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Review Article

Dengue Fever

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Introduction

Dengue infection is Aedes mosquito-borne infectious disease of the tropics caused by dengue virus (DENV). DENV has four distinct serotypes; 1, 2, 3 and 4. Infection by each serovar confers life-long protective immunity to that and partial and transient protection against the other serotypes. Secondary infection is a major risk factor for DHF, mainly due to antibody induced enhancement.[1,2] According to WHO estimates, this disease of the tropics and sub-tropics, affects around 390 million people each year and 3.9 billion people residing in 128 countries are at risk. (WHO 2017).

Dengue in history dates back to 3rd century Chinese literature of Jin Dynasty era and the first confirmed case was reported by Benjamin Rush in 1789. (www.denguevirusnet.com) Dengue has emerged as a disease with significant morbidity and mortality. After several epidemics since 2005, it is now recognized as an important health problem in Pakistan. The incidence is highest for the age group 20 to 30 years (32.0%) with females representing 31.5%. The disease has an overall case fatality rate of 1.86/ 1000 confirmed cases. It is a notifiable disease under the 3 epidemiological categories; suspected, probable and confirmed dengue.

Spectrum of Dengue Infection

The incubation period is from 3 to 14 days.[3] The spectrum of clinical manifestations vary from totally asymptomatic disease to the severe disease, with or without plasma leakage and organ impairment. Understanding the dynamic nature of this disorder is of paramount importance especially for administering right treatment at the right time.

Clinical Course of Dengue Infection

After the incubation period, the illness begins abruptly. Subsequent clinical course, can be broadly, divided in to three phases: febrile, critical and convalescent phase.

Febrile phase typically, begins with sudden onset of high grade fever lasting for 2-7 days. It is common to both DF and DHF patients.[4,5] Fever is variably accompanied by facial flushing, erythema, body aches, anorexia, nausea, vomiting & sore throat.[6,7] On physical examination, mild hemorrhagic manifestations and non-tender hepatomegaly may be observed.[8] The earliest hematological abnormality is a progressive decrease in total white cell count and later a drop in platelet count which usually not precipitous. NS1 antigen and PCR is generally positive during this early stage.

Towards the end of febrile phase, around the time of defervescence (usually between 3rd to 7th day of illness), a few patients enter the critical phase with increased capillary permeability.[9] The critical phase typically lasting 24-48 hours is depicted by varying degree of circulatory disturbances. In less severe cases, these changes are minimal and transient. Many of these patients recover with routine oral fluid and electrolytes or even with non-specific management at home. In more severe forms of plasma leakage, significant volume depletion occurs and the patient has warning signs. of severe dengue with possible progression to shock if fluid resuscitation is not promptly instituted.[9,10,11] Hemoconcentration (a rising trend of hematocrit from the baseline) and thrombocytopenia are usually detectable even before defervescence and onset of shock. Hct level correlates with plasma volume loss and disease severity; it may not be truly representative in cases of frank hemorrhage and /or excessive fluid replacement. Biochemical abnormalities include leucopenia with relative lymphocytosis, prolonged PT/APTT, elevated transaminases (typically AST > 3 x ALT), hypoproteinemia and hypoalbuminemia.[4,5,6]

Plasma leak stops within 24-48 hours from the time of onset as the patient enter convalescent phase. It is followed by reabsorption of extravascular fluid. Patient's

general wellbeing improves, symptoms abate, hemodynamic status stabilizes and diuresis ensues. Some patients may have a classical rash of "isles of white in the sea of red" with or without pruritus.[4] Bradycardia may be observed. HCT level may drop further due to resorption associated hemodilution. The recovery of platelet count is typically preceded by recovery of white cell count (WCC).

Pathophysiology of Plasma Leak

It is speculated that increased plasma permeability is present in all the case of dengue disease. Plasma leak remains small and clinically compensated in most of the patients. Only in a small percentage of patients does this condition cross the critical threshold of compensatory mechanisms to become clinically significant and differentiates DHF and DSS from uncomplicated DF.

The molecular mechanism responsible for the increased vascular permeability seen during DHF/DSS is still not well understood. It appears that immune hyper-drive results in massive over production of cytokines (Cytokine Storm), due to aberrant activation of T-lymphocytes and disturbances of homeostatic system involving Tregs. High concentrations of mediators of inflammation including C3a, C5a, tumor necrosis factor-α, interleukin 2, 6 and 10, interferon- and histamine have also been noted.[5] There is some data to suggest a transient dysfunction of the endothelial glycocalyx layer causing leakage of proteins upto size of albumin.[12,13,14] A second infection with a heterotypic dengue virus may impart increased risk of developing DHF. Antibody-dependent enhancement of viral replication is believed to be responsible for this phenomenon.[15,16,17]

The usual mechanism of hypovolemic shock further complicate the picture. Severity of shock in the face of plasma leak would depend upon state of hydration at the onset of the leak, cardiac reserve, severity of the vasculopathy (rate of plasma leak) and existing comorbidities. Pathophysiological events that occur during DSS are exactly like those of "classical hypovolemic shock" but in DHF the volume lost to the serosal cavities is rich in proteins and is available for reabsorption subsequently and may lead to fluid overload in later stages of the disease.

