

## DENGUE FEVER: A CLINICAL PROFILE

Bharija A., Rehani B., Mohan C., Mohan A.

Departments of Medicine & PET/Nuclear Medicine, Kettering Medical Center, Kettering, Ohio, U.S.A.,  
Department of Medicine, All India Institute of Medical Sciences, New Delhi, India.

**Abstract :** Dengue is the world's most common mosquito borne viral disease. According to WHO dengue fever, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) occur in over 100 countries and 2.5 billion people around the world are at risk of this disease. Its global distribution is comparable to malaria and case fatality rate is approximately 5% with most cases being children and young adults

**Key words:** Dengue fever, dengue hemorrhagic fever, Dengue shock syndrome,

### INTRODUCTION AND HISTORICAL PERSPECTIVE

Dengue, the most significant of all mosquito borne viral diseases, affects humans of all age group worldwide. It has become a significant public health problem in several parts of the world. The first definite clinical report of dengue is attributed to Benjamin Rush in 1789, but the viral etiology and its mode of transmission via mosquitoes (*Aedes aegypti*) were not established until the early 20<sup>th</sup> Century. The first reported epidemics of dengue fever occurred almost simultaneously in 1779–1780 in Asia, Africa and North America. This is an indicator of the fact that the mosquito vector and virus have existed in the tropics for the past 200 years<sup>2</sup>.



Fig.1 World Distribution of dengue and / or Dengue Hemorrhagic fever and *Aedes aegypti* mosquito (courtesy: centre for disease control)

### GLOBAL EPIDEMIOLOGICAL SCENARIO

Fig. 1 shows the worldwide distribution of Dengue and / or Dengue Hemorrhagic Fever and *Aedes Aegypti* mosquito. A global pandemic of dengue began in the 1950s. In the past 50 years, the incidence of dengue has increased 30 fold and is now endemic in 112 countries. These endemic nations are mostly in Africa, The mean number of annual cases of dengue hemorrhagic fever has increased from below 10000 in the 1950s and 60s to over 200000 in the 1990s. Although the major burden is on South East Asia and Western Pacific, rising trends are also reported in

**Correspondence:** Dr. Anant Mohan, Fax. 91-11-26584664  
e-mail : anantmohan@yahoo.com

the Americas, where in the 1980s there were 15000 cases of dengue hemorrhagic fever, in the 1990s there were 56000 cases and in 2001 alone there were 15000 patients<sup>2,3</sup>. Worldwide estimates suggest that 100 million cases of dengue and half a million cases of DHF occur annually, with a case fatality of 0.5% - 3.5% in Asia.<sup>4</sup>

Population growth in the tropics provides many susceptible hosts. Inadequate management of water and waste in rural areas and uncontrolled urbanization provide large water reserves as habitats for the larvae. Lately, air travel has enabled infected humans to import viruses to on – endemic areas. Such factors can change a region from non-endemic (no virus present) to hypoendemic (one serotype present) to hyperendemic (multiple serotypes present)<sup>5</sup>. India has witnessed several dengue epidemics since the last century. Dengue virus was first isolated in India in 1945. DHF is now detected with increasing frequency in different parts of the country. Large number of serologically proven dengue cases, including few with hemorrhagic manifestations appeared first in Calcutta in 1963<sup>6</sup>. Similar outbreaks of dengue was reported from districts of Andhra Pradesh. Similarly, dengue virus outbreaks have been occurring in Chennai regularly for many years. Dengue and DHF cases have also been consistently noted from rural areas of Karnataka, Maharashtra and many other areas including Ajmer, Jaipur in Rajasthan and in Delhi<sup>8</sup>. All outbreaks started in monsoon ( August-November) and subsided with the onset of winter. Fig. 2 outlines the situation of the various major dengue outbreaks in the country from 1974 to 2002. It also highlights the fact that

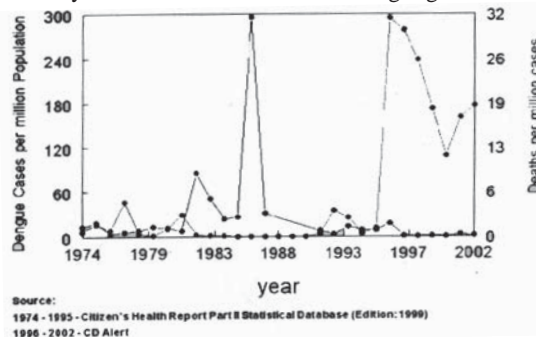


Fig. 2 Major dengue outbreaks in India from 1974-2002.

over the last ten years, although the number of dengue cases have remained stable apart from the big epidemic in 1996, the percentage of death are rising. Another study states that over a five year period (1999-2003) there was a significant increase in the percentage of dengue IgM positive individuals and an increased proportion of children affected by the disease. Approximately 41% of the dengue IgM positive individuals showed positivity for dengue IgG, suggestive of a secondary heterotypic infection<sup>9</sup>.

