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Review Article

Dengue virus: A review

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ABSTRACT

Dengue fever is a mosquito-borne viral illness that is quickly spreading over the globe, with significant death and morbidity rates. Dengue fever is an acute viral infection transmitted by Aedes mosquitos and caused by an RNA virus from the Flaviviridae family. The symptoms might vary from asymptomatic fever to life-threatening complications including hemorrhagic fever and shock. Although dengue virus infections are normally self-limiting, the disease has become a public health concern in tropical and subtropical countries. Dengue fever is a major public health concern owing to its rapid worldwide spread, and its burdens are now unmet due to a lack of accurate therapy and a simple diagnostic approach for the early stages of illness.

1. Introduction

Dengue fever, a mosquito-borne illness spread by the bites of Aedes mosquitos, particularly Aedes aegypti and Aedes albopictus, is the most common human arboviral infection in the world.[1] The dengue virus, a member of the Flavivirus genus and the Flaviviridae family, is an arthropod borne virus with four distinct serotypes (DEN1, DEN2, DEN3, and DEN4). Dengue fever is a severe, flu-like sickness that affects newborns, young children, and adults but rarely kills.

Symptoms typically persist 2–7 days after an incubation period of 4–10 days after an infected mosquito bite.[2] Dengue fever infects over 100 nations, including Europe and the United States (USA). The first dengue viral infection was discovered in South-East Asia, and this region of the globe is home to around 52 percent of the individuals who are at risk of dengue worldwide. The first dengue virus infection was found in South-East Asia and about 52% of the people who are at risk of dengue globally live in this part of the world.[3] The first instance of dengue-like sickness in India was documented in Madras in 1780, and the first virologically proven outbreak of DF in India occurred in Calcutta and the Eastern Coast of India in 1963-1964. A multitude of variables impact dengue incidence and transmission, including uncontrolled population increase, urbanisation, degradation in waste management systems, and a lack of efficient vector control.[4]

1.1. Epidemiology

Dengue epidemiology is a complicated process involving host (man and mosquito), agent (virus) and environment (abiotic and biotic factors). The interplay of these variables affects the amount of endemicity.[5,6]

1.2. Dengue virus

Dengue viruses are classified within the Flavivirus genus. They have single-stranded RNA and are 50 nm in size. Dengue virus has four serotypes: DENV-1, DENV-2, DENV-3, and DENV-4. These serotypes may be in circulation single or in multiples in any given place.

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Despite their antigenic similarities, the four serotypes vary sufficiently to induce cross protection within a few months after infection. A viral serotype infection gives lifetime immunity.

1.3. Molecular epidemiology

The four dengue virus serotypes (DENV-1–4) are phylogenetically related but vary in nucleotide sequence. These are not linked to other flaviviruses and generate their own antigenic complex. Within each serotype, phylogenetic study of the envelope gene genomic area detects the following subgroups or genotypes:

1. DENV-1: 3
2. DENV-2: 2 (one non-human primate)
3. DENV-3: 4 (one non-human primate)

They may coexist in endemic places because immunisation to one serotype does not provide protection against infection by a heterotopous serotype. Anti-dengue antibody responses vary across individuals. Secondary infections raise the chance of serious illness. Antibody responses separate primary and subsequent infections. One of the main differences between DENV and other flaviviruses is the potential of all DENV serotypes to employ pre-existing heterotypic flavivirus antibodies to increase infection. India has all four serotypes.

1.4. Host factor

Dengue virus affects humans and lower primates. All ages and genders are at danger. Passively acquired dengue antibodies in newborns are a risk factor for DHF. Travel to dengue-endemic regions is a major danger. If the patient develops a fever two weeks or longer after travel, it is unlikely to be dengue. Migration of a viremia patient to a no endemic location may bring dengue. Dengue is known to spread geographically through persons travelling from endemic to non-endemic locations.

1.5. Transmission cycle

The female Aedes aegypti gets infected with dengue virus when it feeds on a person's blood during the acute fever (viremia) phase. The mosquito is infected after an 8–10 day extrinsic incubation period. The virus is spread when an infected female mosquito bites and injects saliva into the bite site. This mechanism perpetuates the dengue cycle. Dengue fever starts rapidly after 4–7 days of incubation (range 3–14 days). Virus transfer from infected female mosquitoes to the following generation has been seen.

1.6. Vector

The female Aedes (Ae.) mosquito bites an infected person to spread dengue virus. It is the major vector in most metropolitan areas in India, however Ae. albopictus is also found in several states. Some nations have also implicated Ae. polynesiensis and Ae. niveus as secondary vectors.

