Dengue: Recent health problem in Bangladesh

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Introduction
Dengue is found in tropical and subtropical regions around the world, predominantly urban and periurban areas. It is endemic in more than 100 countries in America, Africa, south east asia and western pacific areas. WHO1 estimates there may be 50 million cases of Dengue infection worldwide every year.

Virus
It is an RNA-containing flavi virus. All its four serotypes can cause Dengue hemorrhagic fever (DHF) / Dengue shock syndrome (DSS). Severe disease is common with Den-2 and Den-3.

Transmission
Dengue is transmitted to human being through the bites of infective female aedes egyptii mosquitoes. Mosquitoes acquire the virus while feeding on an infected individual. Once infected, the mosquito transmit the virus throughout its life, it transmits it to next generation through transovarian transmission

Incubation period
Average incubation period is 3 -13 days.

Primary infection
Once the virus enter the human body, the virus is taken by the monocyte-macrophagereplication of virus occurs within these cells. Cells are destroyed and virus released in the circulation (viremia).

Secondary infection
In secondary infection there occurs antibody dependant enhancement of infection whereby cross-reactive but nonneutralising antibodies from a previous infection bind to a new infective serotype and facilitate virus entry into cells resulting in higher peak viral titres. In primary and secondary infections higher viral litres are associated with severe infections.

Viremia
Viremia is present for about 24 hours prior the onset of illness and for an average of 5 days after the onset of illness. It usually coincides with the period of fever. During this time humans are infective to vector mosquitoes.

Pathogenesis of DF and DSS
- Agent: Dengue Virus (Den-1, Den-2, Den-3, Den-4)
- Viral antigen
  A. Enveloped antigen ‘E’ having
  1. Hem agglutination epitope.
  2. Viral neutralization epitope
  3. Antibody enhanced infection epitope.
- Nonstructural protein NS1
- Membrain Protein M--Pre M
  1. Confer Protective immunity.

  2. May have important role in vaccine production.

Vector
Aedes egyptii. Other aedes compatible of transmmission include
A. albopictus, A polynensiensis, A.scutellaris complexes.

A. egyptii can transmits dengue infection either immediatly by a change of host when its feeding is interrupted or after an inculbation perid of 8 to 10 days. Patients is infective to

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mosquito during viramemia which is present from few hours before the onset of symptoms to an average of 5 days after the onset of symptoms.

- When an individual is infected with any one of the four serotype of dengue virus (DEN-1, DEN-2, DEN-3, DEN-4) for the first time, he/she may develop dengue fever. This is primary infection.
- Primary infection confers lifelong homotypic immunity
- This also confers variable heterotypic immunity against other three serotypes of dengue virus for two to twelve months Fig.I
- In a critical time period (from one year to five years after primary infection) when antibody titer reaches subneutralizing level, second infection with any other virulserotypes can cause antibody hanged infection giving rise to secondary infection that is called dengue hemorrhagic fever (Fig.I)

Figure 1: Immune pathogenesis of DHF by secondary infection

- Third and forth dengue viral infection seldom cause symptoms.
- After single attack of DHF, the chance of second attack of DHF is only 5%
- In fetus with maternal anti dengue IgG can cause DHF with primary viral infection during critical time period (From third to seventh month after birth) when IgG reaches sub-neutralizing concentration (Fig-II)

Figure II: immune petiogeriesus of DHF m infant

- T lymphocytes are activated and produce gamma interferon and interleukin-2 during DF and DHF.
- CD-4 T cells are activated at higher level in DHF than DF.
- CD-8 T Cells are significantly activated only in DHF.
- Rapid release of cytokines and chemicals mediators caused by T cell activation and by cytotoxic T cell mediated lysis of dengue viral infected monocytes, together with complement activation product teakage and coagulation derangement (Fig.I)

- Augmented B cell activation causes increased plasma cell proliferation followed by release of immunoglobulin.
- Immunoglobulin combined with viral protein (antigen-antibody complex) activate
complement and causes increased level of C3a and C5a which cause vascular leakage.