In 1996, Delhi witnessed one of the largest outbreaks of DHF / DSS in South-East Asia. A total of 8900 – 10,000 cases were reported with a death rate of 40.2%<sup>10</sup>. Subsequently in 2003, 723 confirmed cases were reported from 1<sup>st</sup> June to 28<sup>th</sup> October, of which 4 died. This outbreak was less severe as compared to the previous 1996 outbreak 2005 again witnessed a resurgence of dengue cases in the capital with more than 300 serologically proven cases being reported by the local health authorities.

## MICROBIOLOGICAL FEATURES

**Virus:** Dengue viruses are single stranded RNA viruses of the family Flaviviridae and are the most common causes of arboviral disease worldwide. The virus has 4 closely related but antigenically distinct serotypes (DEN-1, DEN-2, DEN-3 and DEN-4). Infection with one serotype is thought to produce lifelong immunity to that serotype but only a few months immunity to the others. Over the last half century, there has been a notable shift in predominant serotypes from DEN 1 to DEN 2, and now to DEN 3 type.

**Vector:** The principal vector of dengue is *Aedes aegypti* mosquito. It is a small dark mosquito with conspicuous white markings and banded legs. *Aedes aegypti* is a domestic, day biting mosquito that prefers to feed on human blood. In many areas, dengue epidemics occur during the warm, humid, rainy seasons, which favour abundant mosquitoes and shorten the extrinsic incubation period<sup>11</sup>.

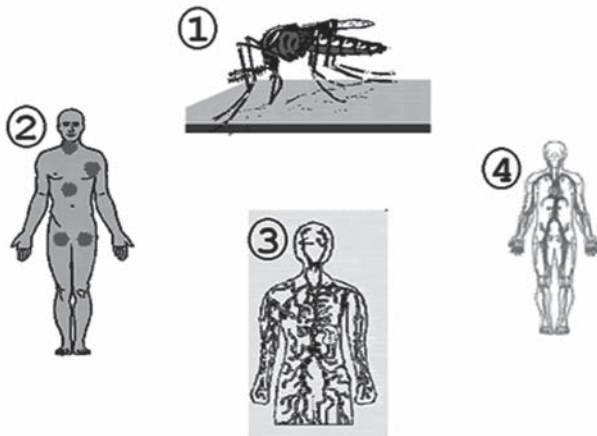


Fig.3 Replication and transmission of Dengue Virus

## LIFE CYCLE (FIG.3)

Humans and mosquitoes are the principal hosts of dengue virus;

the mosquito remains infected for life, but the viruses are only known to cause illness in humans. The transmission of dengue virus occurs through the following steps: (Fig.4)

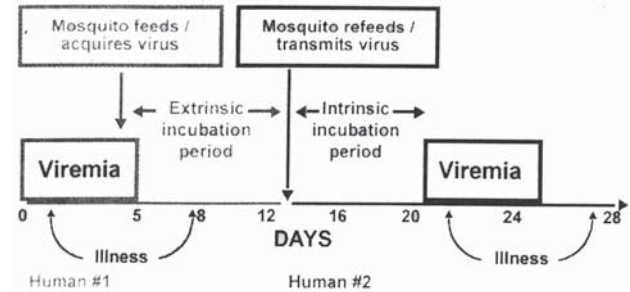


Fig. 4 Relationship of virus transmission with clinical disease

- The virus is inoculated into humans with the mosquito saliva.
- The virus localizes and replicates in various target organs, for example, local lymph nodes and the liver.
- The virus is then released from these tissues and spreads through the blood to infect white blood cells and other lymphatic tissues.
- The virus is then released and circulates in the blood.
- A second uninfected mosquito ingests blood containing the virus.
- The virus replicates in the mosquito midgut, the ovaries, nerve tissue and fat body. If then escapes into the body cavity, and later infects the salivary glands.
- The virus replicates in the salivary glands and when the mosquito bites another human the cycle continues.

Within the mosquito the virus replicates during an extrinsic incubation period of eight to twelve days. The mosquito then bites a susceptible person. Within human the symptoms begin to appear an average of four to seven days after the mosquito bite this is the intrinsic incubation period. This person will have viremia that lasts for about five days<sup>2</sup>.

