Review: Dengue illness

Dr. Ashok Kapse, MD
Kapse Children Hospital, Surat

President Surat branch of Indian Academy of Pediatrics
President Gujarat branch of Indian Academy of Pediatrics
National chairman of Infectious Diseases Chapter of IAP 2004-5.
Section Editor of Journal of Clinical Pediatrics
Section Editor of Journal of Pediatric infectious diseases
published by Elsevier
Recipient of six oration awards By IAP & IMA

- Did original Research in Dengue illnesses in collaboration with CDC Colorado USA.
- Invited to Malaysia, Thailand to deliver talks about need of Dengue vaccines in Asia and operational feasibility.
- Delivered more than 300 lectures across the National and International scientific meetings.
- Invited to deliver talk in World Congress of Pediatrics on 12-12-13 to be held in China.
- Invited as an expert by Zee TV, National Doordarshan and ETV to educate masses about Dengue illnesses.
Review: Dengue Illness

Contents

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>Transmission</td>
<td>2</td>
</tr>
<tr>
<td>Dengue viruses</td>
<td>3</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>4</td>
</tr>
<tr>
<td>Disease classification</td>
<td>6</td>
</tr>
<tr>
<td>Clinical picture</td>
<td>8</td>
</tr>
<tr>
<td>Dengue Clinical management</td>
<td>12</td>
</tr>
<tr>
<td>Management</td>
<td>14</td>
</tr>
<tr>
<td>Monitoring</td>
<td>21</td>
</tr>
<tr>
<td>Complications</td>
<td>22</td>
</tr>
</tbody>
</table>
‘Dengue’ is a Spanish altered word evolved from the roots in the Swahili language as ‘Ki-dinga’. It was labelled as ‘Water poison’ as Dengue like illness was found to be closely associated with most primitive insects thriving near water bodies. This Dengue-like illness also had found its mention in the Chinese Encyclopaedia pertaining to the Chin Dynasty (AD 265-420).

During the 18th and 19th century, Dengue-like diseases were known to be present all over the world excepting Antarctica. Around mid 1950s this disease underwent a strange evolution; compared to its innocuous non fatal existence till then, it suddenly turned out to be deadly; in the South East Asian countries, people started dying due to dengue. Disease exhibited two fatal complications: (1) bleeding diathesis and (2) shock. There after dengue was renamed as ‘Dengue hemorrhagic fever-dengue shock syndrome’. This new evolved form of dengue outbreaks primarily clutched children and despite timely hospitalisation and appropriate treatment many of them succumbed to death.

Figure 1. Current global status 2011.
In the 1980s other Asian countries like India, Sri Lanka, Maldives, Bangladesh and Pakistan came into the gripe of this disease. In India Dengue spread by leap & bound, within a short period it covered every nook and corner of the country, hyperendemicity that is circulation of multiple serotypes become a regular feature. Multiple dengue virus serotypes have been isolated from Indian and Sri lankan epidemics. However, DEN-3 serotype predominates over other strains.

As per latest WHO statistics now around 50 million Dengue cases occur annually resulting in 500,000 hospitalization cases and over 20,000 deaths

With the turn of the last century Dengue moved from Asia to the Pacific regions and the United States of America (Fig-1). As per latest WHO statistics now around 50 million Dengue cases occur annually resulting in 500,000 hospitalization cases and over 20,000 deaths.

TRANSMISSION

Dengue viruses belong to Flaviviridae family which consist of nearly 70 viruses; these are arthropod borne viruses meaning there by that they need vector for life cycle completion; although antigenically distinct yet dengue are four inter related viruses each capable of causing dengue illness.

Vectors:

Aedes mosquitoes serve as vectors for dengue viruses. The Aedes aegypti work as the most efficient carrier however Aedes albopictus could be an effective alternative choice. Vectors not only carry the virus but it also amplifies viral replication.

A. aegypti, the principal vector (Fig-2), is a small, black-and-white, highly domesticated tropical mosquito, it lays its eggs in artificial containers like flower vases, old automobile tires, buckets that collect rainwater, and trash in general commonly found in and around homes, Other important sites in the vicinity of human dwellings which produce large numbers of adult mosquitoes are water storage containers, such as large drums, cement cisterns, and even septic tanks. Female A. aegypti mosquitoes need blood for egg laying. A. aegypti are primarily day
Aedes mosquitoes serve as vectors for dengue viruses. The Aedes aegypti work as the most efficient carrier. Time biters, they prefer to meal between 9 am to 5 pm however if denied day time meals they are capable of night bites also.

The adult female mosquitoes are anxious feeders, little disturbance could disrupt their feeding and they may swap to another person or the same person at a different place, mosquito may bite 5 to 6 persons for completion of one meal.

This particular quality makes the female mosquito an effective and efficient epidemic vector, leaving no room for surprise on finding multiple cases of dengue in the same house within 24 to 36 hours.

Dengue has an incubation period of 8 to 12 days. Viremia may last from three to seven days. An A. aegypti mosquito biting any infected person during this period will carry the virus and while biting another person would infect him.

The climate plays an important factor in the transmission of the virus, fluctuations in temperature and humidity has immediate effects on viral proliferation and transmission. A rise in temperature and humidity results into faster maturation mosquito larvae. In warmer climate mosquito need more and frequent feeds. Based on the WHO estimate, vulnerable population may increase by seven hundred million per annum if temperature rises by 1-2 degree C.

### Dengue Viruses

Enveloped in a lipid envelope the Dengee are small spherical single stranded RNA viruses.

The viral genome encodes three structural proteins (Capsid, C membrane protein, M, envelope glycoprotein, & E protein) and seven non-structural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5).

The antibody neutralizing activity that classifies DENV into 4 serotypes: DENV1, 2, 3 and 4 is determined by the amino acid sequences of the E proteins. Viral entry is initiated by the interaction of the E protein with cellular receptor(s).

Non-structural proteins of DENV function in RNA replication and assembly and in viral protein processing. A few non-structural proteins can also modify the host immune system along with working in viral replication.
viral NS protein is capable of influencing type ‘1 IFN’ signalling and induces cytokine production. The only non-structural protein which exists in a soluble form that can be detected in circulation is NS1.

Infection by one dengue serotype provides lifelong immunity to that particular virus. However, there is no cross protection to other serotypes. Thus, persons living in an area of endemic dengue can potentially be infected with three, and probably four, dengue serotypes during their lifetime

**Reasons for recent rise in dengue and DHF:**

The two principle factors responsible for the exponential increase in the emergence and re-emergence of dengue illnesses are sudden rise in density and geographic distribution of the A. aegypti and a large virus transmission geographically.

The rise in population and unplanned urbanization leading to bad housing, inadequate water supply and poor waste management system are the prime factors which are influencing vector density.

Air travel has facilitated viral movement across the world. Various serotypes, strains, and even genotypes of virus move from one place to another causing hyperendemicity. Viremic individuals play a role in introducing a virus in the new vulnerable population causing epidemics.

