Review Article

Review on Dengue Fever

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Introduction:

Over the last five decades, dengue has emerged globally as a critical threat to population health. The World Health Organization (WHO) estimates that 50–100 million dengue infections occur each year and that almost half the world's population lives in countries where dengue is endemic.[1] Today, dengue ranks as the most important mosquito-borne viral disease in the world. The emergence and spread of all four dengue viruses (serotypes) represent a global pandemic. While dengue is a global concern, currently close to 75% of the global population exposed to dengue are in the Asia-Pacific region.

Dengue is the most rapidly spreading mosquito-borne viral disease of mankind, with a 30- fold increase in global incidence over the last five decades. It is a major public health concern throughout the tropical and subtropical regions of the world. Almost half the world's population lives in countries where dengue is endemic. According to World Health Organization (WHO), about 50–100 million new dengue infections are estimated to occur annually in more than 100 endemic countries, with a steady increase in the number of countries reporting the disease.

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Dengue has been identified as one of the 17 neglected tropical diseases by WHO as mentioned in their first report on neglected tropical diseases in 2010[2]. Although the full global burden of the disease is still uncertain, the patterns are alarming for both human health and the economy. Every year, hundreds of thousands of severe cases arise, of which 20,000 lead to death. The loss to the economy is 264 disability-adjusted life years (DALYs) per million population per year. Approximately 1.8 billion (more than 70%) of the population at risk for dengue worldwide live in South-East Asia Region (SEAR) and Western Pacific Region, which bear nearly 75% of the current global disease burden due to dengue. Of the documented 11 countries of SEAR, 10 countries including Bangladesh are endemic for dengue. The only exception is the Democratic People's Republic of Korea.[3] Approximately 0.29 million cases, of which Thailand contributed almost 30%, Indonesia 29% and India 20%. Similarly, Western Pacific countries have reported 0.33 million cases, of which Philippines contributed almost 52%, Vietnam 24% and Cambodia 14% (source WHO)[3]. The true numbers are probably far more, since severe underreporting and misclassification of dengue cases have been documented. Bangladesh scenario.

Overview

Dengue viruses cause symptomatic infections or asymptomatic sero-conversion.

Symptomatic dengue infection is a systemic and dynamic disease. It has a wide clinical spectrum that includes both severe and non-severe clinical manifestations[4] After the incubation period, the illness begins abruptly and, in patients with moderate to severe disease, is followed by three phases – febrile, critical and recovery (Figure 1). The severity of the disease will usually only be apparent around defervescence i.e. during the transition of the febrile to the afebrile phase,

which often coincides with the onset of the critical phase. The disease has its complex clinical manifestations, on the other hand management is relatively simple, inexpensive and very effective in saving lives. So correct and timely interventions are very crucial. The key to a good clinical outcome is understanding and being alert to the clinical problems that arise during the different phases of the disease with a rational approach in case management.

