10.5005/jp-journals-10036-1083

REVIEW ARTICLE

# Dengue: A Review

[1]Alaka K Deshpande, [2]Shamshersingh G Chauhan, [3]Ankita Sood


## 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.


**Keywords:** Arboviral, Dengue, Shock.

**How to cite this article:** Deshpande AK, Chauhan SG, Sood A. Dengue: A Review. MGM J Med Sci 2016;3(1):26-33.

**Source of support:** Nil

**Conflict of interest:** None

## 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).[1]

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.[2-6] 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.[7] 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.[8]

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.[9] 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 (new Celiata) and the Eastern Coast in 1963–1964,[10-13] 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,

[1]Honorary Professor, [2,3]Resident Physician

[1-3]Department of Medicine, Grant Medical College, Mumbai-400008, Maharashtra, India

**Corresponding Authors:** Alaka K Deshpande, Honorary Professor, Department of Medicine, Grant Medical College JJ Marg, Nagpada-Mumbai Central, Off Jijabhoy Road Mumbai-400008, Maharashtra, India, Phone: +91986916886 e-mail: alakadeshpande@rediffmail.com; and

Shamshersingh G Chauhan, Resident Physician, Department of Medicine, Grant Medical College, JJ Marg, Nagpada-Mumbai Central, Off Jijabhoy Road, Mumbai-400008, Maharashtra, India Phone: +919820396635, e-mail: dr.sgchauhan@gmail.com

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.[14] Transovarian transmission is possible in dengue, but it is unclear how it would affect the epidemiology of the disease.[15] 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).[16,17] 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.[18]

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.[19]

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 there 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.[20]

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.[21] 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 deferevescence phase occurs and fever settles down in patients with dengue, they show a high level of complement activation products C3a and C5a.[22,23] 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.[24]

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)-1β, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ have been found in patients with severe DENV infections, in particular in patients with DSS.[19]

## 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.[25] 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.[26]

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.[27,28]

### 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 hemoconcentration 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."[29] 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, fulminant 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

of its neurotropicity, capillary hemorrhage, disseminated intravascular coagulation, and metabolic disorders.[30] Guillain–Barré syndrome, transverse myelitis, and acute disseminated encephalomyelitis all have been reported to occur in dengue.[31]

Acute hepatitis occurs on the ninth day of illness and enzymes come down after 3 weeks. Acute pancreatitis and acalculous cholecystitis can be seen and the accompanying inflammatory response to them can complicate the primary illness.[30] Deranged liver functions are common in patients with dengue infection due to direct attack on liver cells or unregulated host immune response against the virus.[32] Aspartate aminotransferase levels are more than alanine transaminase levels in patients with dengue hepatitis,[32] and this has been attributed to the more muscle involvement in patients with dengue. Severe involvement has been linked with more incidences of acalculous cholecystitis, encephalitis, renal failure, and coagulopathy.[33]

Acute renal failure mostly happens due to shock and disseminated intravascular coagulation.[34] Pericardial effusion and myocarditis causing ectopic beats can occur in dengue.[35]

Dengue hemorrhagic fever can result in acute respiratory distress syndrome. Dengue virus antigen is found in alveolar lining cells of the lung. Increased permeability of the alveolar-capillary membrane results in edema in the alveoli and interstitial spaces which lead to pulmonary dysfunction.[36] Disseminated intravascular coagulation can occur as a result of ongoing shock and thus help in perpetuating the multiorgan dysfunction or can result because of the virus itself.

## DIFFERENTIAL DIAGNOSIS

- Malaria — also as endemic in India as dengue, has almost the same clinical features as dengue.
- Leptospirosis — prominent myalgias with especially calf tenderness can point to leptospirosis.
- 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[37-40] reporting a high magnitude of scrub typhus, spotted fever, and Indian tick typhus caused by *Rickettsia conori*. Fever, headache, rash myalgias can confuse with dengue and other common infections we see daily. Weil–Felix test helps in diagnosis.
- 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.[41]
- Severe sepsis — it can mimic DHF and DSS but a normal erythrocyte sedimentation rate can differentiate the two.[42]

## 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.[43]

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.[44]

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,[45,46] 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[47-51] 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.[52] 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.[43]

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.[43]

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 cytostatic 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.

