Dengue: A Review

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ABSTRACT

Dengue is the most common arboviral disease in the world with over 50 million people being affected all over. Caused by the virus from genus *Flaviviridae*, it can result from nonspecific viral illness. Early diagnosis, rapid identification of the complications, and fluid restoration are the cornerstone of management of this disease.

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INTRODUCTION

“Dengue is one disease entity with different clinical presentations and often with unpredictable clinical evolution and outcome.” This was the fact that expert consensus groups in Latin America (Havana, Cuba, 2007), South-East Asia (Kuala Lumpur, Malaysia, 2007), and at World Health Organization (WHO) headquarters in Geneva, Switzerland, in 2008, all agreed on. Dengue infections caused by the four antigenically distinct dengue virus serotypes (DENV1, DENV2, DENV3, DENV4) of the family *Flaviviridae* are the most important and most common arbovirus diseases in humans, in terms of geographical distribution, morbidity, and mortality. Dengue infections may be asymptomatic or may lead to an undifferentiated fever (or viral syndrome), dengue fever, or dengue hemorrhagic fever (DHF). The word “dengue” is derived from the Swahili phrase Ka-dinga pepo, meaning “cramp-like seizure.”

Epidemiology

Dengue is currently regarded as the most important arboviral disease internationally as over 50% of the world’s population live in areas where they are at risk of the disease, and approximately 50% live in dengue endemic countries. Dengue virus infection is a major cause of disease in tropical and subtropical areas, with an estimated 50 million infections occurring each year and more than 2.5 billion people being at risk of infection. The virus and its vectors have now become widely distributed throughout the tropical and subtropical regions of the world, particularly over the last half century. Significant geographic expansion has been coupled with rapid increases in incident cases, epidemics, and hyperendemicity, leading to the more severe forms of dengue. Transmission of dengue is now present in every WHO region of the world and more than 125 countries are known to be dengue endemic. Estimates of the global incidence of dengue infections per year have ranged between 50 and 200 million; however, recent estimates using cartographic approaches suggest this number is closer to almost 400 million. The expansion of dengue is expected to increase due to factors such as the modern dynamics of climate change, globalization, travel, trade, socioeconomics, settlement, and also viral evolution.

Dengue has been present for centuries. The first recorded symptoms compatible with dengue were noted in a Chinese medical encyclopedia in 992 AD, however, originally published by the Chin Dynasty centuries earlier (265–420 AD), prior to being formally edited. The disease was referred to as “water poison” and was associated with flying insects.

The first epidemic of clinical dengue-like illness in India was recorded in Madras (now Chennai) in 1780, and the first virologically proved epidemic of dengue fever in India occurred in Calcutta (now Calcutta) and the Eastern Coast in 1963–1964, and routine outbreaks keep on occurring every year with numbers increasing during the monsoon.

Virology

The dengue virus, a member of the genus *Flavivirus* in the family *Flaviviridae*, is a single-stranded enveloped ribonucleic acid (RNA) virus, 30 nm in diameter, which can grow in a variety of mosquitoes and tissue cultures. There are four distinct but closely related serotypes (DENV1–4). They possess antigens that cross-react with other members in the same genus such as yellow fever,
Japanese encephalitis, and West Nile viruses. There is evidence from field and laboratory studies that there are distinct strain differences between dengue viruses. 

Aedes aegypti is the most efficient vector for the virus because of its domestic habits. The female bites during the day and these mosquitoes do not travel much distance from the area of origin and may result in all members of the family being affected. Once a female bites a human with the virus, it undergoes an extrinsic incubation period of about 8 to 10 days and then is able to infect the humans. Once infected, the Aedes mosquito can transmit the virus for about a month. Transovarian transmission is possible in dengue, but it is unclear how it would affect the epidemiology of the disease. Other Aedes mosquitoes capable of transmitting dengue include Ae. albopictus, Ae. polynesiensis, and several species of the Ae. scutellaris complex. These other species also transmit the dengue virus but not as effectively as A. aegypti.

PATHOGENESIS

When mosquitoes feed on humans, DENV is presumably injected into the bloodstream, with spillover in the epidermis and dermis, resulting in infection of immature Langerhans cells, epidermal dendritic cells (DCs). Infected cells then migrate from the site of infection to lymph nodes, where monocytes and macrophages are recruited, which become targets of infection. Consequently, infection is amplified and virus is disseminated through the lymphatic system. Dissemination from the lymphatic system leads to invasion of other cells of the reticuloendothelial system like splenic and liver macrophages, circulating monocytes and bone marrow. Bone marrow stromal cells have also been shown to be susceptible to infection with DENV.

