

## Dengue Fever/Dengue Haemorrhagic Fever: Case Management

Suchitra NIMMANNITYA

*Children's Hospital, 420/8 Rajvithi Road, Bangkok 10,400 Thailand*

Dengue infections caused by the four antigenically distinct dengue virus serotypes (dengue virus 1, dengue virus 2, dengue virus 3, dengue virus 4) of the family *Flaviviridae*, are the most important arbovirus disease in man, both in terms of morbidity and mortality. The infection is transmitted from man to man by *Aedes* mosquitoes. Since 1956, dengue virus infection has resulted in more than 3 million hospital admissions and more than 50,000 deaths in Southeast Asia, Western Pacific countries, Cuba, the Caribbean Islands and Venezuela<sup>1</sup>.

*Key words:* Dengue Fever, dengue haemorrhagic fever, case

Dengue virus infection may be asymptomatic or may lead to simple fever, dengue fever (DF), or dengue haemorrhagic fever (DHF); these manifestations are largely age/immune status dependent<sup>2</sup>. Undifferentiated fever: infants and children infected with dengue virus for the first time (i.e. primary dengue infection) usually develop a simple fever, sometimes with a rash.

Dengue fever is most common in adults and older children; it is an acute biphasic febrile illness with headache, myalgia, arthralgia, rash and leucopenia. Although DF is commonly benign, it may be an incapacitating disease with severe muscle and joint pain ("Breakbone fever"), particularly in adults and very occasionally severe haemorrhage occurs. Infection with one dengue serotype gives partial protection against the others thus DF seldom occurs among indigenous people in dengue endemic areas.

Dengue haemorrhagic fever is most common in children less than 15 years of age and causes a significant number of deaths; acute fever is associated with haemorrhagic diatheses and a tendency to develop fatal shock (dengue shock syndrome). Abnormal haemostasis and plasma leakage are the main pathophysiologic changes and thrombocytopenia with concurrent haemoconcentration are constant findings<sup>3</sup>.

DHF occurs most commonly in children who have experienced a previous primary dengue infection; the reason for this is not well understood. Epidemiological evidences suggest that the sequences of the infecting dengue serotypes and the interval between the two infections (i.e. primary and secondary) may be important factors contributing to the occurrence and/or severity of DHF<sup>1,4</sup>.

## DENGUE FEVER

*Clinical features*

After an incubation period of 4–6 days from the time of the mosquito bite, various non-specific undifferentiated prodromes, such as headache, backache, general malaise may develop. Typically, however, the onset of DF in adults is sudden with a sharp rise in temperature occasionally with chilliness associated with severe headache and flushed or mottled facial skin. Within 24 hours, the following symptoms may develop:

- retro-orbital pain, particularly on eye movement or eye pressure, photophobia
- backache, pain in the muscles and joints of the extremities.

Other common symptoms include:

- anorexia, altered taste sensation
- constipation
- colicky pain and abdominal tenderness
- dragging pains in the inguinal region
- sore throat
- general depression

Symptoms vary in severity and usually persist for several days.

Fever: the temperature is usually between 39°C and 40°C, and the fever lasts approximately 5–7 days. Occasionally a biphasic fever is observed.

Rash: diffuse flushing, mottling or fleeting pinpoint eruptions may be observed on the face, neck and chest during the first half of the febrile period, and a conspicuous rash, that may be maculopapular or scarlatiniform, appears on approximately the third or fourth day. This rash starts on the chest and trunk and spreads to the extremities and face, and may be accompanied by itching and dermal hyperaesthesia. There may be generalized enlargement of the lymph nodes, but the liver and spleen are not usually enlarged.

Towards the end of the febrile period or immediately after defervescence, the generalized rash fades and localized clusters of petechiae may appear over the dorsum of the feet, on the legs, hands and arms. This confluent petechial rash is characterized by scattered pale round areas of normal skin.

Course: the relative duration or severity of DF varies between individuals in a given epidemic, as well as from one epidemic to another.

Convalescence may be abrupt and uneventful but is often prolonged particularly in adults, sometimes taking several weeks, and may be accompanied by pronounced asthenia and depression. Bradycardia is common during this period. Haemorrhagic complication, such as epistaxis, gingival bleeding, gastrointestinal bleeding, haematuria, and hyper-menorrhoea, accompany many epidemics of DF, and on rare occasions severe bleeding has caused deaths in some epidemics<sup>2)</sup>. DF complicated by haemorrhage must be differentiated from DHF.

