Dengue viral infection: An overview of current scenario
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Dengue viral infection: An overview of current scenario

Introduction

Over the last two decades Dengue has emerged as the major vector-borne viral infection worldwide. It is transmitted by the female *Aedes* mosquito to human beings. The dengue virus (DENV) belongs to the Flavivirus family and has four serotypes (DENV1-4), which are clinically indistinguishable. Latest estimates suggest 390 million infections of dengue occur each year, of which 100 million result in symptomatic disease. Infection with DENV results in varying degrees of pathological conditions, ranging from mild asymptomatic dengue fever (DF) to severe dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) which may turn fatal. (Murphy and Whitehead 2011)

Dengue may manifest as a spectrum of clinical syndromes i.e., from dengue fever to severe dengue. The World Health Organization (WHO) Dengue guidelines have identified a number of warning signs to aid in identifying the severity of disease in endemic areas. It is important to be vigilant as the prediction of which patients will progress to severe disease remains challenging. (Yacoub, Mongkolsumapaya et al. 2016)

In severe form of dengue there is increased capillary permeability causing plasma leakage, which results into intravascular volume depletion. If this condition is left untreated can lead to shock and prove fatal. The mechanisms for progression to severe disease is not clearly understood. As there is an association of severe dengue and secondary infection with a different serotype, an immune response could be responsible for the pathogenesis. (Halstead 1988, Mongkolsumapaya, Dejnirattisai et al. 2003). This review will emphasis on current developments in understanding of causes of the dengue pandemic, viral structure and epitope binding, clinical presentation and potential risk factors, pathogenesis, diagnosis, therapeutic options, strategies for disease control and future directions.

**Epidemiology - Disease burden**

Presently around 125 countries are endemic for dengue transmission and are occupied by 50% of the world’s population. (Gubler 2011) Worldwide around 50–200 million dengue infection, 500,000 episodes of severe dengue, and 20,000 dengue-related deaths are reported per year. (Murray, Quam et al. 2013) For individual residing in endemic area there is 40% risk of contracting dengue and out of these, only 0.5% has risk of developing a serious form of the disease. (Ho, Wang et al. 2013)

In India there are cyclic epidemics of dengue over the years. Dengue infection is one of the leading causes of hospitalization and death among children in the country. Concurrent infection in some patients with multiple serotypes of dengue resulted from co-circulation of several serotypes of the virus in India. Overall, India alone possess 34% (about 33 million infections) of the total global threat of dengue leading to hyper-endemicity, prevailing mostly in urban areas. During period 2006 to 2012, an annual average of 20474 dengue cases and 132 deaths by Dengue were reported in India. More than 138 dead due to dengue infection during the first 10 months of 2013, with more than 55,000 cases recorded across the country. The worst affected areas in India in 2015 were Delhi, Punjab, Haryana, Gujrat, Karnataka and Kerala with a range of about 4000–15,000 cases and 9–60 deaths. However, the wide spread problem of under reporting of dengue cases from India has come into focus very recently and the real burden of dengue...
in the country is heavily ignored. (Das, Sarfraz et al. 2017)

Overall, the factors for the global spread of dengue infection include vector and host factors. *Aedes* mosquito vector has adapted itself in urban areas in many parts of the world through dissemination on cargo ships, globalization, and increase in breeding sites through rapid and often poorly planned urbanization of cities. (Kraemer, Sinka et al. 2015) Because of changes in climatic conditions, travel, socioeconomic status, trade, and viral characteristics the incidence and prevalence of dengue infection are expected to rise in future. (Messina, Brady et al. 2014) These factors in addition to ineffective vector control programs and lack of antiviral therapy or vaccines has led to recognize dengue as a public health threat for two-thirds of the world’s population.

**Dengue Viral structure**

The dengue virus is a single-stranded, positive-sense enveloped RNA virus, 50 nm in diameter. It consists of an outer protein shell (E and M), a lipid bilayer, and a less characterized nucleocapsid core (C and RNA genome). Additionally it has seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5).

Dengue virus presents different surface structures during its maturation and infection. These conformational changes are attributed to the inherent flexibility of the envelope protein. E protein is made up of three domains, namely, EDI, EDII, and EDIII, and transitions between its oligomeric states are supported by the hinge motion that occurs between EDI-EDII and EDI-EDIII. The immature virus particle has a spiky appearance with 60 trimeric surface spikes each consisting of three prM-E heterodimers. When mature virus infects a new cell through receptor-mediated endocytosis, the E protein molecules shift to a trimeric conformation in the acidic compartment of an endosome, protrude from the virus surface causing membrane fusion, and facilitate viral RNA release into the cytoplasm. (Khetarpal and Khanna 2016)

The E protein consist of three domains (DI-III), is required for receptor binding and cell fusion and entry. (Kuhn, Zhang et al. 2002) It is the primary target for neutralizing antibodies.

Recent significant development is the discovery of a new class of antibodies directed at a novel epitope: the E dimer epitope (EDE). This is capable of potently neutralizing all four dengue serotypes. (Dejnirattisai, Wongwiwat et al. 2015)

NS1 is a 50 kDa glycoprotein produced by dengue-infected cells. It can be found in the infected patient’s serum from early stage to several days after defervescence. NS1 may have a role in the pathogenesis of severe disease, as higher levels have been detected in dengue shock patients. (Libraty, Young et al. 2002) Antibodies against NS1 may be a potential therapeutic target, and modified NS1 may provide an alternative vaccine strategy. (Wan, Lu et al. 2014)

**Primary and Secondary Dengue Infection**

The first time infection in an individual with any of the four dengue virus serotypes is known as primary dengue infection.

When a mosquito bites a dengue infected person it ingests blood with dengue virus. It takes about 8-10 days for dengue virus to incubate. Dengue infected mosquito bites another person and that person
gets dengue within 4-13 days (Figure 4).

Dengue viruses invade cells by binding to specific receptors on the cell surface. The cells absorb the clinging viruses by receptor mediated endocytosis. The acidic pH of the cell causes transformation of envelope proteins allowing virus to switch form. The viral membrane is able to fuse with endosomal membrane releasing RNA and the cell is taken over for viral replication.

