Emergence of dengue haemorrhagic fever in Bangladesh: Diagnosis, management and prospects for control

Rahman M, Siddique AK, Rahman K

Introduction
Dengue is an acute febrile mosquito-borne disease caused by four antigenically related viruses serotypes of dengue in tropical and subtropical areas of the world putting more than 3 billion people at risk of infection. An estimated 50 -100 million of dengue cases occur yearly resulting in 500,000 hospitalisation and 25,000 deaths. The patterns of dengue viral diseases vary and include commonly mild undifferentiated fever, classical dengue fever (DF) and life-threatening dengue haemorrhagic fever (DHF) frequently leading to hypovolemic shock i.e. dengue shock syndrome (DSS) with a significant case-fatality rate up to 44% if early diagnosis followed by careful and timely proper case-management are not performed.

Classical dengue fever is characterised by fever, pain symptoms (headache, muscle and joints pain, retroorbital pain), rash and gastrointestinal symptoms (vomiting, nausea, loss of appetite and diarrhoea). The febrile phase is usually followed by a short afebrile phase (defervescence phase) and a relatively long convalescence phase. Between 1635 and 1886, dengue infection was primarily clinically expressed as relatively mild dengue fever without a significant morbidity and mortality in the world. However, dengue cases with haemorrhage, shock and death were reported for the first time in 1887 in Queensland, Australia. The severe nature of DHF was not well recognized till 1953 when a large epidemic of DHF (Philippines fever) occurred in Manila, Philippines. The epidemic remained localized in Southeast Asia till the 1970s involving Thailand, Myanmar and other neighbouring countries. In the 1980s and 1990s the epidemic DHF spread west into India, Pakistan, Sri Lanka, Maldives and probably Bangladesh and east into China. Nearly 30 years after its appearance in Asia, the first epidemic DHF emerged in the Americas in Cuba in 1981 and by now many American countries are affected with DHF. Currently, DHF is an important cause of hospitalisation and death in many countries of Asia and the Americas. In July 2000, an outbreak of clinically suspected DHF (not confirmed by virus isolation) suggested by serological evidence, occurred in Dhaka, for the first time in Bangladesh. Sporadic cases are reported from different parts of the country. Thus, an attempt is made to review the current knowledge and experience regarding this emerging dengue infection and their management.

Bangladesh perspectives
Southeast Asia (SEA) is regarded as home of dengue viral diseases. And after the Second World War the periodic DHF epidemics have emerged as an important cause of morbidity and mortality in many countries of SEA. Interestingly, no major epidemic of DHF occurred in Bangladesh in the past. In 1964, dengue serotype 3 was responsible for classical dengue fever in Dhaka (Dhaka fever) and DHF was reported for the first time in Calcutta in India in that year. Apparently, a small outbreak of few cases of clinical DHF was reported in 1968 in an area of Bangladesh close to Myanmar. In 1996 and 1997 multiple dengue serotypes (dengue 2, 3 and 4) were detected for the first time to cause dengue fever in Chittagong, Bangladesh. In 1999, an outbreak of dengue fever with few unconfirmed cases of DHF was reported in Dhaka city, Bangladesh as suggested by positive serologic evidence. The exact dengue situation in Bangladesh is difficult to

1. Mahbubur Rahman, MBBS, MSc, Ph. D (Distinction), Associate Scientist, Laboratory Sciences Division ICDDR,B. Dhaka, Bangladesh. E-mail: mahbubur @ icddrb.org,
3. Khalilur Rahman, MBBS, MRCP (UK), Senior Consultant, Department of Medicine, Holy Family Red Crescent Hospital, Dhaka.

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determine because of lack of facilities for virus culture and other methods for detection of viruses and their serotypes in the past.

**Clinical approach to recognise dengue viral disease patterns**

It has been observed that all dengue infections are not expressed clinically as symptomatic cases and a significant number of infected humans remained asymptomatic or minimally symptomatic for a short period of time. In a prospective study in Thailand, it was observed that 87% of 103 school children infected during the study period by dengue virus were either asymptomatic or minimally symptomatic being absent for a day from the school, 4% and 9% had DF and DHF, respectively. And the majority (78%) of DHF cases required hospitalisation for treatment and pre-existent dengue antibody was a significant risk factor for development of DHF. The clinical presentation depends on age, underlying diseases and immune status of the host and virus strain. The characteristics of different categories of common dengue diseases are summarized in Table 1.

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<th>Table 1. Patterns of Dengue diseases</th>
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<td>Syndrome</td>
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<td>Undifferentiated Fever</td>
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<tr>
<td>Dengue Fever*</td>
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<td>DHF</td>
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DHF = Dengue haemorrhagic fever, DSS = Dengue shock syndrome, 'T' = Tourniquet test
#Other severe dengue syndromes include encephalopathy, hepatic damage, and cardiomyopathy. *Dengue fever may present with severe haemorrhage.

Some dengue infections result in DHF, a syndrome that in its most severe form can threaten the patient's life, primarily by plasma leakage through increased vascular permeability leading to hypovolemic shock usually around defervescence phase (Figure 1).

