

# Dengue : Current Trends and Challenges — An Indian Perspective

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## INTRODUCTION

Dengue is caused by four flavivirus serotypes (DEN-1, DEN-2, DEN-3 and DEN-4). The incidence of dengue fever (DF) and dengue hemorrhagic fever (DHF) has increased thirty-fold globally in the last four decades and more than half the world's population (including developed countries) is now threatened with infection from dengue virus.<sup>1</sup> Epidemiological evidence shows that DHF and dengue shock syndrome (DSS), the more serious manifestations of the disease, occur more frequently on re-infection with a second serotype. The co-circulation of multiple serotypes has also been reported from many countries.<sup>2</sup> The situation in India is reflected by the occurrence of major disease outbreaks in India from time to time over the last few decades.<sup>3,4</sup> However, no reliable data are available to assess the magnitude of the disease in our country. But, obviously, the situation is not very encouraging. In the last seven years, there have been two major disease outbreaks of dengue in north India.<sup>5</sup>

## CLINICAL FEATURES

DF is an acute viral disease manifesting with myalgias, headache, retro-orbital pain, vomiting, maculopapular rash, leucopenia and thrombocytopenia. DHF is characterized by four major clinical features: high fever, hemorrhagic phenomena, hepatomegaly and signs of impending circulatory failure (postural hypotension, resting tachycardia, diaphoresis). Significant thrombocytopenia with concurrent hemoconcentration is a typical laboratory manifestation of DHF. However, in interpreting hematocrit, the potential effect of pre-existing anemia, severe hemorrhage and dehydration needs to be taken into consideration.

The major pathophysiological abnormality differentiating DF from DHF is the plasma leakage syndrome (hemoconcentration, hypoproteinemia and/or serous effusion). In fact, the severity of disease in DHF depends on the quantum of plasma leakage. The patients of DHF presenting with shock due to excessive plasma loss are labeled as dengue shock syndrome (DSS). DHF/DSS are potentially fatal conditions.

The clinicians should be aware of the unusual presentations of DF/DHF. The disease may present as acute acalculous cholecystitis, hepatitis, fulminant hepatic failure, edematous gall bladder wall on ultrasonography, serositis, acute renal failure and neurological manifestations including intracranial bleeding, seizures and myelitis.<sup>6-10</sup> The serositis of dengue involves the pleural and abdominal cavity.

## TRANSMISSION OF DENGUE VIRUS

Over the last few decades, the earlier principal vector of dengue virus in Asia, *Aedes albopictus* has been replaced by *Aedes aegypti*. Interestingly, *Aedes aegypti* has been described as having a relatively low oral receptivity for dengue virus as compared to *Aedes albopictus*.<sup>11</sup> However, it has been recently documented that oral receptivity of *Aedes aegypti* to DEN-2 virus is significantly more than *Aedes albopictus*. Moreover, the infectivity of southeast (SE) Asian genotype of dengue virus vis-à-vis American genotype has also intrigued investigators and it has been suggested that *Aedes aegypti* tends to be more susceptible to infection by DEN-2 virus of SE Asian genotype as compared to American genotype.<sup>12</sup> These observations obviously have important epidemiological implications for Asian countries as the local vector has increased propensity to transmit dengue infection, especially DEN-2 (relatively more virulent serotype).

Different serotypes have been observed in 1996 (DEN-2)<sup>13</sup> and 2003 (DEN-3 and 2)<sup>5</sup> outbreaks in north India. The change in serotypes underscores the role of viral genetic turnover within a focal population and the potential importance of adaptive evolution in viral epidemic expansion. In fact, the mortality observed in 1996 was far greater than the recent outbreak and possibly can be explained by the difference in the serotypes (DEN-2 is more virulent than DEN-3).

## PATHOGENESIS

Various studies of the pathogenesis of DHF have documented the importance of initial high levels of virus replication during acute febrile phase. However, the possible association of viremia during the transition from fever to defervescence, a critical stage in determining the severity of disease, is also being appreciated. It has been observed that there are higher levels of plasma dengue viral RNA in DHF patients as compared to DF patients during the acute febrile stage. Although, during defervescence, the level of plasma

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dengue viral RNA is undetectable in most DF patients, it remains significantly high in all DHF patients. It is being suggested that measurement of increased level of plasma dengue viral RNA during defervescence may serve as a disease marker for DHF in the future.<sup>14</sup>

Animal models infected with DEN-2 have several similarities to human DEN-2 infection.<sup>15</sup> The most notable cytokine amplification is observed with tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). In animal models, treatment with anti-TNF- $\alpha$  serum has been demonstrated to reduce mortality rate significantly. A similar analogy has been tried in human beings, but with limited success. In fact, studies have observed that increase in TNF- $\alpha$  correlates with hemorrhagic manifestations and the increase in interleukin-10 with thrombocytopenia.<sup>16</sup> It has also been observed that anti-platelet IgM levels are higher in DHF/DSS than in DF patients. Moreover, platelet-associated IgG (PAIgG) formation involving anti-dengue virus IgG also plays a pivotal role in the induction of transient thrombocytopenia during the acute phase of secondary dengue virus infection.<sup>17</sup>

Interestingly, acute-phase serum samples obtained from patients of human immunodeficiency virus (HIV) co-infected with dengue virus show reduced HIV infectivity suggesting the possibility that HIV replication is suppressed during acute dengue fever, as occurs during hepatitis GB infection, scrub typhus infection and measles.<sup>18,19</sup> Interestingly, it has also been documented that the African black population have a gene providing nearly complete protection against severe dengue illness.<sup>20</sup> The significance of these observations needs further investigation.

