NATIONAL GUIDELINE FOR CLINICAL MANAGEMENT OF DENGUE IN BHUTAN

Version 1

(20th April 2020)

Vector-Borne Disease Control Program

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Foreword

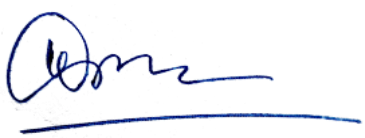
Over the past three decades, the global incidence of dengue fever, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) has increased dramatically. Globally, estimated 3.9 billion people are at risk of infection with dengue viruses. The disease is responsible for 100 million infections and 22,000 deaths every year (WHO). Despite a risk of infection existing in 129 countries, 70% of the actual burden is in Asia. About 4.7 million cases of dengue positive were globally reported in 2019 which was the largest number of dengue cases ever reported. Clearly, dengue virus infection, which is already the most widespread mosquito borne disease in humans is of major public health importance.

In Bhutan, the first ever dengue outbreak was reported in 2004 with a total of 2651 cases compatible with dengue symptoms. During the second upsurge of dengue cases at Phuntsholing in 2006, although morbidity was much less as compared to 2004, there were two deaths associated with dengue. In 2019, 5480 dengue positive cases and 6 deaths (including two pregnant women) were reported. 77% of the cases were reported from Phuntsholing. Of the 20 Dzongkhags, 19 (except Lhuentse) reported dengue cases in 2019, most being imported cases from endemic Dzongkhags. In various studies conducted in Bhutan, Dengue Virus (DENV) serotypes 1, 2 and 3 have been found in circulation, with DENV-1 being predominant. The primary dengue vector Aedes aegypti has been confirmed in Dzongkhags such as Chukha, Samtse, Dagapela, Sarpang, Samdrup Jongkhar, Wangdi, Mongar, Pemagatshel and Tashi Yangtse though mostly seasonally and confined in few places in the abovementioned Dzongkhags.

Though the primary mode of transmission of DENV between humans involves mosquito vectors, there is possibility of maternal transmission (from a pregnant mother to her baby). When a mother does have a DENV infection when she is pregnant, babies may suffer from pre-term birth, low birth weight, and fetal distress. There is no specific treatment for dengue fever dengue hemorrhagic shock and dengue shock syndrome. However, when managed appropriately, the case fatality can be reduced to less than 1%.

This clinical guideline was developed through series of consultations with national specialists in their relevant fields. This guideline is for use in all health centers for appropriate and timely management of dengue cases. This guideline takes into consideration dengue in special situations (children, pregnant mothers and also those with underlying diseases). I hope this guideline will make significant difference in the clinical management of dengue cases in the country from now onwards.

Henceforth, Dengue and suspected dengue is an immediately notifiable disease to National Early Warning & Response Surveillance (NEWARS). All Health workers who come across dengue cases must take the responsibility to report dengue cases immediately so that we can timely avert dengue outbreaks in a Bhutan.



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1. Introduction

Dengue fever also known as "break-bone fever" is a mosquito borne viral disease primarily affecting population in urban areas. The disease is responsible for 100 million infections and 22,000 deaths every year (WHO). In Bhutan, the first ever dengue outbreak was reported in 2004 with a total of 2651 cases compatible with dengue symptoms. During the second upsurge of dengue cases at Phuntsholing in 2006, although morbidity was much less as compared to 2004, there were two deaths associated with dengue. In 2019, 5480 dengue positive cases and 6 deaths (including two pregnant women) were reported. 77% of the cases were reported from Phuntsholing. Of the 20 Dzongkhags, 19 (except Lhuentse) reported dengue cases in 2019, most being imported cases from endemic Dzongkhags. In various studies conducted in Bhutan, Dengue Virus (DENV) serotypes 1, 2 and 3 have been found in circulation, with DENV-1 being predominant. The primary dengue vector Aedes aegypti has been confirmed in Dzongkhags such as Chukha, Samtse, Dagapela, Sarpang, Samdrup Jongkhar, Wangdi, Mongar, Pemagatshel and Tashi Yangtse though mostly seasonally and confined in few places in the above mentioned Dzongkhags. Each serotype provides specific lifetime immunity, and short-term cross-immunity. The mosquito bites mainly during daytime - Two peak biting periods – dawn and dusk (Sun rise &sun set). The *Aedes* mosquitoes have flight range of 100 meters.

Table 1: Risk of dengue transmission in Bhutan

Districts/ Areas	Dengue outbreak year	Presence of vector *Ae. aegypti*	Regular surveillance
High risks areas			
Phuentsholing and Passakha	Since 2004	Confirmed	Yes
Samtse	Since 2012	Confirmed	Yes
Gomtu	Since 2012	Confirmed	Yes
Dagapela	In 2013	Confirmed	No
Gelephu	In 2019	Confirmed	Yes
Samdrup Jongkhar	In 2019	Confirmed	Yes
Doksum in Tashi Yangtse	In 2019	Confirmed	No
Lhamoizingkha	No outbreak	Confirmed	Yes
Along the riverine valley of Punatsangchu (Taksha to Punakha)	No outbreak	Confirmed in Kamichu & Basochu (2010)	No
Gyelposhing, Lingmithang and Thridangbi in Mongar	No outbreak	Confirmed in Gyelposhing (2019)	No
Potential risk areas			
Jomotshangkha, Dewathang, Pemathang Samdrupcholing and Samrang in S. Jongkhar	No outbreak	Not data yet	Yes
Piping, Devitar and lower Sinchula	No outbreak	Not data yet	No
Singay, Sarpangtar, Chokhorling, Sershong, Chuzargang, Norbuling, Umling, Tareythang (SARPANG)	No outbreak	Not data yet	Yes
Arikha, Gedu, Chukha Power colony	No outbreak	Not data yet	No
Sunkosh till Rilangthang in Tserang	No outbreak	Not data yet	No
Tingtibi, Berti, Pangtang till Pangbang	No outbreak	Not data yet	No
Tongtongphy till Khamed in Tongsa including MPH colonies	No outbreak	Not data yet	No
Autso/Tangmachu in Lhuentse	No outbreak	Not data yet	No
T/gang Bazaar, Rangjung & Pam	No outbreak	Not data yet	No

2. Clinical features

- Incubation period: 4-10 days
- Dengue infection can be asymptomatic or symptomatic. The symptomatic presentation can range from undifferentiated fever to rare fatal hemorrhagic death
- Infants and young children may have a non-specific febrile illness with rash, while older children and adults may have either a mild febrile syndrome.
- In general the course of dengue fever consists of three phases: **Febrile, Critical, and Recovery phase.**

2.1 Febrile Phase

- Sudden onset of high grade fever lasting 2-7days, accompanied by facial flushing, headache, skin erythema, generalized body ache, eye pain, myalgia and arthralgia.
- Some patients may have sore throat, injected pharynx, and conjunctival injection. Anorexia, nausea and vomiting are also common.
- Mild hemorrhagic manifestations such as petechial, purpura and mucosal membrane bleeding may be present.
- In some cases easy bruising and bleeding at venipuncture site is present. Rarely massive vaginal and gastrointestinal bleeding may occur.
- Liver may be enlarged and tender after few days of fever. Tender hepatomegaly is indicative of DHF
- Leucopenia of < 5000/cmm of blood and thrombocytopenia of <150,000/cmm.

2.2. Critical Phase

- Occurs generally within 3-7 days of onset of illness, when temperature returns to normal and lasts for 24- 48 hours

- **Plasma leakage**- This phase is characterized by increased capillary permeability leading to plasma leakage and may result in manifestations of warning signs. Progressive leukopenia followed by thrombocytopenia, usually precedes plasma leakage. The period of clinically significant plasma leakage usually lasts 24–48 hours and the degree of plasma leakage varies. The degree of increase above the baseline hematocrit often reflects the severity of plasma leakage.

- **Severe dengue and dengue shock** can occur- Shock occurs when a critical volume of plasma is lost through leakage and is often preceded by warning signs. The body temperature may be subnormal when shock occurs. With prolonged shock, the consequent organ hypoperfusion results in progressive organ impairment, metabolic acidosis and disseminated intravascular coagulation. This in turn leads to severe hemorrhage causing the hematocrit to decrease in severe shock. Instead of the leukopenia usually seen during this phase of dengue, the total white cell count may increase as a stress response in patients with severe bleeding.