**PATHOPHYSIOLOGY**

**Vascular leak:**

A transient increase in vascular permeability that results in the leakage of fluid from the plasma into the interstitium is the fundamental feature which differentiates DHF from DF. The extravasated fluid is collected into serous cavities: peritoneum, pleura and pericardium; and the leakage results into hemoconcentration and hypovolemia. Fortunately in most of the cases leak is transient; the increased vascular permeability spontaneously resolves, the extravasated fluid which gets reabsorbed and the recovery starts. Some of the patients may suffer from a severe leak which leads to hypovolemia, hypotension and shock which could culminate into death.

**Mechanism for vascular leak:**

The pathophysiological mechanisms underlying the capillary leak are not properly understood. Strain gauge plethysmography documents an increase in microvascular permeability which does suggest endothelial dysfunction; however there is no proof that the virus directly infects endothelial cells in vivo, and no structural endothelial abnormalities have ever been demonstrated.

A transient increase in vascular permeability that results in the leakage of fluid from the plasma into the interstitium is the fundamental feature which differentiates DHF from DF.
A layer of glycocalyx is present in the luminal surface of the vascular endothelium. Glycosaminoglycans (GAGs) which are complex, negatively charged polysaccharides are integrated into this layer. The creation of a size selective physical barrier is done by this layer which allows the movement of only some molecules between the fibres. Layer acts as electrostatic barrier which integrates negatively charged molecules like albumin in to it and prevents their loss in to extra vascular space. A transient change in the function of the endothelial glycocalyx at the time of Dengue infection is documented by a recent research. Although a general size-dependent sieving mechanism is partially retained the selective limitation on the negative charge is clearly impaired.

Pathogenesis:
Occurrence of DHF is usually seen in two clinical settings: primary dengue infection in an infant and secondary dengue infection at any age. Various aspects of DENV biology are well understood yet the pathogenesis explaining DHF in two different set of patients is still intriguing. Different factors like total viral virulence, virus burden, host immune response and genetic predisposition are labelled as risk factors for DHF. But still these factors have failed to explain the manifestation of DHF in both clinical settings.

One of the eminent risk factor for DHF is the pre-existence of non neutralizing antibodies either from former infection or transplacental mother to child transmission.

Role of pre-existing antibodies:
In a dengue virgin body first dengue infection manifests as self limiting febrile illness; recovery from this infection is associated with the generation of immunological responses. Epitopes present in E_ protein are capable of inducing homologous as well as heterologous neutralizing and non-neutralizing antibodies. Variations in the levels of these antibodies are the primary determinant of severity of next dengue infection.

Specific protection is insured by neutralizing antibodies to DENV. Infection with one such DENV serotype makes one immune to that infection serotype for lifetime. Antibodies against E, prM proteins and to NS1 are proficient in neutralizing DENV and offering protection against Dengue infection.

Through the initial few months the first infection also provides protection against other serotypes, nonetheless a decline in neutralizing antibodies, and persistence of heterotypic non neutralizing antibodies result into ‘antibody dependent enhancement’ (ADE) of subsequent infection. ADE is a phenomenon when the heterotypic antibodies form complexes with Dengue viruses, which facilitates an enhanced cellular penetration. This transpires only during a secondary infection with a different serotype and on the condition that the heterotypic non neutralizing antibodies are present.

ADE theory explicitly elucidates observed occurrence of DHF in both clinical settings: during primary infection in infants and secondary infection at any age.
DISEASE CLASSIFICATION

Old classification:
Ranging from asymptomatic infection, to mild undifferentiated fever, to fatal shock; dengue illnesses exhibits an extensive array of clinical presentations. Until recent times WHO identified two types of dengue illnesses: dengue fever (DF) a mild self limiting febrile illness and (D) dengue hemorrhagic fever (DHF) a potentially fatal condition pathognomonized by leaky vasculopathy.

According to the disease severity DHF was further divided in to four categories: Grade I:- thrombocytopenia, hemoconcentration, positive TT (Tourniquet Test) and absence of spontaneous bleeding; Grade II:- thrombocytopenia, hemoconcentration, positive TT and presence of spontaneous bleeding; Grade III: -thrombocytopenia, hemoconcentration, positive TT and circulatory insufficiency (fieble pulse, drop of 20 mm Hg or greater in arterial blood pressure, cold extremities and apprehension); Grade IV:- thrombocytopenia, positive TT, hemoconcentration, imperceptible pulse and blood pressure.

DF vs. DHF: Central theme in previous classification:
The core theme in Dengue disease classification is the key dissimilarity that the DF is a non-specific febrile illness and DHF is a potentially serious disorder caused by leaky vasculopathy. Adhering to WHO guidelines, DHF cases should essentially fulfil the following four criteria: (1) Fever or history of acute fever lasting 2–7 days, (2) hemorrhagic tendencies evidenced by at least one of the following: a positive tourniquet test (TT), petechiae, purpura, ecchymoses; bleeding from mucosa, gastrointestinal tract, injection sites or other location haematemesis, and melena, (3) thrombocytopenia [Platelets less than 100 000], (4) evidences for plasma leakage in DHF: >20% rise in hematocrit, fluid in serous cavities documented by x-ray or USG.

Difficulties with previous classification:
The flaring reach of Dengue round the world and also among the older age groups have concerned many clinicians and numerous investigators who have reported multiple problems in the current classification system. Generally the reported difficulties are: [1] the classification makes rigorous efforts to
distinguish between DF, DHF, and DSS, overlooking the overlap between the three for example bleeding or occult bleeding tendency (+ TT) and mild thrombocytopenia could occur in DF as well. [2] documentation of all four requirements for the WHO definition of DHF (fever, haemorrhage, thrombocytopenia, and signs of plasma leakage) needs frequent assessment of packed cell volume and platelet counts which may not always be available or feasible, furthermore a properly fluid managed patient from primary stage of disease may fail to show 20% rise in hematocrit despite vascular leak. [3] TT is an integral part of the existing scheme. However, the test poorly distinguishes between DF and DHF; besides many children with ‘non-dengue’ febrile illnesses may also have positive tests. [4] The DF/DHF/DSS classification disregards severe dengue disease associated with organ involvement like hepatitis, encephalitis and myocarditis, [5] finally, the term DHF places unjustified prominence on haemorrhage when the danger sign that should be watched for and managed is plasma leakage leading to shock.

