

Systematic Review On: Dengue

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ABSTRACT

Dengue fever, a mosquito-borne viral illness caused by the dengue virus (DENV), is a significant global health issue, particularly in tropical and subtropical regions. This review provides an in-depth analysis of dengue fever, covering its structure, history, classification, epidemiology, signs and symptoms, diagnostic approaches, management, treatment options, prevention strategies.

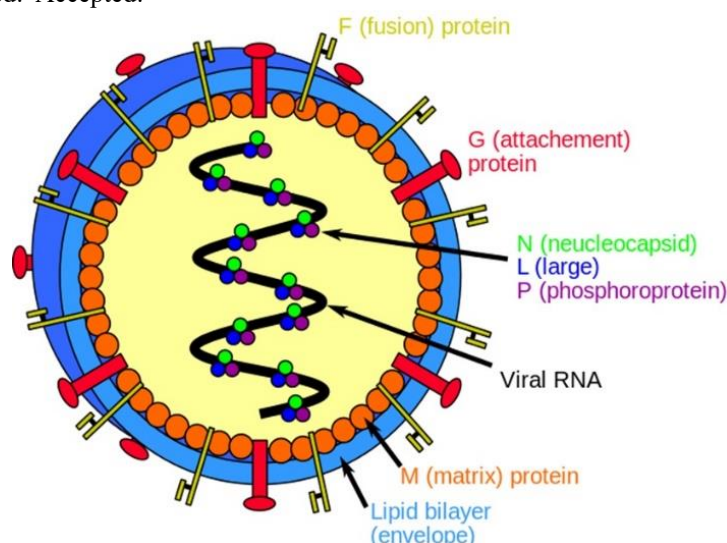
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INTRODUCTION

Dengue fever is a crippling disease spread by mosquitoes that is commonly called "breakbone fever" because of the severe agony it produces. The *Aedes* mosquito species, particularly *A. aegypti* and *A. albopictus*, are principally responsible for its spread, which is commonly referred to as "Fever with broken bones" because of the intense pain in the muscles and joints. There are now a lot of documented cases of dengue fever in India. these days, rare infection syndromes and pathogens are frequently sensationalized in public health headlines, and dengue virus (family Flaviviridae) infection is becoming a more significant endemic issue in many regions of the world. there are 4 type of dengue virus: DengueVirus-1, DengueVirus-2, DengueVirus-3, and DengueVirus-4. Although they have diverse antigenic characteristics, they are connected to one another. Numerous genotypes or subtypes exist within each serotype.[1] Dengue is spread by a variety of *Aedes* mosquito species, chief among them *Aedes aegypti*. There are four different virus species; Infection with one typically results in permanent immunity to that strain and only temporary defense against the other types. Since the 1960s, dengue fever has become much more common, infecting between 50 and 100 million people annually. Early accounts of the illness go back to 1779, and in the early 1900s, the viral cause and mode of transmission were identified. Since the Second World War, dengue has spread around the world and is endemic in more than 110 nations. Apart from eliminating the mosquitos, endeavors are underway to create a vaccine and medications that particularly target the virus.[2] Acute viral infections like dengue can have deadly consequences. The phrase "dengue virus" The phrase "dengue fever" did not become widely used until about 1828, despite the fact that myalgia and arthralgia symptoms were recognized earlier. The family Flaviviridae includes dengue viruses. The virus can be divided into four serotypes, which are called DengueVirus-1, DengueVirus-2, DengueVirus-3, and DengueVirus-4. The positive-sense, enveloped RNA virus known as DV is made up of seven non-structural proteins. Three structural protein genes, which code for the envelope (E), membrane-associated (M), and core (C) glycoproteins, are present in its genome.[3]

