Dengue Fever

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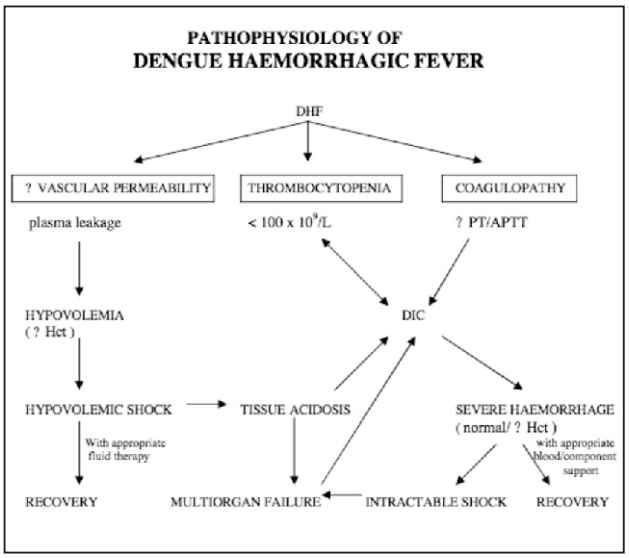
Dengue fever has become a major public health problem in India. It is a systemic viral infection transmitted between humans by *Aedes aegypti* mosquitoes. This mosquito is primarily a daytime feeder that lives around human habitation and lays eggs and produces larvae preferentially in artificial containers There are four dengue virus serotypes: DENV-1, DENV-2, DENV-3, and DENV-4. They belong to the genus *Flavivirus* family It is a single stranded positive sense RNA virus. Infection with one dengue serotype provides lifelong immunity to that virus, but there is no cross-protective immunity to the other serotypes. Sequential infections with more than one serotype are common. One hypothesis for the increased severity seen in secondary infections is antibody-dependent enhancement (ADE) leading to increased replication in Fc receptor-bearing cells. These antibodies are highly cross-reactive among the dengue virus serotypes and, even at high concentrations, do not neutralize infection but potently promote ADE



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Dengue infection is a systemic and dynamic disease. After the incubation period, the illness begins abruptly and is followed by the three phases -- febrile, critical and recovery. Triage and management decisions not only reduces the number of unnecessary hospital admissions but also saves the lives of dengue patients.

FEBRILE PHASE

Patients typically develop high-grade fever suddenly. This acute febrile phase usually lasts 2–7 days and is often accompanied by facial flushing, skin erythema, generalized body ache, myalgia, arthralgia and headache. Some patients may have sore throat, injected pharynx and conjunctival injection. Anorexia, nausea and vomiting are common. Mild haemorrhagic manifestations like petechiae and mucosal membrane bleeding (e.g. nose and gums) may be seen.[1] Massive vaginal bleeding (in women of childbearing age) and gastrointestinal bleeding may occur during this phase.

CRITICAL PHASE

Usually on days 3–7 of illness, the temperature drops to 37.5–38^0 C along with increase in capillary permeability and increase in haematocrit levels lasting up to 24–48 hours.[2]

Progressive leukopenia[2] followed by a rapid decrease in platelet count precedes plasma leakage. At this point patients without an increase in capillary permeability will improve, while those with increased capillary permeability may become worse as a result of lost plasma volume. Pleural effusion and ascites may occur. Hence chest x-ray and abdominal ultrasound can be useful tools for diagnosis. The degree of increase above the baseline haematocrit often reflects the severity of plasma leakage. Shock occurs when a critical volume of plasma is lost through leakage. With prolonged shock, the consequent organ hypoperfusion may result in progressive organ impairment, metabolic acidosis and disseminated intravascular coagulation. This in turn may lead to severe haemorrhage causing the haematocrit to decrease in severe shock. Some times severe organ impairment such as severe hepatitis, encephalitis or myocarditis or severe bleeding may

develop without obvious plasma leakage or shock.[8]

RECOVERY PHASE

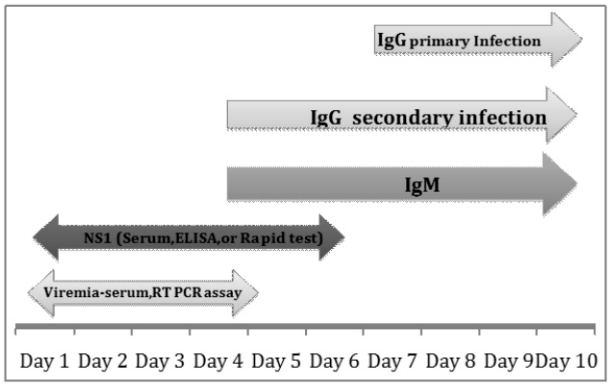
If the patient survives the 24–48 hour critical phase, a gradual reabsorption of extravascular compartment fluid takes place in the following 48–72 hours. General well-being improves, appetite returns, gastrointestinal symptoms abate, haemodynamic status stabilizes and diuresis ensues. Bradycardia and electrocardiographic changes are common during this stage.