- Antibody cross reacted with plasminogen perturbation of coagulation pathway and associated haemostatic mechanism leading to DIC and bleeding.
- Thrombocytopenia and thrombosthenia resulting from early megakaryocyte arrest play and important role by causing bleeding both in DF and DHF.
- DHF/DSS accompanied by the simultaneous and parallel activation of complement and haemostatic system together vascular permeability, The most abnormal values are found in most severely ill patients. The blood levels fof C1q, C3, C4, C5-8, C3 pro-activatots may be depressed. C3 catabolic rate is elevated. Findings are compatible with actinavion of complement, both classicals and alternate pathway. There is also prologed bleeding time, elevated prothrombim time. Prolonged silicon clotting time, reduction in factor II, V, VII, X, Hypo Fibrinogenemia and increased FDP.
- The more reduction of plasma TXA2: PGI2 ratioleads to more overt and serious manifestation of the disease (One of the cause not to give aspirin or alike drugs in gengue).
- High level of NS -1 is found in acute phase serume of serologically proven secondary infection NS -1 could not be detected in serologically confirmed primary infection. These suggests that NS-1 Contributes significantly to the formation f circulating immune complexes that may play an important role in the pathologinesis of service dengue disease.
- Severity of dengue disease correlates with the following factors:
  - High Viremia titer.
  - Secondary dengue virus infection.
  - DEN-2 virus type.
  - Age of patients (in adult hemorrhage and in children shock predominate).
  - Genetic background of patients.
  - Sex of the patients (Female are more susceptible).
  - Time interval between two infection (1-5 years)
  - Sequence of infection (Severe disease DEN-1& DEN-2, less severe disease DEN-2 & DEN-1)

**Histopathological Changes**
- Vascular change include vasodilatation, congestion, perivascular hemorrhage and edema of arterial wall.
- Proliferation of reticuloendithlial cells with accelerated phagocytic activities observed frequently. The lymphoid tissue shows increasing activity of B Lymphocyte system with activity proliferation of plasma cell and lymphoblastiod cells.
- In the liver there is fical necrosis of the hepatic and kupffer cells with formation of councilman like bodies.

**Clinical features**
- Dengue fever is a severe form of flue like illness.

**Manifestations**
It may be
1. Symptomatic
2. Asymptomatic
Symptomatic patients may again be with
a) Undifferentiated fever
b) Classical dengue fever(DF)
c) Dengue hemorrhagic fever(DHF) d) Dengue shock syndrome(DSS)
e) tinusual syndrome such as encephalopathy and fulminant liver failure.

**Phases**
1. Febrile phase(2-7)days
2. Afebrile phase or critical phase(2-3)days-phase for the risk of developing DHF/DSS.
3. Convalescence phase-persists for 7-10 days after critical phase.
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**Classical Dengue Fever**
High rise of temperature (104-1050 F). Fever usually persists for 2-7 days with two peaks during this illness giving saddle back appearance of temperature curve.

**Constitutional features of DF**
Headache, retroorbital pain, bodyache, muscle pain, joint and bone pain, flushed face.

**Rash**
Four types of rashes in dengue.
A. Diffuse flushing
B. Fleeting pinpoint eruptions—they develop in first half of illness.
C. Maculopapular or scarletiform rashes appear on 3rd or 4th day of fever on face and trunk and spread to extremities.
D. Convalescent confluent petechiae—this is typical rash of dengue, appears on 6th day.

**Other features**
Hemorrhage, radicardia, enlarged liver (tender), raised hepatic enzymes, leukopenia, normal platelet count and hematocrits. Hemorrhage can occur in classical dengue fever i.e fever with hemorrhage does not always mean DHF.

**Dengue hemorrhagic fever**
All the features of Dengue fever with followings:

- Hemorrhagic manifestations
  Shown by positive tourniquet test, petechiae, ecchymoses, or purpura or bleeding from mucosa, gastrointestinal tract, injection sites or other locations:
  - **Platelet count <100000/mm³**

Objective signs of plasma leakage due to increased vascular permeability shown by fluctuation of packed cell volume (Hct) by >20% during the course of illness and recovery or clinical signs of plasma leakage such as ascites, pleural effusion or hypoproteinemia.

