# How to manage severe dengue infection

A review of diagnosis and treatment of dengue, a mosquito-borne febrile illness caused by flavivirus with a clinical spectrum ranging from self-limited fever to dengue haemorrhagic fever with shock.

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Dengue is a febrile illness, caused by one of the serotypes of Flavivirus (DENV1-4), transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes during a blood meal (Simmons et al. 2012; Guzman et al. 2015; Pai-Dhungat et al. 2013). The vectors live in an urban habitat and are daytime feeders. *Aedes albopictus* is now spreading to North America and Europe due to international trade. The island of Madeira, Portugal, and five other European countries have witnessed an outbreak of dengue (Guzman et al 2015).

The World Health Organization (WHO) currently estimates there may be 50-200 million dengue infections worldwide every year. Half of the world's population living in endemic areas is at risk (Pai-Dhungat et al. 2013). Recovery from infections in one serotype provides lifelong immunity against that serotype. However, cross immunity is only partial and temporary. Subsequent infection by either serotype increases the risk of developing severe dengue.

## Clinical features

As per the WHO 1997 classification, dengue comprises a clinical spectrum, which consists of
- Dengue fever (breakbone fever)
- Haemorrhagic fever and
- Dengue shock syndrome (WHO 1997)

The revised WHO classification scheme (2012) consists of
- Dengue without warning signs
- Dengue with warning signs
- Severe dengue

Expanded dengue comprises unusual or atypical manifestations of dengue which can happen in the absence of plasma leakage.

**Clinical features of dengue fever without**

**warning signs**
- Fever which lasts 5 to 7 days
- Myalgia/arthralgia
- Retro-orbital pain
- Rash
- Haemorrhagic manifestations – Petechie, ecchymosis, mucosal bleed, positive tourniquet test
- Leucopaenia and thrombocytopaenia

**Clinical features of dengue with warning signs**
- Abdominal pain
- Persistent vomiting
- Mucosal bleed
- Lethargy
- Hepatomegaly
- Rapid decline in platelet count

The differentiating features of dengue with warning signs consist of haemoconcentration with a more than 20% rise in haematocrit, pleural effusion and ascites secondary to plasma leakage because of increased vascular permeability.

**Clinical features of severe dengue**
- Severe plasma leakage leading to cold clammy skin, thready pulse, narrowed pulse pressure, shock, fluid accumulation with respiratory distress
- Severe bleeding
- Organ involvement
- Liver: aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 1000
- Central nervous system (CNS): Impaired consciousness
- Heart and other organ involvement

**Expanded dengue**

Additional manifestations of dengue virus infection may include liver failure, CNS involvement, myocardial dysfunction, acute kidney injury and other organ involvement. Neurological manifestations include encephalopathy and seizures, stroke, Guillain-Barre syndrome, transverse myelitis, mono and poly neuropathies (Solomon et al. 2000). Diagnosis is by serological testing, culture and detection by polymerase chain reaction (PCR) in cerebral spinal fluid. Cardiovascular manifestations include myocardial impairment, arrhythmias and fulminant myocarditis (Miranda et al. 2013). Haemophagocytic lymphohistiocytosis is described in association with dengue virus infection.

## Pathogenesis

After the virus is introduced into the skin by an infected mosquito, viraemia is detected from 6 to 18 hours before onset of symptoms and ends as the fever results. Both innate and adaptive immune responses play a role in clearance of infection. Virus-specific T lymphocytes response and antibody-dependent