After the incubation period, the illness begins abruptly and, in patients with moderate to severe disease, is followed by three phases —febrile, critical and recovery (Figure 5).

Generally primary infection may be symptomatic or asymptomatic. After the onset infection high titers of immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies appear within 3–5 and 6–10 days, respectively. The presence of IgM is transient, disappearing in 2-3 months after the onset of illness, whereas Ig G persists for life. (Guzman, Hermida et al. 2010) Hereafter, primary infection with a particular serotype offers life-long immunity against that serotype, however no continued cross-protective immunity is offered against the remaining serotypes.

When an individual is reinfected with a previously not encountered DENV serotype, it is called as secondary infection. It generally presents as classical DF and 2-3% of secondary infection cases develop into DHF, which may progress to DSS and prove fatal. Secondary infection with a different serotype, the presence of low amounts of heterotypic antibodies (which form complexes with DENVs) promotes the access of the virus to monocytes, via Fc receptors, leading to an increase in viral load and severity of the disease. This phenomenon is known as antibody-dependent enhancement (ADE) which is caused by cross-reactive antibodies elicited against the fusion loop and prM. These are found to be weakly neutralizing leading to enhancement of infection at low concentrations. (Dejnirattisai, Jumnainsong et al 2010, de Alwis, Beltramello et al, 2011) Even though ADE is responsible for disease severity, not all the severe cases are associated with secondary infection nor do all the cases of secondary infection progress to DHF/DSS. (Murphy and Whitehead 2011) Along with the humoral immunity, cross-reactive memory T cells may also participate in either providing protective immunity or causing immunopathology. (Wan, Lin et al. 2013)

Infection with dengue virus may present as dengue fever and progress to DHF or DSS.

**Dengue Fever**

DF is a self-limiting fever, generally lasting for 5 - 7 days. The clinical presentation of DF may differ in different age groups. The infants and young children may present febrile sickness and maculopapular rash, while the older children and adults may present with mild febrile syndrome or severe disease with high fever (usually biphasic), severe headache, retro orbital pain, myalgia, arthralgia, nausea,
vomiting, and petechiae. Leukopenia and thrombocytopenia are generally observed in all ages. In few cases, DF may be associated bleeding from gums, nose, and gastrointestinal tract, haematuria, and menorrhagia. (Khetarpal and Khanna 2016)

Dengue Hemorrhagic fever (DHF)

DHF is associated with symptoms of DF accompanied by thrombocytopenia, hemorrhagic manifestations, and plasma leakage. Generally a positive tourniquet test may be indicative of DHF, although not conclusive due to its low sensitivity/specificity. The severity of disease is determined by amount of plasma leakage. DHF is divided into four grades (I to IV) based on disease severity and clinical manifestations. Frequently patients are manifested with fine petechiae scattered on the extremities, axillae, face, and soft palate, especially observed during febrile period. The critical phase is generally experienced towards the terminal stage of febrile illness, associated with rapid decrease in temperature and usually accompanied by circulatory disturbances including plasma leakage, hem concentration, and thrombocytopenia.

In a study evaluating clinical profile of pediatric patients, it was found that the most common complications were liver dysfunction, acute respiratory distress syndrome, encephalopathy, pleural effusion, ascites, myocarditis, myositis, acute kidney injury, and disseminated intravascular coagulopathy. Platelet count did not always correlate well with the severity of bleeding. There were six deaths (2.3%) and out of them four presented with impaired consciousness (66.6%). The common causes for poor outcome were multiorgan failure, encephalopathy, and fluid refractory shock. (Pothapregada, Kamalakannan et al. 2016)

Dengue Shock Syndrome (DSS)

Dengue shock syndrome (DSS) is a form of hypovolaemic shock and results from continued vascular permeability and plasma leakage. This usually takes place around defervescence, i.e. on days 4–5 of illness (range of days 3−8), and is often preceded by warning signs. From this point onwards, patients who do not receive prompt intravenous fluid therapy progress rapidly to a state of shock.

Dengue shock presents as a physiologic continuum, progressing from asymptomatic capillary

<table>
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<td>Febrile phase</td>
<td>Dehydration: high fever may cause neurological disturbances and febrile seizures in young children</td>
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<tr>
<td>Critical phase</td>
<td>Shock from plasma leakage: severe haemorrhage; organ impairment</td>
</tr>
<tr>
<td>Recovery phase</td>
<td>Hypervolaemia (only if intravenous fluid therapy has been excessive and/or has extended into this period) and acute pulmonary oedema</td>
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Table 1. Medical complications seen in the febrile, critical and recovery phases of dengue
leakage to compensated shock to hypotensive shock and ultimately to cardiac shock. Tachycardia (without fever during defervescence), is an early cardiac response to hypovolaemia. It is important to note that some patients, particularly adolescents and adults do not develop tachycardia even when in shock.

During the initial stage of shock, the compensatory mechanism that maintains a normal systolic BP produces tachycardia, quiet tachypnoea (tachypnoea without increased effort), and peripheral vasoconstriction with reduced skin perfusion (manifested as cold extremities and delayed capillary refill time of > 2 seconds and weak volume peripheral pulses). As peripheral vascular resistance increases, the diastolic pressure rises towards the systolic pressure and the pulse pressure (the difference between the systolic and diastolic pressures) narrows. The patient is considered to have compensated shock if the systolic pressure is maintained at the normal or slightly above normal range but the pulse pressure is ≤ 20 mmHg in children (e.g. 100/85 mmHg) or if they have signs of poor capillary perfusion (cold extremities, delayed capillary refill, or tachycardia). In adults, a pulse pressure of ≤ 20 mmHg may indicate more severe shock. Compensated metabolic acidosis is observed when the pH is normal with low carbon dioxide tension and a low bicarbonate level.

