Dengue and Chikungunya

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AUTHOR DISCLOSURE Dr Lee has disclosed that he was a speaker for Novartis Vaccines. His relationship with them ended in June 2015. Dr Krilov has disclosed that he is site principal investigator for a meningococcal B vaccine trial for Pfizer and that Pfizer provides funding to his institution; site principal investigator for an observational study of respiratory syncytial virus (RSV) infections in preterm infants for AstraZeneca and that AstraZeneca provides funding to his institution; and site principal investigator for a clinical trial of a humanized monoclonal antibody to prevent RSV in high-risk preterm infants for Regeneron. This commentary does not contain discussion of an unapproved/investigative use of a commercial product or device.

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Dengue is caused by 4 related but distinct flaviviruses, DENV1 – 4, which result in 390 million infections annually, with one-third of the world's population at risk. Most flaviviruses are transmitted by arthropods, such as mosquitoes and ticks, and are responsible for diseases such as yellow fever, West Nile fever, and Japanese encephalitis. DENV is primarily transmitted by the bite of an infected female *Aedes aegypti* mosquito, which is endemic to every global region except Europe and Antarctica. Dengue primarily occurs in South and Southeast Asia, Africa, tropical South and Central America, and the Caribbean. In the United States, dengue is a nationally notifiable disease, with 677 cases reported to the Centers for Disease Control and Prevention (CDC) in 2014. It is endemic in Puerto Rico, the US Virgin Islands, and American Samoa. Most US cases result from travel to an endemic area, but locally acquired dengue has been documented in Texas and south Florida.

Seventy-five percent of DENV infections in all age groups are asymptomatic, but a spectrum of disease is seen in the remaining 96 million patients, ranging from self-limited fever to life-threatening shock. Classic dengue fever begins 4 to 7 days after an infected mosquito's bite and typically presents as a flulike illness with a temperature greater than 38.5°C (101.3°F), headache, retro-orbital pain, and severe myalgias, from which its eponym, "break-bone fever," arose. A fine, transient macular rash, nausea, and vomiting may also occur. However, infection may present atypically; the classic findings occur in fewer than 60% of patients. With the exception of high temperatures, children are often less symptomatic than adults during the first phase of infection, which lasts 3 to 7 days. Physical examination may reveal a palpable liver and petechiae and bruising, caused by moderate thrombocytopenia. Other laboratory findings include leukopenia and an aspartate aminotransferase value less than 1,000 U/L (16.7 μkat/L).

Most patients subsequently recover without complications, but about 1%, usually children and young adults, develop systemic vascular leak after defervescing. This leakage causes increased hemoconcentration, hypoproteinemia, pleural effusions, and ascites, resulting in more serious disease, referred to as dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). DHF is defined by a triad of findings: plasma leakage, thrombocytopenia, and hemorrhage. The bleeding is most notable in the skin, but hematemesis, melena, menorrhagia, and epistaxis can also occur. Children rarely have clinically significant bleeding, but adults can have substantial hemorrhage, even with minor plasma leakage. DSS occurs in patients with DHF when the pulse pressure narrows to less than 20 mm Hg from plasma volume loss and peripheral vascular collapse begins. DSS is particularly insidious because patients initially appear well, with normal or elevated systemic blood pressure. However, once they develop hypotension, irreversible shock and death can occur despite aggressive resuscitation. Clinicians

should closely monitor patients for signs of impending shock, such as persistent vomiting, increasingly severe abdominal pain, tender hepatomegaly, mucosal bleeding, lethargy, or restlessness. Helpful diagnostic indicators are the presence of effusions and increasing or high hematocrit as the platelet count rapidly declines. The altered vascular permeability quickly resolves after 48 to 72 hours, and its pathogenesis remains unclear. DHF and DSS do not occur with the initial DENV infection.

Immunity to one serotype after infection may predispose individuals infected with another serotype to severe dengue. Therefore, most travelers, except for those frequently visiting family and relatives, are unlikely to develop what the World Health Organization now classifies as severe dengue.

Dengue is usually diagnosed clinically because most endemic areas lack access to clinical laboratories. Even in developed countries, confirmation is slow and limited to specialized reference laboratories. The gold standard for diagnosis, although it is not helpful in patient care, remains testing paired acute and convalescent (obtained 10 to 14 days later) serum with a DENV hemagglutinin inhibition assay. Newer tests, such as DENV nonstructural protein 1 (NS1) or immunoglobulin (Ig)M enzyme-linked immunosorbent assays or RNA reverse transcription-polymerase chain reaction (RT-PCR), can now diagnose dengue quickly.

Dengue management is largely supportive. Early recognition of shock and careful, frequent assessment of pulse, blood pressure, hematocrit, and urine output, with administration of oral and intravenous fluids and blood products to maintain adequate intravascular volume, is critical. Currently there is no effective antiviral agent for DENV. Prevention is based on mosquito control measures, although a recombinant live attenuated tetravalent vaccine (CYD-TDV) may be approved in 2016.

Chikungunya fever is caused by an alphavirus (CHIKV), which was isolated during an epidemic in 1952 in Tanzania. Its name is the Makonde word for "that which bends upward," describing the bent posture patients that assume from the severe arthralgia CHIKV causes. In 2004, CHIKV made headlines when it spread from Africa to South Asia, causing a number of epidemics affecting millions of people. In October 2013, CHIKV appeared in St. Martin and rapidly spread throughout the Caribbean and Central America, with 1.7 million cases reported within 2 years, 3,270 of which were reported in the United States.

