INTRODUCTION
Dengue is the world’s most common mosquito-borne viral infection and a leading cause of morbidity throughout the tropics and subtropics. Each year, there are about 50-100 million dengue infections and about 5,00,000 individuals hospitalized with DHF, mainly in Southeast Asia. Globally, dengue virus transmission has expanded in recent years, and all four dengue virus serotypes are now circulating in Asia, Africa, and the Americas, representing a global pandemic. Approximately 70% of the population at risk for dengue worldwide lives in the WHO south east Asian region and western Pacific region, which bear nearly 75% of the current global disease burden due to dengue.

Dengue epidemiology in India has dramatically changed over the last few decades. After the first major nationwide outbreak of DHF in the year 1996, gradual dengue virus expansion started in the entire nation. A steady increase in the number and frequency of outbreaks has followed, and, at present, in most of the states of India, all four serotypes are prevalent.

EPIDEMIOLOGY
The epidemiology of dengue depends upon a complex relationship between epidemiological factors, viz. host (man and mosquito), agent (virus) and the environment.

Dengue Virus
Dengue virus belongs to the genus Flavivirus in the family Flaviviridae. It is a positive-stranded encapsulated ribonucleic acid (RNA) virus composed of three structural protein genes that encode the nucleocapsid or core protein, a membrane-associated protein, an enveloped glycoprotein, and seven nonstructural proteins. There are four antigenetically related but distinct serotypes of the dengue virus: DENV-1, DENV-2, DENV-3, and DENV-4. Each serotype has several genotypes. DENV-1 has three, DENV-2 has two, and DENV-3 and DENV-4 each have four. In humans, one serotype produces lifelong immunity against reinfection but only temporary and partial immunity against the other serotypes. Each serotype has unique characteristics and can present with severe manifestations in a particular population depending upon its interaction with the host response.

Host
People of all ages and both genders are at risk of being infected. Travel to dengue endemic areas is a very important risk factor in transmission of disease- it is the commonest cause of fever in the travelers returning from these areas, overtaking malaria and typhoid.

Dengue is transmitted from an infected person to others by the bite of the female Aedes aegypti mosquito (main urban vector) and the Aedes albopictus mosquito. Though transmission primarily occurs through the bite of a vector, there are reports of transmission through blood transfusion, organ transplantation and vertical transmission.

Environment
Ae.aegypti breeds in domestic man-made water receptacles whereas Ae.albopictus prefers natural larval habitats. Seasonal variation in dengue transmission is due to the survival characteristics of vectors, best between 16-30°C at relative humidity of 60-80%.

CLINICAL FEATURES
Dengue viruses cause symptomatic infections or asymptomatic seroconversion. Symptomatic dengue infection is a systemic and dynamic disease. It has a wide clinical spectrum that includes both severe and non-severe clinical manifestations. After the incubation period of 4 to 7 days, it is followed by three phases – febrile, critical and recovery.

Febrile phase: Onset of DF with sudden rise in temperature, lasts for around 4-5 days and is usually associated with severe frontal headache, myalgia, retro-orbital pain, flushing and rash. Rash may be maculopapular or scarlatiniform, usually appears after 3rd/4th day of fever.

A second episode of fever and symptoms can arise, called “saddleback” pattern. Atypical features are enumerated in Table 1.

Potential complications can include

- Dehydration due to decreased fluid intake, emesis, and increased metabolic state.
- Febrile convulsions

Critical phase (Leakage phase): Occurs after 3-4 days after onset of fever. It is characterized by hypovolemia and hemorrhagic manifestations due to increased vascular permeability and plasma leakage, which persists for 36-48 hours.

Potential complications can include

- Unrecognized plasma leakage/hemorrhage leading to shock.
• Pleural effusion

Convalescent phase (Recovery phase): Usually occurs after 6-7 days of fever and lasts for 2-3 days. ECF lost during capillary leakage returns to circulatory system. Clinical improvement is seen.

Potential complications can include
• Intravascular fluid overload due to continual aggressive volume resuscitation during convalescence.

Differentiating Dengue from other febrile illnesses (OFIs) (Table 2):

India, like most developing countries have epidemics of febrile illnesses that can be confused with DF.

At presentation, DF and other febrile illnesses may share similar clinical features, including headache, myalgia, and rash. Early distinction between dengue and OFI would help clinicians to identify patients who should be closely monitored for signs of DHF and stratify them accordingly.

Differences in clinical and laboratory features between dengue and other febrile illnesses have been reported; however, published studies vary considerably in terms of the parameters used, which impacts the clinical applicability of these differences.

