Special Article

Dengue: A Global Threat

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Dengue, a mosquito-borne viral disease, is currently an expanding global problem. The disease is caused by four closely related dengue serotypes; it ranges from asymptomatic infection to undifferentiated fever, dengue fever (DF) and dengue hemorrhagic fever (DHF). DHF is characterized by fever, bleeding diathesis and a tendency to develop a potentially fatal shock syndrome. Dengue infection with organ impairment mainly involves the central nervous system and liver. Consistent hematological findings include vasculopathy, coagulopathy and thrombocytopenia. Laboratory diagnoses include virus isolation, serology, and detection of dengue ribonucleic acid. Successful treatment, which is mainly supportive, depends on early recognition of the disease and careful monitoring for shock. A severity-based revised dengue classification for medical interventions has been developed and validated in many countries. So far, however, there has not been any specific dengue treatment; prevention is currently limited to vector control measures. The world's first, large-scale dengue vaccine, efficacy study demonstrated its efficacy and a reduction of dengue's severity in a study of more than 10,000 volunteers in Asia. Initial safety data are consistent with a good safety profile.

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Dengue is currently the most devastating mosquito-borne viral disease in humans. The disease is caused by the four dengue virus serotypes that range from asymptomatic infection, undifferentiated fever, dengue fever (DF) to severe and fatal dengue hemorrhagic fever (DHF). The clinical spectrum of the infection undermines surveillance activities since the majority of cases are asymptomatic and go undetected. These cases can also be significant sources of infections for dengue virus transmission via the mosquito vector. DHF is characterized by fever, bleeding diathesis and a tendency to develop a potentially fatal shock syndrome. The disease is a major public health concern in several countries with the potential spread of the disease to non-endemic areas. It is one of the leading causes of hospitalization, placing tremendous pressure on strained medical resources with an associated major economic and social impacts on countries where dengue disease is prevalent[1,2].

Epidemiology

Dengue is the most common arboviral infection of humans transmitted by Aedes mosquitoes, principally *Aedes aegypti*. These mosquitoes largely breed indoors in clean water, mainly in artificial water containers, and feed on humans during the daytime. There are four anti-genenically distinct serotypes of dengue virus (DEN 1, 2, 3 and 4) which belong to the genus flavivirus of the family Flaviviridae. Primary infection with a particular dengue serotype confers long-lasting immunity for that serotype (homotypic immunity) while immunity confers to other dengue serotypes (heterotypic immunity) lasts for a few months, after which the patients are still susceptible to heterotypic infection. Four viral serotypes that cause the disease in proportions change over time, and places, even within the same country. Nisalak A, et al reviewed dengue virus incidences from 1973 to 1999 in Bangkok, and demonstrated that all the four dengue serotypes could be found circulating in any year with one predominant serotype emerging and re-emerging as the cause of the epidemic. The authors also concluded that the pathogenesis of DHF is complicated, i.e., a product of host determinants, dengue serotype, and environmental factors[3].

Global phenomenon such as urbanization and international travel are key factors facilitating the spread of dengue. Documenting the type-specific record of dengue virus spread has important implications for understanding patterns in dengue hyperendemicity and disease severity as well as vaccine design and deployment strategies. A series of global maps on

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distribution of confirmed instances of each dengue virus serotype from 1943 to 2013 showed a worldwide expansion of dengue virus, the disease hyper-endemicity and the establishment of an increasingly important infectious disease of global public health significance. About 70% of the overall disease burdens are thought to have increased 30-fold in the last 50 years; this is reported in the Asia-Pacific region. In recent years, there has been an increase in dengue cases in the rural settings, and also a shift towards increased incidence in older age groups in many countries where dengue is endemic. The trend has important implications for dengue control and prevention[4,5]. Vertical transmission of dengue virus from mother to child has also been reported[6].

The severity of DF manifestations increases with age. DF causes fever, rashes, muscle or joint pain, headaches, eye pain but these are rarely fatal. DHF is considered a distinct disease characterized by increased vascular permeability leading to leakage of plasma and dengue shock syndrome (DSS). Unusual manifestations of dengue patients with severe organ involvement such as the liver, kidney, brain or heart associated with dengue infection have been increasingly reported in patients with dengue infection. These manifestations may be associated with co-infections, co-morbidities or complications of prolonged shock. Exhaustive investigations should be done in these cases[1,7-10].

Research into the pathogenesis of dengue infection has exploded over the last five decades with issues that were once considered simple has been becoming more and more complicated as additional data are found. This has led to the development of a number of controversies that are being studied across the globe and debated in the literature and is summarized as follows: the 1997 World Health Organization (WHO) case definition of DHF is not useful; DHF is not significantly associated with secondary dengue infection; DHF results from infection with a virulent dengue virus; DHF is owing to abnormal T-cell responses; DHF results from auto-immune responses and DHF results from direct infection of the endothelial cells. A clinically and physiologically applicable case classification that will allow robust pathological research into the different levels of disease severity is a major priority[1,11-13].