## REFERENCES


1. WHO. Dengue hemorrhagic fever: diagnosis, treatment and control. Geneva: World Health Organization; 2009.
2. Gubler DJ. Dengue, urbanization and globalization: the unholy trinity of the 21(st) century. Trop Med Health 2011 Dec;39(Suppl 4):3-11.
3. Gubler DJ. The global emergence/resurgence of arboviral diseases as public health problems. Arch Med Res 2002 Jul-Aug;33(4):330-342.
4. WHO. TDR Global alert and response dengue/dengue haemorrhagic fever [Internet]. Geneva: World Health Organization (WHO); 2013. Available at www.who.int/tdi/disease
5. WHO. Dengue and severe dengue: fact Sheet No 117 [Internet]. Geneva: World Health Organization (WHO); 2012. Available at www.whoent/mediacentre/foretheetsifs 117/en.
6. World Health Organization (WHO) Global strategy for dengue prevention and control, 2012–2020. Geneva: WHO Press; 2012.
7. Guha-Sapir D, Schimmer B. Dengue fever: new paradigms for a changing epidemiology. Emerg Themes Epidemiol 2005 Mar;2(1):1.
8. Murray NEA, Quam MB, Wilder-Smith A. Epidemiology of dengue: past, present and future prospects. Clin Epidemiol 2013 Aug 20;5:299-309.
9. Gubler DJ. Dengue/dengue haemorrhagic fever: history and current status. Novartis Found Symp 2006;277:3-16
10. Gubler D. Dengue and dengue hemorrhagic fever. Clin Microbiol Rev 1998 Jul;11(3):480-496.
11. Sarkar JK, Chatterjee SN, Chakravarty SK. Haemorrhagic fever in Calcutta: some epidemiological observations. Indian J Med Res 1964 Jul;52:651-659.
12. Chatterjee SN, Chakravarti SK, Mitra AC, Sarkar JK. Virological investigation of cases with neurological complications during the outbreak of haemorrhagic fever in Calcutta. J Indian Med Assoc 1965 Sep;45(6):314-316.
13. Carey DE, Myers RM, Reuben R, Rodrigues FM. Studies on dengue in Vellore, South India. Am J Trop Med Hyg 1966 Jul;15(4):580-587.
14. Cook, GC.; Zumla, AL. Manson's tropical diseases. 22nd ed. Saunders: Elsevier; 2008. p. 753.
15. Gubler, DJ. Dengue. Monath, TP., editor. The arboviruses: epidemiology and ecology. Boca Raton: CRC Press; 1988. p. 223-260.
16. Limon-Flores AY, Perez-Tapia M, Estrada-Garcia I, Vaughan G, Escobar-Gutierrez A, Calderon-Amador J, Herrera-Rodriguez SE, Brizuela-Garcia A, Heras-Chavarria M, Flores-Langarica A, et al. Dengue virus inoculation to human skin explants: an effective approach to assess in situ the early infection and the effects on cutaneous dendritic cells. Int J Exp Pathol 2005 Oct;86(5):323-334.