## PATHOPHYSIOLOGY

Dengue viral antigen has been detected in a various tissues, predominately the liver and reticuloendothelial system<sup>12</sup>. Viral replication is thought to occur primarily in the macrophages. Increased vascular permeability (due to endothelial dysfunction), hemorrhagic manifestations (platelet destruction), and possible disseminated intravascular coagulopathy (DIC) can occur due to severe infection with higher viral titres<sup>13,14</sup>. DHF/DSS usually occurs during a second dengue infection in persons with pre-existing actively or passively (maternally) acquired immunity to any dengue virus serotype<sup>15</sup>.

## CLINICAL FEATURES<sup>2</sup>

The clinical syndromes of Dengue include (a) Undifferentiated fever, (b) Classic dengue fever, (c) Dengue hemorrhagic fever (DHF) and (d) Dengue shock syndrome (DSS). Undifferentiated fever is the most common manifestation of primary dengue infection. Young children often have an undifferentiated febrile illness with a maculopapular rash. Upper respiratory infections,

especially pharyngitis, are common<sup>14</sup>. **Classic dengue fever** presents with abrupt onset of fever accompanied by nausea, vomiting, frontal or retroorbital headache, myalgia, arthralgia and rashes. Fever is usually biphasic and recurs with appearance of a second crop of rash. Although dengue fever is commonly benign, it may be an incapacitating disease with severe muscle and joint pain (break bone fever) This bone pain is usually absent in DHF/DSS. The initial rash is transient, macular, and blanching, and occurs in first 1-2 days of fever. The second rash occurs within 1-2 days of defervescence, morbilliform and maculopopular and spares palms and soles. Miscellaneous symptoms of dengue infection include: Flushing of face, sore throat and cough, cutaneous hyperesthesia, taste aberrations, anorexia, and abdominal pain. Recovery may be prolonged but is usually complete.

**Dengue Hemorrhagic Fever (DHF)** is primarily a disease of children under 15 years in hyperendemic areas<sup>14</sup>. Although DHF generally occurs in secondary dengue infection, it has also been documented in primary infections. Hemorrhagic manifestations affect skin, gingival, nasal, gastrointestinal and genitourinary tracts. *WHO defines a case of DHF as one who fulfills the following four criteria:* (i) Acute high fever for 2-7 days, (ii) hemorrhagic manifestations with positive tourniquet test, (iii) platelet count below one lakh/cmm and (iv) hemoconcentration (rising packed cell volume > 20%) or other evidence of plasma leakage such as ascites or pleural effusion<sup>3</sup>. Furthermore, 4 grades of DHF are recognized depending on severity<sup>3</sup>. These are **Grade-1** fever and constitutional symptoms. A positive tourniquet test is the only finding suggestive of bleeding tendency; **Grade 2** grade 1 manifestations along with spontaneous bleeding; **Grade 3**. Signs of circulatory failure (rapid/weak pulse, narrow pulse pressure, hypotension, cold clammy skin); and **Grade 4**: Profound shock (undetectable pulse and BP).

**Dengue Shock Syndrome (DSS)** is defined as the presence of 4 criteria for DHF (as above) plus circulatory failure presenting directly as frank shock or indirectly as rapid / weak pulse, narrow pulse pressure (< 20 mm Hg or hypotension for age), cold clammy skin and altered mental status. DSS usually occurs 3-6 days after the onset of symptoms. Initial warning signals may be disappearance of fever, rise in hematocrit and drop in platelet count. Presence of severe abdominal pain, intractable vomiting, change, in sensorium or hypothermia, along with any of the features of DHF should send strong alarm signals. Once DSS sets in, mortality is high, to the tune of up to 47%.

**Unusual and rare clinical presentations** of severe dengue infection include severe hemorrhage, hepatic damage, parotitis, cardiomyopathy and neurological complications such as mono / polyneuropathies, encephalopathy, transverse myelitis and Guillain – Barre syndrome<sup>16,17</sup>

## DIAGNOSIS

Clinical diagnosis of dengue depends on the presence of signs of intravascular volume depletion (hypotension or decreased capillary refill), bleeding in to then skin or other sites, positive tourniquet test (Inflate BP cuff to between diastolic and systolic BP for 5 min – appearance of more than 20 petechiae / square

inch indicates a positive test), evidence of increased vascular permeability (pleural effusion/ascites), hepatomegaly, and lymphadenopathy. Dengue needs to be strongly considered in persons who develop fever more than 2 weeks after travel from dengue epidemic area.

Complete blood count may reveal leucopenia, thrombocytopenia (< 100,000/ml), and rising hematocrit (20% increase from baseline). Mild transaminitis may be positive. Imaging studies are useful to document pleural effusion and ascites as well as evidence of intracranial bleed.