She lays her eggs individually on wet surfaces slightly above the waterline. Adults emerge in seven days under ideal circumstances (after the aquatic stages in the life cycle of Ae. aegypti). It may take weeks to emerge at cold temperatures. The eggs may survive desiccation for almost a year and emerge within 24 hours of contact with water. This also hinders dengue prevention and control.

1.7. Dengue symptoms

Dengue fever (40°C/104°F) should be considered when accompanied by two of the following symptoms during the febrile phase:[7]

1. Severe headaches
2. Eye discomfort
3. Muscular and joint pain
4. Vomiting
5. Nausea
6. Swollen glands
7. Rash
8. Severe dengue

The crucial period usually begins 3-7 days following the commencement of the sickness. Symptoms of severe dengue might appear when the patient's temperature drops below 38°C/100°F. Severe dengue may cause death via plasma leakage, fluid buildup, respiratory difficulties, severe bleeding, or organ dysfunction.

1. Severe stomach discomfort
2. Frequent vomiting
3. Fast breathing
4. Bleeding gums
5. Exhaustion
6. Restlessness
7. Blood in vomit

If patients show these symptoms during the critical period, they must be closely monitored for 24–48 hours to provide correct medical treatment and prevent complications and death.

1.8. Laboratory diagnosis

1.8.1. ELISA-based NS1 antigen tests

Dengue NS1 antigen is prevalent in the serum of individuals with early DENV infection. It may be used to diagnose acute dengue infections. It is a simple test with great sensitivity.

NS1 allows early discovery of patients, preventing transmission.

The DENV NS1 ELISA-based antigen assay is commercially available and has been extensively tested for sensitivity and specificity. Due to its specificity, the NS1 test may be used to differentiate between flaviviruses.

1.8.2. IgM-capture enzyme-linked immunosorbent assay (MAC-ELISA)

MAC-ELISA has been frequently utilised recently. It's a basic test that needs no special equipment. MAC-ELISA works by collecting dengue-specific IgM antibodies in the test serum utilising anti-human IgM attached to the solid phase. Then comes dengue antigen. If the patient's serum IgM antibody is anti-dengue, it will attach to the antigen. An enzyme substrate is introduced to produce a colour reaction.

1.8.3. Isolation of dengue virus

Most dengue virus strains may be isolated from clinical specimens if obtained within five days of illness and processed promptly. Autopsy tissues from fatal cases, including liver, spleen, lymph nodes, and thymus, and mosquitoes obtained in nature may be appropriate for viral isolation. Since virus isolation takes 7–10 days, it may be too late to start treating patients with DF/DHF.

1.8.4. IgG-ELISA

An IgG-ELISA has been developed that is comparable to the HI test. Test for primary and secondary dengue infections. The test is straightforward to do but is not considered diagnostic since it simply detects prior illnesses.

1.8.5. Serological tests

Other serological tests for dengue infection include HI, complement fixation (CF), and neutralisation (N) (NT). Due to technological issues, they are seldom utilised.

1.8.6. Management of dengue Fever (DF)[8]

Dengue fever is treated symptomatically. An acute period bed rest is advised. Then sponge to maintain the temperature below 38.5 C.

Antipyretics may help reduce body temperature. Aspirin/NSAIDS such as Ibuprofen should be avoided since they might induce gastritis, vomiting, acidosis, platelet malfunction, and serious bleeding. Paracetamol in the dosages below is preferred:

1. 1-2 years: 60 -120 mg/dose
2. 3-6 years: 120 mg/dose
3. 7-12 years: 240 mg/dose
4. Adult: 500 mg/dose

In youngsters, the dosage is 10 mg/Kg body weight per dose. Dosage may be repeated every 6 hours depending on temperature and bodily soreness.

Excessive sweating or vomiting requires oral fluid and electrolyte treatment.

Patients should be observed for 24–48 hours after becoming afebrile.[8]

1.9. Management during febrile phase

Paracetamol is advised for temperatures below 39 degree celsius. Oral liquids should be suggested to the patient as tolerated. Oral rehydration solutions (ORS) for diarrhoea and/or fruit juices are preferred over plain water. If the patient is vomiting or refuses to eat, intravenous liquids should be given.

Observe patients for early indications of shock. The crucial time comes after the third day of sickness, when the body transitions from feverish to afebrile. Serial haematocrit measurements may help guide treatment plans by indicating plasma leakage and the requirement for intravenous fluids. The haematocrit should be measured every day from the third day until the temperature returns to normal.