**Grades of DHF**
Grade-I: Features of DF plus positive tourniquet test
Grade-II: Above signs plus spontaneous bleeding
Grade-III: Signs of either grade-I or grade-II DHF plus features of circulatory failure viz rapid weak pulse, hypotension apprehension.
Grade-IV: DHF with undetectable BP and pulse.

**DSS²**
Grade III and grade IV together also called Dengue shock syndrome (DSS). A patient is said to have dengue shock syndrome if it has the criteria for dengue hemorrhagic fever and either pulse pressure <20 mm Hg or hypotension defined as systolic pressure < 80 mmHg for those aged < 5 yrs or < 90 mm Hg for those > 5.

A patient with pulse pressure less than 20 even with normal systolic or diastolic pressure may be in DSS.

DHF/DSS usually develop when patient is in afebrile period.

**Diagnosis**
It is described in three ways

**Suspected diagnosis**
For purpose of treatmentsuspicion by a
clinician is sufficient. It is not difficult during the period of outbreak. So in our setting during the period of outbreak (July-October) we can take any febrile patient as Dengue provided we do not forget malaria, typhoid, rickettsias which are common in our clinical practice.

Laboratory investigations
Virus is detectable only in febrile period. Antibodies may not be positive in early stages. It may be false positive in other flaviviruses infection. Antibody tests should not be done before 4th day of infection. It is wise to do it after 7th day. Complete blood picture including Pc, Hct, MP (malarial parasite), LFT (SGOT/SGPT) should be done in early part of infection (3rd or 4th day preferable).

Probable diagnosis
At least one of the followings
• Supportive serology for single serum sample titre >1280 with Hemagglutination inhibition test (HIT), comparable IgG titre with ELISA or positive for IgM antibody test.

• Occurrence at same location and time as confirmed cases of Dengue fever.

Confirmed diagnosis
At least one of the followings:
• Isolation of dengue virus from serum or autopsy samples
• Four-fold or greater increase in serum IgG (by Hct) or increase in IgM antibody specific to dengue virus
• Detection of dengue virus in tissue, serum, or cerebrospinal fluid by immunohistochemistry, immunofluorescence or enzyme-linked immunosorbent assay (ELISA).
• Detection of dengue virus genomic sequences by reverse transcription-polymerase chain reaction.

Exclusion of other diagnosis
A. Febrile phase
1. Complete blood picture including MP
   a. Leukocytosis: A very high leukocyte count virtually exclude the diagnosis of a viral disease.
   b. Leukopenia: A leukopenia or normal blood count having normal platelet count suggests enteric fever, rickettsiosis or other viral disease.

   c. If duration of fever persists for more than 7 days other serological tests for dengue and others are justified (If PC is low and Hct is higher). Fever persisting for more than two weeks exclude the diagnosis of dengue. In the situation of prolonged fever with normal blood picture enteric fever, rickettsiosis should be excluded as these diseases are common in our country.

2. Patients presenting with pain abdomen
Gasritis and hepatitis is the main cause of pain abdomen in dengue. Pancreatitis is a possibility of acute abdomen in dengue, which should be excluded. In case of children rapid distension of abdomen due to ascites may be confused with acute abdomen and an urgent USG abdomen may help.

3. Other investigations
USG abdomen may exclude ascites and effusion (also chest x-ray). Liver function tests, renal function tests, electrolytes should be done in DHF cases. To find out hemorrhagic disorders prothrombin time, APTT, FDP, d-Dimer and fibrinogen level may need to be estimated.
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B. Afebrile phase
In this phase DHF patients are at risk, so monitoring should meticulous for 2-3 days.

Monitoring
Four hourly monitoring of blood pressure, pulse, maintenance of intake and output is mandatory during critical period. At least once a day PC and Hct should be available. This will help prevention of DSS and overhydration as well.