- **Severe organ impairment**- In addition, severe organ impairment such as severe hepatitis, encephalitis or myocarditis and/or severe bleeding may also develop without obvious plasma leakage or shock.
- Some patients progress to the critical phase of plasma leakage and shock without defervescence and,

in these patients, a rising hematocrit and rapid onset of thrombocytopenia or the warning signs, indicate the onset of plasma leakage. Cases of dengue with warning signs will usually recover with early intravenous rehydration. Some cases will deteriorate to Severe Dengue.

The warning signs herald the onset of critical phase. The warning signs

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation (Ascites and pleural effusion)
- Mucosal bleed
- Lethargy and restlessness
- Postural drop
- Liver enlargement >2cm
- Laboratory*:* Increase in HCT (above 20 % of the baseline) concurrent with rapid decrease in platelet count to about 100,000 cells/mm3.

2.3 Recovery Phase

After the critical phase, there is a gradual reabsorption of extravascular compartment fluid over the next 48−72 hours. Recovery phase is characterized by

- A- Afebrile, return of appetite
- B- Blood pressure and other vital normalizes
- C- Confluent itchy erythematous or petechial rash are seen which are described as “isles of white in the sea of red”.
- D- Diuresis
- Stabilization of hematocrit, leucopenia and followed by thrombocytopenia.

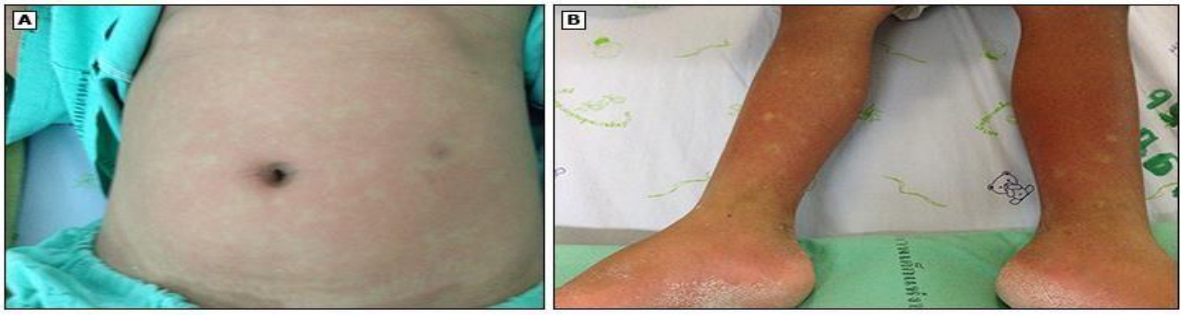

Figure 1: Confluent itchy erythematous rash

Medical complications in the three phases of dengue:

Sl. no	Clinical phases	Common clinical problems
1	Febrile Phase	Dehydration, electrolyte imbalance-hyponatremia, Hypoglycemia Febrile seizures in young children
2	Critical Phase	Shock from plasma leakage: severe hemorrhage, organ impairment. Common complications: acidosis, hypocalcemia, hypoglycemia
3	Recovery Phase	Hypokalemia-due to diuresis Hypervolemia (if intravenous fluid therapy has been excessive and/has been extended to this period) and acute pulmonary edema

3. Revised dengue case classification

The revised dengue case classification (with or without warning signs) is given in **Figure 2** below:

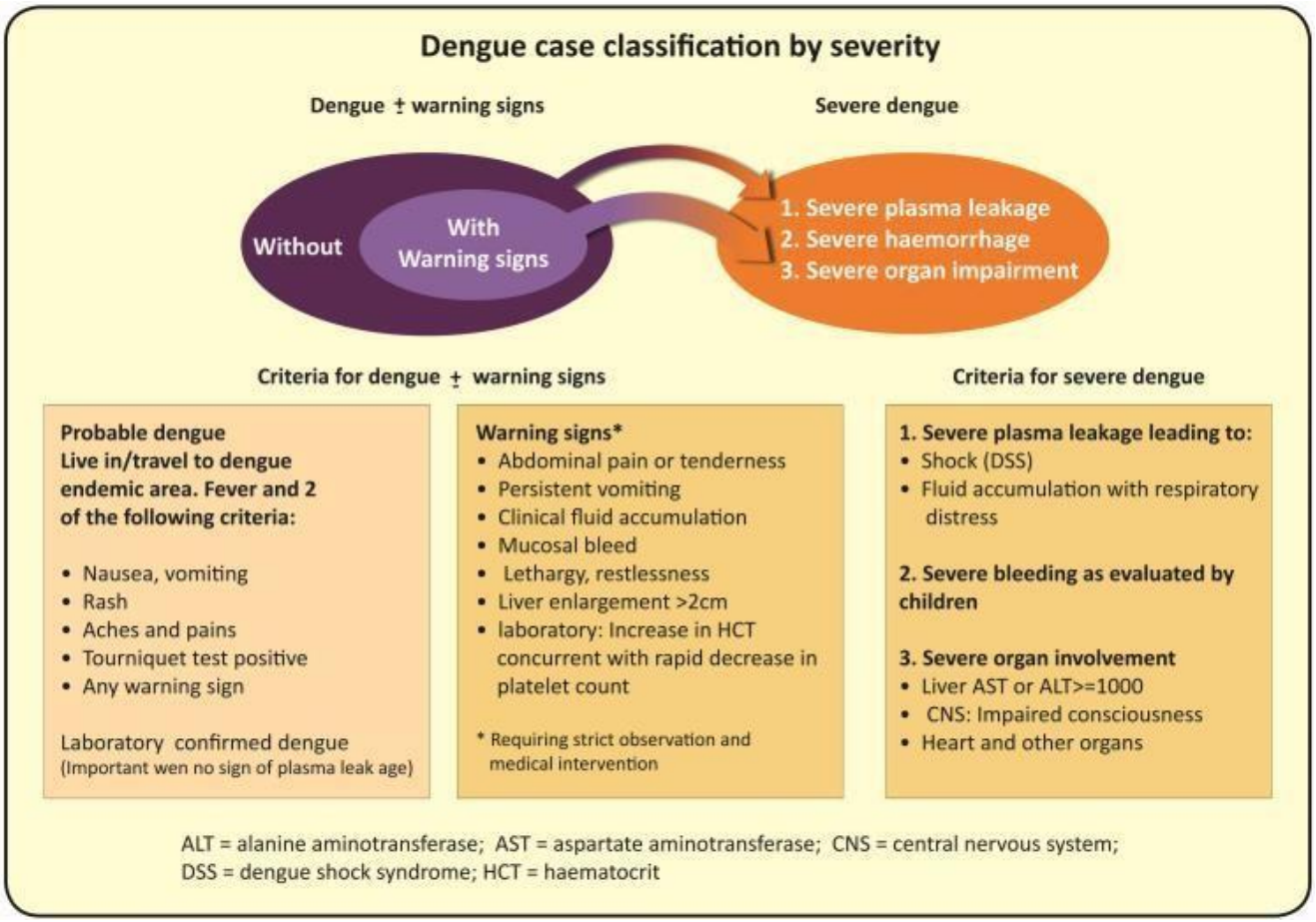

Figure 2: Revised Dengue case classification

4. Case definitions for dengue fever and outbreaks

Confirmed case:

An individual fulfilling suspected case definition and confirmed by rapid test kit detecting NS1 antigen or IgM positive. If IgM is negative on 1st test (acute sample), it should be retested after 5-7 days. Diagnosis of acute dengue infection by IgG is only possible by demonstrating appearance of IgG (convalescent sample) on a previously negative sample (acute sample) or a ≥4-fold rise in titer collected >2 weeks apart.

Note:

Patient management case definition

However, any individual who test positive to IgG (IgM and NS1 negative) and has signs and symptoms consistent with dengue suspected case, it should be managed as probable dengue case. The patient should be retested after 5-7 days and if positive to IgM, it should be considered as a positive dengue case.

Outbreak case definition to trigger dengue outbreak response

Occurrence of confirmed dengue (fulfilling the confirmed individual case definition) of ≥5 or more cases in circumscribed setting (Cluster)) within 7 days period should be considered as an outbreak and should trigger full response activities.