If the loss of volume is not corrected promptly, the patient may progress to decompensated and later refractory shock. In this state neither volume replacement nor vasopressors would restore the normal tissue perfusion or cardiac output.[18] Lactic acidosis has a suppressant effect on myocardium which in turn further worsens the hypotension.[19] Intense vasoconstriction and subsequent ischemic necrosis of the tissues can result in massive bleeding, disseminated intravascular coagulopathy (DIC) and multi-organ failure - a common late complications of prolonged shock.

WHO Dengue Classification

In 2009, WHO suggested an updated classification system to include Dengue fever without warning signs, dengue fever with warning signs and severe dengue. In addition, probable dengue has also been defined for the cases in whom confirmation of the disease is awaited.

Warning signs include abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy, restlessness, liver enlargement >2cm & increase in HCT concurrent with rapid decrease in platelet count. Severe dengue is characterized by DSS or fluid accumulation leading to respiratory distress or severe organ involvement (AST or ALT> =1000, impaired consciousness or involvement of heart and other organs).

Other Important Manifestations

Severe bleeding or organ impairment might occur without plasma leakage. Several important manifestations of dengue infection are often under-recognized. Acute abdominal pain can have diverse etiology ranging from flavivirus associated hepatitis, acalculous cholecystitis, and shock.[20,21,22,23] A few patients (<1%) with dengue infection may develop neurological manifestations, mainly encephalitis, encephalopathy[24,25] and rarely myelitis and Guillain-Barré Syndrome.[26] Renal involvement has been reported in Dengue Hemorrhagic Fever (DHF) ranging from mild proteinuria to acute Kidney injury (AKI), overt proteinria and rarely acute glomerulonephritis. Hemophagocytic Histiolymphocytosis (HLH) syndrome is an uncommon sequel to overactive cytokine productions associated with dysregulated T cell activation and macrophage function, following dengue virus infection.

Laboratory Investigations

Disease is monitored by serial complete blood count with special focus on hematocrit.[22,26] Other biochemical tests like liver function tests may be repeated as indicated.[27] Low cholesterol levels are also indicative of disease severity.[28] Diagnostic tests include Dengue IgM, IgG & NS-1 which may be done by serology or the less validated strip assays (immune-chromatography test).[29,30,31,32,33,34] DENV RNA may be detected by RT-PCR [35,36,37] and viral isolation can be performed in specialized research labs.

Management of Dengue Infection

Currently there is no specific anti-viral medication available against the dengue virus. The mainstay of dengue infection management stays symptomatic and supportive. Dengue is a dynamic disease and it is crucial to recognize plasma leakage & shock at an early stage, to guard against severe organ impairment. This can only

be achieved through frequent clinical and laboratory monitoring.

Based on evaluations from history, physical examination +/- CBC and HCT, the clinicians should be able to determine the diagnosis, phase of illness, hydration and hemodynamic status as well as the need for hospital admission. All patients with warning signs should be hospitalized. Additional indications for admission include inability to tolerate oral fluids, inadequate urine output (less than 0.5ml/kg/hour), clinical signs of dehydration, shock or end organ damage. Pregnancy, extremes of age and co-morbidities confer additional risk factors.

During the critical phase (plasma leakage) which may last for 24-48 hours, monitoring needs to be intensified and frequent adjustments in the fluid regime may be required. Recognition of onset of convalescent phase is also important because intravenous fluid regime needs to be progressively reduced/ discontinued at this stage. Daily or more frequent follow up is necessary especially from day 3 of illness, until the patient becomes afebrile for at least 24- 48 hours without antipyretics.

All inpatients are monitors clinically and on lab parameters. Clinical parameters include general well being, appetite, warning signs, signs of bleeding, ascites, pleural effusion abdominal tenderness, respiratory status, urine output and hemodynamic status (colour & temperature of extremities, capillary refill time, pulse, blood pressure and pulse pressure. These are monitored 4-6 hourly during febrile and convalescent phase and hourly or more frequently during critical phase. CBC and Hct are also checked daily during febrile and convalescent phase and 4-12 hourly during critical phase. Other lab indicators including BUN/Creatinine, LFTs, RBS, Coagulation profile Lactate & blood gases are followed as indicated.[38]

Any patient with significant plasma leak, requirement for respiratory support (non-invasive and invasive ventilation), significant bleeding and encephalopathy or other complications should be managed in high dependency unit (HDU).