New Classification:
The insight that the current classification of Dengue into DF, DHF (Grades 1 and 2) and DSS (DHF Grades 3 and 4) would not be universally applicable for clinical management everywhere had triggered rethinking in WHO. To sort out the issues a global Dengue experts meet was summoned by WHO in 2008 in Geneva. The committee advocated a new case classification for Dengue illnesses and formulated revised guidelines in 2009 for the management of dengue illnesses. Pertaining to the new guidelines this disease is now classified into three categories (1) dengue (2) dengue with warning signs, and (3) severe dengue whereas the clinical course of the disease is divided in three phases: febrile, critical, and recovery. (Fig-3)

![Dengue - Warning signs diagram](image)

**CRITERIA FOR DENGUE - WARNING SIGNS**
- Probable dengue
  - Live in / travel to dengue endemic area.
  - Fever and 2 of the following criteria:
    - Nausea, vomiting
    - Rash
    - Aches and pains
    - Toxoplasma test positive
    - Leukopenia
    - Any warning sign
  - Laboratory-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 > 2 cm
  - Laboratory: increase in HCT concurrent with rapid decrease in platelet count

**CRITERIA FOR SEVERE DENGUE**
- Severe Plasma leakage leading to:
  - Shock (DSS)
  - Fluid accumulation with respiratory distress
  - Severe bleeding as evaluated by clinician
  - Severe organ involvement
    - Liver: AST or ALT ≥ 1000
    - CNS: Impaired consciousness
    - Heart and other organs
Dengue:

Febrile Phase:

Following a short incubation period of two to seven days, a sudden onset high grade fever heralds the dengue illness. A bloachable erythematous flush is usual companion of the fever. (Pic-1) The patients assume a measly look with suffused and swollen face, injected eyes, reddened ears, and crimson maler area, swollen and purplish lips (Pic-2). The flush intensifies with advancing disease. In some patients a classical maculo papular exanthem (Pic-3) may erupt on the top of erythematous flush. Certain patients might develop a sore throat, injected pharynx along with conjunctival injection while catarrh a typical characteristic of respiratory viruses is absent. Adolescents and older children often exhibit symptoms like headache, retro-orbital pain, photophobia, backache, myalgia and arthralgia. Dehydration causing symptoms like anorexia, nausea and vomiting are found to be commonplace in such patients.

A positive tourniquet test in this phase increases the probability of dengue diagnosis

massive gastrointestinal bleeding commonly reported in adults during febrile phase is rare in children.

During the initial febrile phase of the disease it can be challenging to distinguish dengue from non-dengue febrile diseases. A positive tourniquet test in this phase increases the probability of dengue diagnosis (Pic-6).

Luecopenia, atypical lymphocytosis, and mild thrombocytopenia are some of the frequently noticed haematological changes in the febrile phase of dengue illness.

Over a period of 2-7 days an efficient and complete recovery is observed in the majority of patients unfortunately some of the cases may deteriorate with defervescence leading them into a critical phase. Unfortunately preliminary clinical attributes fail to distinguish between severe and non-severe dengue cases; therefore it is imperative that the patient is kept under strict monitoring for warning signs there by facilitating the timely identification of cases evolving to the critical phase.

Dengue with warning Signs:

The below stated warning signs assist to indentify the cases who may pass in to a critical phase: persistent vomiting, abdominal pain, hepatic enlargement, lethargy
Occurrence of warning signs should caution a clinician for regular monitoring and prompt fluid therapy to improve patient’s outcome.

Critical phase:
An increase in capillary permeability sets in around the time of defervescence. Extravasations of plasma, through these leaky capillaries result into progressive hemoconcentration. A parallel drop in platelets usually coincides with plasma leakage. Collectively these changes mark the onset of the critical phase.

In majority cases the leak is transient persisting only for a few hours. On discontinuation of this leak the patient quickly stabilizes and completely recovers. According to the new classification these patients should be classified as Dengue with warning signs.

---

**Days of illness**

<table>
<thead>
<tr>
<th>Days of illness</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Temperature</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Potential clinical manifestations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hemorrhages</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Re-absorption</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overload of fluids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Alterations in organs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical laboratory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hernatoorit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Platelets</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serology and virology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Viremia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ac IgM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stages of the illness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Febrile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Critical Leakage of plasma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recovery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 4 Course of a dengue illness
Severe Dengue:

No sooner did dengue sweep its grip around the world it was realized that this disease can have serious manifestations apart from shock. Hepatitis, myocarditis, encephalitis, and severe bleeding are few of the generally confronted serious manifestations of a dengue illness. A new category: severe dengue is created to include these serious manifestations. This category covers three types of patients: (1) Patients with severe plasma leakage: [A] Shock (cold clammy peripheries, prolonged CRT, narrow pulse pressure, fall in systolic pressure). [B] Fluid accumulation resulting into respiratory distress. (2) Patients with profuse bleeding and (3) Patients with significant organ involvement: [A] Hepatic involvement (Transaminases >1000). [B] Patients with neurological involvement. [C] Patients with cardiac involvement.

Dengue shock:

Patients exhibiting sustained and copious leak would deteriorate. These worsening patients will display signs of impending shock (cold and clammy extremities, feeble or imperceptible peripheral pulse, delayed capillary refill time, narrow pulse pressure and falling blood pressure). For the patients that experience enormous leak, plasma may continue seeping out for two to three days. This extravasated fluid collects primarily in to serous cavities like peritoneum, pleura, and pericardium (Pic-7). Large ascitis and pleural effusion are clinically detectable whereas small effusions would need x-ray chest and abdominal ultrasound for illustration. Amount of vascular leak evidenced as degree of hemoconcentration is the chief determinant of prognosis.

In case of poor monitoring and inadequate fluid replacement patient may gradually pass into hypovolemia, hypotension and shock. Extended shock proceeds to organ hypoperfusion with consequential organ impairment, metabolic acidosis and disseminated intravascular coagulation (DIC). DIC may provoke severe irrepressible bleeding. A sudden depreciation in otherwise elevated hematocrit during critical phase should alert clinician for occult internal bleeding.

Recovery Phase:

Couple of days later the leakage stops and the plasma which had extravasated during the leaky phase resumes to circulation. Patient starts passing copious
amount of dilute urine, develop bounding pulse, wide pulse pressure and rise in blood pressure clubbed with improved appetite. Hemoconcentration resolves; owing to dilutional effect hematocrit may even fall below normal. Around 9th day of the sickness, platelets start increasing and reaches normal over next couple of days. A complete recovery may demand a few more days as effusions are usually slow to resolve. In maximum cases disease recovers in a time span of two weeks.

**Respiratory distress:**

During the critical phase patients exhibiting profound leak usually need massive resuscitative fluid therapy. On the resolution of vascular leak, the extravasated fluid proceeds to the vascular compartment this might cause congestive heart failure manifesting as tachycardia, tachypnea, muffling of heart sounds and basal rales; problem is particularly amplified with colloid uses. Massive pleural effusion and ascitis (Pic-7 & 8) may further add to respiratory distress. Though short lived this stage demands intense monitoring and apt handling; a bad respiratory distress may set in and the patient may need an oxygen support and decongestive (diuretics) therapy. Liver inflection is frequent with dengue viruses.

“The author here in upholds grave reservations in tagging this stage of illness as recovery phase because in this stage severe dengue patient is hemodynamically unstable and necessitates a regular close clinical observations and intensive therapy; which is against the tenet of recovery. In severe dengue cases recovery would be considered only after uneventful passage of this stage of disease. It should better be named as congestive or **regurgitation phase.”**

**Organopathy:**

**Hepatitis:**

Hepatomegaly and liver impairment in form of elevated transaminases is familiar phenomenon in dengue illnesses. The third day after the infection witnesses a rise in the intensity of these enzymes whereas the pinnacle is reached on the seventh or the eighth day and it dwindles to normal values in approximately three to eight weeks. Contradictory to viral hepatitis the rise in the level of SGOT enzyme is usually greater than the increase in the level of SGPT in dengue patients.