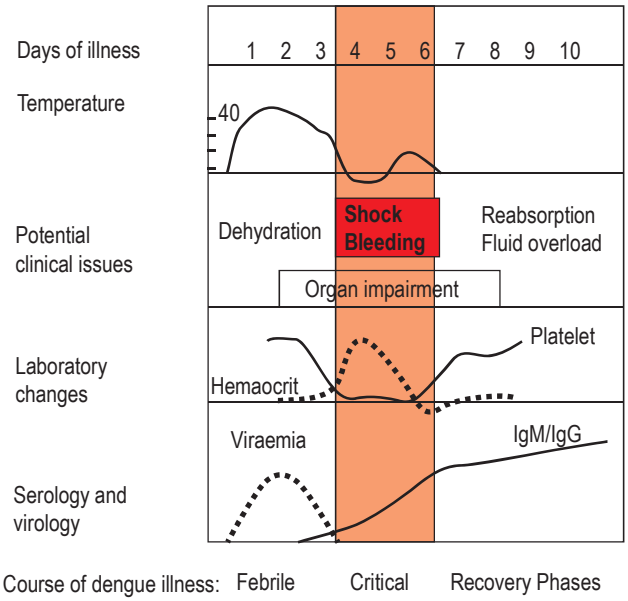

Fig.-1: The course of dengue illness

Febrile phase

Patients typically develop a 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, retro-orbital pain, photophobia, rubeliform exanthema and headache[4]. Some patients may have a sore throat, an injected pharynx, and conjunctiva. Anorexia, nausea and vomiting are common. It can be difficult to distinguish dengue clinically from non-dengue febrile diseases in early febrile phase. A positive tourniquet test in this phase indicates an increased probability of dengue [5,6]. However, these clinical features do not predict the severity of disease. Therefore, it is crucial to monitor for warning signs and other clinical parameters in order to recognize progression to the critical phase. Mild hemorrhagic manifestations such as petechiae and mucosal membrane bleeding (e.g. of the nose and gums) may be seen[7]. Easy bruising and bleeding at venipuncture sites is present in some cases, gastrointestinal bleeding may occur during this phase although this is not common[7]. The liver may be enlarged and tender after a few days of fever[5]. The mearliest abnormality in the full blood count is a progressive decrease in total white cells count, which should alert the physician to a high probability of dengue[5]. In addition to these somatic symptoms, with the onset of fever patients may suffer from an acute and progressive loss in their ability to perform their daily functions such as schooling, work and interpersonal relations[8].

Critical phase

During the transition from the febrile to afebrile phase, patients without an increase in capillary permeability will improve without going through the critical phase. Instead of improving with the subsidence of high fever; patients with increased capillary permeability may manifest with the warning signs, mostly as a result of plasma leakage. The warning signs are mark at the beginning of the critical phase. Warning signs usually precede the manifestations of shock and appear towards the end of the febrile phase, usually between 3-7 days of illness. Persistent vomiting and severe abdominal pain are early indications of plasma leakage and become increasingly worse as the patient progresses to the shock state. The patient becomes increasingly lethargic but usually remains mentally alert. These symptoms may persist into the shock stage. Weakness, dizziness or postural hypotension occurs during the shock state. Spontaneous mucosal bleeding or bleeding at previous venipuncture sites are important hemorrhagic manifestations. Increasing liver size and a tender liver is frequently observed. However, clinical fluid accumulation may only be detected if plasma loss is significant or after treatment with intravenous fluids. These patients become worse around the time of defervescence, when the temperature drops to 37.5–38°C or less and remains below this level, usually on days 3–8 of illness. Progressive leukopenia [5] followed by a rapid decrease in platelet count usually precedes plasma leakage. An increasing haematocrit above the baseline may be one of the earliest additional sign of plasma leakage[9,10] . The period of clinically significant plasma leakage usually lasts 24–48 hours. The degree of plasma leakage varies. A rising haematocrit precedes, changes in blood pressure (BP) and pulse volume. The degree of haemoconcentration above the baseline, haematocrit reflects the severity of plasma leakage; however, this may

be reduced by early intravenous fluid therapy or due to haemorrhage. Hence, frequent assessment of haematocrit are essential because it indicates the need for possible adjustments to intravenous fluid therapy. A right lateral decubitus chest radiograph, ultrasound detects the free fluid in the chest or abdomen, or gall bladder wall oedema may precede clinical detection. In addition to the plasma leakage, haemorrhagic manifestations such as easy bruising and bleeding at venepuncture sites occur frequently. A rapid and progressive decrease in platelet count to about 100 000 cells/mm^3 and a rising haematocrit above the baseline may be the earliest sign of plasma leakage. This is usually preceded by leukopenia (≤ 5000 cells/mm^3)[6] .

