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Dengue Fever in Children

Where Are We Now?

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Dengue fever is the most frequently occurring mosquito-borne viral disease worldwide.¹ Using cartographic approaches, researchers now estimate the number of dengue cases worldwide to have been as high as 390 million in 2010.² The first autochthonous cases reported in France, Croatia and Portugal (island of Madeira) demonstrate that the disease is no longer simply a tropical disease.¹ The wide clinical spectrum, which can range from an asymptomatic or mild febrile illness to a life-threatening hemorrhagic fever syndrome, constitutes a particular challenge for clinicians, particularly in nonendemic areas. This review summarizes current knowledge of dengue fever epidemiology, pathogenesis, diagnostics, prophylaxis and therapy in children. Dengue in children differs significantly from adult disease.³

EPIDEMIOLOGY

Over the last 50 years, the incidence of dengue has increased 30-fold, with the

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highest rates occurring among infants.¹ Moreover, infants are at increased risk of dengue shock. The limited ability of the hemodynamic system in young children to compensate for capillary leakage is believed to contribute to this phenomenon. Yet, the case-fatality rate is generally lower among infants than among adults.¹ Dengue virus infections are endemic in most parts of the tropics and subtropics.¹ Overall, the geographical expansion of the virus has been limited by the temperature sensitivity of its main vector, *Aedes aegypti*. However, the second most important vector, *Aedes albopictus*, has a higher temperature tolerance. This latter vector is most likely responsible for viral transmission in autochthonous dengue cases in Europe.¹ Globalization and anticipated climate changes can be expected to contribute to an increasing number of autochthonous cases in nontropical countries in upcoming years.

PATHOGENESIS

Dengue is caused by a flavivirus. Four different serotypes (DEN1–DEN4) are known. Lack of suitable animal models mimicking the human disease spectrum hampers understanding of dengue pathogenesis.⁴ Viral transmission takes place via a blood meal by infected mosquitoes. Although infections of nonhuman primates do occur, viremic humans are the most important reservoir for dengue viruses. After vector-borne transmission, the virus initially infects macrophages and dendritic cells. Then, it replicates in regional lymph nodes. Infection with the virus is followed by an incubation period of

4 to 10 days, during which the virus becomes disseminated via blood and lymphatic vessels, thereby causing systemic disease. This kinetics is clinically important: dengue infection is highly unlikely if a traveler has left an endemic area more than 3 weeks before the onset of fever.

The pathogenetic mechanisms underlying the variable disease phenotype are only partially understood. Primary infection is considered to result in lifelong protective serotype-specific immunity, whereas serotype cross-reactive protection remains incomplete and is limited to the few months after infection. Moreover, the formation of cross-reactive, non-neutralizing antibodies in the event of a secondary infection with a different serotype may trigger a detrimental systemic inflammatory response via the antibody-dependent enhancement. This phenomenon likely contributes to severe secondary cases and is more common in children.⁵ Although this mechanism may be considered a viral escape targeting the adaptive immune system, the dengue virus may additionally subvert innate immunity by interfering with type I interferon release. Moreover, host genetic determinants such as HLA alleles and variants in cytokine genes may have an impact on disease severity.⁵

CASE DEFINITIONS

According to a formerly accepted definition outlined by World Health Organization, 3 categories of dengue infections were distinguishable: (1) dengue fever, (2) dengue hemorrhagic fever and (3) dengue

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shock syndrome.¹ Although this definition at first was helpful from an educational perspective, it did not fully meet clinical needs with respect to initial risk stratification in individual patients.⁶ A major caveat was that bleeding was defined as the cardinal symptom. However, capillary leakage has proven to be the more important clinical challenge in severe dengue infection—especially in children—because it may cause life-threatening shock without bleeding.⁶ For this reason, the World Health Organization revised its case definitions in 2009 and now distinguishes among: (1) dengue fever, (2) dengue fever with warning signs and (3) severe dengue fever (Fig. 1).¹ It is anticipated that by using these revised definitions, fewer severe cases

will be missed, appropriate treatment will become initiated in a more timely fashion and overall prognosis of severe dengue will improve.⁶

CLINICAL PRESENTATION

The vast majority of patients with dengue infection is either asymptomatic or shows only mild symptoms.⁷ If dengue infections become symptomatic, 3 stages can be distinguished: First, a febrile stage; second, a critical stage during defervescence; and third, a recovery stage. The initial febrile stage begins with rapid-onset, high-grade fever, which is accompanied by retro-orbital headache, severe myalgia and

arthralgia (“break-bone fever”), nausea, vomiting (more common in children³) and general fatigue. A confluent maculopapular rash (more common in children³) appears during the end of the febrile stage. Typically, the face is spared. Other characteristic skin findings are hyperesthesia and hemorrhagic lesions, ranging from petechiae and purpura to bruising around venipuncture sites. Petechiae indicate capillary fragility and may be provoked with the so-called tourniquet test (syn. Rumpel-Leede test). Laboratory investigations generally show thrombocytopenia, leukopenia and a potentially moderate elevation of liver aminotransferase levels. These changes are more profound in adults than in children.³