In majority of cases dengue hepatitis is a self limiting disease however frank hepatic failure culminating in to death has been reported. The exceptionally high levels of LDH enzyme is considered an indicator of life threatening hepatitis in a recently concluded study at Surat, in Gujarat. Fortunately, severe hepatitis is uncommon in pediatric age group.

**Neurological complications:**

An array of neurological manifestations have been reported with dengue infections; most outstanding among them are convulsion, unconsciousness, myositis, spasticity and paresis. Current research proposes that dengue especially DEN-2
DEN- 2 and DEN- 3 has strong neurotropism and is capable of causing encephalitis owing to direct viral invasion of the brain.

Cardiac Complications:
Dengue viral infections pose a threat to the human heart as well. A global hypokinesia, low ejection fraction, ECG changes and rhythm disturbances are marked in a few recent studies. Where majority changes are fleeting and reversible yet a persistent cardiomyopathy is reported from Srilanka.

“Majority of severe dengue patients with organ involvement are seen early in the febrile phase and are unrelated to the perfusion status”.

DENGUE CLINICAL MANAGEMENT

An appropriate dengue management is expected to cater to the following principles:
1) Suspicion of disease.
2) Assessments and management of early febrile phase.
3) Identifying patients with warning signs.
4) Recognizing early critical phase and initiating timely fluid therapy and
5) Recognizing and managing severe dengue shock, massive bleeding, and severe organ impairment.

Suspicion of disease:
As most patients’ exhibit undifferentiated febrile illness, clinicians need to keep a high clinical suspicion index. Certain signs like mealy look, bloachable erythematos flush in a febrile patient presenting particularly during rainy season should instantly stir up suspicion for dengue illness. Respiratory viruses predominant during rainy season could also present with similar erythematous flush although a significant catarrh differentiates them from dengue illnesses.

Signs like mealy look, bloachable erythematous flush in a febrile patient presenting particularly during rainy season should instantly stir up suspicion for dengue illness
Assessments and management of febrile phase:

Clinical History:
Assessing hydration status of suspected patients is a must; diarrhoea, vomiting, anorexia and excessive diaphoresis make dengue patients vulnerable for dehydration therefore a urinary voiding history [frequency, amount and colour] assumes significant importance in a dengue patient.

As vascular leak, the major dengue complication occurs during peri defervescence period, noting the date and time of onset of fever is of vital importance.

Frequent assessments for warning signs, dizziness, and altered mental status are essential to recognize complications at an early stage.

Physical examination:
Vascular leak phenomenon is the major complication related to dengue illnesses, Uncorrected it would progressively lead to dehydration, hypovolemia, hypotension and shock.

Identifying the signs of dehydration and hypotension is thus an important objective of clinical examination. Oliguria, giddiness, inability to walk unsupported and narrow pulse pressure are some significant clinical findings of ongoing vascular leak.

Signs of pleural and peritoneal effusion (dull percussion note, abdominal pain & distension) are other important clinical evidences for vascular leakage.

Enlarged and tender liver with or without icterus may be indicative of liver impairment.

Abnormal mentation, impaired consciousness and convulsions may suggest early neurological dysfunction.

Substantial hemorrhages and mucosal bleed will be clinically evident. However, meticulous search is needed to find out petechiae, purpura and ecchymoses. A tourniquet test must always be performed; positive test suggests underlying bleeding tendency and augments probability of dengue diagnosis.

Investigations:
A haematocrit test in the febrile phase forms a baseline value for the patient which proves to be a vital reference for any change during the course of the disease. Therefore patients should have a CBC performed during early febrile phase.
A progressive thrombocytopenia accompanied with rise in haematocrit hints succession to critical phase (DHF) of disease. These parameters reveal a unique time-bound relationship with the disease. Changes appear a little before the defervescence and peak around second or third afebrile day. Degree of rise in hematocrit exhibits a clear correlation with the severity of the disease.

Serology may not become positive during febrile phase but NS-1, a soluble antigen of dengue virus, appears in patient’s blood as early as on the second day of illness and may live on all through the disease period. Verifiable by ELISA, NS-1 carries a high sensitivity and specificity for dengue diagnosis.

Serum transaminases, creatinine, and electrolytes are some vital tests to be performed.

Clinical signs of fluid leakage may not be perceptible in mild cases. A decubitus x-ray chest used to be employed by past clinicians for signifying mild pleural effusion has become redundant as USG has made the things far more convenient. USG can demonstrate the smallest amount of extravasated fluid in any of the serous cavity. Gall bladder oedema is one of the inexplicable but a consistent sonological conclusion in dengue illnesses.

**MANAGEMENT**

**Out patient management:**

Majority of dengue patients could be treated as out-patients, nevertheless close clinical observations during the febrile period and particularly two to three days beyond the defervescence is absolutely essential.

Care takers should be instructed to observe following commands:

Set appropriate goals for child’s fluid intake (100 to 150 ml/kg, BW). Fluids could be ORS, water, milk, buttermilk, fruit juices, etc. Increased fluid consumption has a potential to reduce the number of hospitalizations. Instruct parents to collect child’s urine and compare the output against fluid intake; passing scanty urine with adequate oral fluid intake should alert clinician for vascular leak.

Use only paracetamol for pain and fever; do not use aspirin, ibuprofen, mfenemic acid, nimesulide or other NSAIDS for fever or pain as these drugs interfere with platelet functioning.

**Close clinical observations during the febrile period and particularly two to three days beyond the defervescence is absolutely essential**
nimesulide or other NSAIDS for fever or pain as these drugs interfere with platelet functioning.

Warn parents for warning signs viz scant urine, giddiness, restlessness, anxiety, severe abdominal pain and cold extremities.

Cautiously assess every patient exhibiting warning signs for impending shock e.g. poor volume pulse, imperceptible pulses, narrowing of pulse pressure, and fall in blood pressure. Patient with such symptoms need immediate hospitalization for intensive IV fluid therapy.

In dengue illnesses crucial pathophysiology starts with defervescence; hence any child deteriorating or failing to improve with subsidence of fever should be sensitively assessed for progression to critical phase.

Instruct the care-givers that the patient should be brought to hospital immediately if any of the following occur: no clinical improvement or deterioration around the time of defervescence, severe abdominal pain, persistent vomiting, cold and clammy extremities, lethargy or irritability/restlessness, bleeding (e.g. black stools or coffee-ground vomiting), not passing urine for more than 4–6 hours.

Majority patients without warning signs would tolerate oral fluids; but patients with anorexia, nausea and vomiting may need intravenous fluid therapy. Normal saline or Ringer’s lactate with or without dextrose given at maintenance rate is adequate in most of the cases till tolerance to oral fluids is regained.

Close medical supervision is mandatory for at least three days beyond defervescence.