Recovery phase

As the patient survives the 24-48 hour of critical phase, a gradual reabsorption of extravascular compartment fluid takes place in the following 48–72 hours. General wellbeing improves, appetite returns, gastrointestinal symptoms abate, stabilization of hemodynamic status and diuresis follows. Some patients have a confluent erythematous or petechial rash with small areas of normal skin, described as "isles of white in the sea of red" [11]. Some may experience generalized pruritus. The haematocrit stabilizes or may be lower due to the dilutional effect of reabsorbed fluid. The white blood cell count usually starts to rise soon after defervescence but the recovery of the platelet count is typically later than that of the white blood cell count. Respiratory distress from massive pleural effusion and ascites, pulmonary oedema or congestive heart failure will occur during the critical and/or recovery phases if excessive intravenous fluids have been administered and if intravenous fluid administration continues even after cessation of plasma leakage. Clinical problems during the different phases of dengue are summarized in Table I.

Severe plasma leakage and dengue shock/ severe dengue

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. As vascular permeability progresses, hypovolaemia worsens and results in shock. It usually takes place around defervescence, usually on day 4 - 5 (range days 3–7) of illness, preceded by the warning signs. During the initial stage of shock, the compensatory mechanism which maintains a normal systolic blood pressure also produces tachycardia and peripheral vasoconstriction with reduced skin perfusion. From this point onwards, patients who do not receive prompt intravenous fluid therapy, progress rapidly to a state of shock. Dengue shock presents as a physiologic continuum, progressing from asymptomatic capillary leakage to compensated shock to hypotensive shock and ultimately to cardiac arrests. Tachycardia (without fever during defervescence), is an early cardiac response to hypovolaemia. During the initial stage of shock, the compensatory mechanism that maintains a normal systolic BP produces tachycardia with quiet tachypnoea (tachypnoea without increased effort)11, and peripheral vasoconstriction with reduced skin perfusion (manifested as cold extremities and delayed capillary refill time of > 2 seconds and weak volume peripheral pulses). As peripheral vascular resistance increases, the diastolic pressure rises towards the systolic pressure and the pulse pressure, the difference between the systolic and diastolic pressures narrows. The patient is considered to have compensated shock if the systolic pressure is maintained at the normal or slightly above normal range but the pulse pressure is ≤ 20 mmHg in children (e.g. 100/85 mmHg) or if they have signs of poor capillary perfusion. Compensated metabolic acidosis is observed when the pH is normal with low carbon dioxide tension and a low bicarbonate level.

Table 1. Medical complications seen in the febrile, critical and recovery phases of Dengue

1	Febrile phase Dehydration:	High fever may cause neurological disturbances and febrile seizures in young children
2	Critical phase Shock from plasma leakage:	Severe haemorrhage; organ impairment
3	Recovery phase	Hypervolaemia (only if intravenous fluid therapy has been excessive and/or has extended into this period) and acute pulmonary oedema

Worsening hypovolaemic shock:

It is manifested as increasing tachycardia and peripheral vasoconstriction. Not only the extremities cold and cyanosed but the limbs become mottled, cold and clammy. By this stage the breathing becomes more rapid and increases in depth – a compensation for the metabolic acidosis (Kussmaul's breathing). Finally, there is decompensation, both systolic and diastolic BPs disappear suddenly and dramatically and the patient is said to have hypotensive or decompensated shock. At this time the peripheral pulses disappear while the central pulse (femoral) will be weak. Hypotension develops when physiologic attempts to maintain systolic BP and perfusion are no longer effective. One key clinical sign of this deterioration is a change in mental state as brain perfusion declines. The patient becomes restless, confused and extremely lethargic. Seizures may occur and agitation may alternate with lethargy. On the other hand, children and young adults have been known to have a clear mental status even in profound shock. Adults have been known to be able to work until the stage of profound shock is reached. The failure of infants and children to recognize, focus or make eye contact with parents may be an early ominous sign of cortical hypoperfusion or failure to respond to painful stimuli such as venepuncture. Parents may be the first to recognize these signs – but they may be unable to describe them, other than to say something is wrong. Listen to parents! Hypotension is a late finding and signals an imminent total cardiorespiratory collapse. Hypotension is associated with prolonged shock which is often complicated by major bleeding[12] . Patients with severe dengue have varying degrees of coagulation abnormalities, but these are usually not sufficient to cause major bleeding[13,14]. When major bleeding does occur, it is almost always associated with profound shock since this, in combination with thrombocytopenia, hypoxia and acidosis, can lead to multiple organ failure and advanced disseminated intravascular coagulation.