**DIRECT METHODS**

Virus isolation | Genome detection | NS1 detection

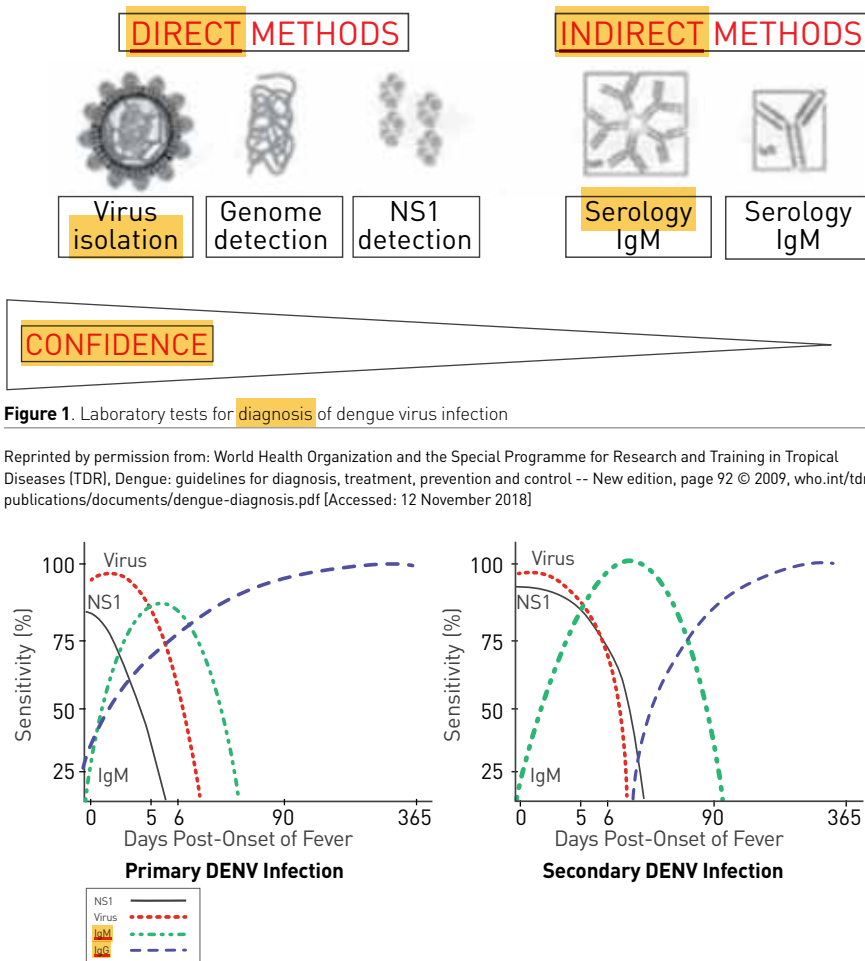**INDIRECT METHODS**

Serology IgM | Serology IgM

CONFIDENCE

**Figure 1**. Laboratory tests for diagnosis of dengue virus infection

Reprinted by permission from: World Health Organization and the Special Programme for Research and Training in Tropical Diseases (TDR), Dengue: guidelines for diagnosis, treatment, prevention and control -- New edition, page 92 © 2009, who.int/tdr/publications/documents/dengue-diagnosis.pdf [Accessed: 12 November 2018]

**Primary DENV Infection**

**Secondary DENV Infection**

NS1
Virus
IgM
IgG

**Figure 2.** Dengue antibody response in primary and secondary infection (CDC 2010)

ity but more accessible and less costly

**1. Direct methods**

During the first week of illness:

- Reverse transcription polymerase chain reaction (RT-PCR) assay for detection of viral nucleic acid
- Nonstructural protein 1 antigen test (NS1Ag): sensitivity 90% in primary infection and 60-80% in secondary infection

**2. Indirect methods (Figure 2)**

- Immunoglobin M antibody (IgM Ab): Detected as early as 4 days after onset of illness
- Immunoglobin G antibody (IgG Ab): In primary infection there is slow rise and low titres, detected after 7 days of onset of illness. In secondary infection, there is rapid rise in titres beginning 4 days after onset of illness.

The ratio of IgG: IgM >1:1.10 on day 2 of illness helps to diagnose secondary dengue infection (Changal et al. 2016).

**3. Direct virus isolation through cultures with delayed results**

**4. Dengue viral proteins detected in tissue samples using immunohistochemical staining**

Liver tissues have highest yield. This is rarely indicated.

