Journal of Pakistan Association of Dermatologists 2009; **19**: 127-130.

Editorial
Dengue fever: the fundamentals

RS Plummer, RP Kulkarni*, A Sethi

Section of Dermatology, Department of Medicine, University of Chicago Medical Center, Chicago, Illinois
*Division of Dermatology, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California

Dengue fever (DF) is a mosquito transmitted disease that is re-emerging as a global threat, resulting in increased morbidity and mortality. Approximately one hundred million cases of dengue fever are reported annually, and it is estimated that two and a half billion people worldwide (two fifths of the global population) are now at risk of contracting this disease.[1,2] This burden is largely borne by tropical developing nations, particularly in rapidly growing urban centers.

Dengue virus, a positive-sense RNA virus, is a member of the Flavivirus genus and is transmitted by the *Aedes* mosquito.[3] There are four serotypes of the dengue virus, labeled DENV1-4. The recent global re-emergence of dengue fever has been largely caused by massive, uncontrolled urbanization, modern transportation, the spread of mosquito vectors, and population growth.[3,4] These processes have also altered the epidemiology of the disease. Once affecting jungles and rural areas, dengue fever is now largely an urban disease. As a result, dengue virus is predominantly transmitted by the domesticated, urban-dwelling *Aedes aegypti* mosquito.

Address for correspondence
Dr. Aisha Sethi,
Section of Dermatology,
Department of Medicine, University of Chicago Pritzker School of Medicine,
Chicago, Illinois.
E-mail asethi@medicine.bsd.uhcicago.edu

Dengue infection can result in a wide variety of illnesses, including subclinical infection, mild febrile disease, classical dengue fever, dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS).[3] Classical DF is an illness characterized by fever, which develops after an incubation period from three to fourteen days.[5] This febrile phase lasts about five days, and is often characterized by high temperatures up to 40°C. The fever may be accompanied by associated symptoms, including headache, retro-orbital pain, myalgias, arthralgias, leucopenia, thrombocytopenia, and/or rash.[3,5,6] DHF is a more severe disease involving a vascular leak syndrome characterized by bleeding, thrombocytopenia, plasma leakage (leading to hemoconcentration with a rise in hematocrit of 20% or greater), effusions, hypoalbuminemia, and/or hypoproteinemia. There have even been reports of DHF cases treated at Pakistan's Aga Khan University Hospital, which presented with neurological involvement, which is unusual for DHF.[6] DSS develops when DHF causes circulatory failure, hypotension, or shock.[5]

Approximately fifty percent of classical DF cases present with a dermatologic component, most commonly a rash.[5,7] This DF exanthem is often observed in two phases. The initial rash, involving face, neck, and chest flushing, is observed within the first twenty-four to forty-eight hours of symptom onset.[8] Later, three to five days after the onset of symptoms, another

rash may appear. This rash is characterized by a generalized morbilliform eruption, often with petechiae and islands of sparing.[5,7,8] If pressure is applied, the lesions will usually blanch. This rash may heal with desquamation and is frequently pruritic at the end of the febrile phase.

Dengue patients also usually test positive to a tourniquet test for capillary fragility, even when presenting with mild clinical symptoms.[1] The tourniquet test involves inflating a blood pressure cuff to a pressure between the patient's systolic and diastolic blood pressures for five minutes; if more than 20 petechiae are present per square inch, the test is considered positive. In the case of more serious disease such as DHF or DSS, petechiae and ecchymoses are more commonly observed. DHF is also associated with mucosal involvement, including conjunctival infection, hemorrhagic crusting of the lips, small vesicles on the soft palate, erythema, and crusting of the tongue.[7]

One major reason that the dengue virus is so troublesome is because infection with one of its four serotypes (DENV1, 2, 3 and 4) provides no cross-protective immunity against secondary dengue infection.[1,3] So although infection by one serotype of dengue virus does provide protection against clinical illness if re-infected by that same serotype, it may actually lead to more severe illness if the same patient is infected by a different serotype. Secondary infection by a different dengue virus serotype is believed to increase the risk of DHF, particularly in children.[1] In addition, each serotype consists of multiple, genetically distinct strains of virus, each of which is associated with a different epidemic potential.[4]

The different serotypes of the dengue virus may correlate with clinical presentation. DENV1 and DENV3 are associated with more severe primary infections while DENV2 and DENV4 tend to cause more severe secondary infections.[4] Primary infection with DENV4 often results in very mild clinical presentations. However, changing strain genotypes and serotype geographical profiles may play a considerable role in the increase in epidemics and increased severity of dengue infections in recent years. The 2006 outbreak of DHF in Karachi, Pakistan, for example, was believed to be caused by co-circulation of DENV2 and DENV3.[9] Khan *et al*. postulate that this severe outbreak may have occurred because DENV3 was a new serotype in the region and/or because the DENV2 strain implicated might have undergone a genotypic shift from its endemic serotype. Rapid urbanization combined with increased global travel have led to the increase in dengue epidemics in part, and it is likely that these continued trends may result in antigenic changes in the virus and more severe forms of disease.