The patient may recover rapidly with volume replacement therapy if initiated within 12–24 h of going into shock or it may prove to be fatal. (Khetarpal and Khanna 2016)

In a study evaluating the clinical profile of pediatric patients, it was found that the most common complications were liver dysfunction, acute respiratory distress syndrome, encephalopathy, pleural effusion, ascites, myocarditis, myositis, acute kidney injury, and disseminated intravascular coagulopathy. Platelet count did not always correlate well with the severity of bleeding. There were six deaths (2.3%) and out of them four presented with impaired consciousness (66.6%). The common causes for poor outcome were multiorgan failure, encephalopathy, and fluid refractory shock. (Pothapregada, Kamalakannan et al. 2016)

Severe disease risk factors and prediction

In a small proportion of patients, severe manifestations of dengue develop relatively late in the course of the illness, usually day 4–6, at the time of fever clearance. The most common severe manifestation is vascular leakage, which can lead to hemodynamic compromise, shock, and death. In addition, bleeding from mucosal surfaces and organ impairment in the form of hepatitis, myocarditis, and encephalitis can occur. The criteria for severe dengue are as follows:

• Severe plasma leakage leading to
• Shock and/or
• Fluid accumulation with respiratory distress
• Severe bleeding
• Severe organ involvement
• Liver: alanine transaminase or aspartate aminotransferase ≥ 1000
• Central nervous system: impaired consciousness
• Heart and other organs

This 48-hour period around defervescence has been classed as the “critical phase” and is the time when patients require closer monitoring. The WHO updated their classification and guidelines in 2009 to
incorporate a set of warning signs to identify higher risk patients. The criteria for dengue warning signs, taken from the 2009 WHO classification are as follows:

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy/restlessness
- Liver enlargement >2 cm
- Laboratory increase in hematocrit concurrent with rapid decrease in platelet count

Several studies have identified certain risk factors that can affect disease severity in dengue which include both host and viral factors. Viral factors include both the infecting serotype and the genotype of the virus. Certain genotypes within each serotype are more virulent than the others which could be linked to outbreaks of severe disease. Higher viral loads have been associated with disease severity in both primary and secondary dengue and with different serotypes. (Libraty, Endy et al. 2002)

The host factors include immune status, age of the host, with children more likely to experience plasma leakage and shock, and adults more likely to develop organ impairment and significant bleeding. (Trung, Thao le et al. 2012) The immune status is one of the most critical factors in determining disease outcome. Elderly patients and those with co-morbidities, including diabetes and hypertension, have also been found to be at an increased risk of severe dengue, possibly due to pre-existing endothelial dysfunction in this group. (Pang, Salim et al. 2012) In a study it was found that hepatitis and thrombocytopenia were present in over 80% of all patients, but severe hepatitis was seen in 11.4% and severe thrombocytopenia in 9.3%. (Krishnamoorthy, Bhatt et al. 2017) Female sex and children under 5 years of age are at risk of poor outcomes. (Anders, Nguyet et al. 2011) Genetic predisposition is also likely to play a role in determining the severity of disease.

### Pathogenesis of severe disease

Although there have been several recent advances in understanding dengue’s pathogenesis; the exact mechanisms remain unclear. Occurrence of severe dengue in secondary infections may be explained by ADE. Heterotypic non-neutralizing antibodies from a prior dengue infection promote viral binding to Fc receptors of monocytes and macrophages, resulting in higher viral loads and more marker inflammatory response. (Guzman, Alvarez et al. 2013)

Additionally, cross-reactive memory T cells may play an important role in triggering the inflammatory cascade. On the other hand HLA-linked protective role of CD8+ cells with a robust multifunctional response being associated with less severe disease. (Weiskopf, Angelo et al. 2013) T cell response is most marked to NS3 protein, with high cytokine and low CD107a (a marker of cell degranulation) predominating. (Duangchinda, Dejnirattisai et al. 2010) The resulting cytokine release, particularly tumor necrosis factor alpha and other vasoactive mediators, may then play a role in the increase in capillary permeability seen in severe dengue. (Butthep, Chunhakan et al. 2012, Sierra, Perez et al. 2012)

NS1 may be involved in pathogenesis of vascular leak as evidenced by its high levels in patients’ plasma, from early in the disease and for up to 2 weeks later. (Duyen, Ngoc et al. 2011) Similar to the viral load, NS1 antigenemia appears to correlate with disease severity. (Libraty, Young et al. 2002) NS1, along with the viral E protein binds to heparan sulfate, one of the major glycosaminoglycans (GAGs) in the glyocalyx of the endothelial cell layer. The glyocalyx consists of a negatively charged network of glycoproteins, proteoglycans, and GAGs that covers the luminal surface of the microvascular endothelium. It provides size and charge selectivity to the capillary wall permeability, as well as acting as a transducer of sheer stress. The adherence of NS1 and of the DENV E protein to the glyocalyx, and the resulting damage, could alter the permeability properties of the microvascular layer, which
may contribute to the characteristic vascular leak that is associated with severe dengue. (Avirutnan, Punyadee et al. 2006, Avirutnan, Zhang et al. 2007)

NS1 and anti-NS1 antibodies are also involved in the pathogenesis of thrombocytopenia and coagulopathy that is characteristic in dengue. NS1 can also activate complement, which may contribute to the vascular leak through the generation of anaphylatoxins and the terminal complement complex SC5b-9. (Avirutnan, Punyadee et al. 2006) In severe dengue cases high plasma levels of NS1 and SC5b-9 correlated with disease severity. They were also found along with the anaphylatoxin C5a in the pleural fluid of dengue shock patients. NS1 can alter endothelial monolayer integrity through the activation of Toll-like receptor 4 on peripheral blood mononuclear cells which is involved in alteration of endothelial permeability. Anti-NS1 antibodies are involved in complement-mediated cytolysis and endothelial cell damage. (Lin, Lei et al. 2003)

**Diagnosis**

Given that dengue virus infection elicits such a broad range of clinical symptoms, early and accurate laboratory diagnosis is essential for appropriate patient management. Virus detection and serological conversion have been the main targets of diagnostic assessment, however cross-reactivity of antibody responses among the flaviviruses has been a confounding issue in providing a differential diagnosis. Furthermore, there is no single, definitive diagnostic biomarker that is present across the entire period of patient presentation, particularly in those experiencing a secondary dengue infection. Nevertheless, the development and commercialization of point-of-care combination tests capable of detecting markers of infection present during different stages of infection (viral nonstructural protein 1 and immunoglobulin M) has greatly simplified laboratory-based dengue diagnosis. (Müller, Depelsenaire et al. 2017)

