Review Article

Current Perspective in Dengue Infection: Review Article

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Dengue infection has been well recognized for more than half a century. However, specific treatment has not existed. The disease is still prevalent in many tropical areas. Trend in epidemiology has noticeably changed recently that more young adults are affected. Many other manifestations other than fever, constitutional symptoms, and bleeding have been recognized. The present review will focus on current epidemiology of dengue infection, diagnosis, and unusual complications. Recommendation of use of dengue vaccine will also be discussed.

Keywords: Dengue infection, Atypical manifestation, Review

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Dengue infection is still prevalent in many tropical countries resulting in 50 to 100 million infections per year[1]. It causes a high economic burden in endemic area and the most important issue is that mortality rate is high in severe cases. Although the disease has been recognized for more than half a century, specific treatment or effective control measures have not been well established. The first dengue vaccine has been released in 2016, however, it does not confer effective immunity to all viral strains.

Dengue infection is caused by dengue virus (DENV) belonging to *Flaviviridae* family. Currently, there are four serotypes (DENV 1 to 4). The virus is transmitted by *Aedes* mosquitoes, both *A. aegypti* and *A. albopictus*. These mosquitoes can also transmit two other well-known viruses, chikungunya and zika viruses. Though the clinical manifestations of these three diseases can be clinically distinguished most of the time, overlapping signs and symptoms exist. Table 1 shows the clinical characteristics of these three diseases. In addition, the serological diagnosis of dengue infection can be complicated by the fact that false positive rates can be high due to cross reactivity of tests with other flaviviruses (e.g., zika and Japanese encephalitis viruses) cocirculating in the same endemic area.

Table 1. Comparison of clinical manifestations of dengue, zika, and chikungunya infections

	Dengue	Zika	Chikungunya
Asymptomatic infection	Common	Common	Not common
Conjunctivitis		✓	
Congenital anomalies		✓	
Neurologic	✓	✓ (congenital)	
Athralgia/myalgia	✓	✓	✓
Headache	✓	✓	✓
Fever	✓	✓	✓
Shock	✓		
Rash	✓	✓	✓

Though the knowledge of management of dengue infection has been quite constant, there has been many new issues regarding dengue infection such as change in epidemiology of infection, atypical manifestations of dengue infection, and vulnerability of infection, etc. The present review will focus on new perspectives of dengue infection at current situation.

Epidemiology

Previously, dengue infection was a childhood disease. However, the number of cases in adolescents and young adults have been increasing recently.

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The reasons behind this shift are not clear but may be due to change in epidemiological, ecological, and demographic dynamics[2]. A study in Thailand proposed that the reduced birth and death rates leading to a shift in the age structure of the population, could contribute to this change[3]. Better control of the disease leading to reduce force of infection, can also cause young adults to be more vulnerable to infection[4]. Another possibility is that the internists are more aware of the disease in adult population resulting in more investigations for the disease and more cases are identified. However, young children still suffer from more severe disease than adults[5]. This shift in age group will have an impact on clinical guideline of dengue infection with more emphasis toward management in adult population including the elderly.

Diagnosis

Diagnosis of dengue infection can be performed by direct antigen detection and serology tests. Direct antigen detection includes polymerase chain reaction (PCR) and NS1 detection. Direct antigen detection is useful during the febrile stage of the disease. NS1 has the highest sensitivity during the first few days of fever[6,7], while PCR assays can be used to detect virus until five to six days after onset of the fever[6]. Overall sensitivity of NS1 for detection of DENV is more than 90% during the first few days after onset of the fever and decreases afterward. It can be as low as 40% on day 4 after onset of fever in cases of secondary dengue hemorrhagic fever[7]. The specificity of NS1 for diagnosis of dengue infection is quite high. A retrospective study conducted by Matheus et al[8] showed that dengue NS1 test did not have positive results in serum of acute Zika infection. IgM is useful in primary infection and can be detected after six days of onset of the fever. The sensitivity is around 80% on day 6 after onset of fever[7].

Clinical manifestations

Dengue infection typically manifests in various clinical spectra, ranging from asymptomatic infection (the most common presentation) to dengue shock syndrome. Mortality rate is high in the latter. Classification of symptomatic dengue infection into dengue fever, dengue hemorrhagic fever (grade I to IV) denotes the pathophysiology of the disease (World Health Organization [WHO] criteria 1997)[9]. Dengue fever is dengue infection without signs of capillary leakage, while dengue hemorrhagic fever represents infection with signs of capillary leakage including rising of hematocrit, pleural effusion, ascites, and hypoalbuminemia. Dengue shock syndrome is dengue hemorrhagic fever with massive leakage to the extent that circulatory collapse ensues. According to this criterion, dengue hemorrhagic fever can be divided into three distinct stages, febrile stage, critical stage or toxic stage, and defervescence stage. However, in 2009, WHO defined a new classification of dengue infection[10]. This classification is based on severity of the disease. There are three categories of severity, dengue without warning signs, dengue with warning signs, and severe dengue. This classification guides clinical management in patients with dengue infection. Patients classified into dengue with warning signs and severe dengue need closed observation.