Non-endemic area

Any single case of dengue confirmed case should be considered as outbreak and should trigger outbreak response activities

5. Investigations

5.1 Laboratory investigations

- Specimen: Blood (Serum/Whole blood),
- Complete blood count:
- Liver Function test
- Renal Function test
- Serum electrolytes, Calcium and albumin(can be used as markers for plasma leakage)
- Random Blood sugar
- Other tests to exclude differentials diagnosis: MP, Scrub Typhus, enteric fever, zika and chikungunya.
- Laboratory diagnosis- **Rapid diagnostic test (RDT)**
    - RDT test kit for Dengue infections are available in various types; detect both antigen (NS1) and antibody (IgM and IgG), NS1or antibody (IgM and IgG) only.
    - NS1 antigen: appears within 24 hours of onset of symptoms and is positive till Day 5
    - IgM: Positive by Day 5 of fever and remains positive till 2-3 months
    - IgG: Positive by Day 7 of illness and lasts lifelong for particular serotype
    - In a secondary infection IgG response is more robust and appears before IgM for the new infection. When lab reports suggest IgG positive with NS1 Ag and IgM negative, Suspect past dengue infection. The guide to rapid test interpretation is given in **Table 2**.

Table 2: Dengue result interpretation table

Test results			Interpretation	Remarks
NS1	**IgM**	**IgG**	Acute dengue infection	
+	-	-	Acute dengue infection	
+	+	-	Acute dengue infection	
-	+	+	Acute dengue infection	
+	+	+	Acute dengue infection	
-	-	+	Past infection	In patient without dengue compatible signs
			Recent infection	In patient with dengue compatible signs

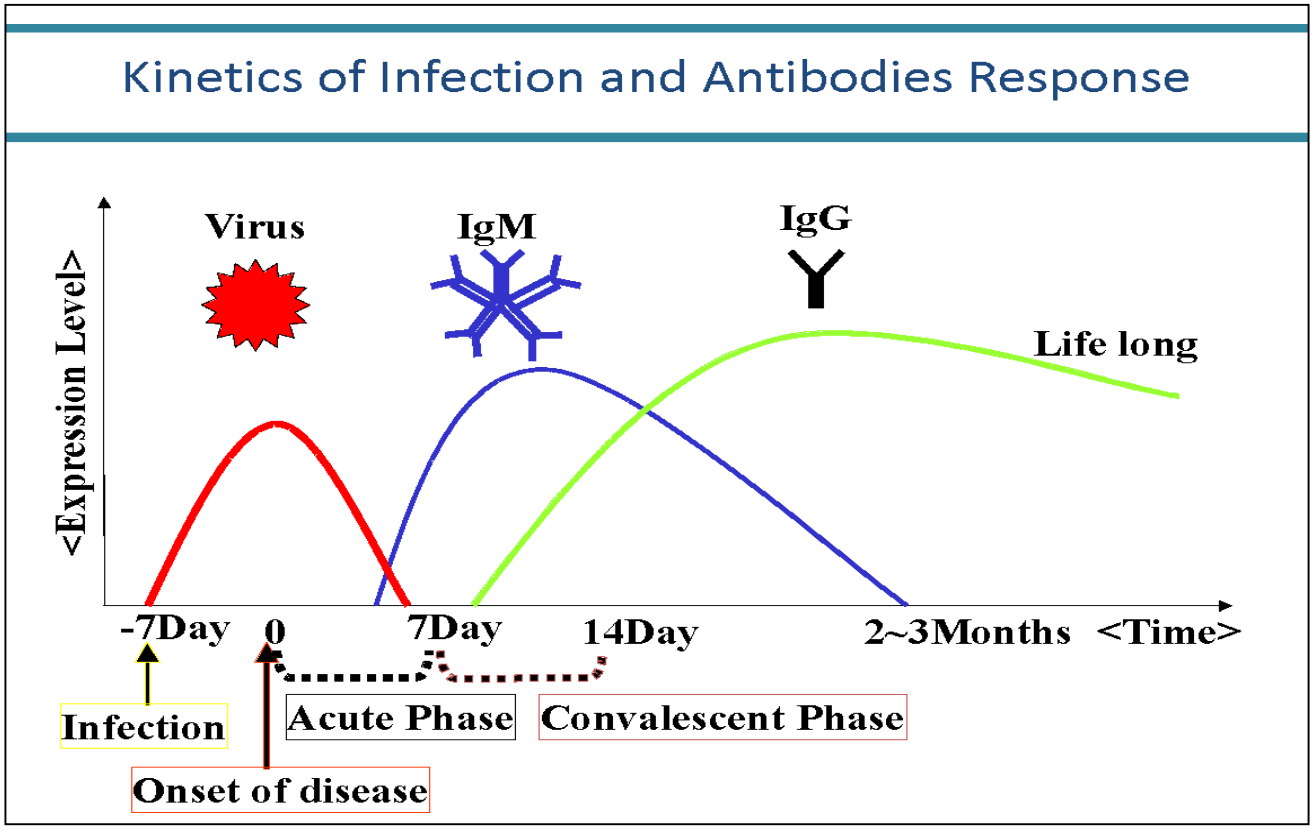

Figure 3: Kinetics of infection and antibodies response

5.2 Confirmatory laboratory testing

PCR and ELISA are done at RCDC, Serbithang, and Thimphu. All RDT positive tests should be sent to RCDC for confirmation using form **Annexure 8**. But the management of dengue should not be withheld till confirmatory test results are known.

The sample when sent for serotyping should contain details of the day of onset of fever ,day of sample collected and other details specifying whether the rapid test was positive to either NS1 antigen or IgM antibody or both or for positive for all NS1,IgM and IgG (In case of an acute infection with old infection).

5.3 Imaging

- **Chest X-ray:** to look for pleural effusion
- **Ultrasound scan chest**: Pleural effusion
- **Ultrasound abdomen:** Enlarged liver and ascites

6. Management

Clinical management of Dengue should be started based on clinical diagnosis without waiting for confirmatory test. Both suspected and confirmed dengue cases should be notified. Mortality from Dengue can be reduced to almost zero by implementing timely and appropriate clinical management. In the management of dengue certain special population needs to be considered separately.

6.1 Special populations to be considered

- Those with underlying conditions: Coronary Artery Disease, Diabetes Mellitus, Chronic Obstructive Pulmonary Disease, hypertension, renal failure, bleeding disorders
- Patients on antiplatelet (aspirin, clopidogrel), anticoagulants(warfarin, heparin) or immunosuppression therapy
- Children
- Pregnant women
- Elderly >65 yrs
- Alcohol abusers
- Past history of dengue
- Living alone or far from hospital/poor accessibility to health facilities /poor social conditions

6.2 Recommendations for clinical management

Health-care workers at the first levels of care should apply a step-wise approach as suggested below in

Table 3: Step wise approach to management of dengue

Step I − Overall assessment	
I.1	History, including symptoms, past medical and family history
I.2	Physical examination
I.3	Investigation, including routine laboratory tests and dengue-specific laboratory test

Step II − Diagnosis, assessment of disease phase and severity	
Step III − Management	
III.1	Disease notification
III.2	Management decisions, depending on the clinical manifestations and other circumstances, patients may : - Manage at OPD (Group A) - Admit for in-hospital management (Group B) - Require emergency treatment and urgent referral(Group C)

Step I – Overall assessment

The **history** should include:

- Date of onset of fever/illness
- Assessment of warning signs
- History of travel or live in endemic areas
- Co-existing conditions (e.g. infancy, pregnancy, obesity, diabetes mellitus, hypertension)
- Jungle trekking and swimming in waterfalls (consider leptospirosis, typhus, malaria), recent unprotected sex or drug abuse (consider acute HIV- seroconversion illness).

The **physical examination** should include:

- Assessment of mental state/level of consciousness
- Assessment of hydration status
- Assessment of hemodynamic status (Check for postural hypotension)
- 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).This test is more specific in children.

How to check for postural hypotension

Let the patient lie down for 5 minutes, measure blood pressure and pulse rate. Thereafter let the patient stand and repeat blood pressure and pulse rate after 3 minutes of standing. A drop in Systolic BP of ≥20mmHg and diastolic of

How to perform tourniquet test

The tourniquet test is performed by inflating a blood pressure cuff to a point mid-way between the systolic and diastolic pressures for 5 minutes.

A test is considered positive when 10 or more petechiae per 2.5 cm2 (1 inch) are observed. In DHF, the test usually gives a definite positive result (i.e >20 petechiae). The test may be negative or mildly positive during the phase of profound shock ≥10 mmHg indicates early shock.

