Dengue Hemorrhagic Fever and Dengue Shock Syndrome — Pertinent Issues in Management

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INTRODUCTION

The Dengue virus is an arbovirus, from genus *Flavivirus* family *Flaviviridae.* It is a single stranded RNA genome surrounded by an icosahedral nucleocapsid and covered by lipid envelope. Four serotypes: DEN-1, 2, 3, 4 have been identified for the virus. Each serotype provides specific lifetime immunity, but only a short-term cross-immunity. All serotypes can cause severe and fatal disease. In the epidemic in Delhi in 2003, Guate96-98 strains of DEN-3 virus were held responsible for the outbreak[1].

The vector for Dengue is the Aedes aegypti mosquito which is also known as the Tiger mosquito, due to the characteristic striped body appearance. It is a highly domesticated mosquito and lays eggs and produces larvae preferentially in artificial containers. Two peaks of biting activity are known for the mosquito – 2-3 hours after the daybreak and in the evening a couple of hours before sundown. The mosquito is a silent and fearless biter and does not buzz. It often feeds on several persons during a single blood meal in a short period of time. If infective, it can transmit the virus even while probing without taking blood meal[1].

Epidemics of an illness resembling dengue have been known to have occurred in 1779, 1780 across three continents of Asia, Africa and North America. The first epidemic of DHF in recent times occurred in Manila, Philippines 1953. In India dengue virus was first isolated in Calcutta in 1945 and the epidemic of DHF first occurred in Calcutta in 1963. Since then epidemics of dengue fever have been reported from Vishakhapatnam, Ajmer, Delhi and Kanpur, mostly attributed to strains DEN 2 and DEN 3. In the recent epidemic Dengue and Chikungunya fever cases were reported from 182 districts in Haryana, Delhi, Rajasthan, Gujarat, Maharashtra, Karnataka, Kerala, West Bengal, Madhya Pradesh, Andhra Pradesh, Tamil Nadu, Pondicherry, Andaman and Nicobar islands. As many as 2300 patients were diagnosed for Dengue Fever in Delhi alone and more than 50 deaths were reported.

PATHOGENESIS OF DENGUE HEMORRHAGIC FEVER AND DENGUE SHOCK SYNDROME

The infected monocytes release vasoactive mediators, resulting in increased vascular permeability and hemorrhagic manifestations that characterize DHF and DSS. Early bone marrow suppression causing leukopenia, thrombocytopenia, decreased neutrophil and monocytes are seen in DHF. Decreased levels of fibrinogen, prothrombin, factor II, VII, VIII, IX, X, XII, ATIII, protein C and S have been reported. The classical markers of disseminated intravascular coagulation may be absent. PT, aPTT, TT may be normal or increased. The levels of C3 and C5 are depressed, and C3a and C5a are elevated[2].

The cause of thrombocytopenia observed in DF is controversial. It has been proposed that there is impaired megakaryocytic production and increased platelet destruction. The causes of platelet injury have been attributed to the virus itself, circulating antiplatelet antibodies, immune complexes and DIC. In addition platelet function abnormalities contribute to bleeding[2].

CLINICAL FEATURES OF DHF AND DSS

Dengue virus infection may be asymptomatic or may cause undifferentiated febrile illness (viral syndrome),
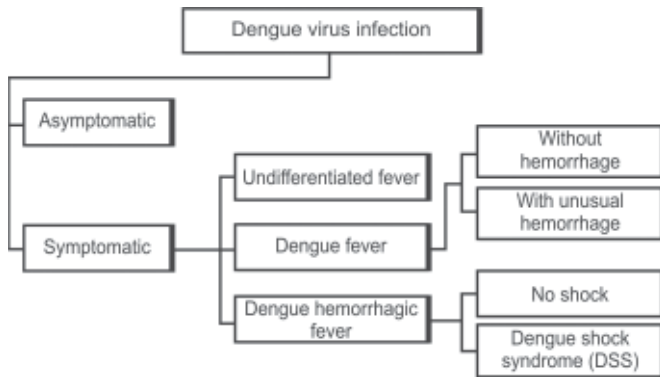
Fig. 1: Clinical spectrum of dengue virus infection

dengue fever (DF) or Dengue Hemorrhagic fever (DHF) including dengue shock syndrome (DSS). Dengue fever could be with or without frank hemorrhage. DHF could present with or without shock. The clinical presentation depends on age of the host and the virus strain. The clinical spectrum of the illness is given in Figure 1.