*Investigation:* Laboratory findings during the acute illness are as follows:

Total WBC is usually normal at the onset of fever, but then leucopenia develops and

lasts throughout the febrile period. Initially, there is a progressive shift of neutrophils to the left – that is an increased proportion of immature non-segmented nuclear forms which persist into convalescence, there is marked depletion of circulating lymphocytes.

Platelet counts are usually normal, as are other components of the blood clotting mechanisms. Infrequently thrombocytopenia may be observed.

Serum biochemistry and enzymes are normal.

### *Diagnosis*

Differential diagnosis of DF includes a wide variety of viral (including chikungunya), bacterial and rickettsial infections that produce a similar syndrome. It is impossible to diagnose mild dengue infection clinically, particularly in sporadic cases. A definite diagnosis is confirmed by virus isolation and/or serology.

### *Management*

The management of DF is symptomatic and supportive.

- Bed rest is advisable during the acute febrile phase.
- Antipyretics or sponging are required to keep body temperature below 39°C.
- Analgesics or a mild sedative may be required for those with severe pain.
- Oral fluid and electrolyte therapy is recommended for patients with excessive sweating, nausea, vomiting or diarrhoea

In areas where DHF is endemic, patients with dengue syndrome should be monitored until they become afebrile, and serial platelet counts and haematocrit determinations are normal.

## DENGUE HAEMORRHAGIC FEVER

### *Pathogenesis and pathophysiology<sup>2,3)</sup>*

The pathogenetic mechanism of DHF is not clear, but two main pathophysiologic changes occurs<sup>2)</sup>:

- Vascular permeability increases that results in plasma leakage, leading to *hypovolaemia* and *shock*.
- Abnormal haemostasis, due to vasculopathy, thrombocytopenia and coagulopathy, leading to various hemorrhagic manifestations.

A constant finding in DHF is activation of the complement system with profound depression of C3 and C5 levels. Immune complexes have been described in DHF associated with secondary dengue virus infection and it is postulated that these may contribute to complement activation and release of C3a and C5a, suspected to be permeability increasing mediators.

The severity of DHF compared with DF may be explained by the enhancement of virus multiplication in macrophages by heterotypic antibodies resulting from a previous dengue infection. There are evidences suggesting that cell mediated immune response may

also be involved in the pathogenesis of DHF.

### *Clinical features*

Typically, DHF begins abruptly with high fever accompanied by facial flushing and headache. Anorexia, vomiting and abdominal pain are common. During the first few days, the illness resembles classical DF, but a maculopapular rash is less common.

A haemorrhagic diathesis is commonly demonstrated by scattered fine petechiae on the extremities, face and trunk, and in the axillae. A positive tourniquet test and a tendency to bruise at venipuncture sites are always present. Bleeding from the nose, gums and gastrointestinal tract are less common. Haematuria is extremely rare.

The liver is usually enlarged, soft and tender. Approximately 50% of patients have generalized lymphadenopathy.

The critical stage is reached after 2–7 days, when the fever subsides. Accompanying or shortly after a rapid drop in body temperature, varying degrees of circulatory disturbance occurs. The child is commonly restless and has cold extremities and sometimes sweats.

In less severe cases, the changes in vital signs are minimal and transient. The patient recovers spontaneously or after a brief period of therapy.

In more severe cases, shock ensues and the patient may die within 12–24 hours. Prolonged shock is often complicated by metabolic acidosis and severe bleeding, which indicate a poor prognosis. If the patient is appropriately treated before irreversible shock has developed, rapid recovery is the rule.

Encephalitic signs associated with intracranial haemorrhage, metabolic and electrolyte disturbances, and hepatic failure (a form of Reye's syndrome) may occur. They are uncommon but carry a grave prognosis.

Course: Convalescence is commonly short and uneventful, and is often accompanied by sinus bradycardia and characteristic confluent petechial rash with scattered round areas of pale skin as described in DF. The duration of DHF is about 7–10 days in most cases.