The diagnosis of Dengue infection is generally made by identification of viral genomic RNA, antigens, or the antibodies it elicits. Antigen detection tests based on NS1 detection have been designed to detect the dengue viral NS1 protein which gets released from the dengue infected cells and appears early in the bloodstream. A three in one test for simultaneous detection of NS1, IgM, and IgG is also available. ELISA-based serological tests are easy to conduct and are cheaper. (Khetarpal and Khanna 2016)

The dengue virus NS1 rapid diagnostic test (RDT) is used for preliminary diagnosis during outbreaks in difficult to reach rural and tribal areas. The diagnosis is confirmed by dengue virus NS1 ELISA in the laboratory. The dengue virus NS1 RDT showed 99.2% sensitivity and 96.0% specificity when analyzed using dengue virus NS1 ELISA as standard. The specificity and sensitivity of the RDT when compared with real time reverse transcriptase polymerase chain reaction (qRT-PCR) was 93.6% and 91.1%, respectively. The serotype specific evaluation showed more than 90% sensitivity and specificity for DENV-1, 2, and 3. The RDT is a good diagnostic tool in difficult to reach rural and tribal areas. (Shukla, Singh et al. 2017)

The NS1/IgM RDT (dengue day 1) showed high sensitivity throughout the acute phase of illness, in primary and secondary infections, in different severity groups, and detected all 4 dengue serotypes, including coinfections. This NS1/IgM RDT is a useful point-of-care assay for rapid and reliable diagnosis of acute dengue and an excellent surveillance tool in our battle against dengue. (Vivek, Ahamed et al. 2017)

Diagnosis of dengue based on clinical features alone is difficult. Rapid diagnostic tests for dengue may need to be routinely used in adult patients presenting with sepsis and septic shock in tropical countries. This approach could improve diagnosis and management of those patients. (Teparrukkul, Hantrakun et al. 2017)

In 1997, the World Health Organization (WHO) listed the tourniquet test (TT) as a criterion for dengue hemorrhagic fever, and that the positive test reflects both capillary fragility and thrombocytopenia. Studies suggested that the test has a greater positivity rate in individuals with more severe forms of the disease but cannot exclude dengue infection. Tourniquet test was more effective in detecting cases that were truly negative than positive and should not be used as diagnosis of dengue. (Furlan, Tukasan et al. 2016)
Current Clinical Management and Treatment

The current management of dengue consists of supportive medical treatment. Continuous monitoring of patient's condition for any of the "warning signs" and careful fluid balance for those with capillary leak are the cornerstones of successful treatment.

As of now, there is no antiviral drug available for dengue. Treatment is usually symptomatic. In case of uncomplicated DF, the treatment consists of bed rest, oral rehydration, and paracetamol as an antipyretic and analgesic. (Dejnirattisai, Jumnainsong et al. 2010)

Adequate oral fluid intake may reduce the number of hospitalizations. Encourage oral intake to replace fluid loss from fever and vomiting. Small amounts of oral fluids should be given frequently for those with nausea and anorexia. The choice of fluids should be based on the local culture: coconut water in some countries, in others rice water or barley water. Oral rehydration solution or soup and fruit juices may be given to prevent electrolyte imbalance. Commercial carbonated drinks that exceed the isotonic level (5% sugar) should be avoided. They may exacerbate hyperglycaemia related to physiological stress from dengue and diabetes mellitus. Sufficient oral fluid intake should result in a urinary frequency of at least 4 to 6 times per day. A record of oral fluid and urine output could be maintained and reviewed daily in the ambulatory setting.

Give paracetamol for high fever if the patient is uncomfortable. The recommended dose is 10 mg/kg/dose, not more than 3−4 times in 24 hours in children and not more than 3 g/day in adults. Sponge with tepid water if the patient still has a high fever. Do not give acetylsalicylic acid (aspirin), ibuprofen or other non-steroidal antiinflammatory agents (NSAIDs) or intramuscular injections, as these aggravate gastritis or bleeding.

Three day post onset of DF the patient's condition needs to be continuously monitored by conducting various blood tests till the condition improves. Clinical signs indicative of progression to serious
condition are low pulse, cold limb extremities, low urine output, abdominal pain and signs of mucosal bleeding. DHF is indicated by a falling platelet count (<100,000/mm$^3$) and rising hematocrit (≥20%) which is suggestive of need of immediate hospitalization is necessary. (Khetarpal and Khanna 2016)

Intravenous fluid is only necessary for patients with significant vascular leak and hemodynamic instability, or patients unable to tolerate oral fluids. It is necessary to maintain effective circulation during plasma leakage. Moreover careful clinical monitoring of pulse rate and blood pressure, hematocrit, platelet count, temperature, urine output, fluid administered, and other signs of shock is required. Patients usually recover within 12 to 48 h of fluid therapy. The current WHO management guidelines recommend the initial use of crystalloid solutions, followed by colloid solutions for patients with profound or unresponsive shock. WHO (2009) In worse case such as internal hemorrhage, whole blood transfusion may be carried out. (Khetarpal and Khanna 2016) Intravenous fluids should be administered with caution.

If the patient has dengue with warning signs or signs of dehydration, judicious volume replacement by intravenous fluid therapy from this early stage may modify the course and the severity of disease. The action plan should be as follows and applies to infants, children and adults:

• Obtain a reference haematocrit before intravenous fluid therapy begins. Give only isotonic solutions such as 0.9% saline, Ringer's lactate or Hartmann's solution. Start with 5–7 ml/kg/hour for 1–2 hours, then reduce to 3–5 ml/kg/hour for 2–4 hours, and then reduce to 2–3 ml/kg/hour or less according to the clinical response

• Reassess the clinical status and repeat the haematocrit. If the haematocrit remains the same or rises only minimally, continue at the same rate (2–3 ml/kg/hour) for another 2–4 hours. If the vital signs are worsening and the haematocrit is rising rapidly, increase the rate to 5–10 ml/kg/hour for 1–2 hours. Reassess the clinical status, repeat the haematocrit and review fluid infusion rates accordingly.