Virus isolation in serum using the shell vial culture technique is considered the gold standard for diagnosing DEN viral infections and is possible within 6 days after onset of symptoms<sup>17</sup>. The presence of viral antigen can be detected using amplified fluorescent ELISA from acute sera collected between 2-7 days after disease onset. This test has a sensitivity and specificity of 90% and 99% respectively. Antibodies against dengue virus (IgM and IgG) can be detected 6-21 days after onset or symptoms by enzyme – linked immunosorbent assay (ELISA) antibody capture which is a relatively inexpensive test with sensitivity of 83.9% - 98.4% and specificity of 100%<sup>18</sup>. In addition, a fourfold or greater rise in antibody titer using on day 5 -6 after symptom onset using the hemagglutination inhibition test is suggestive of flavivirus infection<sup>18</sup>. Reverse transcription – polymerase chain reaction (RT-PCR) is a rapid test (results available by 24 hours ) with high sensitivity and specificity for detecting minute quantities of viral material in the patient's serum. However, the downside is the high cost and expertise needed<sup>19</sup>.

A probable diagnosis of dengue is suggested by the presence of at least one of following<sup>14</sup>. *i) Supportive serology* on single serum sample titres > 1280 with hemagglutination inhibition test, *ii) comparable IgT titre* with enzyme linked immunosorbent assay, or *iii) positive IgM antibody test* and case occurrence at same location and time as confirmed cases of dengue fever. A confirmed diagnosis requires at least one of following<sup>14</sup>: *i) Isolation of dengue virus from serum or autopsy samples*, *ii) fourfold or greater increase in serum IgG (by hemagglutination inhibition test)* *iii) or increase in IgM antibody specific to dengue virus*, detection of dengue virus in tissue, serum, or cerebrospinal fluid by immunohistochemistry, immunofluorescence, or enzyme linked immunosorbent assay, or *i) or detection of dengue virus genomic sequence by reverse transcription – polymerase chain reaction.*

## TREATMENT

No effective antiviral drug is available as yet. Treatment is supportive, where continuous monitoring of vital signs and maintenance of proper hydration play a pivotal role<sup>3</sup>. The role of intravenous immunoglobulins and steroids is not clear. Paracetamol is the only drug recommended for fever at present. Other antipyretics and non steroidal anti inflammatory drugs should be avoided. The recommended dose of paracetamol (60 mg/kg) should not be exceeded. Invasive procedures and intramuscular injections should be avoided unless absolutely necessary.

Outpatient management depends on the presence / absence of hemorrhagic features. Stable patients without any hemorrhagic

manifestations may be treated at home with advice of rest and adequate fluid intake. Instructions regarding danger signs must be given (as outlined above) and frequent reevaluation done. Borderline stable patient with hemorrhagic manifestations must be hospitalized and closely observed. Serial platelet count and hematocrit must be monitored daily until fever subsides. The blood pressure should be measured frequently for any sign of

Adapted from: *Guidelines for the Management of Dengue Fever/ Dengue Haemorrhagic Fever in Small Hospitals*, WHO, 1999

weight in lbs	ml/kg/day	weight in kg	ml/kg/day
< 15	100	< 7	220
16 - 25	75	7 - 11	165
26 - 40	60	12 - 18	132
41 - 88	40	19 - 40	88

Table: WHO guidelines for fluid replacement in dengue fever.

hypovolemia. Patients with hemorrhage with presence of any of the warning signs must be hospitalized immediately. Serial and frequent monitoring of blood pressure, hematocrit and urine output is essential. Intravenous isotonic crystalloids should be given to maintain adequate hydration. The volume of fluid needed is similar as in diarrhea with moderate dehydration (5-8% deficit) as recommended by WHO (Table). Some studies suggest that colloids (dextran 70%) restore the cardiac index and normalize the packed cell volume better than crystalloids. The role of platelet transfusion is not routinely recommended and should be reserved for patients with significant bleeding and severe thrombocytopenia, although the exact platelet count at which to start transfusion is debatable.

## PREVENTION

Preventive strategies for dengue are limited. A live attenuated vaccine against all the 4 serotypes is still under development. An effective vaccine for public use may not be available for 5 to 10 years. Therefore, dengue prevention assumes great importance and revolves primarily around mosquito control measures such as reduction of *A. aegypti* vector populations by preventing accumulation of water in domestic locations, use of mosquito

nets, insect repellents containing diethylmethy ItoLuamide (DEET) in 30% to 35% strength for adults and 6% - 10% for children. Although the above preventive measures may be effective in the long run, they are unlikely to affect disease transmission in the near future. There is thus, an urgent need to develop improved, proactive, laboratory based surveillance systems that can provide an early warning of an impending dengue epidemic. Such surveillance results can, at the very least, after the public to take appropriate preventive measures and physicians to diagnose and properly treat dengue/DHF cases.

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