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An Overview of Eastern Equine Encephalitis (EEE)

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Eastern equine encephalitis (EEE) virus is a mosquito-borne alphavirus endemic to eastern North America and the Caribbean.[1] It is closely related to western equine encephalitis virus, Venezuelan equine encephalitis virus, and Madariaga virus (formerly known as the South American variant of EEE virus). Although EEE virus was first isolated in horses in 1933, it was suspected of causing encephalitis outbreaks among horses (and potentially humans) along the East Coast for several decades prior.[2] The first known human cases of EEE were identified in Massachusetts in 1938.[2]

Eastern equine encephalitis virus circulates between *Culiseta melanura* mosquitoes and birds living around freshwater hardwood swamps.[1] Humans (and horses) are typically infected by other "bridging" mosquitoes (eg, *Aedes, Coquillettidia*, and *Culex* spp.) that acquire the virus from infected birds.[1] Although mosquito bites are the primary mode of EEE virus transmission to humans, transmission through organ transplantation has been documented as well.[3]

In the United States, reported cases of human (and horse) EEE virus disease primarily occur within East Coast, Great Lakes, and Gulf Coast states.[1,4] Most human cases have symptom onset from July through September, typically when the involved mosquitoes are most active.[1,4] Between 2003 and 2016, 121 cases of human EEE virus disease were reported to ArboNET, the national arboviral disease surveillance system managed by the US Centers for Disease Control and Prevention (CDC).[4] Approximately 7 human cases are reported within the United States each year, though this has recently ranged from 3 to 21 (as EEE epidemics are cyclical over years).[1,4] Unexpectedly, 38 cases have been reported so far in 2019, mostly from Massachusetts and Michigan.[1] The exact reasons for this are not currently understood.

Many EEE virus infections are thought to be asymptomatic. Symptomatic infection may either be systemic (eg, fever, myalgias, arthralgias, fatigue) or neuroinvasive (ie, meningoencephalitis).[1] Approximately 5% of EEE virus infections become overtly neuroinvasive with high mortality ($\sim$33%) and high morbidity including permanent neurologic sequelae.[1-4] Lumbar puncture in neuroinvasive cases often shows a cerebrospinal fluid (CSF) pleocytosis (initially neutrophilic or lymphocytic) with normal glucose and potentially elevated protein.[1-3,5] Brain imaging may show lesions particularly in the basal ganglia and thalami but also in brainstem, subcortical, and/or cortical areas.[1,3,5]

Diagnosis is often made based on positive serology (eg, immunoglobulin M tests such as enzyme-linked immunosorbent or microsphere immunoassays followed by confirmatory plaque-reduction neutralizing antibody tests) in the serum and/or CSF.[1] Occasionally, the diagnosis is made based on positive nucleic acid tests (eg, reverse transcription-polymerase chain reaction) in the CSF or tissue,[1,3] particularly among immunosuppressed patients who might not mount an appropriate antibody response. Some state health department laboratories and the CDC are able to provide confirmatory testing of samples, tissues, or postmortem specimens.

Treatment of neuroinvasive EEE virus infection is largely supportive as there are no proven antiviral treatments yet. Seizures, coma, and/or cerebral edema may

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occur and may require intensive care management.[1,3,5] One case report described successfully using intravenous immunoglobulin (which may have provided neutralizing antibodies) with aggressive cerebral edema and seizure management.[5]

Eastern equine encephalitis virus infection can be prevented by avoiding mosquito bites (eg, wearing insect repellant, avoiding outdoors between dusk and dawn, wearing long-sleeved shirts and pants).[1] Clinicians can contact their local and/or state health departments for questions regarding EEE or for assistance with confirmatory testing.

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