Diagnosis:

The diagnostic method to confirm an acute infection depends on the time of clinical illness:

the febrile phase is coincident with the presence of viraemia which is detected by NS1antigen, some viral components and replication products in blood; the critical and convalescent phases coincide with the development of antibodies, IgG and IgM for dengue fever; Specific IgM is the best marker of a recent dengue infection.

Fluid management

The total amount of fluid recommended during the *entire critical phase* (48hrs in patients coming without shock and 24hrs in patients coming in shock) is:

Maintenance (M) + 5% of body weight

Maintenance (M) = 100ml/kg for the first 10kg +50ml/kg for next 10kg + 20ml/kg for balance weight. +5% of body weight (50ml x body weight in kg)

- The maximum weight for which fluid is calculated in any patient *should not exceed 50kg*. Accordingly, M+5% *should not exceed 4000 ml* any patient.

  In all patients entering the critical phase, normal saline or Hartmann solution should be given through an IV cannula in addition to oral fluid. Initial fluid requirement (oral + IV) is 1.5ml/kg/hr. Those who can drink well may be given IV fluids as 0.5ml/kg/hr. to 'keep vein open' and the balance as oral. In infants less than 6 months N/2 saline + 5% dextrose should be used. For those above 6 months when the patient is not taking orally for prolonged periods it is useful to give normal saline in 5% dextrose. Subsequent rate of infusion will depend on the rate of leakage (which will vary from patient to patient and even in the same patient from time to time) judged by pulse, BP, pulse pressure, capillary refill time, Hct and urine output.

  In patients who had been in the critical phase for a significant period but not gone into shock, the amount of fluid needed for maintenance could go up to 7ml/kg/hr. or more but would be unlikely to require the same amount for a long period as leaking will start slowing down. When pulse and BP are stable, it is important to bring down the rate of infusion to avoid fluid overload while repeatedly assessing the UOP, pulse and BP. If a higher rate of maintenance fluid is unable to maintain the pulse pressure, fluid boluses (N saline or colloids 10ml/kg/hr) should be used.

  The rate of IV fluid administration has to be adjusted *frequently* depending on vital signs especially pulse rate, BP, pulse pressure, Hct, CRFT and UOP. Calculate the UOP ml/kg/hr at each void.

  In a patient who is stable, hourly urine output (UOP) is the best guide to decide the rate of infusion. UOP of only 0.5-1ml/kg/hr. is sufficient to maintain renal functions during the critical period. UOP >1ml/kg/hr. suggests that infusion rates are too high. UOP <0.5ml/kg/hr. suggests inadequate fluids. In such

situations catheterisation may be required. Patients who are in shock due to plasma leakage usually have narrowing of pulse pressure ≤20mmHg and patients with bleeding usually present with hypotension. As the peak of leaking occurs around 24 hours, a patient who has gone into significant shock will be in a stage of leaking that has passed about 24 hours and will have only about a further 24 hours before the leaking stops. Hence, if a patient presents with shock (cold, clammy skin, pulse, BP un-recordable) one would assume that the patient had continued to leak before coming to hospital.

There are 2 main indications for colloids (dextran 40 and 6% starch):

- In the management of shock after 2 crystalloid boluses if the pulse/BP has not picked up.
- Development of shock when already having a fluid overload or the amount of fluid received over a period of time appears to be in the direction of exceeding M + 5% deficit.
- While in the critical phase if the patient deteriorates with no haemo-concentration (or if Hct drops) one has to suspect concealed bleeding. In that case bold transfusion is needed
- The end of the critical phase is indicated by stable vital signs, returning of Hct to normal along with clinical improvement and diuresis.
- Consider ABCS (acidosis, bleeding, calcium, sugar) when there is no improvement in spite of adequate fluid therapy.