**Differential diagnoses**

- Viral haemorrhagic fevers like Ebola, Lassa, Yellow fever, Hanta, Crimean congo, Severe fever with thrombocytopaenia syndrome virus (SFTSV)
- Chikungunya
- Malaria
- Typhoid fever
- Leptospirosis
- Rickettsial infection
- Zika virus
- Sepsis due to bacteraemia

**Dengue case management**

Treatment according to groups A to C:
**Group A:** Patients who may be sent home (outpatient management)

1. Bed rest and frequent oral liquids
2. Paracetamol (10mg/kg/dose) not more

enhancement of infection decide severity of the infection. Plasma leakage, haemoconcentration and abnormalities in homeostasis characterise severe dengue.

A transient and reversible imbalance of inflammatory mediators, cytokines and chemokines occurs during severe dengue, probably driven by a high early viral burden, and leading to dysfunction of vascular endothelial cells, derangement of the haemocoagulation system, then to plasma leakage, shock and bleeding.

**Management**

Step I – Overall assessment

- History, onset of symptoms, past medical and family history
- Physical examination, including full physical and mental assessment
- Investigation, including routine laboratory

tests and dengue-specific laboratory tests
Step II – Diagnosis, differentials, assessment of disease phase and severity
Step III – Management

- Disease notification
- Management decisions: Depending on the clinical manifestations and other circumstances, patients may either be:
  o Sent home (Group A) or
  o Referred for in-hospital management (Group B) or
  o Require emergency treatment and urgent referral (Group C)

**Laboratory tests**

See **Figure 1**.

- Directly by detection of viral components in serum—high specificity but labour-intensive and costly
- Indirectly by serology—lower specific-
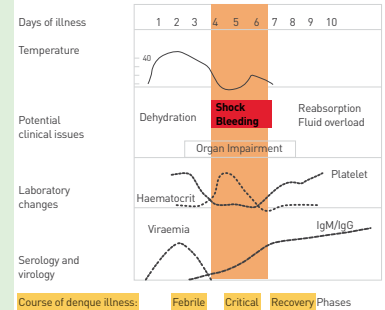
# Dengue Case Management

## Assessment

**Presumptive Diagnosis:**
Live in / travel to endemic area plus
Fever and two of the following:
- Anorexia and nausea
- Rash
- Aches and pains
- Warning signs
- Leukopaenia
- Tourniquet test positive

Lab.confirmed dengue
*(important when no sign of plasma leakage)*

**Warning signs:**
- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy; restlessness
- Liver enlargement >2cm
- Laboratory: Increase in HCT concurrent with rapid decrease of platelet count



| Days of illness | 1 2 3 | 4 5 6 | 7 8 9 10 |
|---|---|---|---|
| Temperature | | 40 | |
| Potential clinical issues | Dehydration | Shock Bleeding | Reabsorption Fluid overload |
| | | Organ Impairment | |
| Laboratory changes | Haematocrit | | Platelet |
| | Viraemia | | IgM/IgG |
| Serology and virology | | | |