Severity of dengue infection

Many factors determine the severity of the dengue infection. Both host and viral factors determine the severity of the disease. Genetic factors have been proven to play a role, meaning that some patients may be more vulnerable to severe infection[11,12]. Obese patients tend to have more disease severity[13]. Subsequent infection with different subtypes of the virus at a certain duration apart from primary infection can lead to severe disease[14,15]. Some subtypes of the virus tend to cause more severe disease than others. DENV subtypes 2 and 3 tend to cause more severe disease that subtypes 1 and 4[16].

Complications of dengue infection

Complications of dengue infection that may encountered include, but is not limited to, bleeding, respiratory distress from massive pleural effusion, or ascites. Bleeding should be suspected if patients had persistent tachycardia, even when adequate fluid is administered or if hematocrit dropped while the vital signs are unstable. Sometimes, bleeding is concealed in the gastrointestinal tract without apparent external bleeding. When bleeding is suspected, blood components (packed red blood cells, fresh frozen plasma, or platelet concentrate) should be administered. Respiratory distress should be managed to ascertain that patients had adequate oxygenation. Mechanical ventilator is needed if the patients developed respiratory failure. Pleural paracentesis is contraindicated in patients with dengue infection as this may cause massive hemothorax. Abdominal paracentesis can be considered. However, if abdominal paracentesis has to be performed, it should be performed by experienced surgeon. Release of abdominal fluid does not only improve

respiratory function but also relieve abdominal pressure. Increased abdominal pressure from rapid accumulation of ascetic fluid can lead to abdominal compartment syndrome, which can compromise renal blood flow and subsequently renal failure[17].

Dengue infection can lead to pathology in many organs. Hepatitis is a well-known end organ disease and can be found in 70% of the dengue infected patients[18]. In addition, myocarditis and encephalitis are not uncommon. The prevalence of myocarditis has been reported to be as high as 11% in one outbreak in southern China[19]. The prevalence of myocarditis was higher in dengue infected patients with warning signs and patients with severe dengue. Patients with myocarditis were also more associated with shock. Manifestations of dengue myocarditis included heart failure, arrhythmia, and heart block[19]. The outcome was quite good in patients with dengue myocarditis[19]. Evidence from myocardial biopsy from a dead patient showed that DENV could be detected in myocytes[20], implying that myocytes can be the target cells of DENV.

Neurological complications of dengue infection include encephalitis, which is the direct viral invasion of brain parenchyma. Encephalopathy can be due to systemic metabolic derangement such as hepatic failure, and post infectious complications such as Guillain Barré syndrome and optic neuritis[21]. Encephalitis could be found in 7% of the dengue infected patients[18]. Patients can present with altered sensorium, or seizure. DENV subtype 2 and 3 are common subtypes that cause dengue encephalitis[22]. Interestingly, common manifestations of dengue infection, for example, myalgia, rash, or bleeding, could be found in less than 50% of the cases with dengue encephalitis[23].

Superimposed infection is another complication in dengue infection. Dengue infection can lead to immune suppression[24,25]. Bacterial infection during the course of dengue infection can occur in patients with comorbidities, advanced age, and more severe dengue manifestations[26]. Superimposed bacterial infection should be suspected in patients with longer duration of fever, and alteration in laboratory parameters such as procalcitonin, leucocyte count, hyponatremia, and renal function tests[26]. Superimposed aspergillosis can be found and is detrimental in dengue infected patients[27,28].

Infection associated hemophagocytic syndrome (IAHS) can be a fatal complication following dengue infection. This condition should be suspected if the patients have recurrence of fever or if the patients do not defervesce as expected in the clinical course. Unexplained decrease of hematocrit or white blood cell count should also raise the possibility of this condition. This condition can be confirmed by bone marrow examination showing increased hemophagocytic activity[29]. Intravenous immunoglobulin (IVIG) is the treatment of choice for this condition[30].

Treatment

Specific treatment of dengue infection is still not available. Appropriate fluid therapy is a mainstay in supportive care of dengue infection.

Vaccine

Currently, only one dengue vaccine (Dengvaxia) has been approved for prevention of dengue infection. The vaccine is live-attenuated and administered for three doses at month 0, 6, and 12[31]. It is recommended for children and adults between 9 and 45 years old. WHO recommends that serological test for dengue infection be done prior to vaccination as seronegative patients who receive vaccine have a higher chance of having severe dengue when infected[32]. However, accurate serostatus of dengue is difficult to obtain. Counseling risks and benefits of vaccination before vaccination is recommended.

Conclusion

Dengue infection is still prevalent in many regions. Recognizing unusual manifestations or complications of the disease is necessary for prompt investigation and treatment. Specific treatment has not existed. Vaccine efficacy is still not optimal. Vector control remains the most important method for disease control.

What is already known on this topic?

Dengue infection still contributes a large burden in tropical area. No effective treatment is available. Previously, this disease was confined to young children, but it now infects adults. It can cause hemorrhage and shock due to capillary leakage. Atypical manifestations or complications have rarely been recognized.

What this study adds?

This review summarized the change in epidemiology of dengue infection, which showed that adult population has been increasingly affected. Many atypical manifestations such as encephalitis, myocarditis, and complications such as abdominal compartment syndrome have been reported.

Conflicts of interest

The author declares no conflict of interest.

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