Management of Dengue
A. Febrile phase
DF and DHF can’t be differentiated initially. DF does not progress to DHF or DHF never begins with DF. Initially management is similar.
1. Reduction of temperature with paracetamol (no other medicine), sponging and adequate hydration
3. Monitoring: Care should be taken about fluid intake from the beginning
4. Rest

Reduction of temperature
1. Aim should be to keep temperature <100°F. Paracetamol may be needed in maximum dose (80 mg/Kg/day) in four divided doses. Rectal route works rapidly.
2. Nontherapeutic means: Sponging with cold water (not ice), regular bathing, nursing in cool open space, thin cloths (avoid woolen blanket) helps reducing temperature.
3. Adequate hydration is a must. About 3L/day (100ml/Kg for children) may be a good amount. Plain water, Oralsaline, dab water, fruit juice (helps with nutrition) all serve purpose.

Clinical clues like repeated vomiting, persistent abdominal pain prehension/restlessness, severe epigastric tenderness are good indicator for DHF.

In DHF grade I and II OPD or home management may be adequate provided bleeding is not severe and adequate fluid and monitoring is ensured.

Ranitidine/Sucralfate/omiprazole/misoprostol all can help. Domperidone may be used for nausea and vomiting.

B. Afebrile phase
In this phase risk of developing DHF is higher so monitoring should be geared.

In DHF III and IV management should be at hospital.

Monitoring of the vital signs and maintenance of near normal blood pressure is the goal. Overenthusiastic or panic parenteral fluid and blood/blood product administration is the most serious mistake happens in these phases.

IV fluid
Normal saline is the best fluid. ICU management was not proved superior for DHF IV patients. Fluid can started @ 3 ml/Kg/hr and changed according to need (BP). In practice if facilities available, fluid can be started from the beginning (grade I) @ 8 drops/min and tailored according to need. Oral fluid should always be encouraged along with IV.

Blood/Blood products
If there is excess bleeding (hematemesismelaena, PV bleeding etc), the Hct is below normal whole fresh blood is indicated. Blood test for grouping should routinely be done for DHF cases. Appraisal of party about group and probable necessity of blood/blood product transfusion before hand should be a routine practice for clinicians. Gum bleeding skin hemorrhages does not need special treatment. Platelet count less than 10000 and higher hematocrit may be an indication for transfusion of platelet concentrate. Platelet concentrate is costly (2500 BDT) and preparation is time consuming (6 hours).

Other drugs
Antibiotics has no role, though severe neutropenia is common accompaniment prophylactic antibiotics are not indicated. Corticosteroidspressor agents (viz dopamine

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etc), antivirals, antileaks(carbazocram)have no role.

C. Convalescence
Most of (even DSS cases) the patients become alright on third day. Patient is discharged when:

a. General condition is acceptable
b. Afebrile

c. PC becomes> 50000. Prolonged fever(hospital stay) may occur in cases with liver necrosis (high S GOT),combined infection(malarialtyphoid, rickettsiosis, hepatitis has been found positive in some of our cases), co-morbid illnesses.

Prevention
May be described in two ways- 1. Primary 2. Secondary

1. Primary prevention
a. Vaccine
Dengue occurs only in humans, lack of a dengue animal model is an obstacle for vaccine development. Phenomenon of antibody dependent enhancement demand the development of a tetravalent vaccine. Live attenuated tetravalent vaccines are being evaluated in phase 2 trials.

b) Mosquito is our target (to date) for prevention. It is also a difficult task owing to it’s intimacy with human. Prevention from mosquito bite is the goal. Mosquito breeding should be prevented by killing larva and destroying receptors for larva viz container /canisters/discarded tyres/small water reservoirs of construction places by not encouraging storage for more than five days. These demands involvement of whole community.

2. Secondary prevention
Adequate management of DHF I and DHF II may prevent development of DSS, thus reduce the mortality in Dengue. Medical persons have great role in secondary prevention.

References
1. WHO Regioanal publication, SEARO, No. 29.