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REVIEW ARTICLE

DENGUE FEVER: A REVIEW ARTICLE

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ABSTRACT: As the outbreaks of Dengue fever increasing in India, one state after other getting affected, it is very essential to know more about this disease and prevalence, any change in the viral strain, severity of the disease pattern, early detection of the virus and early management of the disease resulting in good recovery . Population growth, rapid urbanization, increase in international travel from endemic areas and global warming are playing a major role in disease spread. Measures should be taken to control the aforementioned causes to prevent disease spread and reduce epidemic flare up.

KEYWORDS: Dengue, flaviviridae, polymorphism, MAC-ELISA, NS1 Protein.

INTRODUCTION: HISTORY: The origin of word "dengue" is derived from the Swahili phrase ka-dinga pepo which describes the disease is being caused by an evil spirit. The Swahili word Dinga had its origin from Spanish word dengue, meaning fastidious or careful which would describe the gait of a person suffering the bone pain of dengue fever. The term Break Bone Fever was applied by Benjamin Rush in 1789 report from the Philadelphia epidemic. He used the name "bilious remitting fever". The term dengue fever came into use after 1828. The first record of a case of probable dengue fever is in a Chinese medical encyclopedia from Jin Dynasty (265-420AD) which referred to a "water poison" associated with flying insects.

In 1906, Aedes mosquitoes transmitting the dengue fever was confirmed and in 1907, Dengue was the second disease after "yellow fever" that was shown to be caused by virus. Dengue hemorrhagic fever is first reported in Philippines in 1953, and in 1981 in South America.

EPIDEMIOLOGY: Dengue is believed to infect 50 to 100 million people worldwide in a year.[1] The mortality is 1-5% without treatment and less than 1% with treatment. Severe disease (dengue haemonhagic fever, D. S. S) carry a mortality of 26%. The incidence of dengue in increased 30 fold between between 1960 and 2010. This increase is believed to be to be due to multiple factors like, rapid urbanization, population growth, increase is believed international travel from endemic areas and lastly global warming. The geographical distribution is around the equator mainly affecting Asia and pacific regions.

In India, First outbreak was reported during 1963 in Kolkata.[2] The next major outbreak of Dengue/Dengue Hemorrhagic Fever was reported in Delhi and neighboring states in 1996. Data for the last 10 years reveal maximum number of cases due to. Dengue/DHF were reported in year 1996, (16,000) while the next increase was noted in year 2003. (12,000).

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Dengue cases & death since 2001 (Govt. of India):

Year	2001	2002	2003	2004	2005	2006
No. of cases	3306	1926	12754	4153	11985	12317
Death	53	33	215	45	157	184

Table 1

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Year	Male		Female	
	Total no. of suspected dengue cases	No. of positives (%)	Total No. of suspected dengue cases	No. of positives (%)
2006	370	110 (29.7)	208	94 (45.1)
2007	300	120 (40.0)	217	112 (51.6)
2008	298	126 (42.2)	200	124 (62.0)
Total	968	356 (36.77)	625	330 (52.8)

Table IIa. Year-wise and gender-wise distribution of suspected cases of dengue fever and dengue IgM positive cases over a three year period (2006-2008)

Year	Children		Adults	
	Total no. of suspected dengue cases	No. of positives (%)	Total no. of suspected dengue cases	No. of positives (%)
2006	448	182 (40. 6)	130	22 (16. 9)
2007	388	195 (50. 2)	129	37 (28. 6)
2008	368	202 (54. 8)	130	48 (36. 9)
Total	1204	579 (48. 08)	389	107 (27. 50)

Table IIb. Year-wise and age-wise (children and adults) distribution of suspected cases of dengue fever and dengue IgM positive cases over a three year period (2006-2008)

Virology: Dengue (pronounced Den' gee) is a disease caused by any one of closely related dengue viruses (DEN1, DEN 2, DEN 3 & DEN 4).[3] The viruses are transmitted to human by the bite of an infected mosquito, Aedes Aegypti but 2001 outbreak in Hawaii was transmitted by Aedes Albopictus. The Asian genotypes of DEN-2 and DEN-3 are frequently associated with severe disease.

