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Dengue: Definition, WHO Classification, Pathophysiology, Clinical Manifestation, Investigation, Management

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Abstract
Dengue is endemic throughout the states and union territories of India. According to data released by Director of National Vector Born Disease Control Programme (NVBDCP) for on-going year 2019, India has reported more than 67,000 cases of dengue till Oct 13. Although NVBDCP data confirms that dengue is established and endemic across India, as few as only 0.5% of dengue cases may be captured by NVBDCP due to absence of exclusive dengue surveillance system in India and underreporting. While actions has been taken by the authorities such as fogging breeding sites, all those are seen to be inadequate to curb the momentum of spread of disease. In coming year, dengue is expected to worsen as a public health problem. Adequate reporting by authorities based on a robust surveillance system and action against the risk factors for the spread of the disease are vitally needed to curb cases and prevent the disease's spread.

Keywords: Dengue, Dengue Virus, Dengue Haemorrhagic Fever (DHF), Dengue Shock Syndrome (DSS), Thrombocytopenia, Plasma Leakage, Organ Involvement, Plural Effusion, Ascites

Introduction
Dengue is a viral disease, transmitted by infective mosquito developing symptoms in 5-6 days after bite. Dengue occurs in two forms: dengue fever and dengue haemorrhagic fever (DHF). Dengue fever shows flu like symptoms, while dengue haemorrhagic fever is more sever form of disease which may even lead to death. A person suspected of dengue fever or dengue haemorrhagic fever needs consultation with doctor.
Dengue is caused by Dengue Fever Virus (DENV), an RNA virus which belongs to Flavivirus genus. Four strains of dengue virus are known- DENV-1, DENV-2, DENV-3, and DENV-4 of which all are found in India. Dengue is spread by mosquito named Aedes Aegypti. These mosquito breeds in fresh water in any type of manmade containers or storage containers having even small quantity of water. Eggs of these mosquitos can live without water for more than one year. Aedes Aegypti mosquitos acquires virus from infected human, act as carrier then transfer it to another person spreading infection to him.

Classification
Classification of dengue as per clinical presentation: dengue virus infection can be clinically presented as asymptomatic or undifferentiated fever, dengue fever (DF), Dengue haemorrhagic fever (DHF) with plasma leakage that may lead to hypovolemic shock (Dengue Shock Syndrome-DSS).
Case definition for dengue fever: a patient complaining of acute febrile illness along with two or more following manifestations- headache, retro-orbital pain, myalgia, arthralgia, rash, haemorrhagic manifestation, and leukopenia is a case probable to be a dengue; only when confirmed by serological test like detection of NS-1 antigen, IgG ELISA or positive IgM antibody test, a case is defined as dengue fever.
Case definition for dengue haemorrhagic fever: a patient complaining of acute fever lasting for 2-7 days, along with haemorrhagic tendencies, evidences by positive tourniquet test, petechiae, ecchymoses, bleeding from mucosa gastrointestinal tract, injection site, haematemesis or melena, thrombocytopenia (platelets < 100 000), evidence of plasma leakage due to increased vascular permeability manifested by- rise in haematocrit equal to or greater than 20% above average for sex, age, fall in haematocrit after fluid replacement

therapy equal to or greater than 20%, signs of plasma leakage like plural effusion, ascites and hypoproteinemia

Case definition for dengue shock syndrome: all the above criteria for DHF plus evidence of circulatory failure, manifested by; rapid and weak pulse, narrow pulse pressure, hypotension, cold clammy skin and restlessness.
As per another classification depending on severity of clinical and laboratory parameters patients with dengue are differentiated as patients with non-sever dengue and patients with sever dengue. Further non-sever dengue is split into-patient with warning sign and patient without warning signs.

Non-sever dengue
Probable dengue/ non-sever dengue without warning signs: history of travel to or of living in dengue endemic area, symptoms like nausea- vomiting, rash, aches and pain, tourniquet test positive, leukopenia, laboratory confirmation of dengue.