### *Laboratory Investigations*

Laboratory findings in DHF are as follows:

A normal WBC or leucopenia is common initially with neutrophils predominating. Towards the end of the febrile phase, a relative lymphocytosis with more than 15% atypical lymphocytes is common.

Thrombocytopenia ( $\leq 100,000/\text{cumm.}$ ) and hemoconcentration ( $\geq 20\%$  increase) are constant findings. The platelet count drops shortly before, or at the same time, as the haematocrit increases: both changes occur before the subsidence of fever and before onset of shock.

Chest X-ray: right pleural effusion or bilateral pleural effusion, is commonly found at the peak of plasma leakage.

Liver function test: 80% of DHF patients have slight elevation of AST/ALT (not more than 100U) and AST level is about 2–3 times of ALT. Hypoalbuminemia and reverse

albumin to globulin ratio are frequently observed.

Coagulogram: most cases have slightly prolonged partial thromboplastin time (PTT) and thrombin time (TT). Prothrombin time (PT) is prolonged in about one third of cases.

Pointers to the diagnosis of dengue haemorrhagic fever

- High fever of acute onset, usually in a child
- Petechial haemorrhages and/or a positive tourniquet test often within 24–48 hours of onset
- Tender hepatomegaly
- Normal WBC or leucopenia
- *A fall in platelets preceding or simultaneous with a rise in haematocrit* (Note: this is an important feature, helping to distinguish DHF from DF and other viral infections)
- Pleural effusion (usually on the right side)
- Shock

Differential diagnosis of DHF during the acute febrile phase are many tropical infections including leptospirosis and malaria. With the presence of characteristic manifestations, the clinical diagnosis is confirmed in almost 95% of cases. A rising haematocrit and selective leakage of plasma into pleural and abdominal cavities appear to be unique to DHF. When all the clinical criteria are accompanied by shock, the diagnosis of DHF is definite. The presence of a pleural effusion, commonly on the right side, supports a diagnosis of DHF in cases in which haemoconcentration may be absent due to an untimely test or early fluid replacement, and in cases when severe bleeding has occurred. A normal ESR in DHF/DSS help to differentiate this disease from bacterial infection and septic shock<sup>5</sup>.

#### *Laboratory Diagnosis<sup>2</sup>*

Clinical diagnosis can be confirmed by serological testing and virus isolation from the blood during the early febrile phase. Antibody to all dengue virus antigens increases rapidly in patients with secondary dengue infection. A diagnostic (four fold) increase in dengue virus haemagglutination inhibition (HI) antibody can usually be demonstrated from sera obtained early in the febrile phase on admission, and also 3–5 days later in most DHF cases. A third specimen 2–3 weeks after onset is required to confirm laboratory diagnosis of primary infection, particularly in infants under 1 year of age<sup>7</sup>.

At present, ELISA for IgM and IgG specific dengue antibody has the advantage over HI test in that acute dengue infection could be definitely diagnosed from only acute blood specimen with a sensitivity of 78%. With paired sera (only 2–3 days apart), the sensitivity of the test increases to 97%. The definite diagnosis for acute dengue infection by this method is a detection of more than 40 units of IgM specific dengue antibody. In addition, ELISA technique can differentiate primary from secondary dengue infection and also dengue infection from Japanese encephalitis<sup>6</sup>.

#### *Management<sup>2,3,7</sup>*

The management of DHF during the febrile phase is similar to that of DF. Antipyretics may be indicated but salicylates should be avoided. It should be noted that antipyretics can

not reduce the duration of fever in DHF. Paracetamol is recommended and should be used only to keep the temperature below 39°C. Prognosis of DHF depends on early recognition of plasma leakage which can be achieved by frequent monitoring of patients for a drop in platelet counts and a rise in hematocrit level. The critical period is at the time of defevrescence which occurs approximately on or after the third day of illness. A drop in the platelet count to  $< 100,000/\text{cumm}$  or less than 1–2 platelets/oil field (average of 10 oil field counts) usually precedes a rise in hematocrit and the time of defevrescence. A rise in hematocrit of 20% or more (e. g increase from 35% to 42%) reflects a significant plasma loss and indicates a need for intravenous fluid therapy. Early volume replacement of plasma losses with isotonic salt solution can modify disease severity and prevent shock.

