and management plan
- Based on signs, symptoms and laboratory investigations, important differential diagnoses are toxaemia and HELLP syndrome (Haemolysis, Elevated Liver Enzymes and Low Platelets)
- Normal physiological changes in pregnancy make the diagnosis and assessment of plasma leakage difficult and following baseline parameters should be noted as early as possible

Subsequent management will be based on the changes of baseline levels:

- Pulse, blood pressure (BP), pulse pressure. (Baseline BP is often lower and pulse pressure wider and heart rate may be higher)
- FBC - (Haemoglobin, HCT and platelet count may be lower than in non-pregnant patient)
- SGOT/SGPT
- Clinical detection of pleural effusion and ascites may be difficult due to the presence of gravid uterus
- Ultra Sound scan to detect pleural effusion and ascites
- Fluid volume for the critical period for a pregnant mother should be calculated based on the weight prior to pregnancy

Management of pregnant patients with DF/DHF close to delivery

Risk of bleeding is highest during period of plasma leakage (critical phase). Therefore,

- Unless to save mothers life, avoid LSCS or induction of labour during Critical (plasma leakage) phase
- Obstetric procedures (such as amniocentesis or external cephalic version) should be avoided during the illness

If obstetric procedures are to be undertaken,

- Maintain platelet count above 50,000/mm^3
- Single donor platelet transfusion is preferred, if available, if platelet transfusion is necessary
- If patient goes into spontaneous labour during critical phase, take steps to prevent vaginal tears by performing an episiotomy
- In a case of foetal compromise priority should be given to the mother's life and decision making should involve the multidisciplinary team
- Counselling the family on the probable outcome is essential

Management of patients with DF/DHF during immediate postpartum

- Dengue fever should be suspected in fever in immediate post-partum period
- Early referral to physician

Myocardial involvement in Dengue

- Global dysfunction of myocardial contractility may be seen in DHF with prolonged shock and most likely due to metabolic acidosis
- Hypocalcaemia (a common finding in DHF with moderate to large pleural effusion / ascites) should be considered
- Acidosis and hypocalcaemia should be rapidly corrected if evidence of cardiac dysfunction
- Myocarditis uncommon but can lead to pulmonary oedema with fluid overload; if myocardial involvement is suspected fluid should be given carefully

Liver Disease

- If Dengue is suspected in chronic liver disease, baseline liver function tests (LFT) and prothrombin time (PT)
- Likely to develop hepatic encephalopathy if AST/ALT is very high especially in those with gastrointestinal (GI) bleeding, where liver failure regime should be used early
- Patients may have more plasma leakage if baseline albumin is low; managing these patients with the minimum amount of IV fluid to maintain intravascular volume in order to prevent respiratory distress (acute pulmonary oedema) and/or heart failure
- Prolonged PT or INR (>1.3) indicates a tendency for more bleeding and IV Vitamin K1 recommended
- Assess severity of bleeding and give adequate amount of blood and blood components

Heart Disease

- Identify underlying heart disease and current medication
- Observe carefully and continuous monitoring with echocardiography especially during the critical phase
- Careful adjustment of IV fluid
- Withhold anti-platelet or anti-coagulation therapy for a few days especially during critical phase

Renal Disease

- Baseline renal function tests (U&E, Creatinine), acid-base balance, daily urine output, and urine analysis during early febrile phase and regularly monitored
- Close monitoring of fluid intake and urine output
- Fluid overload during convalescent phase is most important cause of death
- Early consultation with Nephrologist and early planning of renal replacement therapy in those patients who are oliguric with signs and symptoms of fluid overload

Diabetes Mellitus

- Frequent monitoring of blood sugar from admission
- All anti-diabetic drugs switched to insulin to keep blood sugar level below 150-200mg/dl
- Closely monitor and look for development of diabetic ketoacidosis which needs more IV fluid, IV insulin infusion, and monitoring of central venous pressure if possible

5. 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
  - 20% or 50% glucose
  - Vitamin K1
  - Calcium gluconate
  - KCl 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)

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World Health Organization
Myanmar

National Guideline
for Clinical Management of
Dengue

V E R S I O N 0 1

Vector Borne Disease Control Programme
Department of Public Health
Ministry of Health and Sports
The Republic of the Union of Myanmar
June, 2018