Following infection, mononuclear cells predominantly die by apoptosis, while abortively infected or bystander DCs are stimulated to produce the bulk of mediators that are involved in inflammatory and hemostatic responses of the host. In this regard, factors that influence the amount of target cells infected, and consequently the levels of viremia, may determine the ratio of different proinflammatory and anti-inflammatory cytokines, chemokines, and other mediators, as well as the way in which the inflammatory response affects the hemostatic system.

Dengue hemorrhagic fever occurs in a patient who has dengue virus infection and also, in the past, had dengue but with a different serovar. Halstead observed that the incidence of DHF and dengue shock syndrome (DSS) peaked in two populations of young children. One peak occurred in infants (at the age of 6–9 months) who were infected with a DENV serotype different from that which had infected their mothers. The key observation was that severe disease occurred in infants for whom maternal antibodies had declined to low, subneutralizing levels. The other peak was observed in young children who had experienced an earlier, usually mild or subclinical, infection and were later infected with a different DENV serotype. These observations led to the conclusion that subsequent infection of preimmune individuals with a different DENV serotype could exacerbate rather than mitigate disease, a phenomenon that was claimed to be caused by antibodies and termed antibody-dependent enhancement (ADE) of disease. Not all cases of DHF in humans are associated with ADE or high viral loads at presentation. In some cases, when DHF/DSS is seen, the presence of viral RNA became undetectable. In general, however, a high viral load and the presence of virus on the day of defervescence are important risk factors for the development of severe disease.

When defervescence phase occurs and fever settles down in patients with dengue, they show a high level of complement activation products C5a and C5a. Recently, it has been found that nonstructural protein NS1 has a role in complement activation causing local and systemic generation of anaphylatoxin C5a and the terminal SC5b-9 complex. The plasma levels of NS1 and SC5b-9 complexes correlated with disease severity and they were present in the pleural fluid from patients with DSS. This is a novel finding that implicates the major role of NS1 as an important trigger for complete complement activation and the role of the terminal SC5b-9 complex in the pathogenesis of plasma leakage.

It is strongly believed by many scientists studying dengue pathogenesis that a high viral load and activation of high numbers of nonprotective T cells result in a “storm” of inflammatory cytokines and other mediators, leading to the increased plasma leakage characteristic of DHF/DSS. Higher plasma levels of interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL-13, IL-18, tumor growth factor (TGF)-β, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ have been found in patients with severe DENV infections, in particular in patients with DSS.

CLINICAL FEATURES

Dengue has a wide spectrum of clinical presentations, often with unpredictable clinical evolution and outcome. While most patients recover following a self-limiting nonsevere clinical course, a small proportion progress to severe disease, mostly characterized by plasma leakage with or without hemorrhage. 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.
Earlier dengue was classified as undifferentiated fever, classical dengue, and DHF. Dengue hemorrhagic fever was further classified as having four severity grades with grade III and IV being DSS. There have been many reports of difficulties in the use of this classification, which were summarized in a systematic literature review. Due to this discrepancy, the WHO has adopted a new method to classify dengue:

- Dengue without warning signs – nausea, vomiting, rash, leukopenia, positive tourniquet test, body aches and pains.
- Dengue with warning signs – abdominal pain or tenderness, clinical fluid accumulation, mucosal bleed, hepatomegaly >2 cm, thrombocytopenia, and increasing hematocrit.
- Severe dengue – severe plasma leakage leading to shock, severe bleeding, serum glutamate-oxaloacetate transaminase and serum glutamate-pyruvate transaminase in thousands causing severe hepatitis.
- Impaired consciousness, involvement of other organs.

Dengue starts as an acute febrile illness and usually has three phases to the disease – febrile, critical, and recovery.

**Febrile Phase**

Patients typically develop a high-grade fever suddenly. This acute febrile phase usually lasts 2 to 7 days and is often accompanied by facial flushing, skin erythema, generalized body ache, myalgia, arthralgia, retro-orbital eye pain, photophobia, rubeliform exanthema, and headache. Patients may have a sore throat, an injected pharynx with nausea and vomiting being a common finding. It can be difficult to distinguish dengue clinically from nondengue febrile diseases in the early febrile phase. A positive tourniquet test in this phase indicates an increased probability of dengue. Mild hemorrhagic manifestations such as petechiae and mucosal membrane bleeding (e.g., of the nose and gums) may be seen.