STRUCTURE OF DENGUE VIRUS

Dengue has a 50 nm, approximately round virus that is produced from the host cell and is encased in a lipid bilayer membrane. A brief transmembrane region connects the envelope (E) protein, which is present in around 180 identical copies, to the surface of a virus membrane. The other protein, which travels across the lipid Bi-layer with the E type protein, is referred to as the membrane (M) protein. The genome of the virus and the pericapsid C proteins make up nucleocapsid, which is located inside the virion. The one big polyprotein encoded by the roughly 11,000 nucleotides that make up the viral genome is broken into many mature NS (nonstructural) and structural peptides. 3 structure proteins C, prM and E protein, 7 nonstructural proteins (NonStructural-1, NonStructural-2a, NonStructural-2b, NonStructural-3, NonStructural-4a, NonStructural-4b, and NonStructural-5), and brief Non-coding sections at the 3' and 5' close make up is polyprotein. The M and C protein, and the E glyco-protein, are the dengue virus's structural proteins. The prM precursor is cut off into the type M protein by the enzyme furin. The glycoprotein type E carries as the virus neutralizing epitopes and is crucial for the virion's attachment to the receptor. Furthermore, It makes the fusion of the virus envelope and the target cell's membrane easier. Arole role protective immunity has also been linked to one NS protein, NonStructural-1, Together with the glycoprotein E. NonStructural-3 functions as both a Helixase and protease, while NonStructural-5 acts as a polymerase of RNA responsible for replicating the viral RNA.[4]



Figuer-1 structure of dengue virus

HISTORY

The dengue virus was first discovered in Calcutta 1944 saw the creation of kolkata India, from concentrate samples taken from United States warriors, and it was first discovered in Japan in 1943 by inoculating patient serum into nursing mice. The 1st recorded pandemic of a scientific dengue like disease occurred in Maharashtra in 1780. The Philippines saw the 1st significant outbreak of Dengue Hemorrhagic Fever 1952 and 1954. After then, DHF quickly expanded throughout the world. Despite the fact that DHF grew common in nearby nations, India did not record any cases of the condition despite having all the relevant risk factors. The reasons for this are still unknown. DHF has been operating in different parts of India since 1988. In 1996, DHF/DSS saw its first significant nationwide outbreak in India, affecting the regions surrounding Delhi and Lucknow 12, 13, and 14 before spreading over the entire nation. [5] dengue fever in humans may be as ancient as humankind itself. Between AD 265 and 422, a Chinese health care encyclopedia from the Jin Dynasty includes some of the earliest known documents that potentially describe cases of dengue fever. With an epidemiological perspective, the publications characterize the illness as "poisoned water" connected to flying creatures. 2 millennia later, in 1635 and 1699, the Caribbean had the first outbreaks of a disease similar to classical dengue fever, long before the simultaneous epidemics that are claimed to have taken place throughout North America, Asia, and Africa 1779 and 1780. This reports strongly imply that vector dissemination was common 200 years ago. Benjamin Rush created the name "breakbone fever" in 1789 after reporting the first confirmed instance of the illness. Major epidemics have been identified globally every 20–40 years since then. One reason for the absence of epidemic dengue between 1946 and 1963 is that the efforts to eradicate *Aedes aegypti* in order to prevent urban yellow fever were somewhat successful. Dengue has since returned and spread rapidly throughout the area. Significant ecological and demographic changes brought about by World War II, such as increasing numbers of vulnerable people in endemic areas and high civilian and troop mobility, contributed to the dengue virus's proliferation throughout the Asia-Pacific area. Carriers' travel, the growth of the economy, and ongoing urbanization made it easier for adult vectors to reproduce and spread the virus. [6]

CLASSIFICATION

The world health organization started categorizing instances of symptomatic dengue infection as DF or DHF/DSS in the 1960s. When thrombocytopenia (platelet count <100,000), hemorrhagic phenomenon, fever or a history of two to seven days of fever, and proof of plasma discharge due to enhanced permeability of the vessel were all present, DHF was considered to be present. Four severity degrees were used to further categorize DHF, grades 3rd and 4th being regarded as Dengue shock syndrome representatives. 2009 saw the introduction of a revamped World Health Organization (WHO) case categorization system that replaced the previous DHF/DSS and DF classifications with dengue with and without warning symptoms and SD. Nonetheless, the outdated WHO categorization from the 1960s is still often applied. A person must have a history of living in or traveling to an endemic area, have a high temperature, and have at least 2 of the signs listed below in order to be diagnosed with a probable case of dengue: nausea or spitting, unsightly, sores and suffering, neutropenia, or any caution signals. A substantial decrease in platelet count along with an increase in hematocrit levels, lethargy, prolonged vomiting, abdominal discomfort or tenderness, liver enlargement, and apparent fluid accumulation are all warning indications of dengue. Significant bleeding, significant organ damage, or dengue shock-plasma leakage that can result in shock from fluid accumulation-with or without respiratory insufficiency-must all be present in order for SD to be diagnosed. [7]