In patient management:

Any patient exhibiting signs of severe Dengue or warning signs should be hospitalised; although not very common patients with profuse bleeding & with organ impairments need condition specific management and also require hospitalization. In majority of the dengue illnesses intravenous fluid therapy of vascular leak is the most imperative aspect of management. In mild cases (dengue with warning signs, erstwhile DHF Grade 1 & 2), plasma leakage is small and transient, and patients recover spontaneously or shortly after administration of intravenous fluid. In severe cases (Severe dengue, former DHF grades III and IV), there are large plasma losses, hypovolemic shock ensues, and it can swiftly evolve to profound shock. Volume replacement is the foundation for the treatment of this type of severe dengue. The original guidelines for the intravenous (IV) fluid therapy in dengue haemorrhagic fever (DHF) were developed at the Children's Hospital, Bangkok, by Dr Suchitra
In 2009 WHO came out with new set of guidelines with emphasis on resuscitation; accordingly shock is corrected with boluses of (10ml/kg body weight) isotonic fluid while substitution is done by very smaller doses.

Nimannitya. Guidelines were adopted by WHO and proposed as official recommendations in 1975 to 1999. High incessant fluid (7 to 10 ml/kg body weight) substitution was the main theme of these recommendations. Over the last few years it was realized, that many complications and deaths were due to inappropriate fluid replacement leading to fluid overload, and it was felt that dengue vascular leak could be managed with lesser fluid therapy. In 2009 WHO came out with new set of guidelines with emphasis on resuscitation; accordingly shock is corrected with boluses of (10ml/kg body weight) isotonic fluid while substitution is done by very smaller doses.

Choice of fluid:

Two types of intravenous fluids currently used in dengue shock are crystalloids and colloids. Colloid solutions are certainly more advantageous than crystalloid solutions as they provide volume expansion over and above the actual fluid volume infused. The colloid molecules increase plasma oncotic pressure and reverse the net flux of fluid out of the intravascular compartment. Moreover, pathophysiological studies indicate that there is preferential leakage of relatively small plasma proteins (e.g., albumin) as compared with larger molecules (e.g. IgG), which implies that resuscitation with colloid preparations of larger molecular weights may offer therapeutic advantages. Unfortunately, these theoretical advantages have not been substantiated in clinical studies. A recent meta-analysis observed that colloids reduce the hematocrit and pulse rates of children with DSS after the first two hours of fluid resuscitation; but these changes were transient and no relevant advantage was found over crystalloids in reducing the recurrence of shock, the need for rescue colloids, the total amount of fluids, the need for diuretics, and in reducing mortality. General consensus is crystalloids should be used for initial resuscitation while colloid boluses are retained for patients presenting with hypotensive shock, recurrent shock and refractory hypotensive shock.

Management plan:

Dengue with warning signs:

Patients exhibiting warning signs are more likely to pass into critical phase; they need hospitalization for close clinical observations and IV fluid therapy. Platelet count and hematocrit needs to be checked before the fluid therapy. Initial values
serve as an important reference for future changes.

IV fluid therapy should be started with any of the isotonic solutions such as normal saline (0.9%) or Ringer’s lactate. Patients may need 5–7 ml/kg/hour for 1–2 hours for initial hemodynamic stabilization. IV fluid is tapered off to 3–5 ml/kg/hr for 2–4 hours, and then to 2–3 ml/kg/hr or less according to the clinical response. Use just enough intravenous fluid to uphold adequate perfusion. Regular assessment should be done to keep a tab of hemodynamic status (pulse rate, pulse pressure, blood pressure, CR time, urine output) and hematocrit. If the haematocrit remains the same or rises only minimally, continue with the same rate (2–3 ml/kg/hr) for another 2–4 hours.

Destabilization of hemodynamic status associated with increasing haematocrit during critical phase is the indication for stepping up the IV fluid rate. Bolus of to 5–10 ml/kg/hour may be given for 1–2 hours; then modify fluid infusion rates as per the haematocrit.

Over a variable period of few hours to few days (usually 24 to 48 hours) intravenous leak starts decreasing; increasing urine output along with decreasing hematocrit in a stable patient is the excellent indication of ending of critical phase.

Till the risk period is over all the patients should receive regular monitoring for vital signs, peripheral perfusion and detailed fluid balance. The frequency of monitoring depends on the speed of the patient’s recovery, however at least 1-4 hourly watch on vital signs and 4-6 hourly monitoring of urine output is mandatory.

Haematocrit assessments every 6–12 hourly and furthermore before and after every bolus fluid replacement is an essential recommendation from WHO; however it may not always be practicable as facility for micro hematocrit is generally unavailable in field conditions. Regular check on urine output and hemodynamics can avert the need for frequent hematocrit assessment.

**Severe Dengue:**

(Dengue shock and/or fluid accumulation with respiratory distress, severe haemorrhages and severe organ impairment)

Immediate and urgent hospitalization clubbed with emergency treatment is a must for patients with severe dengue. In majority of the cases astute resuscitation is the only intervention needed. Hospital should have intensive care and blood transfusion facilities.

**Dengue shock:**

Intravenous fluid therapy in dengue has experienced a chief conceptual shift over the last few years. Presently fluid therapy is split as fluid resuscitation and fluid replacement. Fluid resuscitation is an approach in which larger volumes of fluids (e.g. 10–20 ml boluses) are dispensed for a limited period of time under close
monitoring. Resuscitation is intended towards improving central and peripheral circulation and end organ perfusion.

Ongoing plasma losses are persistently replaced with intravenous fluid over next 24-48 hours, quantity of this fluid should be just enough to maintain effective circulation and perfusion. In resuscitation and replacement only isotonic fluids must be used; hypotonic fluids have no place in dengue fluid therapy.

Compensated Shock:

(Normal systolic pressure, rising diastolic pressure, narrowing pulse pressure <30, postural hypotension).

Start intravenous fluid resuscitation with isotonic crystalloid solutions at 5–10 ml/kg/hour over one hour (Flow Chart-1). Then reassess the patient’s condition (vital signs, capillary refill time, haematocrit, urine output). The situation will dictate the next step. In case of improvement in the patient’s condition intravenous fluids should be gradually lessened to 5–7 ml/kg/hr for 1–2 hours, then to 3–5 ml/kg/hr for 2–4 hours, and then to 2–3 ml/kg/hr. Patient exhibiting stable haemodynamic status may need only replacement fluid therapy for next 24–48 hours.

In case the vital signs are still unstable even after the first bolus (i.e. shock persists), check the haematocrit. In patients with high or rising haematocrit, replicate a second bolus of crystalloid solution or colloid at 10–20 ml/kg/hr for one hour. Following the second bolus, if there is improvement, reduce the rate to 7–10 ml/kg/hr for 1–2 hours, and then continue declining as above. Patients may need further boluses during next 24-48 hours depending on their progress or regress of the situation.

A falling hematocrit in a hemodynamically unstable patient suggests internal bleeding; a timely blood transfusion is life saving in this type of clinical situation.