Non-sever dengue with warning signs: all the above mentioned criteria along with warning signs like pain in abdomen or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy, restlessness, liver enlargement >2cm, laboratory investigation showing, increase in HCT along with rapid decrease in platelet count.

Criteria for sever dengue: all the criteria for dengue as mentioned above along with sever plasma leakage leading to shock (DSS), fluid accumulation with respiratory distress, sever bleeding as evaluated by clinician, sever organ involvement- liver: SGOT/AST and SGPT/ALT >=1000, CNS: impaired consciousness, kidney heart and other organ involvement.

Pathophysiology
Dengue fever
- Infected Aedes mosquito bite human being, inoculates dengue virus in human body. Virus infects Langerhans cells and keratocytes in skin. Virus multiply in these cells during which NS-1 non-structural protein is released by these infected calls in to circulation.
- NS-1 protein released by infected cell activates inflammatory response through cell mediators like cytokine, interleukins, tumour necrosis factor. These inflammatory mediator produce flu like symptoms-fever, pain, flushing etc.
- In response to NS-1 protein human body produces antibodies which are cross reacting with self-body. This antibodies attack platelets causing their destruction leading to thrombocytopenia. Anti NS-1 antibodies also attack endothelial lining of blood vessels destructing it, causing increase in permeability and plasma leakage.
- Virus infected cells in body are attacked by macrophages. Macrophages engulf infected cells and destroy them by apoptosis. This leads to leukocytopenia. Some of these infected macrophages enter circulation via blood or lymph reaches all organs transmitting infection to all organs.

Dengue haemorrhagic fever
- It not managed adequately dengue fever proceed to dengue haemorrhagic fever subsides but other pathologies continues. Furthermore destruction of thrombocytes increase risk of bleeding with symptoms like petechiae, ecchymosis, bleeding from mucosa gastrointestinal tract, injection site, haematemesis or melena. Also plasma leakage worsens with shift of fluid and accumulation in body space leading to plural effusion and ascites and hypoproteinemia.
- Up to this stage virus reaches all vital organs of the body and infect them. Liver is most commonly affected organ, along with kidney, brain, bone marrow as common sites to be affected. Dengue virus infects hepatocytes and koffer cells of liver causing inflammation leading to dengue related hepatitis. Also plasma leaking along with anti NS-1 antibodies affects renal function by causing glomerular injury-proteinuria, hypoproteinemia, acute kidney injury. Dengue virus infects brain and may lead to encephalitis, myelitis, meningitis**.** Other factors associated with dengue like plasma leakage, hepatitis, AKI along with electrolytic imbalance may also affect normal functioning of brain. Dengue virus supresses the normal functioning of bone marrow resulting in decreased p[production of blood cells especially thrombocytes further worsening thrombocytopenia.
- All above pathologies need to be manage in time, if not; further worsen the patient condition landing him in dengue shock syndrome with circulatory failure, hypotension hypoperfusion and shock leading to death.

Laboratory investigations
- **Isolation of dengue virus** from clinical specimen by cell culture is best way to confirm presence of dengue virus and its infection. But this method is suitable for research or for academic purpose and not for patient care. Nucleic acid detection by PCR, viral antigen detection (NS-1) or serological test to identify specific antibodies can be alternative to this.
- **PCR for dengue virus** detects specific nucleic acids in dengue virus to confirm their presence but being needed higher cost for this test, not widely available.
- **Detection of viral antigen (NS-1)** during febrile phase of infection helps in early identification of dengue infection, with up to 90%of sensitivity. NS-1 test comes positive within 1-2 days of infection even before specific antibodies IgG, IgM appears in blood stream. NS-1 is recommended in first 7-9 days after which it is not recommended. A positive NS-1 test confirms dengue infection, while a negative does not rule out infection. People with negative NS-1 test should be tested for presence of specific antibodies IgG and IgM before ruling out dengue infection.
- **IgM-capture Enzyme linked immunosorbent assay (MAC-ELISA)** is widely used test, recommended by Nation Vector Born Disease Control Programme, Government of India, for final diagnosis of dengue. Anti-dengue IgM antibodies develops with in first five days of infection and remains in circulation for about 90 days. Due to this factor MAC- ELISA can also be used as clinical surveillance of population based on sero-survey in endemic area.
- **Other blood investigations and their findings:**
    - **Complete blood count** shows thrombocytopenia right from early stage of infection, along with leukocytopenia. In later stage (DHF) thrombocytopenia worsens along