**Critical Phase**

Not all patients go into this phase. Only the patients who have significant capillary leakage go into this phase. The onset of the warning signs of dengue, as stated above, herald the onset of critical phase. A fall in temperature is accompanied by plasma leakage which causes exudation of plasma into the third space compartments like pleura, pericardium, and peritoneum. This results in ascites, pleural and pericardial effusions, which, if massive, can lead to respiratory distress. Leakage of plasma leads to increase in hematocrit values.

More than 20% increase in hematocrit values from the baseline signifies hemococoncentration and demands a good hydration therapy. The rise in hematocrit precedes fall in blood and pulse pressure. The significant plasma leakage lasts only 1 to 2 days. Persistent vomiting and severe abdominal pain are early indications of plasma leakage and become increasingly worse as the patient progresses to the shock state. Patient mismanaged or not treated during this phase leads to shock and subsequent multiorgan failure.

**Recovery Phase**

After 48 hours of the critical phase, resorption of the leaked out fluid occurs. The hematocrit falls and may fall below the normal range due to dilutional effect of resorbed fluid and aggressive hydration. Appetite returns and general sense of well-being ensues in the patient. Some patients have a confluent erythematous or petechial rash with small areas of normal skin, described as “isles of white in the sea of red.” Many patients have generalized pruritus in the recovery phase.

If the critical phase continues and adequate hydration has not been received by the patient, then the patients may land into DSS. This usually takes place around defervescence, i.e., on days 4 to 5 of illness (of days 3–8), and is often preceded by warning signs. Tachycardia, as always, heralds the onset of shock. In the initial phase of shock, the increased systolic pressure will maintain the perfusion and with increased peripheral resistance with result in signs of delayed capillary refilling.

A child 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 mm Hg in children (e.g., 100/85 mm Hg) or if they have signs of poor capillary perfusion (cold extremities, delayed capillary refill, or tachycardia). In adults, a pulse pressure of ≤20 mm Hg may indicate more severe shock. Worsening shock can lead to dangerously low blood pressures causing a vicious cycle of multiorgan failure and death.

The dengue virus can have some atypical manifestations. Central nervous system involvement can lead to encephalitis. Encephalopathy in DHF is an atypical manifestation and may appear in various forms, including depressed sensitivity, convulsions, neck rigidity, pyramidal signs, headache, papilledema, myoclonus, and behavioral disorders. Postinfectious sequelae are mainly amnesia, dementia, manic psychosis, Reye’s syndrome, and meningoencephalitis. Neurological involvement may occur because of intracranial hemorrhage, cerebral edema, hyponatremia, cerebral anoxia, fulminating hepatic failure with portosystemic encephalopathy, renal failure, or release of toxic products. Pathophysiology of neurological involvement may include the following factors: Direct tissue lesion caused by the virus because
Dengue: A Review

- Rickettsial infection
- Influenza—pharyngeal and conjunctival injection
- Viral hepatitis—liver enzymes in thousands point
- Chikungunya—usually occurs in localized outbreaks, has similar intensity of bone pain as dengue, thus a differential in early phase.
- Viral hepatitis—liver enzymes in thousands point toward an infective etiology like hepatitis A, B, E, but severe dengue can cause hepatitis which can elevate the enzymes to such proportions.
- Influenza—pharyngeal and conjunctival injection with abdominal pain can mimic influenza.
- Rickettsial infection—rickettsial disease in India has been documented from Jammu and Kashmir, Himachal Pradesh, Uttarakhand, Rajasthan, Assam, West Bengal, Maharashtra, Kerala and Tamil Nadu, with Batra
- Crimean Congo virus—Crimean Congo hemorrhagic fever (CCHF) is a zoonotic viral disease caused by tick-borne virus Nairovirus (family Bunyaviridae). The typical course of CCHF infection has four distinct phases—incubation period, prehemorrhagic phase, hemorrhagic phase, and convalescent phase. The incubation period for CCHF virus is in the range of 3 to 7 days. The mean duration is largely influenced by the route of infection, viral load, and source of infection—blood or tissue from livestock.
- Severe sepsis—it can mimic DHF and DSS but a normal erythrocyte sedimentation rate can differentiate the two.

**DIAGNOSIS**

Specific tests are widely used to detect the presence of dengue. Dengue can be detected using the following:
- Antigen—detection of ns1Ag in sera up to 3 days of fever.
- Seroconversion—detection of immunoglobulin M (IgM) titers in sera from a negative status.
- Virus isolation—using reverse transcriptase polymerase chain reaction (RT-PCR) techniques.

These tests should be done in the first five days of the illness. When a patient is infected with the dengue virus for the first time, there is persistent antigenemia for up to 2 days, after which, IgM antibodies begin to form and is detected in 50% of patients by day 3 and in 98–99% patients by day 9 of illness.