Diagnosis

The incubation period of dengue infection is usually 4-7 days but can range from 3 to 14 days. Clinical and laboratory criteria for the diagnosis of DHF/DSS as established by the World Health Organization in 1997[14] are:

Clinical manifestations:

- Fever: acute onset, high and continuous, lasting two to seven days in most cases;

- Any of the following hemorrhagic manifestations including a positive tourniquet test, petechiae, purpura, ecchymosis, epistaxis, gum bleeding, and hematemesis and/or melena;

- Enlargement of the liver is observed at some stage of the illness in 90-98% of the children; the frequency varies with time and/or the observer;

- Shock, manifested by tachycardia, poor tissue perfusion with weak pulse and narrowed pulse pressure or hypotension with the presence of cold, clammy skin and/or restlessness.

Laboratory findings:

- Thrombocytopenia (100,000 cells per mm^3 or less);

- Hemoconcentration; hematocrit increase of more than 20% from the baseline of patient or population of the same age;

The 1997 WHO Case Classification System for Dengue was revised because of differences across the broad geographical areas and the age groups of people affected by dengue. However, the current 2009 WHO Classification (Fig. 1) has yet to be definitively proved effective. The question still remains, therefore, whether this latest classification requires further modifications[15].

Other common laboratory findings are hypo-proteinemia, hyponatremia, and elevation of hepatic enzymes and blood urea nitrogen levels. Metabolic acidosis may be found in patients with prolonged shock.

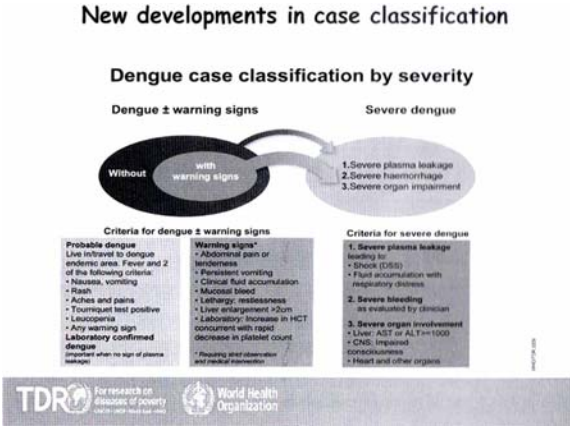

Fig. 1 The 2009 WHO Dengue Case Classification.

White blood cell count is variable, ranging from leukopenia to mild leukocytosis with an increase in the percentage of lymphocytes and presence of atypical forms[1,16,17].

Hematological findings include vasculopathy, reduction of several coagulation factors, reduced platelet count, and platelet dysfunction. The tendency toward bleeding should be monitored in any dengue patients since it may cause severe, uncontrollable hemorrhage. The pathogenesis of bleeding in a dengue patient is not fully understood. The extent of endothelial cells, coagulation, and fibrinolysis activation in children with dengue infection seems to be correlated with dengue's severity[18,19].

The laboratory diagnosis of dengue infection can be confirmed by serological tests, isolation of the virus and detection of viral RNA by reverse transcriptase polymerase chain reaction. Commercial kits for dengue diagnosis are also available for routine use. A pilot evaluation of diagnostic values of ELISA and reverse transcription polymerase chain reaction from oral specimens has yielded promising results. Collection of oral specimens is less invasive and may be more acceptable[1].

Clinical manifestations of dengue infection vary with age as DSS is more common in children than the adult. Infants with dengue infection present more frequently with convulsions, diarrhea, rash, cyanosis, and splenomegaly while co-morbidities in adults are associated with greater risk of mortality[20,21].

Treatment

The treatment of dengue infection is symptomatic and supportive. In most cases, early and effective replacement of lost plasma with fluid and electrolyte solutions, plasma, and/or plasma expanders results in a favorable outcome. The outcome depends on early recognition of the infection and careful monitoring. Blood transfusion is indicated in patients with significant clinical bleeding, mainly from the gastrointestinal tract. Blood components are required when disseminated intravascular coagulation (DIC) has caused massive bleeding. Persistent shock despite adequate fluids and a decline in the hematocrit level suggests significant clinical bleeding requires prompt treatment. DIC that occurs in cases of severe shock may play an important role in the development of massive bleeding and irreversible shock. Coagulation tests should be monitored in all cases of shock to document the onset and severity of DIC. Blood grouping and matching should be carried out as a routine precaution for every patient in shock.

The rate of fluid infusion needs to be carefully tailored according to the patient's vital signs, hematocrit, and urine output. In general, there is no need for fluid therapy beyond 48 hours after the cessation of shock. Reabsorption of extravasated plasma takes place, manifested by a further drop in the hematocrit level. Excessive fluids during the recovery phase may cause hypervolemia, pulmonary edema, or heart failure. An extremely important point is that a drop in the hematocrit level at this stage not be taken as a sign of internal hemorrhage. A strong pulse and blood pressure, with a wide pulse pressure and diuresis, are good vital signs. They ruled out the likelihood of gastrointestinal hemorrhage which is mostly found during the shock stage[1,22].