SEVERE DENGUE is defined by one or more of the following:

(i) Plasma leakage that may lead to shock (dengue shock) and/or fluid accumulation, with or without respiratory distress, and/or
(ii) Severe bleeding, and/or
(iii) Severe organ impairment

DIAGNOSTIC TESTS

1. RTPCR assay of virus[4]
2. Detection of non-structural protein (NS1) by ELISA. Sensitivity during febrile period is 90% in primary infections and 60 – 80% in secondary infections due to anamnestic serological response.[5]
3. Serological diagnosis by serum IgM levels can be detected as early as 4 days.



In secondary infections, IgG antibodies predominate over IgM due to anamnestic response.[6]

MANAGEMENT

There is no effective antiviral drug against dengue and treatment is mainly supportive.

Group A

Patients who are able to tolerate adequate volumes of oral fluids and pass urine at least once every six hours, and do not have any of the warning signs, particularly when fever subside may be sent home. Daily monitoring of haematocrit and platelet count is done.

Group B

Patients with warning signs should be brought to hospital immediately if any of the following occur - no clinical improvement, deterioration around the time of defervescence, severe abdominal pain, persistent vomiting, cold and clammy extremities, lethargy or irritability/restlessness, bleeding (e.g. black stools or coffee-ground vomiting), not passing urine for more than 4–6 hours, those with co-existing conditions that may make dengue or its management more complicated (such as pregnancy, infancy, old age, obesity, diabetes mellitus, renal failure, chronic haemolytic diseases).

- Intravenous fluid given to maintain good perfusion and urine output. They are needed for 24–48 hours.[7]
- Start intravenous fluid resuscitation with isotonic crystalloid solutions at 5–10 ml/kg/hour over one hour. Then reassess the patient's condition (vital signs, capillary refill time, haematocrit, urine output). The next steps depend on the situation.

If the patient's condition improves, intravenous fluids should be gradually reduced based on ideal body weight).

If vital signs are still unstable (i.e. shock persists), repeat a second bolus of crystalloid solution at 10–20 ml/kg/hr for one hour. After this second bolus, if there is improvement, reduce infusion rate. If haematocrit decreases compared to the initial reference haematocrit (<40% in children and adult females, <45% in adult males), this indicates bleeding and the need blood transfusion.

- Patients with warning signs are monitored for haematocrit, blood glucose, and other organ functions - such as renal profile, liver profile, coagulation profile, and treated as indicated.
- Role of steroids in the management of dengue:- There is insufficient evidence to justify the use of corticosteroids in managing dengue shock syndrome. As corticosteroids can potentially do harm, clinicians should not use them unless they are participating in a randomized controlled trial comparing corticosteroids with placebo.[8]
- High-risk patients having platelet count <

20,000/cumm and risk of bleeding require urgent platelet transfusion. Patients with platelet count 21-40,000/cumm are in moderate risk and require platelet transfusion only if they have any haemorrhagic manifestations and other superadded conditions.

Group C

Patients who require emergency treatment and have severe dengue leading to dengue shock or fluid accumulation with respiratory distress or severe haemorrhages or severe organ impairment (hepatic damage, renal impairment, cardiomyopathy, encephalopathy or encephalitis). These patients are managed in critical care settings.

CRITERIA FOR DISCHARGE

- Absence of fever for 24 hours and return of appetite
- Visible improvement in clinical picture
- Stable hematocrit
- 3 days after recovery from shock
- Platelets $\geq 50,000/mm^3$
- No respiratory distress from pleural effusions/ascites

Anti-dengue drugs

A greater understanding of dengue virus biology has meant that targets within the lifecycle have been identified that could potentially be the site of a therapeutic agent.[13] One potential mechanism of action of an anti-dengue drug is through inhibition of viral entry.[15] Other potential targets receiving research attention are the viral proteins NS3 and NS5, which play an integral role in genome replication—their protease domains could be target for protease inhibitors.[16,17]

ENVIRONMENTAL MANAGEMENT

Environmental management seeks to change the environment in order to prevent or minimize vector propagation and human contact with the vector-pathogen by destroying, altering, removing or recycling non-essential containers that provide larval habitats. Such actions should be the mainstay of dengue vector control.

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