In mild to moderate cases (grade I and II)<sup>2)</sup> intravenous fluid therapy may be given for a period of 12–24 hours at an outpatient clinic. Patients who continue to have high hematocrit, platelet counts below  $50,000/\text{mm}^3$  or present with any type of spontaneous hemorrhage other than petechiae should be hospitalized.

The volume and type of intravenous fluids should be similar to that used in the treatment of diarrheal disease with mild to moderate isotonic dehydration (five to eight percent deficit). The required volume should be charted on a two to three hourly basis and the rate of infusion should be carefully balanced throughout the 24–48 hour period of leakage. Serial hematocrit determination every 4–6 hours, frequent record of vital signs and urine output are essential in monitoring the rate of intravenous infusion in order to assure an adequate volume replacement and to avoid over transfusion.

#### *Management of shock*

Dengue shock syndrome (DSS) is a medical emergency that requires prompt and vigorous volume replacement therapy for the rapid and massive plasma losses. There are also electrolyte and acid base disturbances. It must be considered that in DHF there are marked thrombocytopenia, abnormal platelet function, and potential for disseminated intravascular clotting to develop. These abnormal hemostasis are ready factors to cause severe bleeding particularly in cases with prolonged shock.

#### *Treatment of DSS (grade III and IV)*

The following regimen has been used at the Children's Hospital for the past three decades and has been recommended by WHO<sup>2)</sup> since 1974.

##### 1. Replacement of plasma losses.

Immediate volume replacement with isotonic salt solution (5% D in Ringer lactate or Ringer acetate solution or 5% D in normal saline solution) at the rate of 10–20ml/kg/hr or in the case of profound shock (grade IV) as a bolus of 10ml/kg (one to two times). A rapid infusion is continued until improvement is apparent then reduce the rate and adjust thereafter according to the rate of plasma leakage as guided by hematocrit levels.

In case no definite improvement and hematocrit remains high, colloidal e.g. Dextran 40, plasma or the plasma substitute should be given following the initial fluid at a rate of

10–20ml/kg/hr. Blood transfusion is indicated in cases with refractory shock with declining hematocrit value after initial fluid replacement.

2. Continue replacement for further plasma losses for the period of 24–48 hours. Intravenous fluid should be discontinued at the time around 24–48 hours after defevrescence, when hematocrit declines and becomes stable (approximately 40%), with good vital signs and good urine output.

3. Correction of electrolyte and metabolic disturbances. Hyponatremia and metabolic acidosis are common in severe cases. Electrolytes and blood gases should be determined periodically in severe cases and appropriately corrected as indicated.

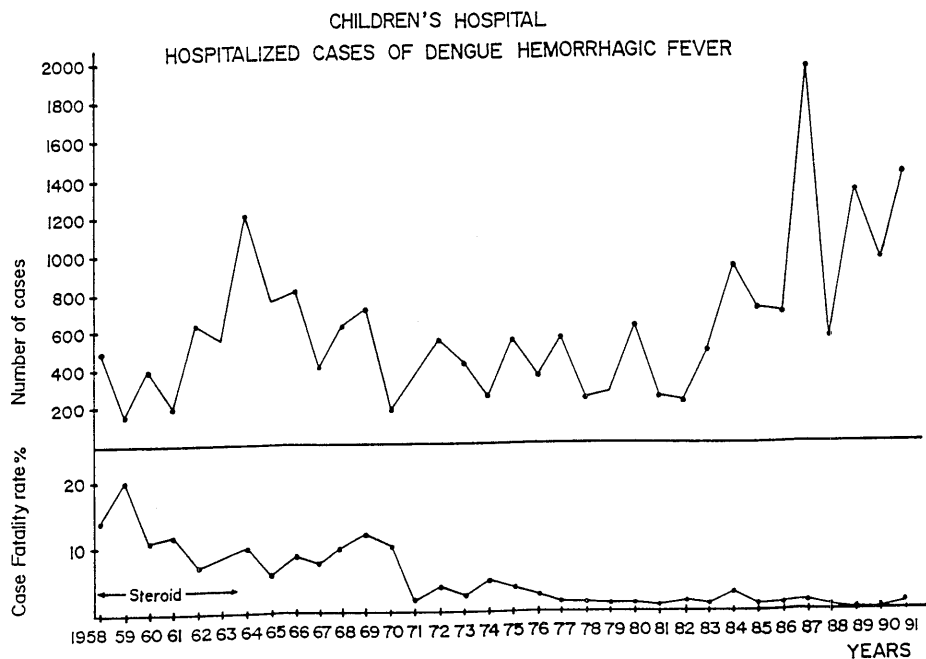
4. Blood transfusion. Severe bleeding mostly from gastrointestinal tract that required blood transfusion was observed in about 15% of shock cases<sup>2)</sup>. A refractory shock despite declining hematocrit level (e.g. from 50% to 40%) after adequate volume replacement with crystalloid and/or colloid indicates significant bleeding that requires blood transfusion. Fresh whole blood (FWB) is preferable and should be given only in such a volume that is needed to restore red cell mass to normal.