EPIDEMIOLOGY

Recent map-based research from the college of Oxford suggests that India is likely to have the highest annual number of dengue cases, with about 33 trillion symptomatic cases and an extra 100 million silent illness. People are traveling to neighboring states more frequently for work and education, which is one of the key causes of the increased epidemic rate. Poor sanitary facilities could also be a contributing factor, as they provide rich environments for vectors to breed. High dengue prevalence has been reported in numerous research conducted around the country. However, The prevalence of dengue in middle India is not well documented. The coexistence of several dengue virus geno-types and sero-types in U.P, India, is alarming. In India, September, October, and November are the months when dengue fever is most commonly transmitted. These results are in line with studies carried out in central India by Gupta and colleagues as well as Ukey and colleagues. They said that there may be more mosquito breeding sites available and that post-monsoon water collecting is the primary cause of this fluctuation. It also display that female are less more probable than males to have dengue. This is supported by other research. still, this runs counter to studies carried out in other Indian locations which reported a female preponderance. The disparity between the sexes in terms of infection rates could be attributed to household orientation and lower female migration in rural areas. Further observation has revealed that the most affected group was North Indian youth, specifically those aged 21 to 30. A Delhi-based study revealed that those in the 21–30 age range are the most affected among the sample population. According to a Kanpur study, people in the 0–15 age range were the most exaggerated.[8]

SIGNS & SYMPTOMS

Approximately 80% of dengue virus infections either have no symptoms at all or only have minor ones, such a low-grade fever. On the other hand, in roughly 5% of cases, the illness might worsen and become potentially fatal. The incubation period, which is the interval between being exposed to the virus and experiencing symptoms, usually lasts between 4 and 7 days. There is therefore little chance that the sickness is caused by dengue fever if symptoms like fever start to show up more than fourteen days following a returns from a place where dengue is prevalent. Early symptoms are usually mild but include high temperature; youngsters are more prone to have serious complications and often have symptoms (vomiting and diarrhea) comparable to gastroenteritis and the common cold. Rapid fever onset, headache, joint or muscle pain, and unsightly are the hallmarks of dengue. A different name for dengue that describes the associated joint and muscle symptoms is "breakbone fever". The course of an infection has three stages: fever, acute illness, and recovery. A high fever, often exceeding 40 °C (104 °F), headache, and generalized discomfort are the hallmarks of the febrile phase, which usually lasts two to seven days. There may also be vomiting. Fifty to eighty percent of persons with symptoms develop a rash. either as flushed skin on the 1st or 2nd day of symptoms, or subsequently in the disease as a rash mimicking the measles outbreaks. This is the time when some petechiae, which are little red spots that bleed slightly from the mouth and nose mucous membranes and do not go away when the skin is squeezed, may start to show.[9]

DIAGNOSIS

1. NS1 Antigen Test

- Procedure:
- Collect blood sample.
- Use NS1 antigen test kit.
- Add serum to the test device and wait 15-20 minutes.
- Interpretation: Positive result indicates active dengue infection within the first 1-7 day of illness

2. Urine Examination

- Purpose: Evaluate renal function and detect hematuria or proteinuria, which may occur in severe dengue.
- Procedure:
- Collect a urine sample.
- Perform a dipstick test and microscopic examination.
- Interpretation: Presence of blood or protein in urine may indicate renal involvement.