1.9.1. Convalescence phase

Stop IV fluids when you see indications of recovery: rash, itching, hunger rise, or 30-60 hours following shock. Some patients have sinus bradycardia.

1. Patients with significant ascites and pleural effusion may need diuretics during this time of re-circulating extravasated plasma.
2. Some people may not recover appetite. This may be caused to diuresis and potassium depletion. Potassium supplementation may be required. Most patients choose potassium-rich fruits (bananas, oranges) and fruit juice.
3. Adults' convalescence might last 2–4 weeks with tiredness.

1.10. Management of DHF grade I and II

Anyone with dengue fever, thrombocytopenia, high hemoconcentration, stomach discomfort, black tarry stools, epistaxis, gum bleeding, etc. should be hospitalised. These patients should be monitored for shock. The key time for shock development is after the third day of sickness, when the disease transitions from febrile to abferile. Increased haemoconcentration implies plasma leakage and volume loss, which requires correct fluid management. Unaffected by the therapy, patients with Grade III/IV DHF/DSS should be managed for Grade III/IV DHF/DSS.

Management of Shock (DHF Grade III / IV)

Immediately after admission, haematocrit, platelet count, and vital signs should be checked, and intravenous fluid treatment started.

The patient must be constantly monitored. If the patient has previously had 1000 ml of intravenous fluid, convert it to colloidal solution (ideally Dextran40) or administer a new whole blood transfusion (10-20ml/kg/dose).[9]

1.11. Pathogenesis of Dengue Fever/DHF

Any of the dengue virus serotypes may cause dengue. Infection with one serotype offers protection against that serotype but not against others. A second infection with a different serotype might result in a more severe illness. This is due to antibody dependent enhancement, where antibodies against one serotype promote infection with another. Because only 2–4% of those with secondary dengue infection become sick, antibody dependent augmentation alone cannot explain this process.[10] Several organisations are actively researching processes that explain why only certain people acquire symptoms of infection. The dengue virus enters the body by a mosquito bite and replicates inside mono nuclear phagocyte cells (macrophages, monocytes, and B cells). Infection of mast cells, dendritic cells, and endothelial cells is also known.[11] Dengue fever has a 7–10 day incubation period. The patient then enters a febrile and infectious phase. The patient may either recover or develop to DHF and/or dengue shock syndrome. Peak plasma viraemia corresponds with dengue severity.[12] Uncomplicated dengue fever and DHF/dengue shock syndrome individuals had different antibody, cytokine, and T-cell responses. Antibody reactions, cytokine responses, and cellular responses to dengue virus will be detailed individually for clarity. Antibody dependent enhancement is hypothesised to be important in severe dengue pathogenesis. In secondary dengue infections, the patient's antibodies form complexes with the virus. The BC component of these antibodies may attach to FcRI and FcRII carrying cells, increasing the number of dengue virus infected cells.[13] TNF, IL-2, IL-6, and IFN are strongest in the first three days of sickness, but IL-10, IL-5, and IL-4 tend to come later, IL-2 and IFN- are Th1 cytokines, IL-5 and IL-4 Th2. Thus, Th1 responses appear first, followed by Th2 responses.[14] There has recently been an increased emphasis on examining features of cell-mediated immune responses in the pathophysiology of DHF. Both CD4+ and CD8+ T-cells may be infected by the dengue virus.[15]

1.12. Researches in progress

Intensive research is being conducted in order to produce antiviral medications that can be used to control DF and prevent life-threatening episodes. Guppies (Poecilia reticulata) or copepods (doridicola agilis) may be kept in standing water to control mosquito (vector) transmission, and the mosquito population can be infected with bacteria from the Wolbachia genus.[16] Future prospects for preventing and treating dengue illness include controlling mosquito (vector) transmission, developing a dengue vaccine, and developing antiviral medications. The need for a dengue vaccine has grown in relevance as the transmission of the disease spreads and the severity of the disease worsens. There is a global public health need for a tetravalent dengue vaccination that is safe, efficacious, and affordable. Vaccine innovation has been hampered by complex pathophysiology, the need to regulate four viral serotypes, and insufficient investment by vaccine inventors.[17]

2. Conclusion

The doctor should be informed of the many clinical signs of this ailment so that therapy may begin as soon as possible. Future efforts to prevent this deadly illness will focus on mosquito control strategies. To raise community knowledge and awareness of Aedes mosquitoes and DF prevention throughout the nation, a focus on health education programmers, particularly on dengue illness, should be placed.

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4. Conflict of Interest

None.

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