Dengue virus is a RNA virus of the family flaviviridae[3]; they are otherwise called arboviruses. The dengue virus genome contains 11,000 nucleotide bones. They have 3 different protein molecules that form virus partied (C, prM and E) and 7 other types of protein molecules (NSI, NS2a, NS2b, NS3, NS4a, NS4b, NS5) that are found in infected host cells and are required for replication of virus. There are 4 strains of virus, ex; DEN1, DEN2, DEN3, DEN4. ALL 4 serotypes can cause full blown disease. Infection with 1 serotype is believed to produce lifelong immunity to that serotype, but he can be infected with other serotypes in future.

The humans are the primary host for dengue viruses & transmitted by Aedes mosquitoes. A mosquito that takes a blood meal from a infected person become infected with virus. In 8 to 10 days,

the virus spreads to tissues like salivary gland from the gut of the mosquito. The virus seems to have no detrimental effect on the mosquito. Aedes mosquitoes live in close proximity to humans. Dengue may also get transmitted via infected blood products and through organ donation. Vertical transmission from mother to child can also occur during pregnancy.

Predisposing Factors: Dengue causes severe disease in babies and children more so in healthy babies. Women are at high risk than men. Dengue many be life threatening in people with diabetes & Br. Asthama – Polymorphisam (Normal variation) in particular genes may decrease the risk of severe dengue complications like TNF Alpha, Mannan – Binding protein, CTLA4, TGFBeta, DC-SIGN, G6PD deficiency individual are at high risk. Polymorphism in the genes for the vitamin D receptor, and Fcr R seem to offer protection.

Mechanism: When a mosquito carrying DENV bites a person, the virus enters the skin together with the mosquito's saliva. It binds to and enter the white blood cells, and reproduces inside the cells while they move throughout the body. The white blood cells respond by producing a number of signalling proteins (Such as interferon) that are responsible for many of the symptoms, such as the fever, the flu-like symptoms and the severe pains. In severe infection, the virus production inside the body is much increased, and many more organs (Such as the liver and the bone marrow) can be affected, and fluid from the bloodstream leaks through the wall of small blood vessels into body cavities. As a result, less blood circulates in the blood vessels, and the blood pressure becomes so low that it cannot supply sufficient blood to vital organs. Furthermore, dysfunction of the bone marrow leads to reduced numbers of platelets, which are necessary for effective blood clotting; this increases the risk of bleeding, the other major complication of dengue.

Severe disease it is not entirely clear why secondary infection with a different strain of DENV places people at risk of dengue hemorrhagic fever and dengue shock syndrome. The most widely accepted hypothesis is that of antibody-dependent enhancement (ADE).

Dengue Fever: Clinical Features: The characteristic symptoms of dengue are: a sudden-onset fever, headache (Typically behind the eyes), muscle and joint pains, and a rash; the alternative name for dengue, "break-bone fever", comes from the associated muscle and joints pains. The course of infection is divided into three phases: febrile, critical, and recovery.

The febrile phase involves high fevers, frequently over 40°C (104°F) and associated with generalized pain and a headache; this usually lasts 2–7 days. Flushed skin and some small red spots called petechiae, which are caused by broken capillaries, may occur at this point.

The critical phase, if it occurs, follows the resolution of the high fever and typically lasts one to two days. During this phase there may be significant fluid accumulation in the chest and abdominal cavity due to increased capillary permeability and leakage. This leads to depletion of fluid from the circulation and organs. During this phase, organ dysfunction and severe bleeding (Typically from the gastrointestinal tract) may occur. Shock and hemorrhage occur in less than 5% of all cases of dengue but those who have previously been infected with other serotypes of dengue virus ("Secondary infection") have an increased risk of this.

The recovery phase occurs next, with resorption of the leaked fluid into the bloodstream. This usually occurs over a period of two to three days. The improvement is often striking, but there may be

severe itching and a rate. It is during this stage that a fluid overload state may occur, which if it affects the brain may reduce the level of consciousness or cause seizures

Associated Problems: Dengue may occasionally affect several other body systems. This may be either in isolation or along with the classic dengue symptoms. A decreased level of consciousness occurs in 0.5–6% of severe cases. This may be caused by infection of the brain by the virus or indirectly due to impairment of vital organs, for example, the liver other neurological disorders have been reported in the context of dengue, such as transverse myelitis and Guillain Barre Syndrome. Infection of heart and acute liver failure are among the rarer complications of dengue.