**Figure 1 : Dengue fever leads to the development of DHF and DSS**

Inflammatory response to dengue infection produces vasculopathy. Extravasation occurs through endothelial gaps, without inflammation and necrosis of capillary endothelial cells resulting in haemoconcentration, pleural effusion, ascites, hypoproteinaemia, hypoalbuminemia. The haemorrhagic phenomenon in dengue infection is complex and not well understood. Reduced formation, function and survival of platelet, action of cytokine, vascular injury and consumption coagulopathy may play role in the causation of bleeding manifestation.

**Danger period** (24-48h, time for development of DHF or DSS): needs observation, clinical and laboratory monitoring for prevention of severe disease.

**Critical period** (time for development of DSS): needs above and require hospital care in outpatient or inpatient for prevention, early recognition and treatment of shock.

**Fatal period** (time for death, 12-24h): needs intensive treatment of hypovolemic shock, nursing and monitoring in special dengue care unit.

Risk factors for dengue infections appear to be many, however, infection of an area with Ades aegypti and introduction of a new serotype where population’s immunity is low are important contributing factors.
Laboratory diagnosis of Dengue infection

Confirmatory laboratory diagnosis of dengue infection include 1) virus isolation 2) detection of specific viral antigen or 3) dengue viral RNA and 4) demonstration of rising titre (4 fold or more) of dengue specific-serum antibodies (Table 2). Laboratory diagnosis is essential for patients and may be necessary for public health surveillance and medical record.

Virus isolation

Isolation of virus is the most definitive approach and is 50% sensitive with ace phase serum in tissue culture after 7 days of incubation. Viremia usually remains for 5 days after onset of symptoms and cleared rapidly with the appearance of antibody. After a week of incubation, cell cultures are stained with fluorescein-conjugated polyclonal antibody to detect virus isolates, and then serotyped with monoclonal antibodies in indirect fluorescent antibody test.

Serological diagnosis

It depends on the detection of presence of dengue-specific IgM or rise in IgG antibody titre in paired acute and convalescent phase sera by enzyme-linked immunosorbent assay (ELISA). The concern is many flavivirus such as Japanese encephalitis, West Nile, tick-borne and St. Louis viruses share group antigens with dengue virus that can cross-react in serological test making results less specific (false positive). IgM antibody becomes detectable in 90% of patients by the sixth day of illness by capture ELISA (MAC-ELISA) and may be detectable for a mean of 60 days. With a single acute phase serum after sixth day, MAC-ELISA has sensitivity of 75%. With paired sera it increased to 95%. IgM negative results on acute phase samples cannot exclude the diagnosis of dengue and convalescent serum should be collected. The IgG antibody appears by fifth day after onset of symptoms in primary dengue. Titre rises slowly for some weeks and then remains detectable for many years. IgG titres rise rapidly in secondary infection in a few days. Indirect ELISA is used to detect IgG. In dengue endemic region high rate of IgG positivity makes analysis of paired sample critical because the presence of IgG antibody in a single serum sample has no clinical significance.

Reverse transcriptase polymerase chain reaction (RT-PCR)

It may be used to detect all four serotypes of viruses and may shorten the detection time compared with viral culture. A multiplex PCR alone or followed by a nested PCR is commonly used in a single tube using four sets of primers. It can detect viruses in samples inactivated by improper storage or containing neutralizing antibody.

Haematological, biochemical and other tests

WBC is normal initially, but leucopenia is common with neutrophil predominating. At the end of febrile phase leucopenia is observed with low neutrophil and lymphocytosis with atypical lymphocytes. Platelet: 100,000/cm3 on 3rd -8th day HCT: increases with plasma leakage in DHS by 20% or more Mild albuminuria or positive
Occult blood test Serum: protein, albumin, C3, C5, prothrombin and fibrinogen may decrease and SGPT, SGOT may increase in DHF / DSS patients. Prothrombin time and partial thromboplastin time may increase.

**Table 2. Laboratory Diagnosis of Dengue Viral Infections**

Other serological tests include hemagglutination and neutralization tests. The results of combined IgM and IgG raft test are difficult for interpretation. The rapid immunochromatographic test may be useful for serosurveillance in association with ELISA.

**Clinical Management of Dengue**

There is no specific treatment of dengue viral diseases. The management is symptomatic and supportive. However, effective case management include following requirements:

- Well-trained Physicians, Nurses
- Reliable laboratory facilities
- Adequate blood supply
- Functioning pharmacy
- Dengue treatment unit during epidemic

**Dengue fever (Classical) - Home management**

- Rest
- Analgesics
- Antipyretics and sponging to keep temperature < 39°C. Use only paracetamol, never use aspirin non-steroidal anti-inflammatory drugs.
- Mild sedatives may be needed

- Oral fluids such as oral saline, fruit juice and soft drinks are very useful and should be used and more so in patients with diarrhoea and vomiting.
- Monitoring of patient is the most important measure for the prevention, early, diagnosis and treatment of DHF and DSS. It includes clinical and laboratory components:

**Clinical monitoring:**

- Fever - very high fever cases frequently develop DHF Bleeding manifestations
- Urinary output
- Level of consciousness
- Blood pressure (pulse pressure)

**Laboratory monitoring:**

- HCT, Platelet count, TC, DC of WBC, Hb%

**Alarm signs** develop usually 3-6 days after onset of symptoms. If alarm signs are noticed during monitoring of patient, the patient may require hospitalisation.