Course of denque illness:  Febrile  Critical  Recovery Phases

## Classification

negative → Co-existing conditions / Social circumstances → positive

positive

negative →

Co-existing conditions
Social circumstances → positive

negative →

**Dengue without warning signs**

**Dengue with warning signs**

**Severe Denque**

## Management

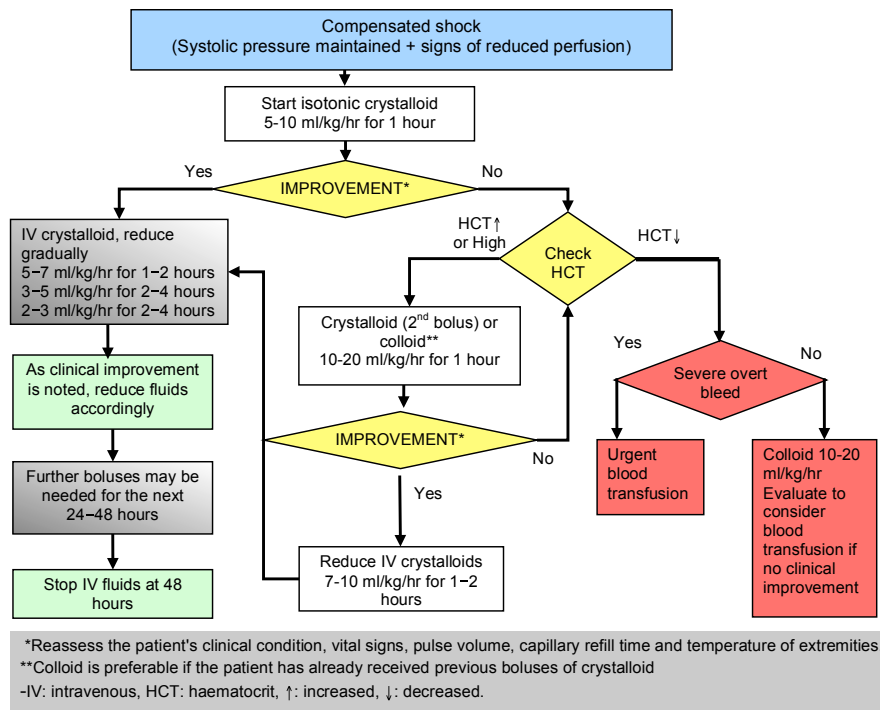| Group A\nMay be sent home | Group B\nReferred for in-hospital care | | Group C\nRequire emergency treatment |
|---|---|---|---|
| **Group criteria**\nPatients who do not have warning signs\nAND\nwho are able:\n• To tolerate adequate volumes of oral fluids\n• To pass urine at least once every 6 hours | **Group criteria**\nPatients with any of the following features:\n• Co-existing conditions such as pregnancy, infancy, old age, diabetes mellitus\n• Social circumstances such as living alone, living far from hospital | **OR**\nExisting warning signs:\n• Abdominal pain or tenderness\n• Persistent vomiting\n• Clinical fluid accumulation\n• Mucosal bleeding\n• Lethargy/restlessness\n• Liver enlargement >2cm\n• Laboratory: increase in Hct | **Group criteria**\nPatients with any of the following features.\n• Severe plasma leakage with shock and/or fluid accumulation with respiratory distress\n• Severe bleeding\n• Severe organ impairment |
| **Laboratory tests**\n• Full blood count (FBC)\n• Haematocrit (Hct ) | **Laboratory tests**\n• Full blood count (FBC)\n• Haematocrit (Hct) | | **Laboratory tests**\n• Full blood Count (FBC)\n• Hae matocrit (Hct)\n• Other organ function tests as indicated |
| **Treatment**\nAdvice for:\n• Adequate bed rest\n• Adequate fluid intake\n• Paracetamol, 4 gram max. per day in adults and accordingly in children\n• Patients with stable Hct can be sent home | **Treatment**\n• Encouragement for oral fluids\n• If not tolerated, start intravenous fluid therapy 0.9% saline or Ringer Lactate at maintenance rate | **Treatment**\n• Obtain reference Hct before fluid therapy\n• Give isotonic solutions such as 0,9% saline, Ringer lactate, start with 5-7mL/kg/hr for 1-2 hours, then reduce to 3-5mL/kg/hr for 2-4 hr, and then reduce to 2-3mL/kg/hr or less according to clinical response\n**Reassess clinical status and repeat Hct**\n• If Hct remains the same or rises only minimally -> continue with 2-3 mL/kg/hr for another 2-4 hours\n• If worsening of vital signs and rapidly rising Hct -> increase rate to 5-10 mL/kg/hr for 1-2 hours\n**Reassess clinical status, repeat Hct and review fluid infusion rates accordingly**\n• Reduce intravenous fluids gradually when the rate of plasma leakage decreases towards the end of the critical phase.\n**This is indicated by:**\n• Adequate urine output and/or fluid intake\n• Hct decreases below the baseline value in a stable patient | **Treatment of compensated shock:**\n• Start IV fluid resuscitation with isotonic crystalloid solutions at 5-10 mL/kg/hr over 1 hr\n• Reassess patient's condition\n**If patient improves:**\n• IV fluids should be reduced gradually to 5-7 mL/kg/hr for 1-2 hr, then to 3-5 mL/kg/hr for 2-4 hr, then to 2-3 mL/kg/hr for 2-4 hr and then reduced further depending on haemodynamic status\n• IV fluids can be maintained for up to 24 - 48 hours\n**If patient still unstable:**\n• Check Hct after first bolus\n• If Hct increases/ still high (>50%), repeat a second bolus of crystalloid solution at 10-20 mL/kg/hr for 1 hr\n• If improvement after second bolus, reduce rate to 7-10 mL/kg/hr for 1-2 hr, continue to reduce as above\n• If Hct decreases, this indicates bleeding and need to cross-match and transfuse blood as soon as possible\n**Treatment of hypotensive shock**\n• Initiate IV fluid resuscitation with crystalloid or colloid solution at 20 mL/kg as a bolus for 15 min\n• If patient improves\n• Give a crystalloid /colloid solution of 10 mL/kg/hr for 1 hr, then reduce gradually as above\n**If patient still unstable**\n• Review the Hct taken before the first bolus\n• **If Hct was low** (<40% in children and adult females, < 45% in adult males) this indicates bleeding, the need to crossmatch and transfuse (see above)\n• **If HCT was high** compared to the baseline value, change to IV colloids at 10-20 ml/kg as a second bolus over ½ to 1 hour; reassess after second bolus\n• **If improving** reduce the rate to 7-10 mL/kgt/hr for 1-2 hours, then back to IV crystalloids and reduce rates as above\n• **If condition** still unstable, repeat Hct after second bolus\n• **If Hct decreases**, this indicates bleeding, see above\n• **If Hct increases/** remains high (> 50%), continue colloid infusion at 10-20 mL/kg as a third bolus over 1 hr, then reduce to 7-10 mL/kg /hr for 1-2 hours, then change back to crystalloid solution and reduce rate as above\n**Treatment of haemorrhagic complications:**\n• Give 5-10 mL/kg of fresh packed red cells or 10-20 mL/kg fresh whole blood |
| **Monitoring**\n• Daily review for disease progression:\n  • Decreasing WBC\n  • Defervescence\n  • Warning signs (until out of critical period)\n• Advice for immediate return to hospital if development of any warning signs\n• Written advice of management (e.g. home care card for dengue) | **Monitoring**\n• Temperature pattern\n• Volume of fluid intake and losses\n• Urine output – volume and frequency\n• Warning signs\n• Hct, white blood cell and platelet counts | **Monitoring**\n• Vital signs and peripheral perfusion (1-4 hourly until patient is out of critical phase\n• Urine output (4-6 hourly)\n• Hct (before and after fluid replacement, then 6-12 hourly)\n• Blood glucose\n• Other organ functions (renal profile, liver profile, coagulation profile, as indicated) | |
| **Discharge criteria:**\n-> all of the following criteria must be present | • No fever for 48 hours\n• Improvement in clinical picture | • Increasing trend of platelet count\n• No respiratory distress | • Stable haematocrit without intravenous fluids |