Case Definition for Dengue Haemorrhagic Fever: The following must all be present: Fever, or history of acute fever, lasting 2–7 days, occasionally biphasic. Haemorrhagic tendencies, evidenced by at least one of the following:

1. A positive tourniquet test petechiae, ecchymoses or purpura bleeding from the mucosa, gastrointestinal tract, injection sites or haematemesis or melaena. Thrombocytopenia (100 000 cells per mm3 or less).
2. Evidence of plasma leakage due to increased vascular permeability, manifested by: — a rise in the haematocrit equal to or greater than 20% above average for age, sex and population;

Indications for hospitalization for bolus intravenous fluid therapy may be necessary where significant dehydration (10% of normal body weight) has occurred and rapid volume expansion is needed.

Signs of significant dehydration Include[4]:

1. Tachychardia
2. Increased capillary refill time (2s)
3. Cool, mottled or pale skin
4. Diminished peripheral pulses
5. Changes in mental status
6. Oliguria
7. Sudden rise in haematocrit or continuously elevated haematocrit despite administration of fluids
8. Narrowing of pulse pressure (20 mmHg (2.7 kPa)).
9. Hypotension (A late finding representing uncorrected shock).

Essential laboratory tests in assessing a patient's condition, the following tests are recommended:

1. Haematocrit.
2. Serum electrolytes and blood gas studies.
3. Platelet count, prothrombin time, partial thromboplastin time and thrombin time.
4. Liver function tests serum aspartate aminotransferase, serum alanine aminotransferase and serum proteins.

Microvascular fragility may be demonstrated by a positive "tourniquet test"[5]; this test is performed by inflating a blood pressure cuff on the arm to midway between systolic and diastolic blood

pressures for five minutes. The skin below the cuff is examined for petechiae, and a finding of greater than 20 petechiae in a one square inch area is considered positive.

Clinicians need to be aware that hemorrhagic manifestations can also be seen with dengue fever. In one study, a positive tourniquet test was noted at presentation in 36 percent of 28 children with DF; spontaneous bleeding may occur as well.[4]

Differential Diagnosis: Dengue virus infection should be considered in the differential diagnosis of a febrile illness in any patient who has resided in or traveled to an appropriate region in the two weeks before the onset of illness. In patients with the features of DF, the differential diagnosis includes: influenza, enteroviral infection, measles, and rubella. In the appropriate epidemiologic settings, malaria, leptospirosis, and typhoid fever must also be considered, and appropriate laboratory testing performed.

Diagnosis: Clinical diagnosis: The clinical manifestations of dengue fever or dengue hemorrhagic fever with or without shock can be helpful in making a provisional diagnosis: One study of children with febrile illnesses in Thailand reported that some clinical features, such as a positive tourniquet test, leukopenia, thrombocytopenia, and increased serum AST levels, were more frequent in patients with dengue fever than in those with other febrile illnesses.

Laboratory Testing: Confirmation of acute dengue virus infection is most frequently accomplished using serology. Tests for detection of viral antigen have recently become commercially available outside the US and show promise for detection of dengue virus infection in the early stages. The following diagnostic approach to the patient with suspected dengue is recommended if laboratory support is available. An acute phase serum or plasma sample should be obtained. The IgM immunoassay (MAC-ELISA or equivalent) is the procedure of choice for rapid confirmation of the diagnosis.[6] This assay may yield a false negative result if obtained within the first six days of illness. To confirm a positive IgM assay result, or if a patient with suspected dengue virus infection has a negative IgM assay result, a convalescent phase serum sample should be obtained at least 10 to 14 days after the acute phase serum. The acute and convalescent specimens should be analyzed together by a hemagglutination inhibition (HI) or enzyme immunoassays to provide definitive serologic testing for acute dengue virus infection. If a patient with suspected dengue virus infection is seen within the first five or six days of illness and has a negative IgM assay result, the acute phase serum sample can be tested for the presence of the dengue viral NS1 antigen.[7]

A more detailed discussion of serologic testing and viral detection methods follows.