Undifferentiated fever: The first infection with dengue virus presents with an undifferentiated viral like illness. Maculopapular rashes may appear during the fever or during defervescence. Fever may be associated with nausea, vomiting, retro-orbital pain, asthenia and myalgias.

Dengue fever: This is an acute biphasic fever with headache, myalgias, arthralgias, rashes and leucopenia.

Although DF is usually a benign illness, however it may present with severe debilitating arthralgias, and myalgia with occasional hemorrhage.

Dengue hemorrhagic fever: DHF is most common in children less than 15 years and is characterized by acute onset of fever associated with non specific constitutional signs and symptoms. There is a hemorrhagic diathesis and tendency to develop fatal shock. Abnormal hemostasis and plasma leakage are the main pathophysiological changes with thrombocytopenia and hemoconcentration presenting as constant findings. DHF has sometimes been documented in primary infections also. Dengue shock has been associated with bronchial asthma and long standing chronic host illness.

The WHO definition of DF is given in Table 1.

Severity of DHF

Grade 1: Fever accompanied by non specific constitutional symptoms and a positive tourniquet test.

Grade II: Spontaneous bleeding in addition to the manifestation of Grade I patients, usually in the form of skin or other hemorrhages.

Grade III: Circulatory failure manifested by rapid and weak pulse with a narrow pulse pressure (< 20 mm Hg) or hypotension with the presence of cold clammy skin and restlessness.

Grade IV: Profound shock with undetectable blood pressure.

Table 1: WHO case definition of dengue fever

Probable	
An acute febrile illness with two or more of the following:	Headache Retro orbital pain Myalgia and arthralgia Nausea and vomiting Skin rash Hemorrhagic manifestations AND Supportive serology OR Occurrence at the same location and time as other confirmed cases of DF
Confirmed	
Confirmation of DF is based on laboratory criteria	Virus isolation from serum or tissue samples; OR Demonstration of 4-fold or more rise in IgG and IgM antibody titers to dengue antigens in paired serum samples; OR Demonstration of dengue antigen in tissue, serum, CSF by immunohistochemistry, immunoflorescence or ELISA; OR Detection of genomic sequences by PCR

Table 2: Clinical profile of DF during epidemic in Delhi in 1996

Feature	Observed percentage
• Bodyaches	45.9
• Rash	36.7
• Purpura	33.6
• Ecchymosis	19.4
• Bleeding (other sites)	52
• Abdominal pain	38.7
• Hematemesis	22.4
• Malena	26.5
• Epistaxis	32.6
• Impaired consciousness	5.1
• Shock	23.5
• Lymph nodes	3.1
• Hepatomegaly	20.4
• Splenomegaly	8.2
• Jaundice	1
• Renal failure	1
• Pleural effusion	8.2
• ARDS	1

The identification of a case of Dengue hemorrhagic fever requires all of four criteria.

1. **Fever** or history of acute fever lasting 2-7 days, occasionally biphasic
2. **Hemorrhagic tendencies** evidenced by at least one of the following:
   - positive tourniquet test
   - petechiae, ecchymosis, purpura
   - bleeding from mucosa, GIT, other
   - hematemesis, malena
3. **Thrombocytopenia** < 100,000 /mm^3
4. **Plasma leakage** evidenced by at least one of the following
   - Rise in hematocrit > 20%
   - Fall in hematocrit > 20% after I/V fluids
   - Pleural effusion, ascitis, hypoalbuminea

Table 3: Risk factors for DHF[4]

Virus factors	Host factors
Virulence of strain DHF risk is greatest when DEN-2 follows DEN-1 Hyperendemic transmission (locations with two or more serotypes circulating simultaneously	Pre-existing anti-dengue antibody due to previous infection or maternal antibodies in the infants A positive association for HLA A2 and negative association for HLA B13 has been reported

Tourniquet test is performed by inflating the sphygmomanometer cuff on the upper arm to midway between systolic and diastolic blood pressures for 5 minutes. A positive test is identified by appearance of more than 20 petechiae per 2.5 cm^2. A variable sensitivity from 56.4 to 90 percent has been reported for the test in diagnosing Dengue hemorrhagic fever[3]. The test may be negative during profound shock and usually becomes positive after recovery from shock.