If there is fluid overload, use packed red cells (PRC) at 5ml/kg once and repeat only if needed.

If there is no fluid overload use 10 ml/kg of whole blood (WB); 5ml/kg of PRBC or 10 ml/kg of whole blood to increases Hct by 5%. Prophylactic platelet transfusions are *not recommended*. Even with low platelet counts (<20 x 109/L) if there is no significant bleeding do not give platelets.

- Recombinant factor VII should be considered only in cases where the cause of bleeding is due to other reasons e.g. trauma.
- Using inotropes should be considered only if there is significant persistent hypotension after adequate resuscitation. IV frusemide is indicated during the recovery phase when there is a suggestion of pulmonary oedema or fluid overload. It is also indicated in patients passing less than 0.5ml/kg/hr of urine despite receiving adequate fluids and having stable BP, pulse, Hct to improve the UOP.[15]

Management of dengue encephalopathy

- Encephalopathy in dengue fever is usually of hepatic origin.
- Ensure adequate airway oxygenation with oxygen therapy. Intubation may be needed for those with respiratory failure or for those in semi-coma/coma.
- Reduction of intracranial pressure (ICP)
    - o Minimal IV fluid to maintain adequate intravascular volume. Ideally total IV fluid should not exceed 80% maintenance.
    - o Switch to colloids earlier if the patient continues to have a rising Hct and a large volume of IV is needed in cases with severe plasma leakage.
    - o Administer diuretic if indicated in cases with symptoms and signs of fluid overload.
    - o Keep in midline position with a tilt up at 15-30 degrees.
    - o Consider dexamethasone 0.5mg/kg/day IV every 6-8 hours to reduce ICP.
    - o Hyperventilation.
- Maintain blood sugar level >60mg/dl. Recommend glucose infusion rate between 4-6ml/kg/hr.
- Correct acid-base and electrolyte balance.
- Intravenous Vitamin K administration: 3mg for <1yr, 5mg for 1-5yrs, 10mg for >5yrs.
- Anticonvulsants (phenobarbitone, phenytoin and diazepam) should be given for control of seizures.
- When high liver enzymes indicate hepatic encephalopathy, other evidence for concealed bleeding should be looked for as it is one of the commonest causes of hepatic failure in DHF. Transfuse blood, preferably fresh packed red cells as indicated. Other blood components such as platelets, FFP may not be given because the fluid overload can cause increased ICP.
- Reduce ammonia production: Use lactulose, neomycin (may not be necessary if systemic antibiotics are given). Empirical antibiotic therapy may be indicated in case of suspected superimposed bacterial infections.

- H2 blockers or Proton pump inhibitors may be given to alleviate gastrointestinal bleeding.

Convalescent phase

This starts after the end of the critical phase and usually lasts 2-5 days. There will be reabsorption of extravasated fluid during this period. Indicators that the patient has reached the convalescent phase includes: Improved general wellbeing and return of appetite. Appearance of convalescent rash (typically appears as white patches in a red background) Generalized itching, hemodynamic stability, bradycardia or normal heart rate, diuresis, stabilization of Hct (Hct may even be lower than baseline due to interstitial fluid reabsorption) Rise of white cell count followed by rise of platelet count. Complications during convalescence include fluid overload, hypokalaemia and nosocomial infections. Hypokalaemia is treated with oral potassium supplements and fresh fruits. Rarely may need addition of potassium chloride to IV fluids.

Conclusion:

Recognize the beginning of the critical phase is very important. Predicting the rate of leak which vary from patient to patient and within the same patient from time to time, so matching the rate of transfusion and rate of leak is very important. Over-transfusion and under-transfusion both should be avoided during the critical phase of illness. Recognize the end of the critical phase is also vital in order to prevent fluid overload. Meticulous monitoring in both the dengue hemorrhagic fever and dengue shock syndrome is essential. Need for crystalloid to colloid and identification for the indications of blood transfusion key point for the management of dengue shock syndrome.

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