• Give the minimum intravenous fluid volume required to maintain good perfusion and an urine output of about 0.5 ml/kg/hour. Intravenous fluids are usually needed for only 24–48 hours. Reduce intravenous fluids gradually when the rate of plasma leakage decreases towards the end of the critical

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<td>Viral isolation</td>
<td>Virus isolated</td>
<td>Serum (collected at 1–5 days of fever)</td>
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<tr>
<td>Genome detection</td>
<td>Positive RT-PCR or positive real-time RT-PCR</td>
<td>Necropsy tissues</td>
</tr>
<tr>
<td>Antigen detection</td>
<td>Positive NS1 Ag</td>
<td>Necropsy tissues</td>
</tr>
<tr>
<td>IgM seroconversion</td>
<td>From negative IgM to positive IgM in paired sera</td>
<td>Acute serum (days 1–5) and convalescent serum (15–21 days after first serum)</td>
</tr>
<tr>
<td>IgG seroconversion</td>
<td>From negative IgG to positive IgG in paired sera or 4-fold increase IgG levels among paired sera</td>
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Table 3: Confirmed and probable dengue diagnosis, interpretation of results and sample characteristic

ELISA = enzyme-linked immunosorbent assay; IgG = immunoglobulin G; IgM = immunoglobulin M; NS1 Ag = non-structural protein 1 antigen; RT-PCR = reverse transcriptase polymerase chain reaction

Figure 9: Laboratory investigations for diagnosis of Dengue infection
phase. This is indicated by urine output and/or oral fluid intake improving, or the haematocrit decreasing below the baseline value in a stable patient.

- Patients with warning signs should be monitored by health-care providers until the period of risk is over. A detailed fluid balance should be maintained. Parameters that should be monitored include vital signs and peripheral perfusion (1–4 hourly until the patient is out of the critical phase), urine output (4–6 hourly), haematocrit (before and after fluid replacement, then 6–12 hourly), blood glucose and other organ functions (such as renal profile, liver profile, coagulation profile, as indicated).

If the patient has dengue with co-existing conditions but without warning signs, the action plan should be as follows:

- Encourage oral fluids. If not tolerated, start intravenous fluid therapy of 0.9% saline or Ringer’s lactate with or without glucose at the appropriate maintenance rate. Use the ideal body weight for calculation of fluid infusion for obese and overweight patients. Patients may be able to take oral fluids after a few hours of intravenous fluid therapy. Thus, it is necessary to revise the fluid infusion frequently. Give the minimum volume required to maintain good perfusion and urine output. Intravenous fluids are usually needed only for 24–48 hours.

**Treatment of shock**

The action plan for treating patients with compensated shock is as follows (see algorithms in Figures 11 and 12): (WHO, 2012)

- Obtain a reference haematocrit before starting intravenous fluid therapy. Start intravenous fluid resuscitation with isotonic crystalloid solutions at 5–10 ml/kg/hour over one hour in adults and 10–20 ml/kg/hour over one hour in infants and children.

Then reassess the patient’s condition (vital signs, capillary refill time, haematocrit, urine output).

- If the adult patient’s condition improves, intravenous fluids should be gradually reduced to 5–7 ml/kg/hour for 1–2 hours; then 3–5 ml/kg/hour for 2–4 hours and finally 2–3 ml/kg/hour which can be maintained up to 24–48 hours. Consider reducing intravenous fluid earlier if oral fluid intake improves. The total duration of intravenous fluid therapy should not exceed 48 hours.

- If the condition in the infant or child improves, intravenous fluids should be reduced to 10 ml/kg/hour for 1–2 hours; then to 7 ml/kg/hour for 2 hours; 5 ml/kg/hour for 4 hours and then to 3 ml/kg/hour, which can be maintained for up to 24–48 hours.

Consider reducing intravenous fluid earlier if oral fluid intake improves. The total duration of intravenous fluid therapy should not exceed 48 hours.

- If vital signs are still unstable (i.e. shock persists), check the haematocrit after the first bolus.

- In adults:

  - If the haematocrit increases or is still high (e.g. haematocrit > 50%), repeat a second bolus of crystalloid/colloid solution at 10–20 ml/kg/hour for one hour.

  After this second bolus, if there is improvement continue with crystalloid solution and reduce the rate to 7–10 ml/kg/hour for 1–2 hours, then continue to reduce as above.

  If haematocrit decreases compared to the initial reference haematocrit (especially if the repeat haematocrit is below the baseline, for example < 35–40% in adult females, < 40–45% in adult males), and the patient still has unstable vital signs, this may indicate bleeding. Look for severe bleeding.

  Cross-match fresh whole blood or fresh packed red cells and transfuse if there is severe overt
bleeding, If there is no bleeding, give a bolus of 10–20 ml of colloid, repeat clinical assessment and determine the haematocrit level. A senior staff member should carry out a review to consider blood transfusion.

• In infants and children:

If the haematocrit increases or is still high, change to colloid solution at 10–20 ml/kg/hour. After the initial dose, reduce the rate to 10 ml/kg/hour for 1 hour, then reduce to 7 ml/kg/hour. As mentioned above, change to crystalloid when the patient's condition improves.

If the haematocrit decreases compared to the initial reference haematocrit (especially if the repeat haematocrit is below the baseline, for example, < 35–40%), and the patient still has unstable vital signs, this may indicate bleeding. Look for severe bleeding. Cross-match fresh whole blood or fresh packed red cells and transfuse if there is severe overt bleeding. If there is no bleeding, give a bolus of 10–20 ml/kg of colloid over 1 hour, repeat clinical assessment and determine the haematocrit level. A senior staff member should carry out a review to consider blood transfusion.

Further boluses of crystalloid or colloidal solutions may need to be given during the next 24–48 hours.

Treatment of profound shock (hypotensive; undetectable pulse and BP). (WHO, 2012)

All patients (infants, children and adults) with hypotensive shock should be managed more vigorously.

For all patients (infants, children and adults), initiate intravenous fluid resuscitation with crystalloid or colloid solution at 20 ml/kg as a bolus given over 15–30 minutes to bring the patient out of shock as quickly as possible. Colloids may be the preferred choice if the BP has to be restored urgently, i.e. in those with pulse pressure less than 10 mmHg. Colloids have been shown to restore the cardiac index and reduce the level of haematocrit faster than crystalloids in patients with intractable shock (4–6).