Hypotensive shock:

A hypotensive shock demands a more aggressive approach. (Flow Chart-2). An initial resuscitative bolus of 20ml/kg body weight of colloid is pushed over 15 min so as to rescue patient from shock. On improvement a further bolus of IV fluid (crystalloid/colloid) 10ml kg/hr is infused over next one hour. In a hemodynamically stable patient fluid is gradually tapered over following 6-8 hours. Further fluid replacement for subsequent 24-48 hours is undertaken with maintenance doses of isotonic crystalloid infusion.

In a hemodynamically unstable patient (i.e. shock persists) prior to the second bolus review the haematocrit; low haematocrit indicates bleeding and necessitates blood transfusion. In case the initial haematocrit was high compared to the baseline value; a second bolus of colloid solutions at 10–20 ml/kg is pushed over next 30 minutes to one hour. Review the hemodynamics after the second bolus if the condition stabilizes; reduce the rate to 7–10 ml/kg/hr for 1–2 hours, then switch over to crystalloid solution and decrease the rate of infusion as stated above.

Assessment of haematocrit will decide the further management for a patient showing up unstable hemodynamics. Falling hematocrit is a signal for blood
Decompensated shock
Fluid resuscitation with 20 ml/kg/hr isotonic crystalloid or colloid over 15-30 min
Try to obtain a HCT level before fluid resuscitation
FBC, HCT, before and after fluid resuscitation.

IMPROVEMENT

Crystalloid/colloid 10 ml/kg/hr for 1 hour, then continue with
- IV crystalloid 5-7 ml/kg/hr for 1 - 2 hours;
- reduce to 3-5 ml/kg/hr for 2 - 4 hours;
- reduce to 2-3 ml/kg/hr for 2 - 4 hours.
If patient continues to improve fluid can be further reduced.
Monitor HCT 4-hourly or more frequent as indicated
If the patient is not stable, act according to HCT levels:
- If HCT increases, consider bolus fluid administration or increase fluid administration;
- If HCT decreases, consider transfusion with fresh whole blood
Consider to stop iv fluid at 48 hrs of plasma leakage/defervescence

Review 1st HCT

HCT ↑ or High
Administer 2nd bolus of fluid
10-20 ml/kg over 1/2 to 1 hour
Consider significant occult/overt bleed
Initiate transfusion with fresh blood (whole blood/packed cell)

HCT ↓

Improvement

Repeat 2nd HCT

HCT ↑ or High
Administer 3rd bolus fluid (colloid)
10-20 ml/kg over 1 hour

HCT ↓

Repeat 3rd HCT

Yes
Fluid Management in compensated shock

Compensated shock
Systolic pressure maintained but has signs of reduced perfusion
Fluid resuscitation with isotonic crystalloid 5-10 ml/kg/hr over 1 hr
FBC, HCT, before and after fluid resuscitation.

**IMPROVEMENT**

- IV crystalloid 5 - 7 ml/kg/hr for
  1 - 2 hours, then
  - reduce to 3 - 5 ml/kg/hr for 2 - 4 hours
  - reduce to 2 - 3 ml/kg/hr for next 2 - 4 hours.
- If patient continues to improve fluid can be further reduced.
- Monitor HCT 4-6 hourly
- If the patient is not stable, act according to HCT levels:
  - If HCT increases, consider bolus fluid administration or increase fluid administration;
  - If HCT decreases, consider transfusion with fresh whole blood
- Consider to stop iv fluid at 48 hrs of plasma leakage/defervescence

**Check HCT**

- HCT↑ or High
  - Administer 2nd bolus of fluid
    10-20 ml/kg/1 hr
- HCT↓
  - Consider significant occult/overt bleed
  - Initiate transfusion with fresh blood (whole blood/packed cell)

**IMPROVEMENT**

- Administer 3rd bolus fluid (colloid)
  10-20 ml/kg over 1 hour
transfusion while rising hematocrit is a hint for further colloid boluses. Until the patient stabilizes this practice is followed. Improvement in the patient calls for a reduction in the rate to 7-10 ml/kg/hr for 1-2 hours, later change back to crystalloid solution and reduce the rate of infusion progressively over next 6-8 hours to maintenance doses. A need to give multiple fluid boluses may arise during critical phase in a dengue shock patient. Extent and frequency of such boluses again depends on the patient’s hemodynamic response. In case of unresponsive dengue shock patients 5% albumin boluses have found to be an effective treatment.

**MONITORING**

As dengue shock exhibits a highly dynamic clinical course it is vitally important that the patient remains under regular scrutiny. Though frequency of assessment is often dictated by patient’s condition, it should at least be done at an hourly interval till patient is haemodynamically unstable.

Consistent monitoring (no less than 4hourly) is mandatory even in a haemodynamically stable patient till fluid regurgitation is complete and patient is absolutely out of risk. Frequent assessment of vitals, pulse (peripheral pulses), blood pressure, pulse pressure, heart rate, abdominal girth, and urinary output are mandatory.

**Peripheral pulses:**
By and large perceptible peripheral pulse is indicates an adequate perfusion. Imperceptible or feeble peripheral lower limb pulses (posterior tibialis & dorsalis pedis) particularly during replacement fluid therapy are a definite indicator of higher fluid requirement.

**Pulse pressure:**
A slow leak in dengue permits a compensatory mechanisms to operate; prior to the occurrence of overt cardiovascular collapse, the diastolic pressure rises to reach and meet the systolic pressure, and the pulse pressure narrows down. This makes narrowing of the pulse pressure a very significant parameter for defining dengue shock. Sustaining pulse pressure of more than 20mm of Hg is the most important aspect of IV fluid therapy. Narrow pulse pressure less than 20mm of Hg has to be taken as an indication for stepping up IV fluid rate.
Urine output:
Maintaining a fluid input-output chart is of key importance. The urine output gives essential information about end organ perfusion; it should be checked hourly till the patient is out of shock and later on 1 to 2 hourly till the patient is out of risk. A continuous bladder catheter enables correct monitoring of urine output. An appropriate urine output would be more than 0.5 ml/kg/hour.

Haematocrit:
Haematocrit assessment (before and after fluid boluses until stable, then 4–6 hourly) is the central theme in dengue shock management. Variations in hematocrit are important therapeutic guides. These changes should always be interpreted along with the haemodynamic status. Few examples of precise hematocrit interpretation would be as follows: (1) a high haematocrit together with stable haemodynamic status and adequate urine output does not call for further intravenous fluid. In such situation, it is probable that the haematocrit will start declining within the next 24 hours as the plasma leakage stops. (2) A rising or persistently high haematocrit together with unstable vital signs (particularly narrowing of the pulse pressure) highlights active plasma leakage and the requirement for a further bolus of fluid replacement. (3) A declining haematocrit clubbed with unstable vital signs (particularly narrowing of the pulse pressure, tachycardia, metabolic acidosis, poor urine output) points to a major haemorrhage and the need for urgent blood transfusion and (4) Reduction in haematocrit together with stable haemodynamic status and adequate urine output shows hemodilution and/or intravasation of fluids suggestive of discontinuing of further intravenous fluids.