**Figure 4.** Algorithm for fluid management of compensated shock

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than 3-4 times/day in chidren and not more than 3g/day in adults. Tepid water sponging if high grade fever persists

3. Patients with more than 3 days of illness need to be reviewed daily for disease progression (Look for leukopaenia, thrombocytopaenia, increasing Hct, defervescence and warning signs).

**Group B:** Patients with warning signs, co-existing conditions and those with social circumstances need inhospital management for close observation.

Warning signs: no clinical improvement, deterioration around the time of defervescence, abdominal pain, vomiting, cold peripheries, obtundation, bleeding, breathlessness, oligo-anuria. Refer to **Figure 3** (previous page) for fluid management of Group B patients.

**Group C:**
- Patients with severe plasma leakage causing shock, third spacing, respiratory distress
- Severe haemorrhages
- Severe organ impairment

Further divided into patients with compensated and uncompensated shock (**Figures 4-5**).

## When to stop IV fluids
- Signs of cessation of plasma leakage
- Stable haemodynamics
- Decreasing haematocrit with stable haemodynamics
- Apyrexia for > 24-48 hours
- Resolving abdominal symptoms
- Improving urine output

Prophylactic transfusion of platelet concentrates in absence of bleeding, even if profound thrombocytopaenia and use of steroids, unless proven haemophagocytic syndrome, has not been shown to improve outcome (Dondorp 2016).