The intra-osseous route should be attempted if peripheral venous access cannot be obtained.
• If the patient’s condition improves:

  • In adults, give a crystalloid/colloid infusion of 10 ml/kg/hour for 1 hour. Then continue with crystalloid infusion and gradually reduce to 5–7 ml/kg/hour for 1–2 hours, then to 3–5 ml/kg/hour for 2–4 hours, and finally to 2–3 ml/kg/hour (or less), which can be maintained for up to 24–48 hours. Consider reducing intravenous fluid earlier if oral fluid intake and urine output improve. The total duration of intravenous fluid therapy should not exceed 48 hours.

  • In infants and children, give colloid infusion of 10 ml/kg/hour for 1 hour. Then continue with crystalloid 10 ml/kg/hour for 1 hour, then to 7.5 ml/kg/hour for 2 hours, to 5 ml/kg/hour for 4 hours and to 3 ml/kg/hour, which can be maintained for up to 24–48 hours. Consider reducing intravenous fluid earlier if oral fluid intake and urine output improve. The total duration of intravenous fluid therapy should not exceed 48 hours.

  • For all patients, if vital signs are still unstable (i.e. shock persists), review the haematocrit obtained before the first bolus.

    • If the haematocrit was normal or low (< 30–35% in infants, < 35–40% in children and adult females, < 40–45% in adult males), this may indicate bleeding. Look for severe bleeding. Cross-match fresh whole blood or fresh packed red cells and transfuse if there is severe overt bleeding. If there is no bleeding, give a second bolus of 10–20 ml/kg of colloid over 30 minutes to 1 hour, repeat clinical assessment and haematocrit level plus a review by senior staff to consider blood transfusion.

    • If the haematocrit was high compared to the baseline value (if not available, use population baseline), change intravenous fluids to colloid solutions at 10–20 ml/kg as a second bolus over 30 minutes to 1 hour. After the second bolus, reassess the patient. If the condition improves, reduce the rate to 7–10 ml/kg/hour for 1–2 hours, then change back to crystalloid solution and reduce the rate of infusion as mentioned above.
• If the condition is still unstable, repeat the haematocrit after the second bolus.

• If the haematocrit decreases compared to the previous value (< 35% in infants, < 40% in children and adult females, < 45% in adult males), this indicates bleeding and the need to cross-match and transfuse blood as soon as possible.

• If the haematocrit increases compared to the previous value or remains very high (> 50%), continue colloid solutions at 10–20 ml/kg as a third bolus over 1 hour. After this dose, reduce the rate to 7–10 ml/kg/hour for 1–2 hours, then change back to crystalloid solution and reduce the rate of infusion as mentioned above when the patient’s condition improves. If the condition is still unstable, repeat the haematocrit after the third bolus.

• Further boluses of fluids may need to be given during the next 24 hours. The rate and volume of each bolus infusion should be titrated to the clinical response. Patients with severe dengue should be admitted to the high-dependency or intensive care area and be managed by senior staff.

Clinicians who take care of dengue shock infants should remember that an infant with a low baseline haematocrit of 30%, presenting with dengue shock and a haematocrit of 40%, is relatively more haemoconcentrated than another child with a baseline value of 42% and haematocrit of 50% at the time of shock.

**When to stop intravenous fluid therapy**

Recognizing when to decrease or stop intravenous fluids as part of the treatment of severe dengue is crucial to prevent fluid overload. When any of the following signs are present, intravenous fluids should be reduced or discontinued:

• signs of cessation of plasma leakage;
• stable BP, pulse and peripheral perfusion;
• haematocrit decreases in the presence of a good pulse volume;
• apyrexia (without the use of antipyretics) for more than 24–48 hours;

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**Fig. 13. Algorithm for fluid management in hypotensive shock – infants, children and adults**
• resolving bowel/abdominal symptoms;
• improving urine output.

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

Management of thrombocytopenia

The most striking laboratory finding in dengue is thrombocytopenia. Mucosal bleeding may occur in any patient with dengue but if the patient remains stable with fluid resuscitation/replacement, this should be considered as a minor issue. The bleeding usually improves rapidly during the recovery phase. In patients with profound thrombocytopenia, ensure strict bed rest and protection from trauma. Do not give intramuscular injections. No evidence exists (from observational studies) that prophylactic platelet transfusions are beneficial in haemodynamically stable patients.

To prevent the lethal outcome, the dengue patients are often hospitalized and serial platelet counts are monitored. When the platelet count is severely low, prophylactic platelet transfusions are given to circumvent hemorrhagic manifestations despite the dearth of robust evidence. The proportion of dengue patients receiving platelet transfusion ranged from 7% to 50.3% in studies from Trinidad and Tobago, India, Taiwan and Singapore. (Lee, Wong et al. 2016) This wide range reflects varying local practices and general lack of consensus with regards to the management of thrombocytopenia in dengue. In a global survey, 190 out of 306 (62.1%) respondents did not advocate prophylactic platelet transfusion in the absence of bleeding. (Horstick, Tozan et al. 2015) However, there was also a wide geographic variation in their responses.

Recent clinical trial demonstrated that prophylactic platelet transfusion was not superior to supportive care in preventing bleeding, and might be associated with adverse events. (Lye, Archuleta et al. 2017) Platelet transfusion in absence of bleeding in adult dengue with platelet < 20,000/mm3 did not reduce bleeding or expedite platelet recovery. There was potential harm by slowing recovery of platelet count to > 50,000/mm3 and increasing length of hospitalization. (Lee, Wong et al. 2016) Moreover there was significantly higher fluid balance, incidence of pulmonary edema and increased length of hospital stay associated with preventive transfusion. (Lum, Abdel-Latif Mel et al. 2003)

Blood transfusion is life-saving and should be given as soon as severe bleeding is suspected or recognized. However, blood transfusion must be given with care because of the risk of fluid overload. Do not wait for the haematocrit to drop too low before deciding on blood transfusion.

The action plan for the treatment of haemorrhagic complications is as follows: (WHO, 2012)

• If possible, attempts should be made to stop bleeding if the source of bleeding is identified e.g. severe epistaxis may be controlled by nasal adrenaline packing.