I**nvestigations**

- Do CBC on **first visit** (it may be normal); and repeat daily until the critical phase is over
- Use the HCT in the early febrile phase as the patient's own baseline.
- If the patient's baseline HCT is not available use age-specific population HCT levels as a surrogate during the critical phase
- Decreasing Total Leucocyte Count and platelet counts make the diagnosis of dengue very likely
- Leukopenia usually precedes the onset of the critical phase and has been associated with severe disease
- A rapid decrease in platelet count, concomitant with a rising HCT compared to the baseline, is suggestive of progress to the plasma leakage/critical phase of the disease
- Dengue test

Step II – Diagnosis, assessment of disease phase and severity

On the basis of evaluation of the history, physical examination and/or full blood count, hematocrit and dengue specific tests, clinicians should determine whether the disease is dengue, which phase it is in (febrile, critical or recovery), whether there are warning signs, the hydration and haemodynamic state of the patient, and whether the patient requires admission.

Step III – Disease notification and management decision (Groups A–C)

Disease notification: Cases of suspected or confirmed dengue should be notified to RCDC through NEWARS and VDCP immediately.

7. Management decisions

Depending on the clinical manifestations and other circumstances, patients may either be categorized as

- Group A: Can be managed on OPD basis
- Group B: Admit for in-hospital management - B1- special population, B2- dengue with warning signs
- Group C: Require emergency treatment and urgent referral

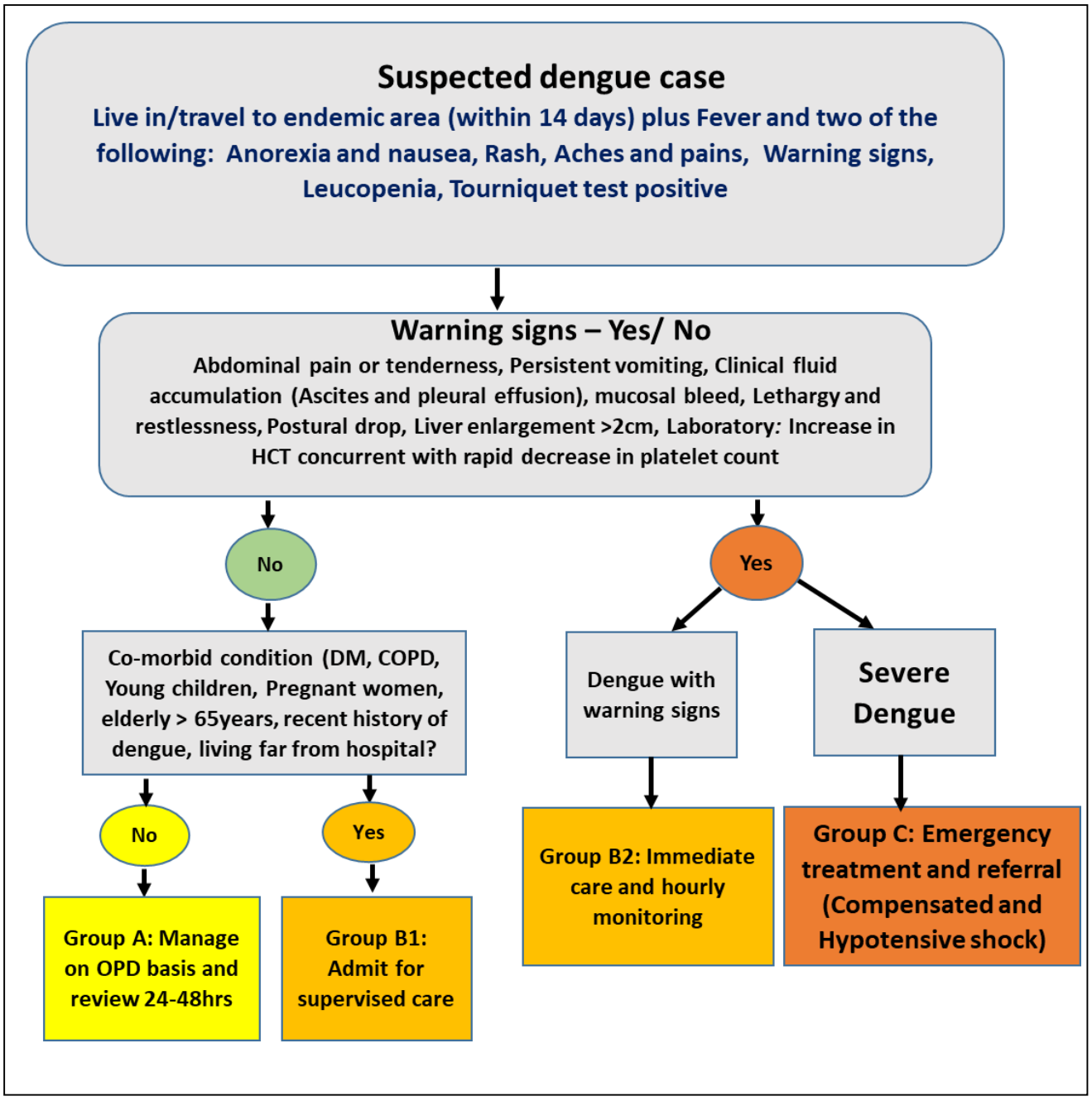

Figure 4: Treatment according to Groups A–C

7.1 Group A

Criteria for management of patients on OPD basis

- Not having any of the warning signs
- Able to tolerate adequate volumes of oral fluids
- Able to pass urine at least once every six hours
- No underlying medical conditions or those who don't fit in the special population group
- Normal blood counts

OPD management

Treatment:

- Tablet Parecetomol for fever (not to exceed 4gms/24 hours; do not give NSAIDs/Aspirin and avoid Intramuscular mode of administering injections.
- Give ORS /adequate fluid intake
- Adequate bed rest

Monitoring

- Daily review for disease progression and repeat CBC testing
- Decreasing WBC and platelets(<100,000/cumm)
- Warning signs until out of critical phase
- Ensure adequate oral fluids intake and urine output
- Advise for immediate return to hospital if development of any warning signs

7.2 Group B

- Includes (**B1-all special populations) and (B2-dengue with warning signs)**
- Should be admitted for hospital management.
- In special populations without warning signs encourage oral fluids. If not tolerated, start intravenous fluid therapy of 0.9% NS or RL at maintenance rate.
- Meticulous initiation of fluid replacement in patients with warning signs is the key to prevent progression to the shock state.
- Monitor vital signs every 4 hourly or more frequently

The action plan should be as follows and applies to infants, children and adults

If the patient has dengue with warning signs:

- Obtain baseline HCT and body weight before fluid therapy
- Use ideal body weight for fluid calculations for obese and overweight patients
- Give IV 0.9% NS or RL
- Give the minimum intravenous fluid volume required to maintain good perfusion and urine output of about 0.5 ml/kg/hour. Intravenous fluids are usually needed for only **24−48** hours
- Start fluid at **5–7 ml/kg/hr** for 1–2 hours then reduce to **3–5 ml/kg/hr** for 2–4 hrs and further reduce to **2–3 ml/kg/hr for 2-4 hours.**

Reassess clinical status and repeat HCT and review fluid infusion rates accordingly

- If hematocrit remains the same or rises only minimally, Continue fluid 2–3 ml/kg/hr for another 2–4 hours
- If the vital signs are worsening or HCT rising rapidly increase the rate to (5–10) ml/kg/hour for 1–2 hours

Monitor vital signs and peripheral perfusion as follows (Annexure 2)

- TPR, BP 1-4hourly until patient is out of critical phase
- Urine output 6 hourly
- HCT : before and after fluid replacement, then 8 hourly
- Blood glucose, other organ functions (renal profile, liver profile, coagulation profile, as indicated.
- Maintain intake/output chart

7.3 Group C

These are patients with severe dengue who require emergency treatment and urgent referral because they are in the critical phase of the disease and have severe plasma leakage leading to dengue shock and/or fluid accumulation (pleural effusion, ascites) with respiratory distress. Dengue shock is classified into:

I. **Compensated shock** is defined as **normal systolic BP** with tachycardia and narrow pulse pressure ≤ 20 mmHg or cold extremities and delayed capillary refill time of > 2 seconds.
Monitor vitals every 1 to 2 hours (**Annexure 3**)