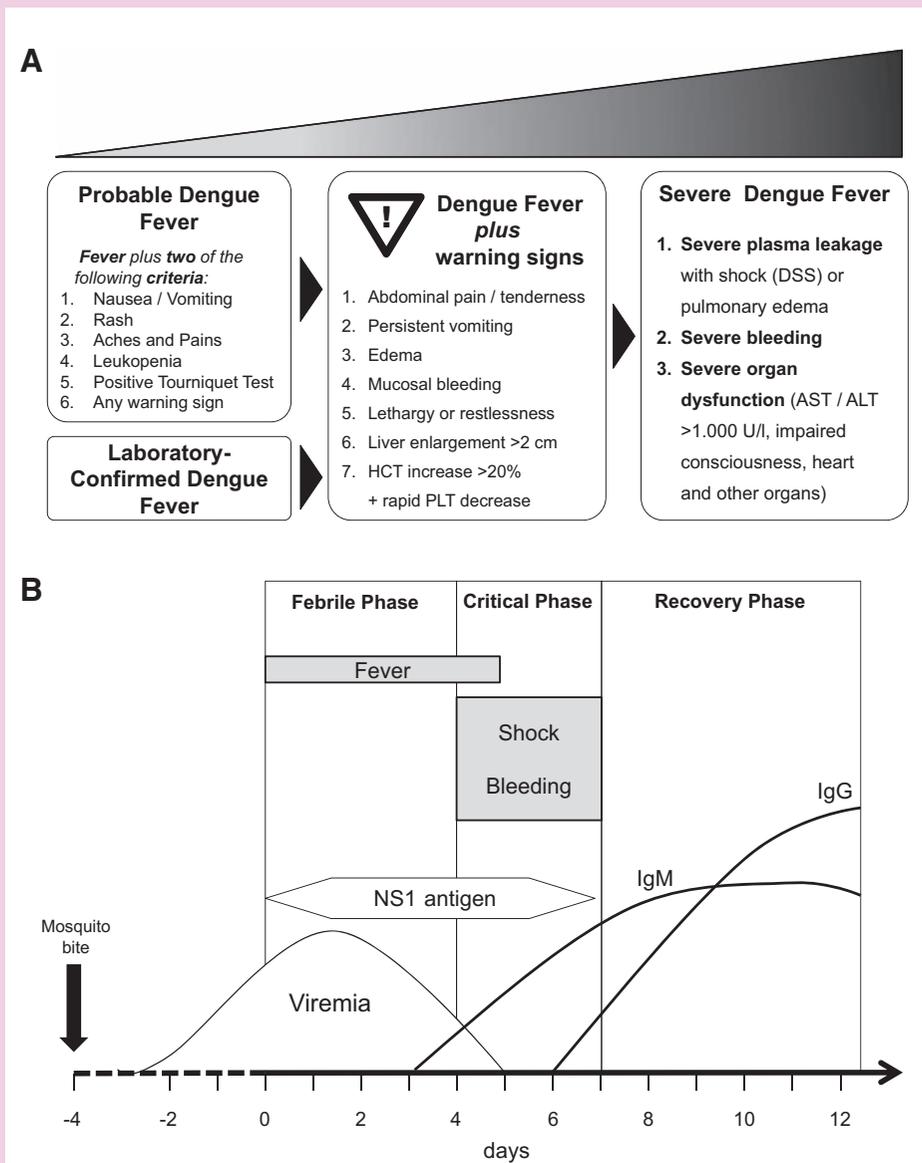


FIGURE 1. A, Revised dengue fever case classification, adapted from World Health Organization 2009.¹ B, Clinical course and laboratory diagnosis of dengue fever. AST indicates aspartate transaminase; ALT, alanine transaminase; DSS, dengue shock syndrome; HCT, hematocrit; NS1, nonstructural protein 1; PLT, platelet count.

Although most children recover directly after the initial stage, a small proportion will develop systemic capillary leakage during defervescence (days 4–7), which is the most critical stage of the disease. Capillary leakage can rapidly lead to severe shock. Accordingly, the decline of fever is the critical time point for both diagnoses of the disease and for starting appropriate fluid management. Delayed diagnosis of severe dengue is associated with high mortality (up to 40%).¹ Therefore, the following warning signs for deterioration are of utmost clinical importance (Fig. 1A): (1) severe abdominal pain or tenderness, (2) persistent vomiting, (3) mucosal bleeding and (4) behavioral changes such as lethargy or restlessness. Additional signs of capillary leakage include pleural effusions, gallbladder wall thickening and ascites. Thus, repeated abdominal ultrasound examinations are important for monitoring the risk for developing severe disease in all dengue patients. Laboratory changes of note include hemoconcentration (defined as increase in hematocrit of $\geq 20\%$), progressive thrombocytopenia and hypoproteinemia. Increased vascular permeability during the critical stage of dengue infection is usually short, which limits shock duration to 48–72 hours. The last stage may manifest with a secondary maculopapular rash, which may be accompanied by severe itching, but eventually heals with desquamation. The duration of the recovery period is variable.