17. Wu SJ, Grouard-Vogel G, Sun W, Mascola JR, Brachtel E, Putvatana R, Louder MK, Filgueira L, Marovich MA, Wong HK, et al. Human skin Langerhans cells are targets of dengue virus infection. Nat Med 2000 Jul;6(7):816-820.
18. Nakao S, Lai CJ, Young NS. Dengue virus, a flavivirus, propagates in human bone marrow progenitors and hematopoietic cell lines. Blood 1989 Sep;74(4):1235-1240.
19. Martina BE, Koraka P, Osterhaus AD. Dengue virus pathogenesis: an integrated view. Clin Microbiol Rev 2009 Oct;22(4):564-581.
20. Halstead SB. Observations related to pathogensis of dengue hemorrhagic fever. VI. Hypotheses and discussion. Yale J Biol Med 1970 Apr;42(5):350-362.
21. Libraty DH, Endy TP, Houng HS, Green S, Kalayanarooj S, Suntayakorn S, Chansiriwongs W, Vaughn DW, Nisalak A, Ennis FA, et al. Differing influences of virus burden and immune activation on disease severity in secondary dengue-3 virus infections. J Infect Dis 2002 May;85(9):1213-1221.
22. Nishioka K. Serum complement level in dengue hemorrhagic fever. Allerg Immunol (Leipz) 1974-1975;20-21(4):385-392.
23. Shaio MF, Chang FY, Hou SC. Complement pathway activity in serum from patients with classical dengue fever. Trans R Soc Trop Med 1992 Nov-Dec;86(6):672-675.
24. Avirutnan P, Punyadee N, Noisakran S, Komoltri C, Thiemmeca S, Auethavornanan K, Jairungsri A, Kanlaya R, Tangthawornchaikul N, Puttikhunt C, et al. Vascular leakage in severe dengue virus infections: a potential role for the nonstructural viral protein NS1 and complement. J Infect Dis 2006 Apr 15;193(8):1078-1088.
25. Bandyopadhyay S, Lum LC, Kroeger A. Classifying dengue: a review of the difficulties in using the WHO case classification for dengue haemorrhagic fever. Trop Med Int Health 2006 Aug;11(8):1238-1255.
26. Rigau-Pérez JG, Clark GG, Gubler DJ, Reiter P, Sanders EJ, Vorndam AV. Dengue and dengue haemorrhagic fever. Lancet 1998 Sep 19;352(9132):971-977.
27. Kalayanarooj S, Vaughn DW, Nimmannitya S, Green S, Suntayakorn S, Kunentrasai N, Viramitrachai W, Ratanachueke S, Kiatpolpoj S, Innis BL, et al. Early clinical and laboratory indicators of acute dengue illness. J Infect Diseases 1997 Aug;176(2):313-321.
28. Balmaseda A, Hammond SN, Pérez MA, Cuadra R, Solano S, Rocha J, Idiaquez W, Harris E. Assessment of the World Health Organization scheme for classification of dengue severity in Nicaragua. Am J Trop Med Hyg 2005 Dec;73(6):1059-1062.
29. Nimmannitya S. Clinical spectrum and management of dengue haemorrhagic fever. Southeast Asian J Trop Med Public Health 1987 Sep;18(3):392-397.
30. Gulati S, Maheshwari A. Atypical manifestations of Dengue. Trop Med Int Health 2007 Sep;12(9):1087-95.