The identification of Dengue Shock syndrome requires all four DHF criteria and in addition a circulatory failure manifested by:

1. Rapid and weak pulse and
2. Narrow pulse pressure (< 20 mmHg)
3. Hypotension for age < 5 yr- < 80 mmHg

   ≥5 yr- < 90 mmHg
4. Cold clammy skin, restlessness.

Risk factors for developing DHF and DSS

Several factors have been identified and proposed for the development of DHF following an infection by the dengue fever virus. These have been shown in Table 3. The risk factors for development of Dengue Shock Syndrome[4] have been listed in Table 4.

Laboratory and Radiological Features Observed in Dengue Fever

Various laboratory abnormalities are observed in Dengue fever. These have been detailed in Table 5.

Table 4: Risk factors for DSS

Criteria for DHF	Warning signs	Time factor	Alarm signs
Fever	Disappearance of fever	3 to 6 days after onset of	Severe abdominal pain
Hemorrhagic manifestations	Drop in platelets	symptoms	Prolonged vomiting
Increased capillary permeability	Increase in hematocrit		Hypothermia
Thrombocytopenia (Platelets < 100,000/mm^3			Irritability or somnolence

Table 5: Laboratory features observed in DF epidemic in Delhi in 1996

Feature	Mean
• Hemoglobin g/dl (n=88)	11.6 (2.9)
• Hematocrit % (n=71)	39.0 (8.6)
• TLC (n=73)	7163 (10365)
• Platelets (n=98)	30000 (25000)
• Bilirubin mg/dl (n=34)	0.9 (0.6)
• AST IU/l (n=43)	274 (634)
• ALT IU/l (n=43)	143 (242)
• SAP IU/l (n=29	196 (155)

Radiological investigations and ultrasound examination in patients with Dengue fever have revealed ascitis, hepatomegaly, splenomegaly, gallbladder wall edema, perihepatic fluid collection, acalculous cholecystitis, sludge in gallbladder.

Gallbladder wall thickness (GBWT) of > 3 mm on U/S in DHF patients can be used as a criterion indicating the need of hospitalization. GBWT $\geq$ 5 mm is useful as a criterion for identifying DHF patients at high risk of developimg hypovolemic shock with sensitivity of 93.8% and specificity of 91.7%.

Complications and Unusual Presentations

Features of encephalitis such as seizures and coma are rare in DHF but have been observed in the recent epidemic in various parts of the country. These may occur as a result of prolonged shock and bleeding within internal organs.

Inappropriate use of water in treatment leading to hyponatremia may cause features of encephalopathy. Subdural effusions have been observed in some cases. Febrile convulsions may be seen in infants. Fatal cases of encephalitis have been reported. In unusual cases the dengue virus has been reported to cross the blood brain barrier and infect the central nervous system.

Acute liver failure and renal damage usually occur at the terminal stage and may be associated with encephalopathic features. There is a marked rise in AST and ALT in these cases. Renal failure and hemolytic uremic syndrome are observed in some cases. Some of the cases are seen in patients with underlying factors such as G6PD or a hemoglobinopathy causing an intravascular hemolysis.

Dual infections with other endemic diseases such as leptospirosis, viral hepatitis, falciparum malaria have been reported with unusual manifestations.

Differential Diagnosis of DHF

In the febrile phase of the illness, there is usually an absence of physical localizing signs and the differential diagnoses associated with DF are diverse, including viral bacterial and protozoal infections. Leptospirosis, malaria, infectious hepatitis, chikumgunya, meningococcemia, rubella and influenza are included in the differential diagnosis of DF.

The presence of hemoconcentration along with thrombocytopenia, differentiates DHF from other diseases. A normal ESR differentiates this illness from bacterial infection and septic shock.

Management of Dengue Hemorrhagic Fever and Dengue Shock Syndrome

Dengue fever can be best managed at home, with an advice to take bed rest, consume plenty of oral fluids and paracetamol for control of fever. Patients should be advised to monitor platelets and hematocrit regularly at home and report to the hospital if patient has persistent vomiting, refuses fluids and food, resides away from the hospital or is unable to comply with medical advice. Patients with Grade II, III or IV illness should be hospitalized.