A diagnostic accuracy study done in Brazil showed that conjunctival redness and decreased leukocyte count were independent predictors of DF.

A systematic review of literature published by NIH showed that patients with dengue had significantly lower platelet, white blood cell and neutrophil counts, and a higher frequency of petechiae than OFI patients. Higher frequencies of myalgia, rash, hemorrhagic signs, lethargy/prostration, and arthralgia/joint pain and higher hematocrits were reported in adult patients with dengue but not in children.

More prospective studies are needed to construct a valid and generalizable algorithm to guide the differential diagnosis of dengue in endemic countries.

**APPROACH TO DENGUE**

1. Assessment:
   a. History
   b. Examination
INFECTION

INFECTION

c. Investigations and Diagnosis
2. Grading of severity, case classification
3. Management and Disease Notification
4. Prevention of Dengue
1. Assessment:
   a. Obtain complete history:
      - Onset of fever/illness,
      - Associated symptoms: diarrhea, respiratory
      - Fluid intake and Urine output
      - Warning signs
      - Prior episodes of dengue
      - Travel history, Family history
      - Presence of co-existing conditions: infancy, pregnancy, obesity, diabetes mellitus, hypertension
   b. Evaluation:
      - Hemodynamic status: heart rate, capillary refill, skin color and temperature, peripheral pulse volume, pulse pressure, blood pressure, mentation.
      - Hydration status
      - Bleeding manifestations, Rash, positive tourniquet test
      - Evidence of plasma leakage: pleural effusions, ascites, hemoconcentration, abdominal tenderness, hepatomegaly, acidic breathing
   c. Investigations: All patients:
      i. Complete Blood count including Hematocrit
      ii. Dengue serology for diagnosis:
         - NS1 Ag is a marker of acute dengue infection: first 3 days of illness.
         - Single sample after day 5: Specific IgM detection, up to 3 months after onset of fever.
         - Primary infection: High IgM, Low IgG.
         - Secondary infection: Low IgM, High IgG
   iii. Specific tests:
      - Blood Sugar Level
      - Organ Function tests
      - Coagulation profile
      - Blood culture
2. Grades:
   2009 WHO case classification for Dengue:
   - Dengue Viral Infection
     - Mild
     - Moderate
     - Severe
   Table 3: Classification of Dengue Fever
<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>DF</td>
<td>Fever of 2-7 days with 2 or more of the following:</td>
</tr>
<tr>
<td></td>
<td>- Headache</td>
</tr>
<tr>
<td></td>
<td>- Retro-orbital pain</td>
</tr>
<tr>
<td></td>
<td>- Myalgia</td>
</tr>
<tr>
<td></td>
<td>- Arthralgia</td>
</tr>
<tr>
<td>DHF I</td>
<td>DF features + Positive Tourniquet test and evidence of plasma leakage</td>
</tr>
<tr>
<td></td>
<td>Platelet count &lt; 1,00,000/cu.mm + Haematocrit rise &gt; 20% over baseline</td>
</tr>
<tr>
<td>DHF II</td>
<td>DF + evidence of spontaneous bleeding and abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Platelet count &lt; 1,00,000/cu.mm + Haematocrit rise &gt; 20% over baseline</td>
</tr>
<tr>
<td>DHF III (DSS)</td>
<td>DF + circulatory failure: weak rapid pulse, narrow pulse pressure &lt;20 mm Hg, Hypotension, cold clammy skin, restlessness</td>
</tr>
<tr>
<td></td>
<td>Platelet count &lt; 1,00,000/cu.mm + Haematocrit rise &gt; 20% over baseline</td>
</tr>
<tr>
<td>DHF IV (DSS)</td>
<td>Profound shock with undetectable blood pressure/pulse</td>
</tr>
<tr>
<td></td>
<td>Platelet count &lt; 1,00,000/cu.mm + Haematocrit rise &gt; 20% over baseline</td>
</tr>
</tbody>
</table>
   - Laboratory confirmed Dengue
   - Management algorithms:
     - Dengue Viral Infection
     - Asymptomatic
     - Symptomatic
     - Mild
     - Moderate
     - Severe
   - 1) Severe plasma leakage
     - Deterioration
     - Shock
   - 2) Severe bleeding
   - 3) Severe organ involvement
   - 4) Severe neurological manifestations
   - 5) Other severe complications

   Management algorithms:
   (Adapted from 46)
Capiillary leakage syndrome

- **1. Afebrile > 48 hours**
- **2. Clinical improvement**
- **3. Platelet count increasing**