5. Unusual manifestations/complications<sup>8)</sup>.

The most frequently encountered are acute hepatic failure and renal failure (which usually follow a complicated case with prolonged shock) that required specific and appropriate treatment. Early blood exchange transfusion in case of hepatic encephalopathy or Reye's like syndrome has proved to be life saving in a number of cases, as is hemodialysis in renal failure.

Some DHF patients present unusual manifestations with signs and symptoms of CNS involvement, as convulsion and/or comatose. This has been shown to be encephalopathy not encephalitis which may be a terminal stage of DHF cases with intracranial hemorrhage or occlusion associated with DIC. Electrolyte and metabolic disturbances are found to be associated factors of encephalopathy. The most commonly found is encephalopathy associated with hepatic failure which is a major contributing cause of death in DHF now.

The experience at the Children's Hospital where a great number of DHF cases were seen each year, the treatment with this regimen, without using corticosteroid or any vasopressure drugs, has resulted in a steady decline in mortality of shock cases. The case fatality rate drops from about 10% in 1970 to 2% in 1984 and 0.2% in 1990 (Fig. 1.). Results of the studies from various places on the use of corticosteroid in treating DSS showed no benefit either in fatality rate or a reduction in volume of fluid therapy or duration of therapy<sup>9)</sup>. The prognosis of DHF, a disease of potential fatal shock, thus depends on early diagnosis and early recognition of shock which could be done with careful clinical observation and simple laboratory tests.



**Fig. 1.** Hospitalized cases of dengue hemorrhagic fever, children's Hospital, Bangkok, Thailand

#### REFERENCES

- 1) Halstead, S B (1993): Global epidemiology of dengue: health systems is disarray, *Trop. Med.* 35 (4), 137-146.
- 2) WHO (1986): *Dengue hemorrhagic fever: diagnosis, treatment and control.* Geneva. World Health Organization.
- 3) Nimmannitya S. (1987): Clinical spectrum and management of dengue hemorrhagic fever, *Southeast Asian J. Trop. Med. Pub. Hlth.*, 18: 392-397.
- 4) Sangkawibha N., Rojanasuphot S., Ahandrik S. *et al.* (1984): Risk factors in dengue shock syndrome. A prospective epidemiological study in Rayong. Thailand, *Am. J. Epid.*, 20: 653-669.
- 5) Kalayanarooj S, Nimmannitya S. (1989): A study of erythrocyte sedimentation rate in dengue hemorrhagic fever. *Southeast Asian J. Trop. Med. Pub. Hlth.*, 20: 325-330.
- 6) Innis BL., Nisaluk A., Nimmannitya S. *et al.* (1989): An enzyme linked immunosorbent assay to characterize dengue infections where dengue and Japanese encephalitis co-circulate. *Am. J. Trop. Med. Hyg.*, 40 (4): 428-27.
- 7) Nimmannitya S. (1993): Management of DF/DHF, *In Monograph on Dengue/Dengue Hemorrhagic Fever.* WHO Regional Publication, SEARO No. 22: 48-61.
- 8) Nimmannitya S, Thisyakorn U, and Hemsrichart, V. (1987): Dengue hemorrhagic fever with unusual manifestations. *Southeast Asian J. Trop. Med. Pub. Health.*, 18: 398-406.
- 9) Sumarmo, Talago W and Asrin A. (1982): Failure of hydrocortisone to effect outcome in dengue shock syndrome. *Pediatr.* 69 (1) : 45-49.