## Treatment of haemorrhagic complications
- Strict bed rest and protection from trauma
- Avoid intramuscular injections
- Cautious insertion of urinary/nasogastric tubes/central line insertion under ultrasound guidance
- Stop the bleeding
- 5-10mL/kg of fresh packed red blood cells (PRBCs)
- Platelet transfusion (if <10,000 or active bleeding) and occasionally fresh frozen plasma (FFP).
- Vitamin K if international normalised ratio (INR) deranged or liver disease
- In gastrointestinal bleeds, H2 blockers/ proton pump inhibitors (PPIs) but doubtful efficacy

### Risk factors
- Patients with refractory shock
- Patients on non-steroidal anti-inflammatory agents, anticoagulant therapy
- Patients with pre-existing peptic ulcer disease

## Glucose control
Both hypoglycaemia and hyperglycaemia can occur in the same patient during critical phases.

## Electrolyte and acid base imbalances
- Hyponatraemia secondary to GI losses or use of hypotonic solutions
- Hypo- or hyperkalaemia in association with acute kidney injury or gastrointestinal losses or stress-induced hypercortisol state.
- Hypocalcaemia: after massive blood transfusions or use of sodium bicarbonate
- Hypophosphataemia
- Hyperuricaemia
- Lactic acidosis secondary to tissue hypoxia and hypoperfusion
- Hyperchloraemic metabolic acidosis due to administration of large volume of normal saline

## Complications
- Prolonged shock
- Severe bleeding with disseminated intravascular coagulation
- Fluid overload
- Respiratory distress and failure
- Multiorgan failure (MOF)
- Abdominal compartment syndrome
- Irreversible shock and death
- Co-infections and nosocomial infection: Gram-negative sepsis, co-existing tropical diseases like malaria, leptospira, typhus, enteric fever, chikungunya
- Haemophagocytic syndrome: Manifested as persistent high-grade fever, cytopaenia and MOF associated with macrophage activation, haemophagocytosis and hypercytokinaemia with raised serum ferritin levels.

- o Diagnosed by bone marrow biopsy demonstrating haemophagocytic activity
- o Treatment mainly with steroids (Methylprednisolone) and IV immunoglobulin

## Dengue prevention
Prevention includes mosquito control, personal protective measures and vaccination.

- **Mosquito control:**
  - o Reducing breeding sites
  - o Larva control
  - o Use of insecticide
  - o Endosymbiotic control: a novel strategy consists of releasing mosquitoes infected with the intracellular endosymbiotic bacterium *Wolbachia*, thereby reducing mosquito lifespan and inhibiting viral replication.

- **Personal protective measures:** A combination of chemically-treated gear and clothing and a strong chemical repellent may be necessary in areas with high concentrations of disease-carrying arthropods.

- **Vaccine:** CYD-TDV is a formulation of four chimeric yellow fever 17D-dengue vaccine viruses. In April 2018 the World Health Organization (WHO) advised that it should be administered only to individuals with a history of previous dengue virus infection or laboratory evidence of previous dengue virus infection. It is administered in three doses at months 0, 6, and 12.
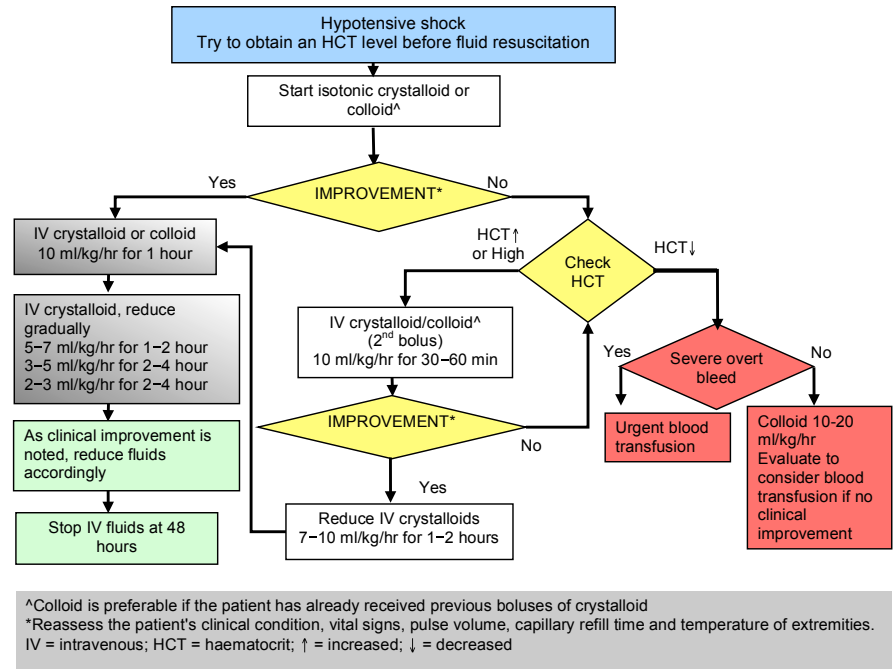