Serologic Testing: The most frequently used serologic tests for the diagnosis of acute dengue virus infection are the hemagglutination inhibition (HI) assay and IgG or IgM enzyme immunoassays.[8] Complement fixation and neutralizing antibody assays are more technically demanding and are used in specialized laboratories only.

The HI assay historically has been and remains the gold standard for serologic testing for dengue virus-specific antibodies. Analysis of paired acute and convalescent serum samples is essential; a fourfold or greater rise in HI antibody titer between acute and convalescent samples defines acute infection. The antibody response will depend on whether the patient has primary or secondary dengue

virus infection. In primary infection, HI antibodies develop late (After the fifth day of illness) and reach titers of less than 1:1250 in the convalescent phase. By contrast, HI antibodies rise early in secondary infection and reach titers above 1:1250 (often 1: 10,240 or higher) in the convalescent phase.

Immunoassays for the detection of dengue virus-specific IgG antibodies have demonstrated sensitivity and specificity of approximately 99 percent and 96 percent, respectively, compared to the HI assay. As with the HI assay, diagnosis of acute dengue virus infection using the IgG enzyme linked immunosorbent assay (ELISA) requires testing of paired acute and convalescent serum samples, showing a greater than four-fold rise in antibody titer.[7]

One assay that can use a single blood specimen for diagnosis of dengue infection is the IgM antibody capture ELISA or MAC-ELISA. Dengue virus-specific IgM antibodies are typically detected by the MAC-ELISA by about the sixth day of illness and persist for 30 to 90 days. If positive, this test can assist in rapid diagnosis of the patient with dengue infection. However, the sensitivity and specificity of this assay is much lower than the HI assay. In one study of Thai children with predominantly secondary dengue virus infections, only 29 percent of subjects had a positive result in the MAC-ELISA by the time of defervescence. Factors that reduce the sensitivity or specificity of the MAC-ELISA include occasional blunting of the IgM antibody response in secondary dengue virus infections and the potential for positive results to reflect recent rather than acute dengue virus infection.

Virus detection Isolation of dengue virus or detection of dengue viral RNA or protein in an acute phase serum or tissue specimen provides the most definitive confirmation of infection. Virus isolation and RT-PCR should generally be performed only when needed for epidemiologic purposes or as part of clinical research studies.

Serum or plasma are the preferred specimens for virus isolation, although virus can occasionally be isolated from liver tissues after clearance of virus from the serum. Regardless of the specific method used, optimal detection is achieved when specimens are obtained early after the onset of symptoms, during the febrile period].

Reverse transcriptase-polymerase chain reaction (RT-PCR) has comparable sensitivity to viral isolation. Although technically demanding and not widely available, RT-PCR is the only method that can detect virus within a clinically meaningful time frame (one to two days).[9]

Dengue viral proteins can be detected in tissue samples using immunohistochemical staining. Liver tissues appear to have the highest yield. However, since liver biopsy is rarely indicated in patients with suspected dengue virus infection, this method is generally only used for postmortem diagnosis.

The dengue viral nonstructural protein 1 (NS1) can be detected in plasma, especially during the first five to six days of illness. In one study, high levels early in infection were associated with DHF.

Ultrasound: Ultrasound was demonstrated to be useful in the detection of plasma leakage in DHF in one study of 158 suspected cases in Thailand.[10] Plasma leakage occurred as early as three days after the onset of fever; pleural effusions were most common.

Treatment: Since, as noted above, there is no specific therapy available for dengue virus infections, it is important to exclude other treatable diagnoses. Patients at risk for dengue can acquire other diseases with similar clinical features, such as malaria, typhoid fever, and leptospirosis. Symptoms in patients with dengue virus infections resolve in five to seven days.

Supportive treatments are available for the specific disease manifestations of dengue virus infection.

Dengue Fever: Patients with dengue fever should be cautioned to maintain their intake of oral fluid to avoid dehydration. Fever and myalgias can be managed as needed with acetaminophen. Aspirin or nonsteroidal antiinflammatory agents should generally be avoided because of the risk of bleeding complications and in children because of the potential risk of Reye's syndrome. The most important measure to assist the patient with dengue fever is to carefully evaluate the patient for impending complications, such as early evidence of DHF, as described below.