### Group A: Home Management

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>No warning signs</td>
<td>Bed rest</td>
</tr>
<tr>
<td>Adequate oral fluid intake</td>
<td>Adequate fluid intake</td>
</tr>
<tr>
<td>Good urine output (every 6 hours)</td>
<td>Paracetamol up to 4gm/day</td>
</tr>
</tbody>
</table>

### Group B: Referral for In-Hospital Care

### Warning Signs
- Recurrent Vomiting
- Abdominal pain
- Lethargy/ Restlessness
- Clinical Fluid accumulation
- Hematocrit > 2cm
- Bleeding manifestations

### Warning Signs Present

#### Home Based Management

- Improvement?
- NO/Worsening

#### Hospitalization

- Check Haematocrit, Pit, BSL, UOP, perfusion, organ function
- Intravenous fluids
- Isotonic solution @ 5-7 ml/kg/hr over 1-2 hours

#### Clinical Response

- Fluids:
  - 3-5 ml/kg/hr
  - 2-3 ml/kg/hr
- Reassess Hematocrit

#### Same/ Minimal Increase

- Continue @ 2-3 ml/kg/hr for 2-4 hrs
- Adequate fluid intake, Urine Output

#### Worsening/ Increase to 5-10ml/kg/hr for 1-2 hrs

- Reassess and review fluid intake rates
- Decrease IVF Gradually

### SEVERE DENGUE

#### Group C: Emergency Hospitalisation

- Isotonic Crystalloids @ 5-10 ml/kg/hr * 1 hr
- IV Isotonic Crystalloid/Colloid @ 20ml/kg/hr *15 mins

#### Improving?

- NO

#### Decompensated Shock

- Urgent Blood Transfusion

- Urgent Blood Transfusion

### Conditions

- Infants/ Old Age
- Diabetes Mellitus
- Hypertension
- Pregnancy
- Coronary Artery Disease
- Hemoglobinopathies
- Immunocompromised status

### Criteria for Discharge

1. Afebrile > 48 hours
2. Clinical improvement
3. Platelet count increasing
4. No Respiratory distress
5. Stable haematocrit without intravenous fluids

The principal underlying the treatment of dengue is the correction of the volume contraction in the vascular system due to the capillary leak syndrome. This has been shown to correspond to the risk of complications. Early and continual assessments of the fluid volume status as reflected in changes to haematocrit is reasonably accurate to follow.

It is important to ensure that patients do not have a sudden rise in values during the critical phase of capillary leak. The approach to dehydration depends on clinical scenario and the severity of volume loss during evaluation. This determines the speed of replacement of volume and additional measures for support.

Most patients can be managed at home with daily outpatient reviews with a checklist to assess severity and alarm symptoms. This can prevent overcrowding of hospitals without endangering patient care. However, it is important to remember that the risk of complications is most just after the patient becomes afebrile, and appropriate counseling is imperative to ensure that monitoring is continued into this critical phase.

Patients who may be at risk, including those with other medical conditions may be best cared for in the wards of hospitals, where regular monitoring and hydration should suffice. Patients with severe symptoms are best managed in areas with access to good monitoring and intervention services.

For most patients, only crystalloids are required for volume expansion, and colloids including blood may be considered in those in the most severe category. The role of platelet is minimal, if any, and is best restricted to those with active bleeding.

Discharge may be considered once the patient has crossed the critical phase. Again, those with difficulty handling the volume that is reabsorbed, like those with renal or...
cardiac disease, may need additional observation during this phase as well. Patients may experience additional manifestations during the recovery phase in addition to post viral asthenia like pruritus, joint pain and bradycardia. These tend to resolve spontaneously over time, and may only require reassurance.

There are many unusual manifestations of dengue, and should be considered in all patients with a short febrile illness. Raised liver enzymes are very common, and usually the AST is higher than ALT. However, severe liver injury is rare. Other unusual manifestations include Gullian-Barre syndrome, myocarditis, renal failure, and lung injury. In most cases, these resolve with appropriate symptomatic management.

**PREVENTION OF DENGUE: (47)**

<table>
<thead>
<tr>
<th>ENVIRONMENTAL MEASURES</th>
<th>PERSONAL PROTECTION</th>
<th>MOSQUITO CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Improving water supply</td>
<td>- Protective clothing</td>
<td>- Larvivorous fish in large water bodies</td>
</tr>
<tr>
<td>- Environmental sanitation improvement</td>
<td>- Mosquito repellants</td>
<td>- Bacillus thuringiensis serotype H-14, endotoxin producing bacteria.</td>
</tr>
<tr>
<td>- Mosquito-proofing overhead tanks, screens on doors/windows.</td>
<td>- Insecticide-treated mosquito nets</td>
<td>- Chemical Larvicide: Temephos(50 EC)</td>
</tr>
<tr>
<td>- Education to public</td>
<td>- Dengue vaccine</td>
<td>- Adulticide: Pyrethrum spray (indoor)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malathion/ Ultra Low volume spray (fogging)</td>
</tr>
</tbody>
</table>