31. Rao SM, Pradeep M, Dnyaneshwar M, Alai T. Dengue encephalitis – clinical spectrum and outcome. Intern Med Inside 2013 Oct;1:8.
32. Wong M, Shen E. The utility of liver function tests in dengue. Ann Acad Med Singapore 2008 Jan;37(1):82-83.
33. Parkash O, Almas A, Wasim Jafri SM, Hamid S, Akhtar J, Alishah S. Severity of acute hepatitis and its outcome in patients with dengue fever in a tertiary care hospital Karachi, Pakistan (South Asia). BMC Gastroenterol 2010 May;10:43.
34. Hommel D, Talarmin A, Reynes JM, Hulin A. Acute renal failure associated with dengue fever in French Guiana. Nephron 1999;83(2):183.
35. Nagaratnam N, Sripala K, De Silva N. Arbovirus (dengue type) as a cause of acute myocarditis and pericarditis. Br Heart J 1973 Feb;35(2):204-206.
36. Lum LCS, Thong MK, Cheah YK, Lam SK. Dengue associated adult respiratory distress syndrome. Ann Trop Paediatr 1995 Dec;15(4):335-339.
37. Batra HV. Spotted fevers and typhus fever in Tamil Nadu – commentary. Indian J Med Res 2007 Aug;126(2):101-103.
38. Mahajan SK, Kashyap R, Kanga A, Sharma V, Prasher BS, Pal LS. Relevance of Weil-Felix test in diagnosis of scrub typhus in India. J Assoc Phys India 2006 Aug;54:619-621.
39. Mathai E, Lloyd G, Cherian T, Abraham OC, Cherian AM. Serological evidence of continued presence of human rickettsiosis in southern India. Ann Trop Med Parasitol 2001 Jun;95(4):395-398.
40. Sundhindra BK, Vijaykumar S, Kutti AK. Rickettsial spotted fevers in Kerala. Natl Med J India 2004 Jan-Feb;17(1): 51-52.
41. Appannanavar SB, Mishra B. An update on Crimean Congo hemorrhagic fever. J Global Infectious Dis 2011 Jul-Sep;3(3): 285-292.
42. Kalayanarooj S, Nimmannitya S. A study of erythrocyte sedimentation rate in dengue hemorrhagic fever. Southeast Asian J Trop Med Public Health 1989 Sep;20(3):325-330.
43. WHO. Handbook for clinical management of dengue. Geneva: World Health Organization; 2012.
44. De Paula SO, Fonseca BA. Dengue: a review of the laboratory tests a clinician must know to achieve a correct diagnosis. Braz J Infect Dis [Internet] 2004 Dec [cited 2015 Oct 14];8(6): 390-398.
45. King A, Innis BL, Caudle L. B-cells are the principal circulating mononuclear cells infected by dengue virus. Faseb J 1991;5a:9998.
46. Guzman MG, Kouri G. Advances in dengue diagnosis. Clin Diagn Lab Immnunol 1996 Nov;3(6):621-627.
47. Rothwell SW, Putnak R, La Russa VF. Dengue-2 virus infection of bone marrow: characterization of dengue-2 antigen-positive stroma cells. Am J Trop Med Hyg 1996 May;54(5):503-510.
48. Butthep P, Bunyaratvej A, Bhamarapravati N. Dengue virus and endothelial cell: a related phenomenon to thrombocytopenia and granulocytopenia in dengue hemorrhagic fever. Southeast Asian J Trop Med Public Health 1993;24(Suppl 1): 246-249.
49. Wong KF, Chan JKC, Chan JCW, Lim WWL, Wong WK. Dengue virus infection associated hemophagocytic syndrome. Am J Hematol 1991 Dec;38(4):339-340.
50. Jacobs MG, Weir WR, Bannister BA. Dengue hemorrhagic fever: a risk of returning home. BMJ 1991 Apr;302(6780):828-829.
51. Hathirat P, Isarangkura P, Srichaikul T, Suvatte V, Mitrakul C. Abnormal hemostasis in dengue hemorrhagic fever. Southeast Asian J Trop Med Public Health 1993;24(Suppl 1):80-85.
52. Dadu T, Sehgal K, Joshi M, Khodaiji S. Evaluation of the immature platelet fraction as an indicator of platelet recovery in dengue patients. Int J Lab Hematol 2014 Oct;36(5):499-504.
53. Damonte EB, Matulewicz MC, Cerezo AS. Sulfated seaweed polysaccharides as antiviral agents. Curr Med Chem 2004 Sep;11(18):2399-2419.
54. Crance JM, Scaramozzino N, Jouan A, Garin D. Interferon, ribavirin, 6-azauridine and glycyrrhizin: antiviral compounds active against pathogenic flaviviruses. Antiviral Res 2003 Mar;58(1):73-79.
55. Yin Z, Chen YL, Schul W, Wang QY, Gu F, Duraiswamy J, Kondreddi RR, Niyomrattanakit P, Lakshminarayana SB, Goh A, et al. An adenosine nucleoside inhibitor of dengue virus. Proc Natl Acad Sci USA 2009 Dec;106(48):20435-20439.
56. Luzhkov VB, Selisko B, Nordqvist A, Peyrane F, Decroly E, Alvarez K, Karlen A, Canard B, Qvist J. Virtual screening and bioassay study of novel inhibitors for dengue virus mRNA cap (nucleoside-2'O)-methyltransferase. Bioorg Med Chem 2007 Dec;15(24):7795-7802.
57. Rajapakse S. Intravenous immunoglobulins in the treatment of dengue illness. Trans R Soc Trop Med Hyg 2009 Sep;103(9): 867-870
58. Senaka R. Corticosteroids in the treatment of dengue illness [Abstract]. Trans R Soc Trop Med Hyg 2009 Feb;103(2):122-126.
59. Guy B, Almond JW. Towards a dengue vaccine: progress to date and remaining challenges. Comparative Immunol, Microbiol Infect Dis 2008 Mar;(2-3):239-252.