Five types of serological tests have been used for the diagnosis of dengue infection: Hemagglutination-inhibition, complement fixation, neutralization test, IgM capture enzyme-linked immunosorbent assay (ELISA), and indirect IgG ELISA. The limitations of these techniques are the high cross-reactivity observed with these tests, requiring a comprehensive pool of antigens, including all four serotypes, another Flavivirus (yellow fever virus, Japanese encephalitis virus, or St Louis encephalitis virus), and in some areas, another virus that causes similar clinical manifestations but that is not Flavivirus, such as Oropouche, Mayaro, or Chikungunya viruses. Furthermore, the dengue antibodies are better detected around the 5th day of disease onset, making this technique unfeasible for rapid diagnosis.

Four methods of viral isolation have been routinely used for dengue viruses: intracerebral inoculation of newborn mice, inoculation on mammalian cell cultures, intrathoracic inoculation of adult mosquitoes, and inoculation on mosquito cell cultures but they are done only in a handful of patients and in research centers.
According to the WHO, RT-PCR is a powerful method to be used for dengue diagnosis, but it still needs to be better standardized. Other laboratory tests may show leukopenia, thrombocytopenia, and rise in hematocrit. Liver enzymes may be deranged as well in dengue hepatitis and coagulopathy may result in deranged prothrombin time.

Thrombocytopenia of moderate degree is a usual finding associated with dengue, the reasons for which are multifactorial, which include early transient marrow suppression with damage to megakaryocytes, platelet aggregation to endothelial cells targeted by dengue fever viruses, hemophagocytosis, and finally, immune destruction of platelets, with dengue antibody complexes being found on their membrane and falling platelets the cause of admissions and worries for the treating clinicians.

Immature platelet fraction (IPF) is a laboratory parameter which helps in diagnosing the cause of thrombocytopenia. The IPF is elevated in cases of thrombocytopenia which happens due to peripheral destruction and is depressed when the cause is bone marrow suppression. One study has found out the relation and utility of IPF in dengue. According to it, when the IPF is repeated after obtaining its basal value on day 1, it shows a rising trend, and then the rise in platelet count is imminent within 24–48 hours. Thus, prophylactic transfusions of platelets can be avoided in many cases.

TREATMENT

For a disease that has such complex pathology and such diverse clinical features, the treatment remains fairly simple. Adequate hydration can well save a patient suffering from severe dengue and decrease his mortality. The WHO has formulated complete guidelines on the management of dengue including the admission and discharge criteria.

The following patients, who are diagnosed with dengue, need to be admitted to the hospital:

- Any patient with warning signs of dengue (see above)
- Unable to tolerate oral feeds and dehydrated look
- End organ damage suspicion
- All pregnant patients and patients with other comorbidities like diabetes mellitus, anemia, and obesity.
- Infants and elderly.

Other patients can be effectively monitored at home under close supervision of the health care provider. Adequate hydration using coconut water, juices, oral rehydration solution can be administered to the patient. If the patient cannot tolerate the same, then admission to a hospital is necessary. Paracetamol up to 4 gm/day can be used for fever. Nonsteroidal anti-inflammatory drugs should be avoided as they may increase the risk of bleeding by functional defects of platelets and also may precipitate Reye’s syndrome, especially in children. Tepid sponging can be used to decrease the temperatures as well. Daily, or in resource-limited settings, every third day, hematocrit and platelet counts need to be done to monitor the disease.

Patients who are admitted to the hospital need hydration by oral and preferably by intravenous route. The goals of fluid resuscitation include improving central and peripheral circulation, i.e., decreasing tachycardia, improving blood pressure (BP) and pulse volume, warm and pink extremities, a capillary refill time <2 seconds, improving end-organ perfusion i.e., achieving a stable conscious level (more alert or less restless), and urine output ≥0.5 ml/kg/hour or decreasing metabolic acidosis.

Obtain a reference hematocrit 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 hematocrit. If the hematocrit 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 hematocrit is rising rapidly, increase the rate to 5–10 ml/kg/hour for 1–2 hours. Reassess the clinical status, repeat the hematocrit, and review fluid infusion rates accordingly. Give the minimum intravenous fluid volume required to maintain good perfusion and urine output of about 0.5 ml/kg/hour. Intravenous fluids are usually needed for only 24–48 hours. Reduce intravenous fluids gradually when the rate of plasma leakage decreases toward the end of the critical phase. This is indicated by urine output and/or oral fluid intake improving, or the hematocrit 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), hematocrit (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).