with changes in haematocrit indicating plasma leakage and reduced hemoglobin levels indicating signs of internal bleed.
- Bio chemistry shows deranged liver enzymes- SGOT/SGPT indicating liver is affected, electrolytic imbalance along with increased blood urea indicating renal impairment. This finding should be co-related with clinical findings and vital signs.

- **Radiological investigation: X-ray** should be done for patient with DHF to detect collection of fluid in pulmonary space- signs of plural effusion. Ultrasound sonography should be done for client complaining of pain in abdomen and tenderness, USG finding shows collection of fluid in abdominal space indicating ascites.

Management

Management of Dengue Fever (DF)

Management of Dengue fever is symptomatic and supportive

1. Bed rest is advisable during the acute phase.
2. Use cold sponging to keep temperature below 39oC.
3. Antipyretics may be used to lower the body temperature. Aspirin/NSAID like Ibuprofen etc. should be avoided since it may cause gastritis, vomiting, acidosis and platelet dysfunction.
4. Oral fluid and electrolyte therapy are recommended for patients with excessive sweating or vomiting.
5. Patients should be monitored in DHF endemic area until they become afebrile for one day without the use of antipyretics and after platelet and haematocrit determinations are stable, platelet count is >50,000/ cu mm.

Management of DHF (Febrile Phase)

The management of febrile phase is similar to that of DF. Paracetamol is recommended to keep the temperature below 39º C. Copious amount of fluid should be given orally, to the extent the patient tolerates, oral hydration solution (ORS), such as those used for the treatment of diarrhoeal diseases and/or fruit juices are preferable to plain water. IV fluid may be administered if the patient is vomiting persistently or refusing to feed. Patients should be closely monitored for the initial signs of shock. The critical period is during the transition from the febrile to the afebrile stage and usually occurs after the third day of illness. Serial haematocrit determinations are essential guide for treatment, since they reflect the degree of plasma leakage and need for intravenous administration of fluids. Haematocrit should be determined daily from the third day until the temperature has remained normal for one or two days. If haematocrit determination is not possible, haemoglobin determination may be carried out as an alternative.

Management of DHF Grade I and II

Any person who has dengue fever with thrombocytopenia and haemoconcentration and presents with abdominal pain, black tarry stools, epistaxis, bleeding from the gums and infection etc. needs to be hospitalized. All these patients should be observed for signs of shock. The critical period for development of shock is transition from febrile to afebrile phase of illness, which usually occurs after third day of illness. Arise of haemoconcentration indicates need for IV fluid therapy. If despite the treatment, the patient develops fall in BP, decrease in urine output or other features of shock, the management for Grade III/IV DHF/DSS should be instituted. Oral rehydration should be given along with antipyretics like Paracetamol sponging, etc. as described above.

Management of DHF Grade III and IV (DSS)

Common signs of complications are observed during the afebrile phase of DHF. Immediately after hospitalization, the haematocrit, platelet count and vital signs should be examined to assess the patient's condition and intravenous fluid therapy should be started. The patient requires regular and sustained monitoring. If the patient has already received about 1000 ml of intravenous fluid, it should be changed to colloidal solution preferablyDextran40/ haemaccele or if haematocrit is decreasing, fresh whole blood transfusion 10ml/kg/dose should be given.

However, in case of persistent shock when, after initial fluid replacement and resuscitation with plasma or plasma expanders, the haematocrit continues to decline, internal bleeding should be suspected. It may be difficult to recognize and estimate the degree of internal blood loss in the presence of haemoconcentration. It is thus recommended to give fresh whole blood in small volumes of 10ml/kg/hour for all patients in shock as a routine precaution. Oxygen should be given to all patients in shock.

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