**SPECIAL CIRCUMSTANCES**

1. Dengue in immunocompromised patients:

   - Patients on cancer chemotherapy
   - Patients with haematological disorders
   - Post transplant patients on immunosuppression
   - Primary/congenital immunodeficiency disorders
   - Chronic steroid therapy
   - Autoimmune diseases on immunomodulator therapy
   - HIV/AIDS with CD4 count <500

Clinical presentation is similar in immunocompromised patients, although the course is usually prolonged. Principles of treatment remain the same, although close monitoring is preferred.

Transplant and Dengue: In post-solid organ transplant patients, dengue usually follows a benign course with no evidence of longterm damage / rejection episodes. Thrombocytopenia is more severe in patients receiving steroids, azathioprine and cyclosporine concomitantly. Tacrolimus is found to prolong duration of thrombocytopenia. Graft survival and outcome following dengue fever was not affected in the studies.

In studies involving renal transplant recipients, likelihood of developing severe forms of dengue was found to be low, probably due to diminished T-cell responses.

There are reports of dengue in stem cell recipients, sometimes donor-derived. Dengue fever complicating patients with aplastic anemia have been salvaged with stem cell therapy. However, this disease appears to be more severe in this population and poor outcome is reported.

A case series of patients on biotherapy for rheumatological diseases, infected with dengue, found that none of them developed severe dengue. However there are no guidelines regarding continuing biological therapy during the course of treatment.

2. Dengue in Pregnancy:

   - High index of suspicion for diagnosis is necessary as the consequences due to dengue infection are multifold. Multiple studies have shown complications ranging from miscarriages, preterm births, haemorrhages in labour, perinatal deaths, adverse maternal outcomes and vertical transmission of infection to the fetus.

Serial Haematocrit measurement is crucial for disease monitoring. Unless imperative, to avoid induction of labour / Caesarian section during critical phase, as risk of bleeding is at its peak during that period.

Baby should be evaluated and monitored post-
delivery as vertical transmission of disease has been observed.\(^\text{60}\)

- Breastfeeding has been shown to transmit dengue in a case study, however there are no clear guidelines on the same.\(^\text{61}\)

3. Dengue in patients on Antithrombotic treatment:\(^\text{62}\)

4. Surgery and Dengue:

- Acalculous cholecystitis due to plasma leakage leading to gall bladder wall edema is a clinical manifestation of Dengue Fever. The patient presents with right hypochondrial pain. The course is usually self-limiting and surgery is not warranted unless there is diffuse peritonitis.\(^\text{63}\)

There are no guidelines on management of surgical patients with Dengue. Post-operative bleeding from surgical sites should be closely monitored. As removal of in-dwelling vascular catheters may cause hemorrhage, it could be deferred till critical phase is over. Platelet transfusion is not necessary in all surgical patients.\(^\text{64}\)

5. Dengue and Diabetes Mellitus: Diabetes Mellitus is an independent risk factor for developing profound thrombocytopenia and severe forms of dengue infection.\(^\text{65-67}\) Studies have shown DM to be a predictor of mortality in dengue.\(^\text{66-67}\) A study has shown that stress-induced hyperglycemia found at the time of acute infection disappeared after recovery, warranting use of HbA1c for checking glycemic status. (68) Early diagnosis of dengue in diabetics is hence of importance. It will ensure closer glycemic control and adjusted fluid management in this population.

6. Dengue and Zika: Zika virus (ZIKV), an emerging arboviral infection also transmitted by Aedes spp belonging to genus Flavivirus is an important public health issue.\(^\text{69}\)

A recent report on coinfection between dengue and Zika raised the concern of missed / under-diagnosis of Zika. The effect of coinfection needs to be studied further.\(^\text{70}\)

Data suggests that there is an interplay between host antibody response to ZIKV and DENV, with concern of DENV being a cofactor for increasing severity of Zika infection.\(^\text{71}\)

There is speculation that this could affect how Zika behaves in pregnant women, and more research on this is ongoing.

That dengue has become a major public health issue is beyond doubt; following well established protocols and pathways for assessment and management is the only way to reduce the morbidity, mortality and the financial impact of this disease, not to mention the overcrowding of already over burdened medical facilities.

**REFERENCES**


16. Lum LC, Lam SK, Choy YS, George R, Harun F. Dengue