• If blood loss can be quantified, this should be replaced. If not, give aliquots of 5–10 ml/kg of fresh - packed red cells or 10–20 ml/kg of fresh or fairly fresh whole blood (FWB) at an appropriate rate and observe the clinical response. It is important that fresh whole blood or fresh red cells are given. Oxygen delivery at tissue level is optimal with high levels of 2,3 diphosphoglycerate (2,3 DPG). Stored erythrocytes lose 2,3 DPG, low levels of which impede the oxygen-releasing capacity of haemoglobin, resulting in functional tissue hypoxia. A good clinical response includes improving haemodynamic status and acid-base balance.

• Consider repeating the blood transfusion if there is further overt blood loss or no appropriate rise in haematocrit after blood transfusion in an unstable patient.

• There is no evidence that supports the practice of transfusing platelet concentrates and/or fresh-frozen plasma for severe bleeding in dengue. Nevertheless, in certain situations such as obstetrical deliveries or other surgeries, transfusions of platelet concentrates with or without fresh frozen plasma should be considered in anticipation of severe bleeding.

ABO identical and compatible pooled platelet transfusions were more successful in increasing the post transfusion platelet counts as compared to ABO incompatible pooled platelets in dengue patients. (Bhat, Chowdappa et al. 2016)
• In gastrointestinal bleeding, H-2 antagonist and proton pump inhibitors have been used, but their efficacy have not been studied.

• Great care should be taken when inserting a nasogastric tube or bladder catheters which may cause severe haemorrhage. A lubricated orogastric tube may minimize the trauma during insertion. Insertion of central venous catheters should be done with ultra-sound guidance or by an experienced person.

• It is essential to remember that blood transfusion is only indicated in dengue patients with severe bleeding. Unnecessary blood transfusions cause the haematocrit to rise sharply, thus giving a false impression of haemoconcentration and severe plasma leakage leading to unwarranted fluid therapy.

Altered sensorium on presentation, lower hemoglobin and hematocrit levels, higher serum creatinine, higher serum transaminase and lower serum albumin levels to be significantly associated with mortality in dengue. Identification of these parameters early in the course of disease should prompt intensification of treatment in dengue cases. (Saroch, Arya et al. 2017)

Patients with DHF/DSS are more susceptible to develop renal failure compared to DF group. Patients in the RF have higher percentages of shock, haemoconcentration, thrombocytopenia, raised AST and low serum cholesterol. (Vakrani and Subramanyam 2017)

**Novel therapeutic options**

Development of effective vaccines many of which are undergoing clinical trials could be breakthrough in the prevention of Dengue infection. Moreover several traditional medicines are being evaluated for their usefulness in managing dengue.

The carica papaya leaves extract (CPLE) possibly benefits in dengue is by increasing the platelet counts. The research has demonstrated membrane stabilizing properties of CPLE in *in vitro* studies. Carica papaya leaf extracts inhibited heat-induced and hypotonicity-induced hemolysis of erythrocytes obtained from both healthy individuals and individuals with dengue infection. The extracts are likely to possess membrane-stabilizing properties and protect blood cells against stress-induced destruction. This property may be useful in patients with dengue infection where the leaf extracts could possibly prevent platelet lysis which could be attributed to the actions of flavonoids and other phenolic compounds in the papaya leaves. (Ranasinghe, Ranasinghe et al. 2012)

Arachidonate 12-lipoxygenase (ALOX 12) also known as the platelet type lipoxygenase (ALOX 12) gene aids in the production and differentiation of megakaryocytes which leads to the production of 12-hydroxyeicosatetraenoic acid and therein production of platelets. Adding on, platelet-activating factor receptor (PTAFR) gene, expressed in megakaryocytes is involved in platelet aggregation. This gene is platelet-specific and is a direct target of transcription factor RUNX1 in megakaryocytes and platelets. Carica papaya leaf extract has been found to increase the ALOX 12 activity by 15 fold and 13.42 fold increase in PTFAR activity which increases the platelet production. (Subenthiran, Choon et al. 2013)

Moreover two components of a viral serine protease, NS2B and NS3, play a pivotal role in viral replication. It is crucial for the production of the polyprotein precursor before the assembly of the viral complex. Flavonoid components of papaya leaves has significant inhibitory activity against NS2B-NS3 serine protease, particularly against Dengue virus serotype 2 and exerts its antiviral property by preventing viral assembly. (Senthilvel, Lavanya et al. 2013)

A randomized controlled trial was conducted in Malaysia on 290 patients between the ages of 18 and 60 years with platelet counts ≤100,000/L. The patients were confirmed to be suffering from dengue using a rapid dengue bedside test. Patients in the intervention group were administered fresh juice from 50 g of C. papaya leaves once a day 15 min after breakfast for 3 consecutive days. In addition, they received the standard treatment for dengue. The controls only received the standard treatment. The study found that there was a significant increase in the platelet counts in the intervention group at the end of 40 h when compared to the counts 8 h after the intervention began. This significant increase was not observed in the control group. An increase in arachidonate 12-lipoxygenase and the platelet-activating factor receptor gene expression was also observed in the intervention group. These genes are associated with increased platelet production. (Subenthiran, Choon et al. 2013)
A study conducted in Indonesia used CPLE capsules, which contained 70% ethanol extract of C. papaya leaves. The 80 patients included in the study had high continuous fever for 2-7 days, thrombocyte count of <150,000/L and hematocrit of 20% or more. They were randomized into two groups; one group received CPLE capsules in addition to standard treatment, whereas the other group received only standard treatment for dengue. The study found that platelets in patients with dengue increased faster in those who were administered the CPLE. The authors thus conclude that treatment with CPLE can hasten recovery of patients and therefore reduce hospitalization. (Yunita F, 2012)

A randomized controlled clinical trial was carried out in India to evaluate effect of CPLE on platelet count in dengue fever. Patients were randomized into two groups wherein, the study group was given CPLE of 500 mg once daily and routine supportive treatment for consecutive five days whereas the controls were given only routine supportive treatment. It was found that on 3rd, 4th and 5th day platelet count of study group was significantly higher than control group (p value < 0.05). (Figure 14). Average hospitalization period of study group v/s control group was 3.65±0.97 v/s 5.42±0.98 days (p value < 0.01) (Figure 15). Average platelet transfusion requirement in study group was significantly less than control group (0.685 units per patient v/s 1.19 units per patient) (p value <0.01). (Gadhwal, Ankit et al. 2016)