Dengue virus infection with significant Bleeding: Gastrointestinal bleeding or menorrhagia in patients with DHF, and occasionally in patients with dengue fever as well, can be severe enough to require blood transfusion. Factors that contribute to bleeding include thrombocytopenia due to decreased platelet survival and, in severe cases, frank disseminated intravascular coagulation. . Platelet transfusions are rarely given, but may be warranted in patients with severe thrombocytopenia (<10,000/mm3) and active bleeding.

Dengue Hemorrhagic Fever: Plasma leakage in DHF is important to manage with aggressive intravascular volume repletion to prevent or reverse hypovolemic shock. In mild cases, particularly when medical attention is received early, oral rehydration may be sufficient. However, in patients with established intravascular fluid loss, intravenous fluid administration is recommended. Blood transfusion is appropriate in patients with significant bleeding.

Treatment of Shock: A protocol for intravenous fluid therapy has been developed by the World Health Organization (WHO) based upon clinical experience mainly in children from Southeast Asia.[11] For patients with shock, an initial bolus of five percent dextrose in normal saline or Ringer's lactate (10 to 20 mL per kg of body weight) infused rapidly is recommended, followed by continuous infusion (10 to 20 mL/kg per hour) until vital signs and urine output normalize. The infusion rate can then be gradually reduced until it matches plasma fluid losses.

The adequacy of fluid repletion should be assessed by serial determination of hematocrit, blood pressure, pulse, and urine output. Patients with shock on presentation should initially have vital signs measured at least every 30 minutes and hematocrit measured every two to four hours. Narrowing of the pulse pressure is an indication of hypovolemia in children even with a normal systolic blood pressure. Normalization of the hematocrit is an important goal of early fluid repletion; however, a normal or low hematocrit may be misleading in patients with overt bleeding and severe hypovolemia.

Close clinical observation is essential, even after normal blood volume is restored, because patients can develop shock for one to two days after initial fluid resuscitation, which represents the period of increased vascular permeability in DHF. Most patients who present for medical attention before profound shock develops and who receive appropriate fluid therapy will recover quickly.

The fluids that are lost into tissue spaces during the period of plasma leakage are rapidly reabsorbed. Thus, intravenous fluid supplementation should be discontinued once patients are taking oral fluids and have normal hematocrit, vital signs, and urine output. Usually no more than 48 hours of intravenous fluid therapy are required. Excessive fluid administration after this point can precipitate hypervolemia and pulmonary edema.

In the absence of complications from prolonged hypotension or from medical interventions, most patients with DHF will have stabilized within a few days of admission. Discharge from the hospital

is appropriate when patients have been afebrile for at least 24 hours and have normal oral intake, urine output, and hematocrit.

The basis of DHF pathogenesis is hypothesized to be immunologic, which has led to interest in immunomodulatory drugs for therapy. However, a meta-analysis of four trials involving 284 participants found that corticosteroids were no more effective than placebo in reducing the number of deaths, the need for blood transfusion, or the number of serious complications.

Unusual Complications: Encephalopathy and liver failure are uncommon manifestations of DHF, which are associated with a high mortality rate.[12] While seizures or jaundice should always be regarded as indicative of severe disease, no specific treatment is available.

Outpatient management and early recognition of DHF: Because dramatic plasma leakage can develop suddenly, substantial attention has been placed upon the early identification of patients at higher risk for shock and other complications.[3] The following clinical features are helpful in this determination: Duration of illness: The period of maximum risk for shock is between the third and seventh day of illness. This tends to coincide with resolution of fever. Plasma leakage generally first becomes evident between 24 hours before and 24 hours after defervescence. "Alarm signs"[6] Severe abdominal pain, persistent vomiting, abrupt change from fever to hypothermia, or abnormal mental status, such as disorientation, are noted in a minority of patients. In one study, these signs developed less than one day prior to hospitalization. Hematocrit. An elevation of the hematocrit is an indication that plasma leakage has already occurred and that fluid repletion is urgently required. Platelet count: Severe thrombocytopenia (<100,000/mm 3) is one of the clinical criteria for DHF and usually precedes overt plasma leakage. Serum aspartate transaminase (AST) Mild elevations in serum transaminases are common in both dengue fever and DHF. However, levels are significantly higher in patients with DHF, and elevated AST levels are noted earlier in illness than the other signs listed above. . Soluble dengue NS1 protein — Blood levels of soluble dengue NS1 protein (>600 mg/mL) were predictive of DHF in one study of Thai children with secondary dengue 2 virus infections.[13]