Supervising arterial or venous blood gases and other organ functions such as: renal profile, liver profile, coagulation profile, should be performed as per individual case indications and demand.

Severity markers:
Noteworthy thrombocytopenia, clinical signs of vascular leak, and narrowed pulse pressure materializing early during febrile phase of sickness are indicators of serious course of disease.

---

**COMPLICATIONS**

Haemorrhagic complications:
Minor Bleed:
In Dengue infected patients a little mucosal bleeding in the form of epistaxis, gum bleed, conjunctival haemorrhages might occur. Such patients typically remain stable
and require only fluid resuscitation/replacement; such bleeds rapidly improve during the recovery phase.

Major Bleed:

Reports of unusual bleeding symptoms with some of the dengue outbreaks are seen but normally major bleeding in pediatric age group is uncommon in dengue. Major bleeding in the form of Gastrointestinal and vaginal hemorrhages may occur in adult patients. Bleeding complications can take place in patients who have pre-existing acid peptic disease, are on anticoagulant therapy and/or are treated with non-steroidal anti-inflammatory agents. In pediatric patients major bleeding is almost always subordinate to poorly managed shock culminating into multi organ dysfunction and consequential DIVC.

Recognizing major bleed:

Gastrointestinal tract is the site where major internal bleeding takes place. It may destabilize hemodynamics in a critically placed dengue shock patient nonetheless many hours might elapse before it would manifest as ‘malena’. Falling haematocrit associated with unstable haemodynamic status is the early indicator of internal bleeding and has to be taken as an alarming signal for blood transfusion irrespective of the then absolute hematocrit level.

Plan for treatment of major Bleed:

10 ml/kg of fresh-packed red cells or 20 ml/kg of fresh whole blood should be transfused at an apt rate. Improvement in hematocrit, haemodynamic status and acid-base balance are indicators of successful therapy. In case of inappropriate rise in haematocrit and inadequate clinical response, a repeat transfusion turns out to be necessary. Stored blood loses 2, 3 DPG, low levels of which hinder the oxygen-releasing capacity of haemoglobin; resulting in functional tissue hypoxia therefore it is important that only fresh whole blood or fresh red cells are given.

Platelet transfusion:

Unless substantial bleeding platelets are not indicated even with a count as low as 10,000 per cu mm. Platelets transfusion is required only in case of significant bleeding. Prophylactic transfusion with platelets has

In pediatric patients, major bleeding is almost always subordinate to poorly managed shock culminating into multi organ dysfunction and consequential DIVC

Falling haematocrit associated with unstable haemodynamic status is the early indicator of internal bleeding and has to be taken as an alarming signal for blood transfusion irrespective of the then absolute hematocrit level

Plan for treatment of major Bleed:

10 ml/kg of fresh-packed red cells or 20 ml/kg of fresh whole blood should be transfused at an apt rate. Improvement in hematocrit, haemodynamic status and acid-base balance are indicators of successful therapy. In case of inappropriate rise in haematocrit and inadequate clinical response, a repeat transfusion turns out to be necessary. Stored blood loses 2, 3 DPG, low levels of which hinder the oxygen-releasing capacity of haemoglobin; resulting in functional tissue hypoxia therefore it is important that only fresh whole blood or fresh red cells are given.

Platelet transfusion:

Unless substantial bleeding platelets are not indicated even with a count as low as 10,000 per cu mm. Platelets transfusion is required only in case of significant bleeding. Prophylactic transfusion with platelets has

Prophylactic transfusion with platelets has no therapeutic status irrespective of any platelet count
no therapeutic status irrespective of any platelet count. On the contrary incongruous transfusion of blood components increases the risk of pulmonary oedema and respiratory distress.

**Respiratory distress:**

**Causes:**

Acute pulmonary oedema, severe metabolic acidosis from severe shock and ARDS all contribute to respiratory distress yet polyserositis (severe ascitis, & pleural effusions) due to fluid over dose is the commonest cause for this complication.

**Fluid overload:**

Fluid over dose can be an outcome of the following: (1) Unwarranted and/or too rapid intravenous fluids. (2) Erroneous use of hypotonic instead of isotonic crystalloid solutions. (3) Inadvertent continuation of intravenous fluids even after leakage has stopped. (4) Over use of colloids. (5) Inappropriate transfusion of blood products: fresh-frozen plasma, platelet concentrates, and cryoprecipitates and (6) Co-morbid conditions such as congenital heart disease, chronic lung and renal diseases.

Polyserositis in severe dengue may not always indicate fluid overload; in severe dengue vascular leak invariably is massive; infused fluid, however appropriate it may be, is bound to leak into serous cavities causing polyserositis.

**Clinical features:**

Tachypnoea, dyspnoea, wheezing, chest wall in-drawing are some of the initial signals of fluid overload. Tense ascitis and pleural effusions may cause severe respiratory distress. Cough with frothy pink sputum herald the inception of pulmonary oedema and congestive heart failure.

**Management plan:**

As soon as the vascular leak is over intravasation of fluid starts. This is indicated by the widening of pulse pressure, stable blood pressure, bounding peripheral pulses and rise in urinary output. Speedy gush of intravasating fluid would cause fluid overload and vascular congestion particularly if patient keeps receiving intravenous fluids.

Oxygen supplementation is a must for patients with respiratory distress, the management of fluid overload is dictated by hemodynamics, hematocrit and phase of the disease.

---

A wide pulse pressure and increased urinary output clubbed with falling hematocrit are indications to stop further intravenous fluid. Furosemide 0.1–0.5 mg/kg/dose intravenously once or twice daily serves to decline respiratory distress in a fluid overloaded patient. Monitoring of serum potassium and correcting the ensuing hypokalaemia is important for patients treated with Furosemide. If
there is any doubt that critical phase [vascular leak] is still on then better avoid diuretic therapy.

Any patient still suffering from shock having low haematocrit levels and exhibits signs of fluid overload might be suffering from occult haemorrhage. Fresh blood transfusion given to such a patient can prove to be immensely advantageous.

If the patient remains in shock and has an elevated haematocrit repeated small boluses of a colloidal solution will prove to be profitable.

**Dyselectrolytemia, Blood glucose disturbances:**

Prospects of electrolyte disturbances like hyponatraemia, hypokalaemia, hyperkalaemia, serum calcium imbalances and metabolic acidosis need to be retained in mind while treating dengue shock. Although dyselectrolytemia is uncommon it may occur either due to inappropriate use of hypotonic solutions for resuscitation and replacement or diarrhoea vomiting consequential in to gastrointestinal electrolyte losses.

Blood sugar needs to be under close monitoring as both hypoglycaemia and hyperglycaemia could transpire and destabilize a precariously positioned hemodynamics.

**Adjuvant therapy: Vasopressors and inotrops:**

During a severe fluid unresponsive hypotensive dengue shock Vasopressors and inotrops can be utilized as temporary measures, however Vasopressors and inotrops should always and just be used as supportive measure and never ever as a substitute to fluid therapy in a severe fluid unresponsive hypotensive dengue shock.