Although dengue infections during pregnancy may cause premature birth or abortion, vertical infection of the fetus is rare. Malformations are not known to be associated with dengue infections during pregnancy.

DIAGNOSIS

Dengue infection can be diagnosed directly through detection of virus components or else indirectly via serological methods (Fig. 1B). Viral components can be detected by reverse-transcriptase polymerase chain reaction or by immunoassays for the soluble nonstructural protein 1 antigen. Both polymerase chain reaction and nonstructural protein 1 antigen assays show comparable sensitivity (80–90%) during the first 3 days of the illness.¹ Serologic diagnosis is possible 4 to 5 days after fever onset for anti-DEN-IgM and after 7 to 10 days for anti-DEN-IgG antibodies. In secondary infection, IgM production is often absent, whereas IgG titers rapidly rise to exceedingly high levels. Anti-DEN-IgG persists for life. Discrimination between serotypes is not possible by serology.

The type of diagnostic test used depends upon the stage of the disease. Due to the acute onset and severity of the symptoms,

patients with dengue usually present within the first 2 days of disease at healthcare facilities. At this stage, diagnosis only can be established by direct viral detection assays. However, once hemorrhagic fever or dengue shock syndrome has developed, diagnosis can only be established by serology because the viremic phase is over.

The differential diagnosis includes any undifferentiated febrile syndrome, especially malaria, typhoid fever, leptospirosis, melioidosis, rickettsial diseases, as well as acute viral infections with human immunodeficiency, Epstein-Barr, chikungunya and West Nile virus. In addition, other viral hemorrhagic fevers and measles need to be considered.

THERAPY AND PREVENTION

Currently, effective antiviral treatment for dengue infection is not available. For example, balapiravir, a polymerase inhibitor, has not shown beneficial effects compared to placebo.⁸ Therefore, disease management is primarily supportive and centers on appropriate fluid management. Patients with mild symptoms and sufficient oral fluid intake are treated symptomatically with bed rest and acetaminophen/paracetamol. Due to their platelet-inhibiting effects, nonsteroidal anti-inflammatory drugs and acetylsalicylic acid should be avoided. Daily clinical evaluation and laboratory monitoring of complete blood count is necessary in order to detect thrombocytopenia or—most importantly—capillary leakage. An increase in hematocrit levels of more than 20% is a sign of significant plasma loss and an indication for transfer of the patient to the intensive care unit.⁷ During the critical phase of defervescence, careful monitoring of warning signs is important so that intravenous fluid therapy can be started as soon as necessary. In the event of dengue shock, rapid resuscitation with crystalloid solutions is essential for the prognosis. Colloid solutions should be reserved for patients with severe and persistent shock. The current World Health Organization guidelines on dengue fever offer a precise algorithm with respect to fluid management in dengue patients.¹ After hemodynamic stabilization, infusion rates should be reduced in order to avoid iatrogenic fluid overload. This is important because the duration of dengue-associated shock is typically short. Blood transfusions are necessary in the event of severe bleeding.¹

Currently, a licensed dengue vaccine is not available, but several preparations are under investigation.⁷ The provision of cross-reactive protection against all 4 serotypes is 1 of the major challenges in vaccine development. Recently, an attenuated tetravalent

vaccine based on a recombinant virus constructed from yellow fever virus was able to show an efficacy of 30% in preventing virologically confirmed dengue infections in a trial conducted in over 3000 Thai school children aged 4–11 years.⁹ Nevertheless, despite the overall efficacy of this vaccine, protection was not satisfactory for serotype 2 strains (<10% efficacy).⁹

Due to the absence of both specific treatment options and a vaccine, prophylaxis by avoidance of mosquito bites by *Aedes* mosquitoes remains the cornerstone of dengue prevention. This is especially true for children who have had a first dengue infection and are returning to dengue-endemic areas. Classical but still up-to-date measures include the wearing of protective, insecticide-impregnated clothing and the usage of mosquito repellents, for example, N,N-diethyl-metatoluamide. In contrast to malaria, insecticide-treated bed nets are of very limited value because *Aedes* mosquitoes bite during the day.¹

CONCLUSIONS

Due to the lack of an effective dengue vaccine as well as to the absence of targeted treatment options, the knowledge and skills to recognize and diagnose the disease before it reaches its critical phase are of utmost importance for clinicians treating dengue patients.

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