II. **Hypotensive shock (decompensated):** is defined as worsening tachycardia, fall in both systolic and diastolic BP, worsening acidosis (kussmaul breathing), and altered sensorium. Monitor vitals every half an hour (**Annexure 4**)

III. **Profound shock**: Organ dysfunction and worsening metabolic acidosis associated with following complications
   - DIC
   - ARDS
   - Acute liver failure
   - AKI
   - Cardiac arrest
   - Severe hemorrhages
   - Severe organ impairment (hepatic damage, renal impairment, cardiomyopathy, encephalopathy or encephalitis)

7.4 Principles of management

- Refer all patients for admission to a hospital with blood transfusion facilities.
- Judicious intravenous fluid resuscitation is the essential and usually sole intervention required
- Use crystalloid solution (NS or RL) sufficient to maintain an effective circulation during the period of plasma leakage (usually for 24-48 hrs) and adjust fluid accordingly
- Replace plasma losses immediately and rapidly with crystalloid solution
- Use colloid solution in case of hypotensive shock/intractable shock resistant to crystalloid resuscitation
- Obtain HCT levels before and after fluid resuscitation.
- Use ideal body weight for overweight and obese patients while calculating fluid rates (As given in the

Table 4)

- All shock patients should have their blood group taken and a cross-match carried out
- Blood transfusion with either Whole blood (WB) or Packed Red Cell (PRC) units should be given only in cases with established severe bleeding, or suspected severe bleeding (fall in HCT) with unexplained hypotension.
- Refer Figure 5 for treatment of compensated shock in adults
- Refer Figure 6 for treatment of compensated shock in infants and children.
- Refer Figure 7 for treatment of hypotensive shock in adult, children and infants.

Dosage for Blood/ blood component transfusions

1. Packed red cell (PRC) transfusion: 5ml/kg body weight
2. Whole blood (WB) : 10ml/kg body weight
3. Fresh frozen plasma(FFP) :15ml/kg body weight
4. Platelet concentrates(PC):1unit for every 10kg body weight

For detailed guidelines on selection of blood components, please refer to 'National Guidelines for Appropriate Clinical Use of Blood for doctors and nurses' available via this link; https://www.bloodsafety.gov.bt/wp-content/uploads/2017/05/clinicalblooduse.pdf

Normal maintenance fluid per hour can be calculated on the basis of the following formula* (equivalent to Holliday Segar formula):

- 4 ml/kg/hr for first 10 kg body weight
- + 2 ml/kg/hr for next 10 kg body weight
- + 1 ml/kg/hr for subsequent kg body weight

*For overweight/obese patients, calculate normal maintenance fluid based on ideal body weight (IBW) **Table 4**, using the following formula:

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

Table 4: Estimated ideal body weight for overweight or obese adults

Height (cm)	Estimated, IBW (kg) for adult males	Estimated IBW (kg) for adult females
150	50	45.5
160	57	52
170	66	61.5
180	75	70

Table 5: Requirement of fluid based on body weight

Body weight (in Kgs)	Volume of fluid to be given in 24 h	Rate of fluid (ml/hour)			
		Regimen 1 3ml/kg/hr	Regimen 2 6ml/kg/hr	Regimen 3 10ml/kg/hr	Regimen 4 20ml/kg/hr
10	1500	30	60	100	200
15	2000	45	60	150	300
20	2500	60	90	200	400
25	2800	75	120	250	500
30	3200	90	150	300	600
35	3500	105	180	350	700
40	3800	120	210	400	800
45	4000	135	240	450	900
50	4200	150	270	500	1000
55	4400	165	300	550	1100
60	4600	180	360	600	1200

Please note:

- The fluid volume mentioned are approximations.
- Normally changes should not be drastic.
- Do not jump from R-2 to R-4 since this can cause fluid overload.
- Similarly reduce fluid volume from R-4 to R-3, from R-3 to R-2 and from R-2 to R-1 in a stepwise manner.