Another Indian multi-centric, double blind, placebo controlled, randomized, prospective study was conducted in 300 patients across 5 centers, to evaluate the efficacy and safety of CPLE, as empirical therapy for thrombocytopenia associated with dengue fever. The intervention group received CPLE tablet three times daily for five days. Moreover both the groups were managed by the standard care for dengue. The results indicate that CPLE had significant increase (p< 0.01) in the platelet count over the therapy duration, in dengue fever patients, confirming CPLE accelerates the increase in platelet count compared to the control group. There were few adverse events related to GI disturbance like nausea and vomiting which were similar in both groups. (Kasture, Nagabhushan et al. 2016)

A systematic review and meta-analysis was conducted to find out the level of evidence on the efficacy and safety of CPLE in dengue. It was found that Carica papaya leaf extract was associated with increase in platelet count in the overall analysis. (Mean difference [MD] =20.27 [95% confidence interval (CI) 6.21-34.73; P = 0.005]). There was significant decrease in hospitalization days in the CPLE group (MD = 1.90 [95% CI 1.62-2.18; P < 0.00001]). (Charan, Saxena et al. 2016)

Several clinical trials have failed to demonstrate efficacy of both antivirals and adjunctive therapies. Two recent antiviral trials studying balapiravir in Vietnam and celgosivir in Singapore failed to demonstrate any beneficial effect on viremia or clinical outcome. (Nguyen, Tran et al. 2013, Low, Sung et al. 2014)

Lovastatin studies in vitro studies was able to interrupt the DENV assembly pathway and increase survival in animal models. (Martinez-Gutierrez, Castellanos et al. 2011) However these findings were not replicated in human study investigating lovastatin in early dengue. (Whitehorn, Nguyen et al. 2016)

No adjunctive therapies have demonstrated any disease-modifying effect. The anti-malarial drug chloroquine, although possessing some antiviral effects in vitro, (Farias, Machado et al. 2014) failed to demonstrate reduction in viremia or NS1 duration in a randomized controlled trial in adult dengue patients. (Tricou, Minh et al. 2010) Moreover corticosteroids also failed to demonstrate its immunomodulatory effect in alteration of disease severity both in patients with established dengue shock and also when given early in the disease course. (Tassniyom, Vasanawathana et al. 1993, Tam, Ngoc et al. 2012) Intravenous immunoglobulin use did not impact on the development of severe thrombocytopenia. (Dimaano, Salto et al. 2007) Nor did prophylactic platelet transfusions have any benefit on bleeding manifestations in adult patients with severe thrombocytopenia. (Lye, Lee et al. 2009)

New strategies for dengue control

Efforts over the several year to control the spread of dengue have been unsuccessful, mainly because of lack of a vaccine and problems in keeping check on the major global vectors Aedes aegypti mosquitoes and, more recently, Aedes albopictus. (Paupy, Delatte et al. 2009) These mosquitoes bite during the day and have adapted very well to the urban environment, breeding primarily in man-made water containers. Vector control strategies are directed towards elimination of the container breeding sites, improved access to piped water supplies, and improved management of water storage. The larvicides
and insecticides are generally used during outbreaks and had many limitations, including resistance. (Luz, Vanni et al. 2011)

Novel technologies showing some potential for future dengue control are biologic and genetic modification of mosquitoes. Recently dengue vaccine (CYD-TDV, Sanofi-Pasteur) was introduced in Mexico followed by the Philippines. Moreover several candidate vaccines are in different phases of development, e.g. live attenuated, inactivated whole virus, and subunit and recombinant vaccines. (Capeding, Tran et al. 2014) Vaccine studies have also emphasized the need to improve our understanding of the immunological correlates of disease, as neutralizing antibodies to all four serotypes were demonstrated among vaccines in an earlier phase of the study but did not translate to equal protection.

Conclusion and way ahead

Dengue is one of the world’s most rapidly emerging diseases. As incidence continues to rise in endemic areas, and transmission in new regions of the world becomes established, there are many public health challenges ahead to tackle dengue. Currently there is no antiviral drug available for dengue and treatment is usually symptomatic. Continuous monitoring the patient’s condition for any of the “warning signs” and careful fluid balance for those identified to have capillary leak are the cornerstones of the success of treatment. There have been recent advances in our understanding of the epidemiology, risk factors for severe disease, and pathogenesis, plus the identification of therapeutic targets, which may lead to novel treatments.

On the contrary awareness of the disease and its symptoms are at medium levels in India and an effective knowledge about the process of vector transmission and ways to prevent it are not
consistently well understood. These issues are certainly more acute in islands of urban areas as it is difficult to maintain regular surveillance and control of the mosquito breeding sites. (Daude, Mazumdar et al. 2017) There has been a resurgence of dengue fever with a change in the pattern of presentation during the recent epidemics. It is also difficult to estimate the prevalence of dengue when sick people do not have access to health services and are not recorded in sentinel hospitals. In the absence of a vaccine, it is fundamental that people act against the disease and its local risk of transmission in an efficient and appropriate manner by ensuring vector control in their neighborhood, notably by eliminating stagnant water within and around their homes in order to limit the presence of mosquitoes. Clinical vigilance and awareness regarding the changing epidemic pattern and timely detection of cases are vital to reduce mortality and morbidity due to severe dengue infection.

References


Dear Doctor,

It gives me immense pleasure to present to you this QMR issue by eminent physician Dr. Rajesh Sinha, from Patna.

Over the last two decades Dengue has emerged as the major vector-borne viral infection worldwide. In India there are cyclic epidemics of dengue over the years. Dengue infection is one of the leading causes of hospitalization and death among children.

In this issue on Dengue Viral Infection, Dr. Rajesh Sinha, has emphasized the current developments in understanding of causes of the dengue pandemic, viral structure and epitope binding, clinical presentation and potential risk factors, pathogenesis, diagnosis, therapeutic options, strategies for disease control and future directions.

With best regards,

Dr. Balaji More  
Vice President - Medical