Prevention

Prevention of dengue depends on the control of the mosquito vector by limiting its breeding places and treatment of stored water with larvicide. These measures against dengue are effective only with a high level of government commitment, education, and community participation. Development of a dengue vaccine is seen as the best hope to fight this disease[1,23].

The first phase III efficacy trial for a recombinant, live, attenuated tetravalent dengue vaccine in highly dengue-endemic areas in Asia demonstrated that the dengue vaccine is efficacious when given as a 0-6-12 month schedule to 2-14 year-old children. The vaccine has an efficacy against symptomatic dengue regardless of severity by 56.5%. Secondary analyses showed the contribution of each of the four serotypes to the overall efficacy. Clinically important reduction of severe disease and hospitalizations associated with evidence of reduced symptomatology was also observed. Higher efficacy was observed in the immunogenicity subset seropositive at baseline. The safety profile is consistent with good safety profiles observed in previous studies over the 25-month follow-up showing no evidence of antibody dependent enhancement in partial or completely vaccinated individuals.

Results support the vaccines potentiality in reducing the public health burden of dengue[24].

An independent scientific and educational Association of South East Asian Nations (ASEAN) Members States Dengue Vaccination Advocacy Steering Committee (ADVASC) was established in 2011 to address the practical challenges faced by the ASEAN countries as they were preparing for the eventual

introduction of a dengue vaccine. ADVASC convened workshops that drew together public health representatives and dengue experts from the ASEAN countries in order to make practical recommendations to improve the current surveillance and diagnostic for dengue to enable the countries to assess consistently and accurately communicate, the impact of a dengue vaccine[25,26].

Better understanding of new paradigms for a changing dengue epidemiology will not only feed into operational policy for dengue control but also provide fertile terrain for vaccine application strategies in the future. Epidemiological data of this kind will be both valuable for dengue vaccine efficacy trials and for consideration of the age group to be vaccinated leading to universal dengue vaccine implementation in the future.

In summary, dengue poses a heavy economic cost to the healthcare system and society. The potential economic benefits are associated with promising dengue prevention interventions, such as dengue vaccine and vector control innovations[27].

Potential conflicts of interest

None.

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เดงกี: วิกฤติโลก

อุษา ทิสยากร, จุล ทิสยากร

เดงกีเป็นไวรัสที่มียุงลายเป็นพาหะนำโรคซึ่งในปัจจุบันพบการแพร่ระบาดไปทั่วโลก เดงกีมี 4 สายพันธุ์ โดยการติดเชื้ออาจเป็นการติดเชื้อที่ไม่มีอาการหรือเป็นไข้ที่ไม่รุนแรงไปจนถึงเป็นไข้เดงกี (dengue fever, DF) และไข้เลือดออก (dengue hemorrhagic fever, DHF) ลักษณะของโรค DHF คือมีไข้ มีอาการเลือดออกและมีการรั่วของพลาสมาซึ่งอาจทำให้ผู้ป่วยมีภาวะช็อกเกิดขึ้น โรคติดเชื้อเดงกียังอาจทำให้เกิดอาการจากอวัยวะต่าง ๆ ของร่างกายเช่น อาการทางสมอง อาการทางตับ การเปลี่ยนแปลงทางโลหิตวิทยาได้แก่ vasculopathy, coagulopathy และ thrombocytopenia การวินิจฉัยโรคติดเชื้อเดงกีทางห้องปฏิบัติการประกอบด้วยการแยกเชื้อไวรัส การตรวจทาง serology และการตรวจด้วยวิธีการทางชีวโมเลกุล การรักษาโรคติดเชื้อเดงกีเป็นการรักษาตามอาการซึ่งมักจะได้ผลดี เมื่อสามารถวินิจฉัยโรคได้แต่เนิ่น ๆ ตลอดจนการติดตามดูแลผู้ป่วยอย่างใกล้ชิด องค์การอนามัยโลกได้ปรับเปลี่ยนนิยามของโรคติดเชื้อเดงกีโดยจำแนกตามความรุนแรงของโรค เพื่อประโยชน์ในการดูแลรักษาผู้ป่วย และได้มีการนำนิยามของโรคติดเชื้อเดงกีดังกล่าวไปใช้อย่างแพร่หลาย การป้องกันโรคติดเชื้อเดงกีทำโดยการควบคุมยุงลาย ซึ่งเป็นพาหะนำโรค การศึกษาประสิทธิผลและความปลอดภัยของ dengue vaccine ในอาสาสมัครมากกว่า 10,000 รายในทวีปเอเชียพบว่าวัคซีนดังกล่าวสามารถป้องกันการติดเชื้อและลดความรุนแรงของโรคได้และวัคซีนมีความปลอดภัย