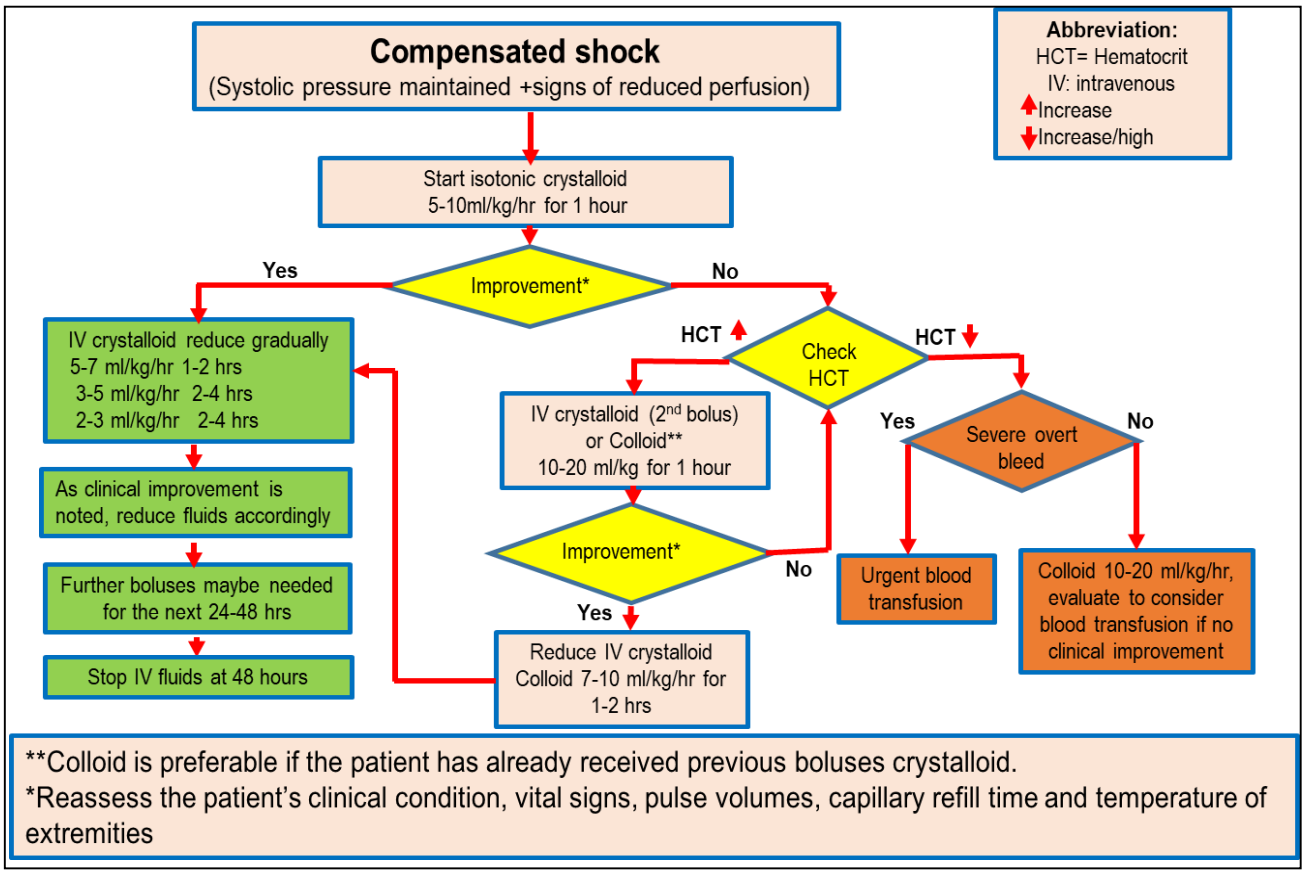

Figure 5: Algorithm for fluid management of compensated shock in adults

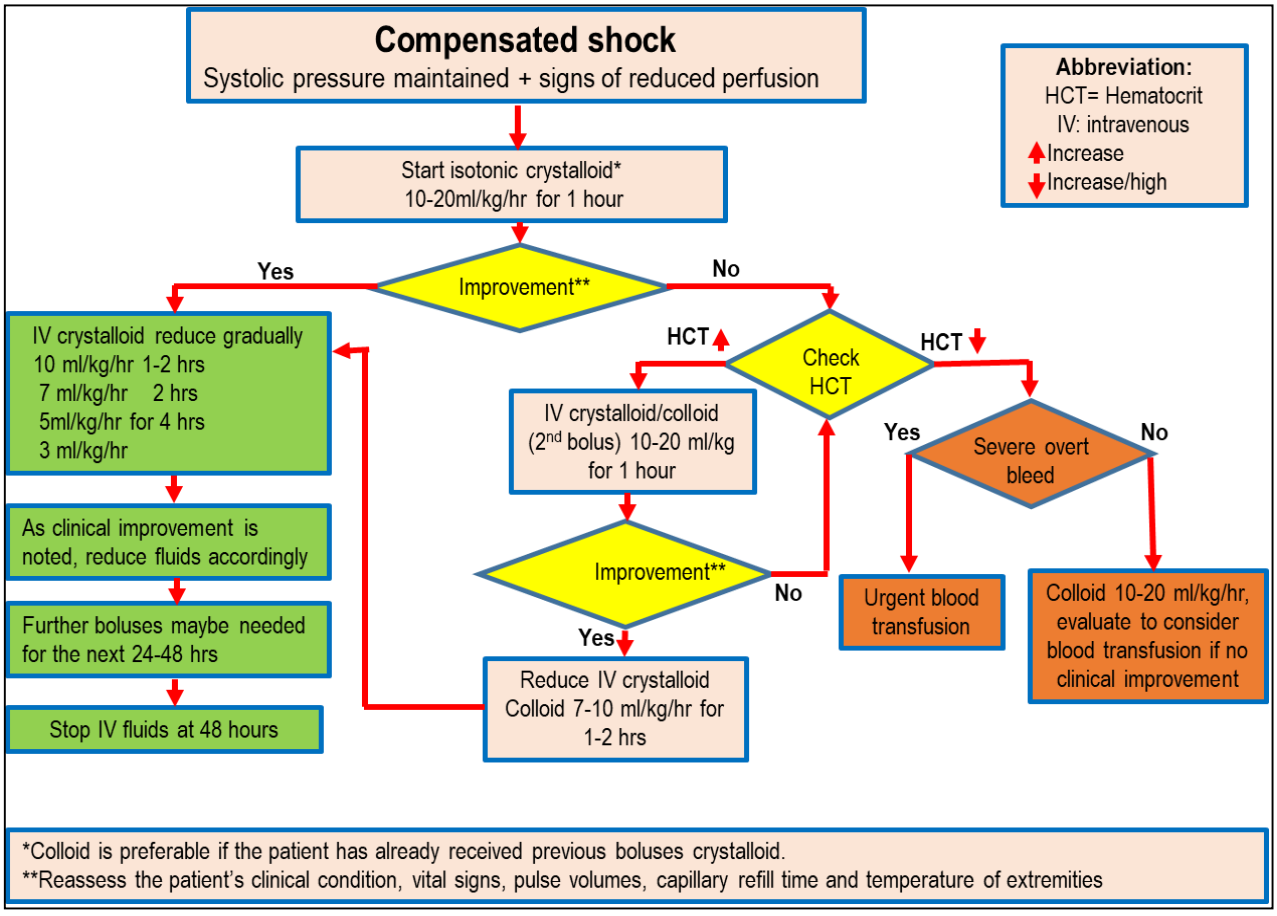

Figure 6: Algorithm for fluid management of compensated shock in infants and children

When to stop intravenous fluid therapy

Intravenous fluids should be reduced or discontinued when any of the following signs are present,

- Stable BP, pulse and peripheral perfusion;
- Haematocrit decreases in the presence of a good pulse volume;
- Apyrexia (without the use of antipyretics) for more than 24–48 hours;
- Resolving bowel/abdominal symptoms;
- Improving urine output.

Continuing intravenous fluid therapy beyond the 48 hours of the critical phase will put the patient at risk of pulmonary oedema and other complications such as thrombophlebitis.

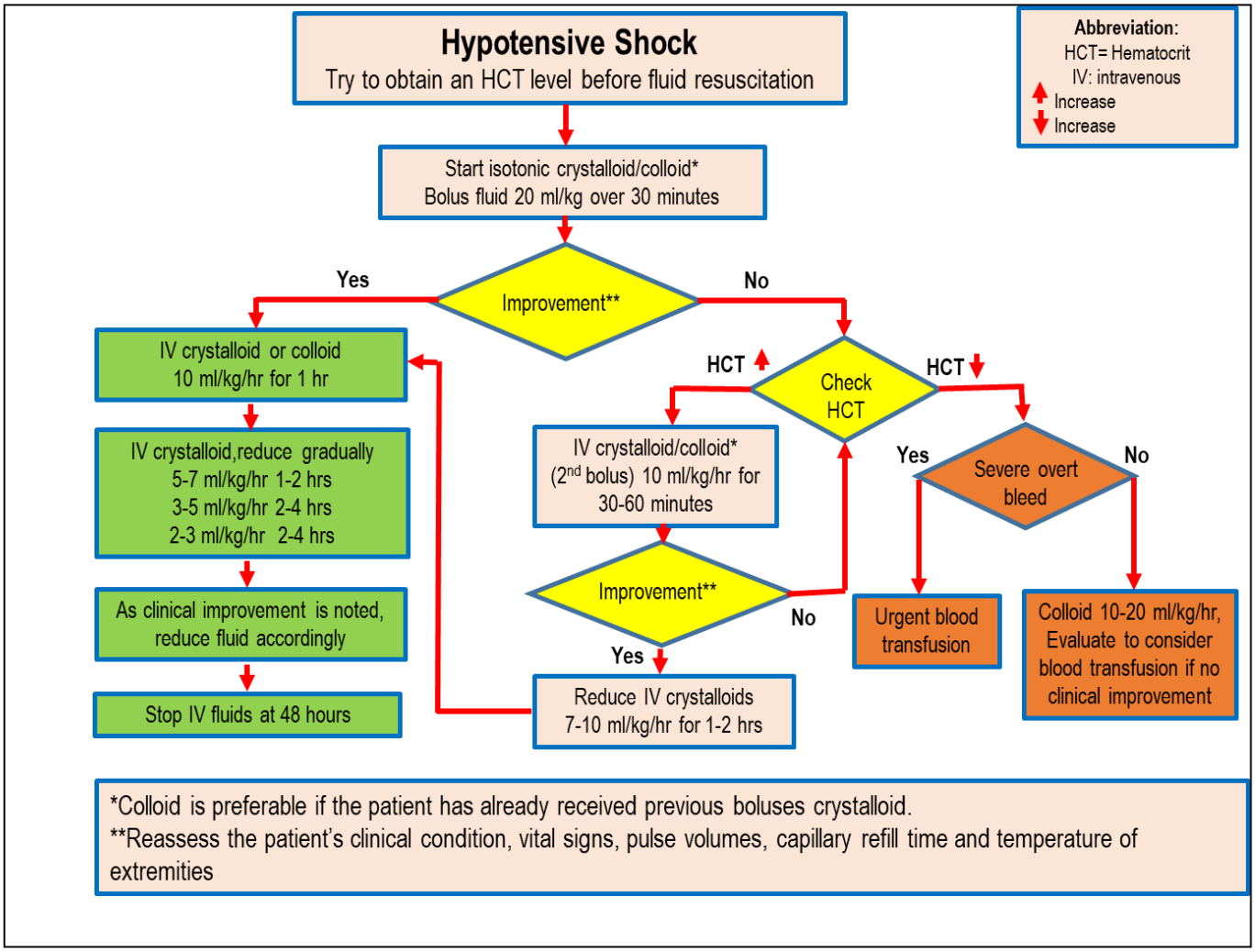

Figure 7: Algorithm for fluid management of hypotensive shock in adult, infants and children

Platelet transfusion

- Prophylactic platelet transfusion may be considered for counts < 10,000/cumm in absence of bleeding manifestations
- Transfuse platelet only if bleeding manifestations is present.
- Platelet transfusion may be considered for those who may need emergency surgery.

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

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

8. Discharge criteria

All of the following conditions must be present:

Clinical

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

Laboratory

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

9. Referral

Primary Healthcare Centres (PHCs) can treat dengue cases with no warning signs but will need to refer to hospital for patients with warning signs and patients who fit under the special population group. Before referring a patient, it is advised to consult the specialist and initiate necessary appropriate management before and during the transfer of the patient from one health center to another.

Criteria for referral from district hospitals to higher centres

Rarely patients with dengue need referral to higher centers, if close monitoring and careful fluid management is administered at the district hospital. Referrals may be considered according to the availability of blood products and the need for ICU care in case of multi-organ dysfunction. Referred cases should be discussed with the concerned specialists prior to the referral. A detailed input output chart should be maintained throughout the journey. Proper fluid instructions should be given en-route.