Although CHIKV is spread by the same mosquitoes as DENV, it can be more readily transmitted. Paired with the vulnerability of a population that has no prior immunity to CHIKV, efficient transmissibility has led to large-scale outbreaks. One outbreak in northeastern Italy in 2007 was caused by the local *Aedes aegypti* and *Aedes albopictus* mosquitoes biting an infected traveler and then infecting the local population with an adapted CHIKV that had enhanced transmissibility. Both of these mosquito species are present in the United States, and at least 11 endemic cases have been documented. Estimates of CHIKV incidence and prevalence are not as well defined as for DENV.

In sharp contrast to DENV, 85% of CHIKV infections are symptomatic, with rapid onset of a temperature of 39° to 40°C (102.4° to 104°F) after a brief incubation of 2 to 4 days. Polyarthralgia begins 2 to 5 days after fever, frequently involving more than 10 joint groups. The arthralgia tends to be symmetric and more common in distal than proximal joints, especially large joints, although the axial skeleton may be involved. Patients are often immobilized by pain. Macular or maculopapular rash is also common, appearing 3 or more days after fever and lasting 3 to 7 days. The rash begins on the trunk or extremities, can be patchy or diffuse, may involve the face as well as the palms and soles, and may be pruritic in up to 50% of patients. Children may develop bullous lesions, but petechiae and bruising are uncommon. Gastrointestinal symptoms and erythematous ears from CHIKV chondritis occur as well.

Similar to DENV, CHIKV is usually diagnosed clinically. Marked lymphopenia is characteristic as well as thrombocytopenia, elevated aspartate aminotransferase/alanine aminotransferase, and hypocalcemia. RT-PCR can diagnose CHIKV in the first week of illness, and IgM can be positive before the fifth day of illness and persist for months. A fourfold rise in IgG between acute and convalescent serum also confirms CHIKV. Treatment of CHIKV is supportive, and prevention is through mosquito control, with vaccine research still in early stages.

Differentiating DENV and CHIKV can be difficult because both are acute systemic febrile illnesses with rash that occur in the same world regions. The Table highlights important differences between the two. The differential diagnosis also includes malaria, rickettsial disease, typhoid, leptospirosis, Epstein-Barr virus infection, measles, rubella, and other hemorrhagic fever viruses.

COMMENT: Dr Anthony Fauci, Director of the National Institute of Allergy & Infectious Diseases, has called mosquitoes the most destructive animals on earth, without any

TABLE. **Differentiating Dengue from Chikungunya**

	DENGUE	CHIKUNGUNYA
Fever	Longer duration (5–7 days)	High-grade, shorter duration (3–5 days)
Arthralgia	Common	Common, but characteristically severe **polyarthralgia**
Rash	Fine, faint transient macules; spares the palms/soles	Maculopapular, can be bullous, pruritic, and on the face, palms/soles
Petechiae/ecchymoses	**Common**	Uncommon
Joint swelling	Very uncommon	**Common**
Abdominal pain	Common	Uncommon
Respiratory symptoms	Can occur	Not seen
Leukopenia	Common	Uncommon
Symptoms	Resolve within 1 week, except for fatigue	Frequently persist
Severe complications	Can occur	**Rare**

apparent redeeming characteristics. Within the family of mosquitoes, the *Aedes,* along with the *Anopheles* (the vector for malaria), is at the top of the list of villains. In addition to dengue and chikungunya, *Aedes* species carry the arboviruses responsible for yellow fever, West Nile fever, eastern equine encephalitis, and now the most recent addition to the catalog of pandemic threats: Zika virus.

Initially identified serendipitously in Uganda in 1947, the Zika virus spread locally in West Africa and then eastward to the Pacific, causing outbreaks of infection in Micronesia and Southeast Asia that were characterized by fever, rash, arthralgias, and conjunctivitis. Until recently it raised no special concern because the virus appeared to cause only transient illness, if any at all; up to 80% of infected individuals remained asymptomatic. However, in 2015, if I may paraphrase W.B. Yeats, all changed, changed utterly; a terrible pandemic was born.

By the year's end, Brazil reported more than 1 million cases of Zika infection and with them came an alarming rise in cases of microcephaly as well as of Guillain-Barré syndrome. Brazil hosted the World Cup in 2014, and some have speculated that one of the myriad visitors from around the globe transported the Zika virus as unwanted baggage. When an infected human is bitten by an *Aedes* mosquito, the insect ingests the virus, and its next bite passes the virus on to another human host – and so an epidemic is born. When newly infected travelers return to homelands infested with *Aedes,* the epidemic becomes a pandemic. More than 20 countries in the Americas have now reported indigenous cases of Zika virus. As of this writing, no locally acquired Zika infections have been reported in the United States, but several travelers returning from areas of active infection have been identified with the virus, and possibly some southern states harbor mosquitoes that could become a reservoir for the regional spread of Zika.

The Centers for Disease Control and Prevention have urged women who are pregnant or trying to become pregnant to avoid travel to areas where Zika virus has been identified and has issued guidelines for the management of pregnant women who may have been infected and for the evaluation of infants with possible congenital infection. Early in 2016, the World Health Organization (perhaps belatedly) declared the neurologic complications associated with Zika virus infection to be an international health emergency, which is the same classification it gave to the Ebola epidemic in West Africa several years ago. As pediatricians, we know the devastating consequences of microcephaly. It is a terrible price to pay, even for the miracle of modern air travel.

—Henry M. Adam, MD
Associate Editor, In Brief

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