Like many other viral illnesses, there is currently no chemotherapeutic treatment for DF; it must be treated supportively.[1,3,10] Although supportive treatment can prove effective, dengue viral infections can still cause significant morbidity and mortality. Children less than fifteen years of age are less likely to present with classical DF, yet they have disproportionately higher mortality rates when presenting with DHF.[1]

Because of this lack of treatment options, vector control is of the utmost importance. Insecticides, barrier measures, protective clothing, bed netting, and insect repellents can be used to defend against insect bites.[1] Vertical control methods are also important in limiting the breeding of mosquitoes. *A. aegypti* largely relies on stagnant water sources to breed, which are often found in man-made containers. Increased vigilance and sanitation to limit such breeding areas can effectively limit the mosquito vector

population. Additionally, education about the transmission cycle of the *Aedes* mosquito and the clinical signs and symptoms of early dengue infection can be useful to reduce the burden of disease. Increased public health surveillance efforts are necessary in order to combat dengue fever.[10]

Ultimately, vaccine research promises to be the best defense against dengue. Although many successful vaccines have been produced to protect against other Flaviviruses, the dengue virus poses unique challenges. An effective vaccine must protect against all four serotypes and be safe for young children.[11] Five candidate vaccines are now in preclinical or clinical evaluation. Two of these vaccines, both live attenuated vaccines, are in advanced stages of evaluation. One has been tested on children, the other on adults.[2] Both demonstrate eighty to ninety percent seroconversion rates. One of the concerns with live-attenuated vaccines, however, relates to their susceptibility to rapid genetic mutation and recombination, which could result in a reversion back to a non-attenuated, virulent phenotype. Vaccine researchers are also working to develop chimeric virus vaccines as well as genetic vaccination procedures that use recombinant virus vectors, such as attenuated adenoviruses.[11] It is hoped that these efforts will eventually lead to a successful vaccine candidate, thereby reducing the burden of dengue infection. Until that time, vigilance and vector control will remain the most important strategies in the fight against dengue fever.

It is evident that the threat from the dengue virus is large and growing. The past six decades have witnessed a worrisome rise in epidemics as well as an increase in disease severity.[7,9] Currently, there is no frontline treatment or vaccination against this disease. Therefore, the rapid response and detailed knowledge of medical personnel is of the utmost importance. Although the most striking features of this disease are not always dermatological, there are several significant dermatological features of dengue fever and dengue hemorrhagic fever, and dermatologists can play an important role in diagnosing and treating this disease within a crucial timeframe. Detailed understanding of the exanthema of dengue fever is extremely important, as recognition of the classical dengue rash can help rapidly narrow a differential diagnosis. The skilled eye of a dermatologist can lead to prompt diagnosis and institution of rapid treatment, both of which are critical for reducing the morbidity and mortality associated with the dengue virus.

References

1. Lupi O and Tyring SK. Tropical dermatology: viral tropical diseases. *J Am Acad Dermatol* 2003; **49**: 979-1000.
2. Stephenson, JR. Understanding dengue pathogenesis: implications for vaccine design. *Bull World Health Organ* 2005; **83**: 308-14.
3. Mackenzie JS, Gubler DJ, Petersen LR. Emerging flaviviruses: the spread and resurgence of Japanese encephalitis, West Nile and dengue viruses. *Nat Med* 2004; **10**: S98-109.
4. Kyle JL, Harris E. Global spread and persistence of dengue. *Annu Rev Microbiol* 2008; **62**: 71-92.
5. Wilson ME, Chen LH. Dermatologic infectious diseases in international travelers. *Curr Infect Dis Rep* 2004; **6**: 54-62.
6. Wasay M, Channa R, Jumani M, Zafar A. Changing patterns and outcome of dengue infection; report from a tertiary care hospital in Pakistan. *J Pak Med Assoc* 2008; **58**: 488-9.
7. Thomas EA, John M, Bhatia A. Cutaneous manifestations of dengue viral infection in Punjab (North India). *Int J Dermatol* 2007; **46**: 715-9.
8. Pincus LB, Grossman ME, Fox LP. The exanthem of dengue fever: clinical

features of two US tourists traveling abroad. *J Am Acad Dermatol* 2008; **58**: 308-16.

9. Khan E, Hasan R, Mehraj V *et al*. Co-circulations of two genotypes of dengue virus in 2006 out-break of dengue hemorrhagic fever in Karachi, Pakistan. *J Clin Virol* 2008; **43**: 176-9.
10. Chang AY, Parrales ME, Jimenez J *et al.* Combining Google Earth and GIS mapping technologies in a dengue surveillance system for developing countries. *Int J Health Geogr* 2009; **8**: 49.
11. About Dengue Vaccines. [internet]. Pediatric Dengue Vaccine Initiative, 2009. [cited 2009 July 31]. Available from http://www.pdvi.org