10. Dengue in co-morbid conditions

Dengue infections in patients with underlying diseases or co-morbid conditions can be severe and may lead to more complications or even death if not managed properly during the early Febrile Phase. Making an early diagnosis of dengue illness in such patients will be challenging. Therefore, early suspicion and close follow-up is important**.**

Liver Disease: Baseline liver function tests (LFT) including prothrombin time (PT) is of value when dengue is suspected in patients with chronic liver disease. If AST/ALT is very high the patient is likely to develop neurological involvement (Hepatic Encephalopathy) especially in those with gastrointestinal (GI) bleeding. In such patients liver failure regime should be used early. If baseline albumin level is low these patients may have more plasma leakage. Managing these patients with the minimum amount of IV fluids to maintain intravascular volume in order to prevent respiratory distress (acute pulmonary oedema) and/or heart failure is crucial.

Heart Disease: The key consideration in patients with heart diseases would be to identify the underlying

heart disease and the current medication. These patients should be observed carefully with close and continuous monitoring preferably echocardiography especially during the critical phase. Careful adjustment of IV fluid is the key to success and to prevent complications. Those who are on anti-platelet or anti-coagulation therapy are recommended to stop the medication for a few days especially during the critical phase.

Renal Disease: The baseline renal function tests (Blood Urea, Creatinine), electrolytes, acid-base balance, GFR, urine output per day and urine analysis should be performed during the early febrile phase and regularly tested during the course of the illness. Close monitoring of fluid intake and urine output is very important. Fluid overload during convalescent phase is the most important cause of death among these patients. Early consultation with a Nephrologist and early planning of any renal replacement therapy in those patients who are oliguria with signs and symptoms of fluid overload is important.

Diabetes Mellitus: Frequent monitoring of blood sugar is important from the time the patients are admitted to hospital. All anti-diabetic drugs have to be switched to insulin in order to keep blood sugar level preferably below 150-200mg/dl. Closely monitor the patient and look for the possible development of Diabetic Ketoacidosis where patient will need more IV fluid, IV insulin as an infusion and monitoring of central venous pressure if possible

11. Dengue in children

Dengue infection occurs in all age groups however pediatric age group are at a high risk for morbidity and mortality.

Neonatal dengue

If there is vertical transmission of dengue, the newborn may or may not present with shock, which can be confused with septic shock. Therefore, history of febrile illness or confirmed dengue during pregnancy is important to diagnose a dengue shock among neonates and young infants. Admit all neonates suspected dengue for close observation. The main stay of management of neonatal dengue is symptomatic and supportive treatment.

Management dengue in infants

Severe dengue is less common in infants but when it does occur the risk of dying is higher than in older children and adults. Infants with dengue should be referred for hospital management. Management of dengue in infants with and without warning signs can be summarized as in table below in **Table 6**:

Table 6: Summary of dengue management in infants with and without warning signs

Dengue infants without warning signs	Dengue infants with warning signs
• Supportive treatment. • Oral rehydration-ORS, fruit juices and other fluids containing electrolytes and sugar. • Continue breastfeeding/formula feeding and/or solid food. • Fever control-antipyretics and tepid sponging.	• Start IV fluid- isotonic crystalloid solutions like Ringer's lactate, Ringer's acetate or 0.9 % saline should be used. 5-7 ml/kg/hrs for 1-2 hrs. Then, adjust according to patient's clinical response. • IV fluid therapy is only required for 24-48 hrs. In most infants since the capillary leak resolves spontaneously after this time.

Points to be considered when managing infants with severe dengue

- Infant with a low baseline hematocrit of 30%, presenting with dengue shock and a hematocrit of 40%, is relatively more hemoconcentrated than another child with a baseline value of 42% and a hematocrit of 50% at the time of shock.
- In infants, IV fluids must be administered with special care to avoid fluid overload.
- Fluids account for a greater proportion of body weight in infants than children and minimum daily requirements are correspondingly higher. Infants have less intracellular fluid reserve than older children and adults. Moreover, capillary beds are intrinsically more permeable than those of older children or adults. Both early cardiovascular compromise and significant fluid overload are more likely if capillary leaks occur in these circumstances.
- Blood transfusion is only indicated in dengue infants with severe bleeding.

12. Dengue in pregnancy

The clinical manifestations, treatment and outcome of dengue in pregnant women are similar to those of non-pregnant women but with some important differences. In order to recognize and diagnose dengue disease early in pregnancy, clinicians need to maintain a high index of suspicion when dealing with pregnant women who present with febrile illness after travelling to, or living in dengue-endemic areas. Physiologic change during pregnancy and some more common obstetric complications may cause misdiagnosis, delayed diagnosis, or delayed treatment. Pregnant women were at increased risk of developing severe dengue [dengue hemorrhagic fever (DHF)] and mortality when compared with non-pregnant women

Effect of Dengue on pregnancy outcomes.

- High rates of cesarean delivery, preeclampsia, and preterm birth
- Higher risk of low birth weight
- Higher risk of miscarriage.
- Increase risk of vertical transmission and symptomatic disease in the newborn.
- Significant impact of dengue at parturition-severe bleeding

Challenges in recognition of dengue and plasma leakage in pregnancy

Hyperemesis during the first trimester of pregnancy can resemble the warning signs of severe dengue and this may delay the recognition of severe dengue. After the second trimester of pregnancy it is normal to see an increase in circulating blood volume with generalized vasodilatation, resulting in an increased baseline heart rate and lower baseline BP, as well as a lower baseline hematocrit. This can confuse the diagnosis of dengue and therefore clinicians need to be alert to the following:

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

presence of a gravid uterus.

Management of Dengue during Pregnancy

- All pregnant patients with dengue fever irrespective of the trimester should be first admitted to the Obstetric ward where initial assessment and management plans are to be decided.
- Conservative medical and obstetrical management is the treatment of choice
- There is no difference in fluid therapy compared with the non-pregnant state
- Obstetric assessment should be done daily or more often depending on the trimester. Medical assessment should include;
    1. Febrile phase monitoring
    2. Critical phase monitoring in a patient with plasma leakage
    3. Fluid management should be done like that of non-pregnant women.
- In the woman using aspirin for prevention of preeclampsia, the drug should be withheld.
- Woman should be monitored for the warning signs of severe dengue infection- Vital signs (1-4hourly), urine output (4-6 hourly), hematocrit (6-12 hourly), blood glucose, renal function tests, liver function tests, and coagulation profile.
- Avoid Induction of labor or elective Caesarean section during the critical phase of the illness. It is best to delay until the critical phase is over and the patient reaches recovery phase.
- During the critical phase vaginal delivery or Caesarean section should be undertaken only if the mother's life is at risk or the patient develops spontaneous labor during this period. If there is a fetal indication (Fetal Distress) for delivery, it is recommended not to intervene and deliver during critical phase.
- If premature labor occurs during critical phase, it is advisable to delay the delivery until the leaking resolves by using tocolytic drugs such as Nifedipine. The most commonly used regimen for acute tocolytic treatment is 20mg of Nifedipine initially, and if contractions persist and no hypotension, followed by another 20mg 30 minutes later followed up with 20mg 8 hourly.
- If delivery is inevitable, blood and blood products should be prepared. Platelet transfusion is indicated when the platelet count is <50,000/mm3 during labor and should be initiated during or at delivery.
- Transfusion of packed red cells should be administered if indicated.
- Intense active management of third stage of labor in preventing postpartum hemorrhage is required by the use of IV uterotonic agent. Since this is a high-risk situation, give 05 IU of Oxytocin slow IV bolus (No IM injections due to bleeding tendency in Dengue). This should be followed by oxytocin 10 IU per hour as a concentrated infusion or alternatively Misoprostol (800micrograms) could be used rectally.
- The newborn whose mothers had dengue just before or at delivery should be closely observed.

13. Prevention and Control

- The vector consists of two Aedes (Stegomya) species namely *Ae. aegypti* and *Ae. albopictus.*
- Ae. aegypti is usually domestic and considered efficient vector in urban areas while *Ae.albopictus* in rural and peri-urban areas
- Dengue can be prevented through collaborative efforts among various stakeholders
- Breeding sites are normally man-made or natural containers that can hold domestic water or rain during monsoon season. Therefore, the disease occurs during monsoon or just after the rainy season.