**Figure 5.** Algorithm for fluid management in hypotensive shock

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## Conclusion
Dengue, as a mosquito-borne disease, can be prevented by effective mosquito control measures and vaccine development, which is under evaluation. Suspected dengue cases should be assessed carefully and directed to the appropriate care setting. Early recognition of severe dengue infection is essential as it needs prompt initiation of more aggressive therapy. Outpatient management is appropriate for patients without warning signs, with plenty of fluids and advice to watch for signs of dehydration, clinical deterioration or lack of improvement with defervescence or impending shock. Inpatient management is warranted for patients with dengue with warning signs, severe dengue infection or with coexisting conditions. They should be closely watched for signs of bleeding or worsening shock. Thus, high clinical suspicion, appropriate diagnostic measures and treatment at the right time is the key to achieve good outcomes in these patients and reduce morbidity as well as mortality. ■

## References

Centers for Disease Control and Prevention (CDC) (2010) Dengue: Laboratory guidance and diagnostic testing. [Accessed: 29 August 2018] Available from cdc.gov/dengue/clinicallab/laboratory.html

Changal KH, Raina AH, Raina A et al. (2016) Differentiating secondary from primary dengue using IgG to IgM ratio in early dengue: an observational hospital based clinico-serological study from North India. BMC Infectious Diseases, 16: 715.

Dondorp AM (2016). Other tropical diseases in the ICU. In: Webb A, Angus D, Finfer S et al., eds. (2016) Oxford textbook of critical care. 2nd edition, pp. 1404-7.

Guzman MG, Harris E (2015) Dengue. Lancet, 385: 453-65.

Kularatne SA (2015) Dengue fever. BMJ, 351: h4661.

Miranda CH, Borges Mde C, Matsuno AK et al. (2013) Evaluation of cardiac involvement during dengue viral infection. Clin Infect Dis, 57: 812-9.

Pai-Dhungat JV, Parikh F (2013) Medical philately. Dengue an escalating problem. J Assoc Physicians India, 61(8): 582.

Simmons CP, Farrar JJ, Nguyen vV et al. (2012) Dengue. New Engl J Med, 366: 1423-32.

Solomon T, Dung NM, Vaughn DW et al. (2000) Neurological manifestations of dengue infection. Lancet, 355:1053-9.

World Health Organization (1997) Dengue haemorrhagic fever: diagnosis, treatment, prevention and control. 2nd edition. Geneva: WHO. [Accessed: 29 August 2018] Available from who.int/csr/resources/publications/dengue/Denguepublication/en

World Health Organization (2012) Handbook for clinical management of dengue. Geneva: World Health Organization. [Accessed: 12 November 2018] Available from wpro.who.int/mvp/documents/handbook_for_clinical_management_of_dengue.pdf

World Health Organization (1997) Dengue haemorrhagic fever: diagnosis, treatment, prevention and control. 2nd Edition. Geneva: WHO. [Accessed: 29 August 2018] Available from who.int/csr/resources/publications/dengue/Denguepublication/en

World Health Organization and the Special Programme for Research and Training in Tropical Diseases (TDR) (2009) Dengue guidelines for diagnosis, treatment, prevention and control: new edition. [Accessed: 12 November 2018] Available from who.int/rpc/guidelines/9789241547871/en