Patients who have severe plasma leakage and severe end organ involvement require aggressive fluid management. Fluid boluses at the rate of 10–20 ml/kg may be required over 15–30 minutes in DSS. In patients with compensated shock, start intravenous fluid resuscitation with isotonic crystalloid solutions at 5–10 ml/kg/hour over 1 hour. If the 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 shock persists, and the hematocrit increases or is still high (e.g., hematocrit > 50%), repeat a second bolus of crystalloid/colloid solution at 10–20 ml/kg/hour for 1 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 hematocrit decreases compared with the initial reference hematocrit (especially if the repeat hematocrit is below the baseline, e.g., <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 hematocrit level. If the condition improves, give fluids accordingly to patients who do not have shock (see above).

If shock persists, change to colloid solution at the same rate with frequent boluses. Parameters to be monitored include alertness and comfort levels, vital signs, and peripheral perfusion (every 15–30 minutes until the patient is out of shock then 1–2 hourly). In general, the higher the fluid infusion rate, the more frequently the patient should be monitored and reviewed in order to avoid fluid overload while ensuring adequate volume replacement. If previously not detectable, pleural effusion and ascites should be detectable after fluid boluses. Monitor their effects on breathing. A decrease in hematocrit together with stable hemodynamic status and adequate urine output indicates hemodilution and/or reabsorption of extravasated fluids. In this case, intravenous fluids must be discontinued immediately to avoid pulmonary edema.

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
- Hematocrit decreases in the presence of a good pulse volume
- Apyrexia (without the use of antipyretics) for more than 24–48 hours
- Resolving bowel/abdominal symptoms
- Improving urine output.53

Studies have shown several sulfated polysaccharides extracted from seaweeds have been studied and high antiviral activity against dengue virus has been observed.53 In modern medicine, ribavirin, glycyrrhizin, and 6-azauridine have been reported to have cytoplastic and inhibitory effects on the dengue virus.54

An adenosine analog is another promising drug currently being studied. The chemical “NITD008” is the best example.55 Currently, the most advanced targets are the NS3/NS2B protease and NS5 RNA-dependent RNA polymerase, which have undergone high throughput screening and lead compound optimization. New targets including E, NS3 helicase, and NS5 methyltransferase are being explored.56

Dysregulation of the immune system with its hyperactive state has been a part of the pathophysiology of dengue, and some investigators have sought for the use of intravenous Ig for the management of severe dengue, but the results are not very productive.57

Although corticosteroids are not mentioned in the WHO guidelines on the management of dengue, clinicians use corticosteroids empirically based on the presumed immunological basis of the complications of dengue. The evidence base for the benefit or lack of benefit of corticosteroids in dengue is limited; previous studies have been small, with methodological flaws, less stringent randomization, and unclear allocation concealment, and were performed a long time ago. Studies so far have only been in patients with shock syndrome, and the possible effects of corticosteroids on thrombocytopenia and bleeding as well as other complications of dengue are unknown. All previous studies have been in children; the effect of corticosteroid treatment in adults with dengue infection has not been evaluated.58

A primary immunological mechanism that confers protection from dengue illness is virus neutralization through antibodies, and all current dengue vaccine candidates aim to elicit high levels of neutralizing antibody. The increasing cocirculation of the four dengue virus types means that a vaccine is needed that protects against all four of them; hence, the vaccine needs to be tetravalent. Moreover, the induction of protective, neutralizing antibody responses against all four serotypes of dengue virus simultaneously should avoid the theoretical concern of vaccine-induced ADE in vaccine recipients. Dengue vaccines in development are of four types: Live attenuated viruses, chimeric live attenuated viruses, inactivated or subunit vaccines, and nucleic acid-based vaccines.1

One is a chimeric tetravalent vaccine in which the structural genes (prM and E) of each of the four dengue viruses were inserted individually to replace those of yellow fever virus in the backbone of the yellow fever 17D vaccine. Thus, the nonstructural genes of yellow fever are provided to allow replication of the chimeric
virus, and attenuation is imparted by the yellow fever portion of the chimera. Monovalent vaccines, as well as tetravalent mixtures of all four viruses, have been given to human volunteers of varying aged in phase 1 and 2 trials in both nonendemic and endemic regions. At least two doses were required to achieve high rates of tetravalent neutralizing antibodies, and somewhat higher seroconversion rates were observed in subjects with preexisting immunity to yellow fever.59

CONCLUSION

Dengue is the most common arboviral disease in the world and is approaching pandemic proportions. Currently, early diagnosis and correct treatment offers the only hope for curing the disease. Environmental measures would also help in curbing the numbers by decreasing the host.

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