3. Kidney Function test:

- Purpose: Asses renal function, which can be affected in severe dengue cases.
- Procedure:
- Collect blood sample.
- Take a blood urea nitrogen (BUN) and serum creatinine reading.
- Interpretation: levels of Elevated suggest impaired kidney function.

4. Liver function test:

- Purpose: Evaluate liver function, as dengue can cause hepatic injury.
- Procedure:
- Collect blood sample.
- Measure level of ALT, AST, bilirubin, and alkaline phosphate.

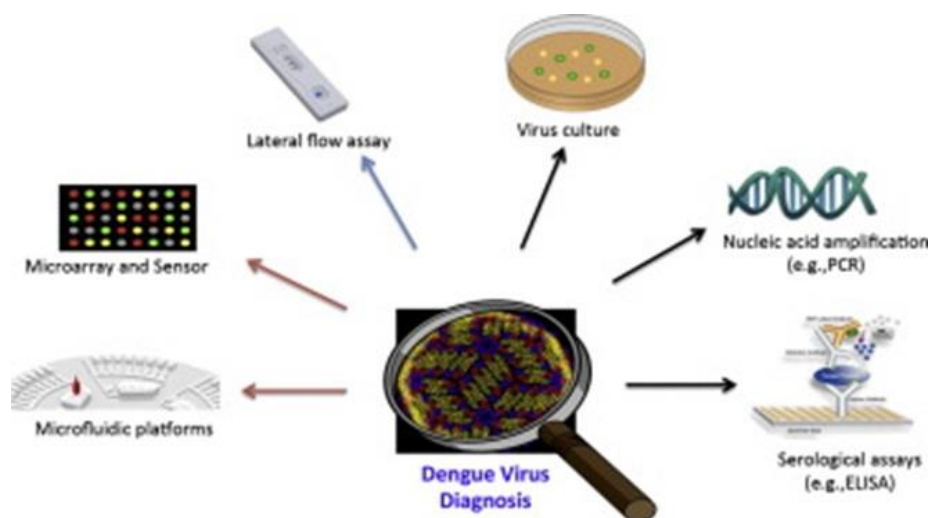
- Interpretation: Elevated liver enzymes and bilirubin level indicate liver damage.

5. Compleat blood count (CBC) Test:

- Purpose: monitor the blood cell counts and detect dengue-induced changes.
- Procure:
- Collect blood sample.
- Use an automated hematology analyzer to measure WBC, RBC, hemoglobin, hematocrit, and platelet count.
- Interpretation: Leukopenia and thrombocytopenia are common findings in dengue.

6. Differential leukocyte count:

- Purpose: Analyze the proportion of different type of white blood cells.
- Procedure:
- Collect blood sample.
- Perform a peripheral blood smear and manual differential count or use an automated analyzer.



Figuer-2 diagnosis of dengue virus

MANAGEMENT

Fluid administration in cases of severe dengue

Vascular permeability is markedly increased in DSS, the most serious form of DHF. The difference in heart rate between the Systolic and diastolic measurements phases, or pulse pressure, is a crucial marker of plasma leakage. "Diastolic blood pressure usually starts to rise before overt shock appears, and pulse pressure may narrow. pulse rate of under 20 millimeters per hour is indicative of disseminated intravascular coagulation (DIC), As stated to the WHO. Treating this illness effectively requires restoring circulating plasma volume as soon as possible." There is disagreement over the ideal intravenous fluid selection. According to the 1975 World Health Organization's care guidelines, patients with refractory shock were formerly instructed to refill their volume first with crystalloid solutions and then with colloids.

Exchange of Blood Products

The medical personnel treating dengue patients frequently faces the difficult decision of if a patient should receive a platelet transfuse or not. The country's platelet inventory is in danger due to the exponential increase in demand for platelet concentrates that follows most dengue epidemics. In the course of the 2013 Dengue outbreak in India, a single-center study carried out by AIIMS, New Delhi, found that 531 patients got 1750 RDPs (random donor platelets) and 114 SDPs (single donor platelets); of these, 23.2% of the transfusions were considered inappropriate. Furthermore, tendency to bleed typically doesn't correspond with normal number of platelet in youngsters, but can occur in them. Thus highlights the need to clarify the appropriate use of platelet transfusions in patients with thrombocytopenic dengue who have visible bleeding, regardless of size.