Table 7: Source reduction and its management

I. *Ae. aegypti* breeding sites	Container management
Barrel drums and other water containers in bathrooms and toilets	Change water and wash weekly by scrubbing containers with abrasive material to remove eggs that are usually glued to container sides
Open overhead water tanks	Should have tight fitting lids to prevent breeding
Flower pots with water	Avoid water collection at the base of flower pots
Blocked roof gutters	Clean roof gutters regularly during rainy seasons
Flower vases	Change the water weekly
Refrigerator dipping pans with water collection	Empty the pan weekly and wash properly by rubbing with abrasive cloths

Note: *Ae. aegypti* rarely breed in natural containers

II. *Ae. albopictus* breeding sites	Container Management
Old containers in open areas in scraps	Advocate and ensure owners to cover or dispose off scraps before onset of and during monsoon.
Unused tyres and drums in open areas	The owners should be informed to dispose or cover before monsoon.
Plastic and bottles thrown in open areas	Conduct cleaning campaigns regularly in collaboration with relevant stakeholders
Fallen beetle nut (Doma) leaves	Advocate owners to cut into pieces and use as green manure.
Natural Breeding sites	
Rock and Tree holes, bamboo stumps	Fill the holes with gravels and sand if located near houses.

Personal protection:

- Use LLIN both during day and night
- Wear long-sleeve clothes at dusk and dawn to prevent mosquito bites
- Use mosquito repellents on exposed body parts
- Advice compulsory use of LLIN or repellents for dengue patients to prevent further transmission

Chemical control

- Indoor Residual Spraying during transmission season
- Thermal Fogging during outbreaks
- Larvicides inoculation

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References

1) Chaithongwongwatthana, S. (2017). Dengue in pregnancy. *Southeast Asian J Trop Med Public Health, 48,* 1.
2) Handbook for Clinical Management of Dengue WHO. 2012
3) Dengue guidelines for diagnosis, treatment, prevention and control. WHO 2009.
4) Guideline on management of dengue fever and dengue haemorhage fever in adults Nov. 2012. Ministry of health. Sri Lanka.
5) National guidelines on clinical management of dengue in pregnancy, July 2019. Ministry of health, Sri Lanka.

Annexures

Annexure 1: Monitoring chart in dengue fever during febrile phase (Patient to be monitored every 3-6 hourly)

Name…… ……Age/Sex……..weight ……..

Date of onset of fever……. Date/time of admission……..

Date/Time	Input (ml) both oral/IV	HR/min	BP in mmHg	Pulse pressure (SBP-DBP)	RR/min	CRT (<2 sec/>2sec)	Extremities (warm/cold)	UOP every 6 hrly (Diaper/leakage)	WBC once a day	HCT once day	Platelet count once day

Annexure 2: Monitoring chart for dengue with warning signs (critical phase) Patient to be monitored every 2 hourly

Crystalloids (NS/RL) Fluid ml/kg/hr																								
7																								
6																								
5																								
4																								
3																								
2																								
1																								
Time (in hour)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Used % of fluid																								
HR																								
BP																								
Pulse pressure																								
RR																								
CRT																								
Extremities(warm/cold)																								
UOP (void/catheter) every 6hrly																								
HCT every 6 hrly																								
Platelet every 6 hrly																								
WBC every 6 hourly																								

Annexure 3: Monitoring chart for Dengue with Compensated Shock (Patient to be monitored every 1-2 hourly)

Name……Age/Sex……..Weight……
Date/time of admission……
Fluid Boluses given: …….Other fluids:
Dextran/PRC/WB……..

Crystalloids (NS/RL) Fluid ml/kg/hr																								
10																								
7																								
6																								
5																								
4																								
3																								
2																								
1.5																								
(Time in hr)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
UOP (ml/kg/hr)																								
Cumulative volume																								
HR																								
BP																								
Pulse pressure																								
RR																								
CRT																								
Extremities(warm/cold)																								
HCT every 2 hourly																								
Platelet every 2 hourly																								
WBC every 2 hourly																								
LFT																								
RFT																								
S. Albumin																								

Annexure 4: Monitoring chart for Dengue with Hypotensive Shock (Patient to be monitored every 15 minutes and vitals hourly)

Name……Age/Sex…….. Weight…… Date/time of admission…… Fluid Boluses given: ……. Other fluids: Dextran/PRC/WB……..																							
Crystalloids (NS/RL) Fluid ml/kg/hr																							
10																							
7																							
6																							
5																							
4																							
3																							
2																							
1.5																							
Time																							
UOP (ml/kg/hr)																							
HR																							
BP																							
Pulse pressure																							
RR																							
CRT																							
Extremities (warm/cold)																							
HCT every 2 hourly																							
Platelet every 2 hourly																							
WBC every 2 hourly																							
LFT																							
RFT																							
S. Albumin																							

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Annexure 5: Normal Vital Signs for children

Age	Estimated weight	Normal Heart Rate Range	Normal Respiratory rate range	Hypotension level (systolic BP)
1 month	4kg	110-180	40-60	<70
6 months	8kg	110-170	25-40	<70
12 months	10kg	110-170	22-30	<72
2 years	12kg	90-150	22 - 30	<74
3 years	14kg	75-135	22 - 30	<78
4 years	16kg	75-135	22 – 24	< 80
5 years	18kg	65-135	20- 24	< 82
6 years	20kg	60-130	20- 24	< 86
8 years	26kg	60-130	18- 24	< 90
10 years	32kg	60-110	16-22	< 90
12 years	42kg	60-110	16-22	< 90
14 years	50kg	60-110	14-22	< 90
≥ 15 years		60-100	12-18	<90

Annexure 6: Hemodynamic Assessment

Hemodynamic parameters	Stable circulation	Compensated shock	Hypotensive Shock
Conscious level	Clear	Clear	Restless
Capillary refill	Brisk (≤ 2sec)	Prolonged (>2sec)	Very prolonged, mottled skin
Extremities	Warm and pink	Cool peripheries	Cold, clammy
Peripheral pulse volume	Good volume	Weak and thread	Feeble and absent
Heart rate	Normal heart rate for age	Tachycardia for age	Severe tachycardia
Blood pressure	Normal blood pressure or pulse pressure for age	Normal systolic BP but rising diastolic pressure. Narrowing pressure pulse pressure. Postural hypotension	Narrow pulse pressure (≤ 20mmHg). *Hypotension. Recordable blood pressure
Respiratory rate	Normal respiratory rate for age	Tachypnea	Hyper apnea or kussmaul's breathing (metabolic acidosis)
Urine output	Normal	Receding trend	Oliguria or anuria

*Definition of Hypotension:

1. For adults - systolic BP of <90mmHg or mean arterial pressure (MAP) < 70mmHg or Systolic BP decrease of >40mmHg or < SD below normal for age
2. For children, refer Annexure 5

Annexure 7: Age specific Hematocrit level (HCT)

Age	HCT (%)	Remarks
1 month	44	***Note:*** *Leucopenia in children with dengue if total leucocytes count ≤ 2000 & Thrombocytopenia if platelets count <100,000.*
2 month	35	
6 month	36	
6month- 2 year	36	
2-6 year	37	
6-12 year	40	
12-18 year	41-43	

Annexure 8: Surveillance Clinical Data Form (For sample send to RCDC)

Demographic Information

Hospital:_____ Date (DD/MMM/YYYY): _ _/_ _ _/_ _ _ _

Patient Name: _____

Age ……. Sex…….Occupation ……

Residential address ……..Contact Numbers…….

History of Illness:

Date of first symptoms (DD/MM/YY): …….

Tick any of the following systems:

	Symptoms	**Yes**	**No**	**Remark**
1	Fever			
2	Headache			
3	Retro-orbital pain			
4	Muscle pain			
5	Severe back-ache			
6	Joint pain			
7	Rash			
8	Positive tourniquet test			
9	Petechaie, ecchymoses, or purpura			
10	Bleeding from nucosa, GI or any other sites			
11	Hematemesis or melena			
12	Rapid and week pulse			
13	Hypotension			
14	Cold, clammy skin			
15	Restlessness			
16	Altered mental status			

Note: Copy of 1st CBC result of the patient should be attached.

Patient disposition: outpatient	Emergency (casualty)	Admitted
☐	☐	☐

Case enrolled #……Lab ID#.....

Date of sample collection …….....