Fluid Management

Dengue with Warning Signs

Stable patients may be given oral fluids only while IV fluids are indicated in cases of vomiting and increasing hematocrit despite increased oral intake. Crystalloid (0.9% Saline) is the fluid of choice. Frequent adjustment of maintenance fluid regime is often needed during the critical phase. If patients deteriorate and progress to shock, a more aggressive fluid resuscitation is indicated.[39,40]

IV fluid therapy may be reduced or discontinued when patients begin to show signs of recovery (usually after 24-48 hours of beginning of critical phase) or the HCT drops in a hemodynamically stable patient.

Dengue Shock Syndrome (DSS)

Dengue shock syndrome is a medical emergency. All patients with dengue shock should be managed in high dependency intensive care units and fluid resuscitation must be initiated promptly.[38] In spite of successful initial resuscitation the patient may experience recurrent episodes of shock because of continuing capillary leakage which can last for 24-48 hours.

Intravenous fluid therapy is the mainstay of treatment for dengue shock.[41,42] There is no clear advantage of using any of the colloids over crystalloids but colloids (dextran 40, gelatin solution & and hetastarch solution) may be preferable as the fluid of choice in patients with intractable shock after crystalloid resuscitation fails to restore the cardiac index. Colloids reduce the level of HCT faster than crystalloids in patients with intractable shock.[7,41] The volume and rate of fluid replacement should be carefully titrated to the clinical response to maintain an effective circulation while avoiding an over replacement. Improvement in the clinical parameters, decreasing Hct and improvement in metabolic acidosis indicates adequate fluid resuscitation.

HCT drops after fluid resuscitation while the patient remains in shock, indicates significant bleed (often occult) and blood transfusion should be instituted as soon as possible. In patients with persistent shock, the aim is to identify and correct overt/occult bleeding, hypocalcemia, acidosis and hypoglycemia, sepsis and cardiogenic shock.

Fluid therapy has to be judiciously controlled to avoid fluid overload which could result in massive pleural effusion, pulmonary edema or ascites.[11] To address this potential problem, fluid is infused according to calculated quotas. The formula applied is M+5% and this quota is given over 48hours of critical illness.

Management of Bleeding/Haemostasis

The hemostatic changes that occur in dengue infection are considered to be the result of thrombocytopenia as well as activation of coagulation pathways due to endothelial dysfunction.[43,44,45] Bleeding is considered significant when it results in hemodynamic instability. Minor mucosal bleeds are common and usually cease spontaneously.[7] Significant bleeding can be a consequence of disseminated intravascular coagulation which usually occurs following prolonged shock and acidosis.[46] Blood transfusion is life- saving and should be given as soon as severe bleeding is suspected or recognized. Most of the GIT bleed will improve after 48-72 hours of the defervescence; only persistent bleed requires further investigation.

There is no role for prophylactic transfusion with platelets and fresh frozen plasma to prevent bleeding in the dengue patients. There is insufficient evidence to support the use of recombinant activated factor VII, Vitamin Km tranexemic acid, IV immunoglobuoins and steroids in dengue patients with significant bleeding.[47,48,49,50,51]

Discharge Criteria

Patients may be discharged once afebrile for 48 hours (without antipyretics) if 40,46 their general condition and vital signs are stable with no or minimal visible bleeding, no dyspnea or respiratory distress, stable hematocrit, rising trend in platelet count (PLTs > 40,000) and fully recovered organ dysfunction.

Vaccination

There are four distinct types of dengue. First infection with any one of them can increase the chances of severe disease in secondary infection when exposed to a different serotype.[52,] For a vaccine to be effective for its treatment, it must protect against all four types at once. A weak response to one of them could act like a first infection and leave a person vulnerable to severe disease when exposed second time.

In December 2015, Dengvaxia, the world's first vaccine against dengue virus developed by French pharmaceutical company Sanofi Pasteur, was licensed and approved for use in 19 dengue endemic countries for individuals 9 years of age and older. Vaccine recipients with evidence of prior dengue infection benefited from vaccination, exhibiting a substantial cumulative decrease in hospitalized and severe dengue. However, vaccine recipients without such infection were shown to have an increased risk of hospitalized and severe dengue specially in third year after vaccination. This led to withdrawal of this vaccine from market from many countries.[52,53] The other vaccine trials in pipeline are by Takeda and NIH.[54,55]

Conclusion

This analysis highlights the unique features of patients with dengue infection and also addresses the key points of management.

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