**Alarm signs are:**

- Drop in BP
- Platelet count < 50,000 / cm³
- Increase in HCT (>20%) or rising HCT
- Major haemorrhage
- Patient with altered consciousness or convulsion

**DHF Grade I & III**

Patients with fever, platelet count (< 100,000 / cm³), increased HCT (≥20%) and minor bleeding including a positive TT test may be treated in outpatient observation clinic or may require hospitalisation.

**Treatment in Observation ward or OPD like a Diarrhoea Treatment Corner**

**Fluid therapy:** isotonic fluid, half strength saline in Glucose or Ringer's lactate for 24-48 h and plenty of fluid orally. Antipyretics and sponging to keep temperature < 39°C. Monitoring: Clinical and laboratory, input-output and vital signs for prevention, early diagnosis and treatment of DSS cases.

**Hospitalisation of dengue patient: When?**

DF or DHF patient not improving during observation and has any one of following needs immediate hospitalisation:

- Drop in BP
- Platelet count < 50,000
- Increase in HCT (>20%) or rising HCT
- Major haemorrhage
- Patient with altered consciousness or convulsion
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f) All DSS patients (DHF grade III & grade IV)
g) Patient with severe abdominal pain with hepatomegaly

Principles for the optimum treatment of severe dengue diseases (DSS / DHF)
Fluid therapy (replacement of plasma loss): Correct loss immediately (10 -20 ml/kg/hr) as required and maintain it for 2 to 4 days. Fluid replacement is performed as in the case of diarrhoeal patient. Replace loss immediately as bolus and then maintain it usually for 24 to 72 h depending on clinical response. The amount of fluid is usually daily maintenance plus 5% of body weight. Type of Fluid: isotonic crystalloid fluid (half strength saline in glucose or Ringer's lactate or 5% dextrose in aqua) and Dextran 40 in severe cases if no improvement occurs with crystalloid fluid. In severe cases, initial hydration with Dextran 40 provides better results.

Electrolyte and metabolic corrections: Fresh Blood is indicated in severe bleeding, in refractory shock (no improvement with crystalloid or colloidal fluid) and DSS with DIC. Only 15% -20% of DSS patients may require blood.

Platelet concentrate usually offers no benefit in case of thrombocytopenia as shown by different studies.

Steroid and vesopressive drug are not useful
No role of antibiotics and vitamin C Antiviral drugs are not effective
Monitoring of patients: Clinical and laboratory, input-output and vital signs for prevention of death.

Intensive care and treatment are required for the first 48-hour for preventing case fatality in DSS as most case-fatality occurs during the first 12 -24 h.

Prospects for control
Vaccine Development
Live attenuated vaccine containing four dengue serotypes, developed by Mahidol University, Thailand, are undergoing commercial production. Preliminary clinical studies suggest that they can be safe and immunogenic. Concerns remain regarding the conversion to virulent strain. Inactivated vaccine candidates are safer and the immunogenicity of formalin-inactivated dengue 2 virus is encouraging. However, the cost of vaccine appears to high because of insufficient and slow growing nature of dengue virus in tissue culture. The recent exciting development of complete infectious cDNA clones of dengue virus holds a great promise as the basis for a dengue vaccine.

Vector control
Control of dengue currently depends on controlling its vector Aedes mosquito (Ae aegypti, Ae albopictus). Aedes is peridomestic mosquito with a short flight range (100 yards) and breeds exclusively in artificial habitats such as water-storage container and discarded items that collect rainwater and particularly rainwater-filled tree-holes. Elimination of these peridomestic larval sources is the most effective way to control mosquitoes that transmit dengue. Space spraying with insecticides to kill adult mosquitoes is usually ineffective. The aerosols are particularly recommended for emergency control during epidemic transmission as part of an integrated vector elimination effort including environmental management, source reduction and use of larvicides.

Community participation
In recent years, the emphasis has shifted towards community- based approaches, based upon health education and individual responsibility to eliminate peridomestic mosquito larval habitats. However, it takes long time to control wide geographical area.

Protection of host from mosquitoes bites
The bites can be avoided by covering body with clothes and shoes, using repellents such as DEET (30%) and coils. It may be remembered that the peak bitting time is early morning and late evening, though it can bite any time. Visiting a dengue endemic area is a risk factor for dengue infection. Thus, special care must be taken to avoid this infection. Bitting of an infected person (patient) must be prevented by keeping in mosquito net and in relatively mosquito-free area to prevent
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transmission and spread of diseases in order to break the cycle of mosquito-human-mosquito. It is wise to use mosquito nets to babies, old people and others who may rest during the day.

References