## MANAGEMENT

### Hydration

The conventional management principles of DF/DHF include rehydration therapy (preferably oral and/or intravenous replacement in hospitalized patients), control of high fever by sponging and paracetamol (non-steroidal anti-inflammatory drugs are absolutely contraindicated due to bleeding diathesis).<sup>21</sup> In fact, oral rehydration therapy (ORT) should be initiated on the first day of the illness in DF as it prevents DHF and decreases risk for hospitalization in these patients.<sup>22</sup>

### Platelet Transfusion

The role of platelet transfusion as a panacea for the management of dengue needs special mention. In fact, the platelet count is not predictive of bleeding. The duration of shock and low-normal hematocrit at the time of shock are risk factors of severe hemorrhage and subsequent mortality.<sup>23</sup> However, theoretically, thrombocytopenia is a risk factor for hemorrhage and the threshold for prophylactic platelet transfusion is 10,000/mm<sup>3</sup> in non-dengue patients.<sup>24</sup> It can be suggested that since there is no other specific therapy for DHF/DSS, patients with bleeding tendency and/or a platelet count less than 20,000-25,000/mm<sup>3</sup> may be empirically transfused platelets. It has been documented that non-dengue

patients receiving multiple transfusions may be alloimmunized to many HLA- and platelet-specific antigens and demonstrate no increase in their post-transfusion platelet count. In dengue patients, this trend may be all the more evident in view of the other factors contributing to thrombocytopenia. Therefore, dengue patients should preferably receive single donor apheresis platelets (SDAP) as compared to random donor platelets (RDP) to lower the risk of alloimmunization.<sup>24</sup>

Unfortunately, patients as well as health care workers tend to “chase” platelet counts. As discussed earlier, the crux in treatment of dengue patients is maintenance of good hydration, monitoring for any overt bleeding and not “panic” if the platelet count is more than 50,000/mm<sup>3</sup> but less than 150,000/mm<sup>3</sup> (normal platelet count is 150,00-450,000/mm<sup>3</sup>). In fact, most of these patients are recovering from DF viz. patients are afebrile, appetite is normal and have a feeling of well being, but the platelet count is on the “lower side”. This “syndrome” of chasing platelet count in dengue patients who are otherwise completely asymptomatic and improving can be labeled as “Dengue panic syndrome”. This panic syndrome was quite evident in the outbreak of dengue in northern states of India in 2003. Therefore, the role of media and health care workers in dissemination of the simple strategy of hydration from day one of the illness needs to be emphasized. It will not be an exaggeration to state that appropriate hydration is the only therapeutic modality that makes the difference between life and death in dengue patient.

The flip side of the “dengue panic syndrome” is the overloading of the already strained emergency services of tertiary care hospitals by these patients. Consequently, the “true” DHF/DSS patients needing urgent attention in the emergency may not get the desired care, in spite of the best efforts of the hospital personnel.<sup>25</sup>

### Ancillary Therapeutic Modalities

The newer strategies (supportive and pharmacological) are also being tried to combat the mortality associated with DHF/DSS. The patients with DSS may develop acute respiratory distress syndrome (ARDS). This was also observed during the recent outbreak in north India. Previously, these patients were treated with oxygen through a nasal cannula and/or tracheal intubation and mechanical ventilation, as necessary. A recent study has proposed the role of non-invasive ventilation in improving the morbidity and mortality of ARDS in children with DHF/DSS in dengue-endemic areas.<sup>26</sup> The role of mycophenolic acid (MPA), an immunosuppressive agent, is also being investigated in the treatment of dengue.<sup>27</sup>

## PREVENTION

Obviously, the core strategy for the reduction in transmission of dengue is the role of community participation in vector control. *Aedes aegypti* feeds during the day, rests indoors and lays its eggs in artificial water containers. Therefore, vector control includes simple measures like eliminating larval habitats, using insect repellents/indoor space-spray insecticides and mosquito nets while sleeping.

The widespread use of chemical insecticides over the years has exposed *Aedes* mosquito to an intense selection pressure of resistance against these compounds. Therefore, programs will have to be designed to monitor the resistance of *Aedes aegypti* to insecticides in our country. This assumes greater importance now as dengue is rapidly emerging as a major threat to public health in India and an effective dengue vaccine is still eluding us.

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