There were no deaths among 162 adults studied (Average age 27 years), of whom 28 (17 percent) had DHF; the overall hospitalization rate was 44 percent. All of the subjects with DHF either were hospitalized or qualified for hospitalization according to the protocol, whereas 89 (66 percent) of the subjects without DHF were managed without hospitalization.

FUTURE DIRECTIONS: To develop an anti-dengue drug, animal model systems are needed for drug testing. A dengue mouse model has been validated and demonstrated to be a suitable test system for antiviral drugs. In one study, administration of an antiviral agent targeting dengue RNA-dependent RNA polymerase significantly reduced viremia in a dose-dependent manner

PREVENTION: The greatest risk for dengue virus infection is in individuals residing in endemic areas and not in travelers.

Public health efforts in endemic areas: Control of the Aedes aegypti mosquito, which transmits dengue virus, and the development of vaccines are two potential approaches in preventing dengue virus infections.

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Mosquito Control: Mosquito control is the most effective approach to the prevention of dengue transmission. Programs targeting the Aedes aegypti mosquito as a means to eliminate urban yellow fever in the Americas from the 1940s through 1970s were quite successful. These programs were also effective at reducing dengue transmission in the region. These programs were based on a "top down" approach involving aggressive mosquito surveillance and insecticide use. However, lack of attention and funding of these programs in the 1970s led to re-emergence of A. aegypti throughout its former region and the corresponding re-emergence of dengue.

Insecticide spraying, in response to dengue outbreaks, is not highly effective against A. aegypti mosquitoes, which frequently breed inside houses. Community-based approaches involving education of the population in efforts to reduce breeding sites, such as discarded tyres and other containers that accumulate standing water.

In one study, a comprehensive community and governmental control strategy, including the seeding of water vessels with Copepods (Fish) that feed on mosquito larvae, was successful in eliminating A. aegypti and dengue transmission in 32 communities in rural areas of Vietnam.

Vaccination: Infection with dengue provides long-term protection against the particular serotype that caused the disease, supporting the feasibility of a dengue vaccine. However, it provides only short-lived immunity to the other three dengue serotypes. In view of the association of DHF with previous exposure to dengue viruses and the recognition that all four serotypes are capable of inducing DHF it is the general consensus in the scientific and public health communities that any candidate vaccine should produce protective immunity against DEN 1-4. Since waning immunity might also increase the risk for DHF in vaccinees, vaccine-induced protective immunity should also be long-lived.

Animal studies indicate that protective immunity against dengue can be mediated by neutralizing antibodies, especially those directed against the envelope (E) glycoprotein. However, natural dengue infection induces low levels of cross-reactive antibodies that are detected in neutralization assays, but do not prevent infection with the other dengue serotypes. Studies have shed light on the molecular basis for antibody neutralization of virus infection; however, until improved assays are available the cross-reactivity will continue to complicate the laboratory assessment of vaccine-induced immunity.

Tetravalent vaccines that induce immunity against all four serotypes are in development. In a rhesus monkey model, one tetravalent live attenuated dengue virus vaccine demonstrated seroconversion rates of 100, 100, 90 and 70 percent against dengue serotypes 1, 2, 3, and 4. In addition, vaccination resulted in complete protection against viremia from inoculation with serotype 2; challenge with the other dengue serotypes demonstrated protection in 50 to 80 percent of animals compared to controls.

Recommendations for travelers: Most travelers from non-endemic countries are at exceedingly low risk for DHF because they lack previous exposure to dengue viruses.[14] Avoidance of exposure to infected A. aegypti mosquitoes is the primary approach to prevention of dengue virus infections in travelers. These mosquitoes predominantly live in urban areas in and around houses.

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