Intravenous Fluid Therapy for Dengue Fever

Intravenous fluid therapy is the cornerstone for the management of Dengue fever. The amount of fluid and the nature of fluid should be decided judiciously. Crystalloids are used in fluid resuscitation. Dextrose normal saline and ringer lactate can be used for fluid replacement.

In DF Grades I and II, fluids are started at an initial rate of 6 ml/kg/hour for the first two hours and the patient is reassessed. If there is improvement in clinical features the fluid rates may be reduced to 3 ml/kg/h for the next 6 to 12 hours and discontinued after 24 hours in case of continued improvement. If no improvement is noticed during reassessment, fluid rates should be increased to 10 ml/kg/h for the next one hour. If a rise in hematocrit is noticed despite crystalloid therapy, the patient should be put on colloids, plasma or dextran at the rate of 10 ml/kg/h.

In grades III or IV, in presence of unstable vital signs, a falling urine output or signs of shock, immediate volume replacement should be attempted with crystalloids at the rate of 10-20 ml/kg/h for the first hour and the patient should be reassessed. In case of improvement the fluid therapy may be tapered of

gradually over the next 24 to 48 hours. However, if no improvement is noticed and despite adequate replacement and oxygenation, and the hematocrit is found to rise, colloid replacement may be needed at the rate of 10-20 ml/kg/h.

Monitoring in DHF and Shock

The patients should be monitored for measurement of vital signs every 30 minutes. The hematocrit should be measured every 2 hour for 6 hours and then 4 hourly till the patient is stable. Besides, platelets should be monitored every twelve hours. A fluid balance sheet should be religiously maintained and urine output should be recorded. Any bleeding manifestations should be recorded and seriously considered.

Role of Platelet Transfusion in DHF

There are no clear indications of platelet transfusion in Dengue fever as no benefit has been reported or recorded following platelet transfusion. Platelets should not be transfused blindly and decisions should be based on clinical judgment. The World Health Organization recommends that platelets should be transfused only if the patient is bleeding or has a platelet count less than 10,000/cmm.

Role of Steroids in Dengue Hemorrhagic Fever

It has been shown that corticosteroids which have been inadvertently used in treatment, have no clear indication or therapeutic benefit in the management of Dengue Fever and Schock[5].

Management of Uncommon Manifestations and Complications of DHF

Patients with acute hepatic failure should be given early blood transfusion. Those with renal failure would benefit from aggressive hemodialysis. Encephalopathy evidenced by increased irritability, somnolence or behavior changes, in absence of meningism should alert the physician of an impending intracranial hemorrhage or occlusion associated with DIC. In recent years, however, several cases with CNS infections have been documented by virus isolations from the CSF or brain.

Criteria for Discharge

A patient may be discharged from the hospital if there is absence of fever for at least 24 hours without the use of antipyretics, there is return of appetite, visible clinical improvement, adequate urine output, no vomiting, no bleeding, a stable hematocrit, convalescent confluent skin rash, a platelet count > 50,000 /cmm and no respiratory distress.

Vaccine Against Dengue

Currently there is no licensed vaccine against dengue virus. Field testing of an attenuated tetravalent vaccine are currently underway. An effective vaccine must be tetravalent. Effective, safe and affordable vaccine will not be available in the immediate future.

REFERENCES

1. Gubler DJ. Dengue and dengue hemorrhagic fever. Clin Microbiol Rev 1998;11(3):480-96.

2. Wills BA, Oragui EE, Stephens AC, et al. Coagulation abnormalities in dengue hemorrhagic Fever: Serial investigations in 167 Vietnamese children with Dengue shock syndrome. Clin Infect Dis 2002;35(3):277-85.

3. Wali JP, Biswas A, Aggarwal P, Wig N, Handa R. Validity of tourniquet test in dengue haemorrhagic fever. J Assoc Physicians India 1999;47(2):203-4.

4. Sangkawibha N, Rojanasuphot S, Ahandrik S, et al. Risk factors in dengue shock syndrome: A prospective epidemiologic study in Rayong, Thailand. I. The 1980 outbreak. Am J Epidemiol 1984;120(5):653-69.

5. Sumarmo, Talogo W, Asrin A, Isnuhandojo B, Sahudi A. Failure of hydrocortisone to affect outcome in dengue shock syndrome. Pediatrics 1982;69(1):45-9.