(a) Transfusions of platelets for prevention

Prophylactic platelet transfusion did not significantly improve supportive treatment alone, nor did it stop bleeding or speed platelet recovery in a number of studies conducted on adult dengue patients. Based on current research, Platelet transfusions for prophylaxis are usually not necessary in adult dengue patients with thrombo-cytopenia who are not bleeding actively. Further solid evidence is necessary to assess the necessity of such therapies for pediatric cases or those with severe dengue. When the count falls below 10,000/mm³, many units think about transfusing platelets.

(b) Patients undergoing platelet transfusion for both minor and serious bleeding

Forty-four dengue patients who were bleeding because their platelet counts were low had their absolute platelet count raised by 50% to 100% by platelet infusions. However, thromboelastography (TEG) measurements of clot strength showed no discernible improvement or clinical bleeding outcomes impact from these transfusions. This preliminary investigation was conducted on these patients. In a different trial, platelet transfusion was linked to a severe adverse reaction rather than preventing the progression of mild to severe bleeding in youngster dengue fever patients with thrombo-cytopenia and No or minimal hemorrhage.

Platelet Fraction of Immature (PFI)

One measure of bone marrow healing in patients with idiopathic pulmonary fibrosis (IPF) is the amount of reticulated platelets in the incidental blood. Analyzing red blood cells' reticulocyte count—which sheds light on bone marrow activity—is comparable to this procedure. As a result, PMP levels were higher in dengue patients with thrombocytopenia who did not have bleeding than in those who did. This led to the hypothesis that PMPs' procoagulant effect might be protecting these patients; PMPs might also be a biomarker for determining whether to administer prophylactic platelet transfusion.

Co-infection of SAR-CoV-2 with dengue

Serious health problems and a more intense course of COVID-19 are linked to co-infection with dengue virus and SARS-CoV-2. According to studies, individuals who have both viruses tend to have more severe illnesses, a greater admission rate to the intensive care unit, and a higher death rate than those who just have one virus infection. This has been linked to the 2 pathogens' similar pathophysiology for cause thrombocytopenia, coagulopathy, artery leakage, and cytokine storms; in a coinfection, both viruses damage different organs either independently or together.

Anti-dengue Medicines

There isn't currently a licensed anti-viral drug reachable for the therapy of dengue. Still, a number of anti-DENV drugs that show promise are being examined on people and are in several phases of growth. NonStructur-5 methyltransferase, NonStructural-3pro/NonStructural-2B protease, NonStructural-3 helicase, RNA-depending RNA poly-merase of NonStructural-5, and the E protein are among the dengue virus proteins that are being looked into as potential treatment targets. The dengue virus enters, translates, and replicates in host cells by using a number of host proteins. Anti-DENV medications may also target host proteins such as kinases, glucosidases, and proteases. [10]

TREATMENT

There is no specific antiviral treatment for dengue fever. Management focuses on supportive care:

Hydration: Adequate fluid intake to prevent and treat dehydration is crucial, particularly in severe cases.

Pain and Fever Management: Paracetamol is recommended for fever and pain; NSAIDs are avoided due to bleeding risks.

Monitoring: Regular monitoring of vital signs, platelet counts, and hematocrit levels is essential for managing complications and guiding treatment.

PREVENTION

Effective prevention strategies include:

Vector Control: Reducing mosquito breeding sites through environmental management and the use of larvicides.

Personal Protection: Use of mosquito repellents, wearing long-sleeved clothing, and utilizing insecticide-treated nets.

Community Engagement: Public health campaigns to educate communities about mosquito control and personal protection.

CONCLUSION

Dengue fever remains a major global health issue, with increasing incidence and impact. Effective management involves early diagnosis, supportive care, and robust preventive measures. Continued research into vaccines, vector control, and treatment options is vital for reducing the burden of dengue fever and preventing future outbreaks.

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