Dengue and Dengue Hemorrhagic Fever

David M. Morens, MD

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Dengue is an acute influenza-like disease caused by any of 4 genetically similar mos-
quito-borne arboviruses of the Flavivirus family.1 Dengue viruses are thus related to yellow fever virus, West Nile virus, Japanese encephalitis virus, and several other human pathogens. Although flaviviruses have historically been linked to specific geographic locales, in recent years many have been extending their geographic ranges. Among the most important examples of this phenomenon, dengue has been re-emerging globally,2 along with a potentially fatal, and poorly understood complication known as dengue hemorrhagic fever.

Importance

The importance of dengue to pediatric infectious disease practice has been increasing.1–4 As dengue has expanded globally into new tropical and subtropical areas, the risk of infection to travelers returning to the United States (US) has risen. Moreover, dengue has for decades caused serious problems in such US jurisdictions as Puerto Rico, the US Virgin Islands, American Samoa, and other Commonwealths/Territories, has caused epidemics in Hawaii (as recently as 2001–2002) and recurrent cases/small outbreaks in Southern Texas, and is believed by some to pose the threat of urban outbreaks in the 24 other States with vector mosquito prevalences. The once-rare complication known as dengue hemorrhagic fever (see below) has not only become more highly incident in persons with dengue infection, but has in recent decades “spread” from Southeast Asia to the Western Hemisphere.

Epidemiology

Dengue viruses are sustained in mosquito-human-mosquito transmission cycles, the major vectors being the “classical” African-descended vector Aedes aegypti, and more recently a less-efficient but more adapt-
able vector Aedes albopictus. These mosqui-
to-borne peridomestic, breeding in or very near households, in flower pots, cans, jars, discarded car tires, and in other receptacles where fresh water meets a solid surface. Dengue is thus an urban problem.2–5 Although dengue epidemics once ravaged the US eastern seaboard as far north as Philadel-
phia, the fact that mosquitoes may not sur-
vive year round in northern latitudes, as well as modern sanitation (refuse collection, screen-
ing, air conditioning), now afford a degree of “protection.” Nevertheless, the experience of Singapore, a modern, wealthy, and air-conditioned country with the world’s most ag-
gressive dengue control program, proves that dengue epidemics may be nearly impossible to prevent.

Clinical Picture

Historically, dengue and dengue hem-
orrhagic fever/dengue shock syndrome have been considered childhood diseases, but this is largely a function of their recognition and study in highly endemic and hyperendemic areas where adults are immune. As dengue expands globally, more adult cases of dengue hemorrhagic fever are being seen. The incubation period averages 5 days after the bite of an infected mosquito. With the exception of a variable and transient maculopapular rash that may be faint or unrecognizable in dark-skinned persons, the clinical picture of uncomplicated dengue is almost indistin-
guishable from that of influenza and of a number of other alphavirus and flavivirus infections, eg, chikungunya: sudden onset of fever, myalgia and prostration, with variable symptoms/signs (Figure).6–8 The fe-
ver course has been classically described as “saddle back,” with a relative lowering of fever on about the third day, followed by a return on days 4 and 5, after which deferves-
cence occurs. The so-called pathognomonic symptom of “retro-orbital pain” (severe move-
ment-associated ocular myalgia) is seen in a number of other arboviral diseases and occa-
sionally in influenza. Minor bleeding phe-
nomena such as epistaxis, gingival bleeding, petechiae, and thrombocytopenia appear in about 10% of patients without dengue hem-
orrhagic fever, and do not by themselves predict progression of disease severity. Prolonged convalescence associated with intractable fatigue (up to 2 months) is not uncommon.

Complications: Dengue Hemorrhagic Fever and Dengue Shock Syndrome

Dengue hemorrhagic fever and its most severe form, dengue shock syndrome are potentially fatal dengue complications of obscure pathogenesis caused by any of the 4 viral types.1 Despite its name, and even though hemorrhagic phenomena are near-
universal and may occasionally be serious, almost all deaths are caused by hypotension rather than by hemorrhage. Since hemor-
rhagic signs are commonly seen in both den-
gue hemorrhagic fever and in uncomplicated dengue, the term “dengue hemorrhagic fe-
ver” is something of a misnomer. The under-
lying pathogenesis of dengue hemorrhagic fever includes a rapidly developing capillary leakage syndrome with hemoconcentration and venous pooling. If uncorrected by fluid admin-
istration, it may quickly lead to hypotension and shock. The diagnostic criteria for dengue hemorrhagic fever/dengue shock syndrome and for staging of severity were developed decades ago by the World Health Organization (Figure).7,9,10 but have recently become contro-
versial in their applicability to adults patients because of newer diagnostic tests.1,7

Pathogenesis

Although dengue hemorrhagic fever/ dengue shock syndrome pathogenesis is largely uncharacterized, it has become clear in recent decades that, as had been observed by Halstead and colleagues in the 1960s, major risk factors seem to be secondary (sec-
ond dengue or other flavivirus followed by dengue) infections in older children/adults, as well as primary (first dengue) infections in infants.1 The prevailing hypothesis to ex-
plain this observation is that cross-reacting/ nonneutralizing IgG antibody against a pre-
viously infecting dengue serotype (in the case of infants, transplacentally acquired IgG antibody), upregulates infection by dengue bound virus into FcR-bearing cells (antibody-dependent enhancement, or ADE).11

Diagnosis

The most important elements in diag-
nosing dengue are often travel history, a high index of suspicion, and familiarity with the clinical signs and the epidemiologic picture. In a clinical setting, available diagnostic tests
such as serologies and PCR may be unreliable. For whatever reason, dengue hemorrhagic fever/dengue shock syndrome in travelers returning to the US has to date (2009) been extremely rare. During epidemics it is impossible to predict which patients will progress to dengue hemorrhagic fever/dengue shock syndrome, but in hyperendemic areas like Thailand, where parents have become highly educated about dengue, it is nowadays rare that children are brought to hospitals in the late stages of disease, leading to a substantial drop in dengue hemorrhagic fever deaths over recent decades. Hemoconcentration without dehydration is an early warning sign of dengue progression (Figure); pericardial and pleural effusions may also be documented on X-rays or echograms.

Treatment

Treatment strategies and protocols for dengue hemorrhagic fever/dengue shock syndrome have been developed by the World Health Organization and are available online (http://www.who.int/csr/disease/dengue/DengueResources.pdf). These rely largely on anticipation of shock and prompt administration of standard available fluid/electrolyte solutions, eg, lactated Ringer’s solution. Severe shock can be treated with dextran 70 or 6% hydroxyethyl starch. Uncomplicated dengue rarely requires specific treatment. Rest, hydration, nutrition, and antipyretics are the mainstays of supportive care in uncomplicated cases; obviously, aspirin should not be used. No specific drugs or antiserum preparations are available.

Prevention

Development of dengue vaccines has been a high priority for decades. Several are in phase 1 or 2 clinical trials, but it will probably be a number of years before any one becomes available for routine use. Travelers should be educated about avoiding Aedes mosquitoes by learning about their bionomics and by wearing protective clothing and using insect repellants. In endemic communities, dengue epidemics represent public health crises. Anti-dengue public health measures rely on public education via schools, radio/television, and leaflets/posters, and by mosquito control including adulticiding (chemical spraying), larvicide, and source reduction (elimination of breeding sites by clean up of debris).

REFERENCES