**Avoidable ancillary treatment:**

In some of the dengue studies Steroids, intravenous immunoglobulins, and of recombinant Activated Factor VII has been tried but none of them were found to be fruitful in dengue management.

**Reasons for mortality in Dengue Shock:**

Failing to appreciate that patient is passing in critical phase of disease:

When temperature subsides in a febrile illness parents and treating physician tend to feel relaxed and reassured considering it a sign of clinical recovery. It is unfortunate enough that a dengue patient develops pathognomonic vascular leak with defervescence and worsens during this period; failure to grasp this is the commonest cause of death in dengue shock. It is imperative on the treating clinician’s part to regularly evaluate every patient for warning signs at this stage of disease. Warning signs like anxiety, apprehension and giddiness at

| Reasons for mortality in Dengue Shock: |
| 1) Failing to appreciate that patient is passing in critical phase of disease |
| 2) Failure to appreciate internal Bleeding |
| 3) Failure to appreciate vascular congestion |
| 4) Organ Impairments |
defervesence should siren a physician for a possible development of shock and an impending death could be evaded by hospitalising the patient for IV fluid therapy in the nick of time.

**Failure to appreciate internal bleeding:**

Major clinical hemorrhages are never common place in pediatric dengue though rarely enough an occult massive bleed may ascertain to be life threatening. Declining hematocrit and a destabilized hemodynamics should signal the clinician for such an eventuality; a timely blood transfusion would save a life.

**Failure to appreciate vascular congestion:**

Unintentional continuation of IV fluid in the wake of intravasation of leaked out fluid would cause cardiac overload and consequential CHF and death. Receding hematocrit with raised urinary output is an indicator to intravasation of leaked out fluid and should be treated as a pointer to terminate IV fluid therapy.

Dengue hemorrhagic fever exhibits a set clinical pattern and observes a fixed time bound course of events despite being a complex disease but cognizance and acquaintance with its course immensely facilitates in diagnosis-making and offering proper therapy. Alongside appropriate IV fluid management and recurrent monitoring, mortality in dengue shock could be significantly minimized.

**Organ Impairments:**

In clinical situation of hepatitis, encephalopathy, encephalitis, and cardiac abnormalities organ specific standard management requires to be carried out.

**Dengue anti viral drugs:**

Clinical studies in recent times have noted that the viral load is pretty higher in blood of the patients who develop severe dengue (DHF, DSS) compared to patients experiencing the milder dengue fever (DF). From this observation it can be deduced that any drug which could lower the viral load can prove to be effective in curbing the disease progression and would bring the improvement in morbidity. Exploration for molecules which could interfere with viral replication is on. Numerous potential viral targets have been found out; presently the most advanced targets are the NS3/NS2B protease and NS5 RNA-dependent RNA polymerase.

**Dengue vaccine:**

An intensified research is on to come up with a dengue vaccine. The prevalent challenge is to find out a tetravalent vaccine which can induce long lasting protective immunity against all four viruses. Dengue vaccines under development are of four types: live attenuated viruses, chimeric live attenuated viruses, inactivated or sub-unit vaccines, and nucleic acid-based vaccines. A DEN-DEN chimera is a dengue vaccine which is in advanced preclinical development stage. The tetravalent vaccine produced by combining the four chimeric dengue viruses is protective when administered to mice. Monkey challenge experiments have been conducted and
provisions for clinical trials are proceeding.
Despite the arduous challenges posed by multiplicity of viral serotypes useful strides have been made in the fields of dengue antivirals as well in dengue vaccine.

Bibliography:

18. Sumarmo H. Wulur E. Jahja, Gubler DJ. et al. Clinical observations on virologically confirmed fatal
701 (1983).
20. Nimmannitya S. clinical spectrum and management of dengue haemorrhagic fever. Southeast
21. Kalayanarooj S, Chansiriwongs V, Nimmannitya S. Dengue Patients at the Children’s Hospital,
22. Kalayanarooj S, 0. Clinical presentations of dengue hemorrhagic fever in infants compared to
23. Kliks SC, Nimmanitya S, Nisalak A, Burke DS. Evidence that maternal dengue antibodies are
important in the development of dengue haemorrhagic fever in infants. Am J trop med hyg 1988;
38:411–19.
24. Capeding RZ , Brion JD , Caponpon MM , Gibbons RV et al. The Incidence, Characteristics, and
25. Kapse AS. A study of an epidemic of dengue at surat; Clinico-investigative analysis. In
environment & health in developing country1998; 339-50.
involvement in dengue hemorrhagic fever with classic dengue fever. SOUTHEAST ASIAN J
TROP MED PUBLIC HEALTH. 2000: Vol 31 No. 2; 259-263.
proceedings of the international conference on dengue/dengue hemorrhagic fever; Kuala
29. Wills BA, Nguyen MD, Loan HT, et al. Comparison of Three Fluid Solutions for Resuscitation in
Syndrome: A Randomized Double-Blind Comparison of 4 Intravenous Fluid Regimens in the
31. Sharon LR, Michelle DV, Marissa MA. The Use of Colloids and Crystalloids in Pediatric Dengue
Shock Syndrome: a Systematic Review and Meta-analysis. BMC Infectious Diseases 2011,
11:52.
Dear Doctor,
Come monsoon and with it comes a horde of infectious diseases. One such disease which is being encountered quite often these days during rains is Dengue illness. This issue on Dengue illness has been authored by Dr. Ashok Kapse. Dr. Kapse is a practicing Pediatrician at Surat in Gujarat. He has been associated with CDC, Colorado (USA) for his research on Dengue illness. He has been invited to Malaysia and Thailand to deliver talks on Dengue vaccine. He has also been invited to talk at the World Congress of Pediatrics to be held at China in December this year. In a very simple and lucid manner, Dr. Kapse has reviewed various aspects of Dengue illness, with special emphasis on fine points that would be of help to a practicing clinician in the diagnosis and management of Dengue illness. We are sure you would enjoy and gain tremendously from this review.

This booklet is presented to you by Raptakos, Brett & Co. Ltd.
We would very much like to have your valuable suggestions and comments to make our future issues more meaningful to you.
We will appreciate if you could spend a few minutes to fill in your comments and mail the same to us. You can also view the QMR on our website: www.raptakos.com and e-mail your feedback to following e-mail id: medical1 @raptakos.com

Thanking you,
Medical Director

---

**Feedback form: July - Sept. 2013 (Dengue illness)**

1. Your comments on this issue of Q.M.R.

   

2. Please suggest medical topics for our QMR which could be printed in future.

   

3. Any other suggestions / comments:

   

4. Name : Dr. ___________________________ M □ F □

   Clinical Address : __________________________

   City : _____________ State : _______________ Pin □□□□□□□□

   Tel.: ___________________ E-mail : ________________

   Qualifications :

---

Please mail this form to: Medical Director, RAPTAKOS, BRETT & CO. LTD.
21 A, Mittal Tower, 210, Nariman Point, Mumbai 400 021. India