Case Follow-up

Rather than follow Mr. P.'s suggestion to increase his medication doses and emphasize how poorly he was doing, his psychiatrist highlighted the ways in which his psychiatric illness interfered with his ability to seek and sustain competitive employment. He wrote a letter for Mr. P. to submit with his next SSI application. Mr. P.'s case manager worked with him on his reapplication and accompanied him to his interview, and Mr. P. ultimately received SSI.

An audio interview with Dr. Kalofonos is available at NEJM.org

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Disclosure forms provided by the author are available at NEJM.org.

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Eastern Equine Encephalitis Virus — Another Emergent Arbovirus in the United States

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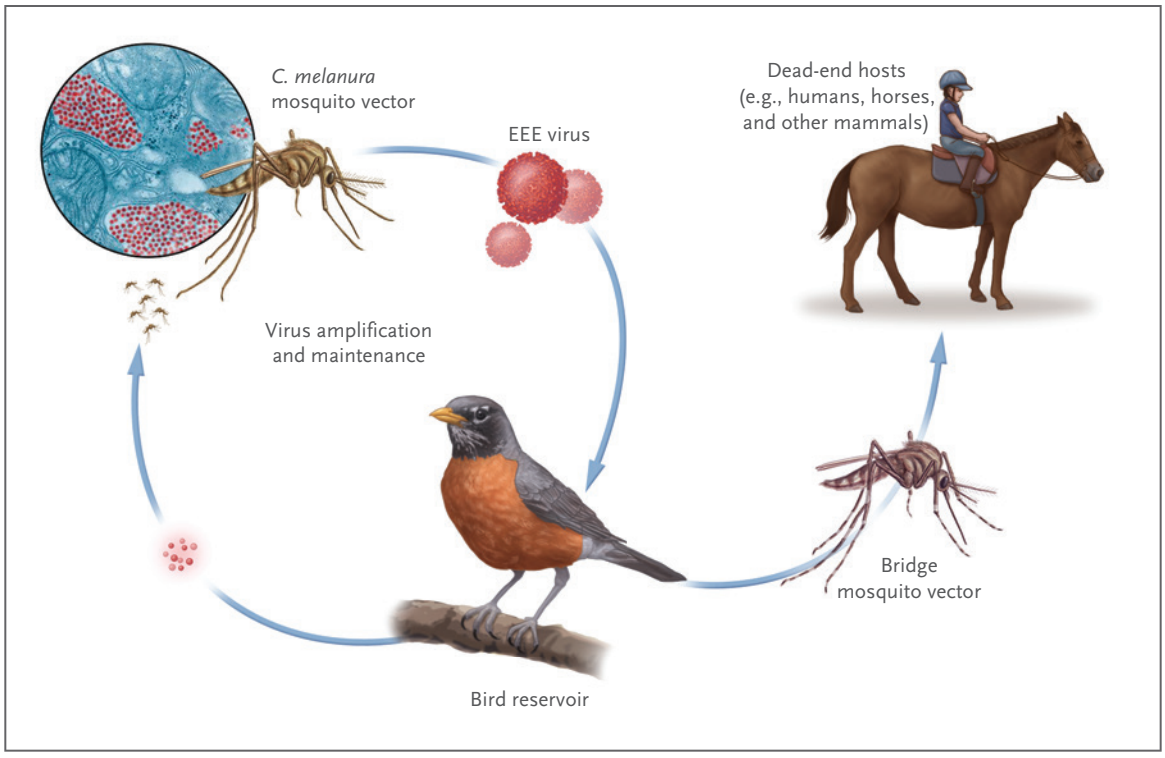
Humans have always lived in intimate association with arthropods that transmit pathogens between humans or from animals to humans. About 700,000 deaths due to vectorborne diseases occur globally each year, according to World Health Organization estimates. In the summer and fall of 2019, nine U.S. states have reported 36 human cases (14 of them fatal) of one of the deadliest of these diseases: eastern equine encephalitis (EEE), an arthropod-borne viral (arboviral) disease transmitted by mosquitoes. In recent years, the Americas have witnessed a steady stream of other emerging or reemerging arboviruses, such as dengue, West Nile, chikungunya, Zika, and Powassan, as well as increasing numbers of travel-related cases of various other arboviral infections. This year's EEE outbreaks may thus be a harbinger of a new era of arboviral emergences.

EEE has probably prevailed for centuries, and 12 U.S. EEE epidemics or epizootics were documented between 1831 and 1959. Most known arboviruses that can infect humans, such as EEE virus (EEEV), circulate generally unnoticed in enzootic reservoirs of arthropods and vertebrate hosts such as birds and mammals.[1] EEEV spreads between *Culiseta melanura* mosquitoes and various passerine (tree-perching) birds found in forested wetlands (see figure). Small mammals, reptiles, or amphibians may also be involved in its environmental circulation.

The virus occasionally spills over from its usual reservoirs to infect dead-end hosts such as humans, equids, swine, pheasants, various game and exotic birds, and gallinaceous poultry. These spillovers occur at unpredictable intervals and are usually mediated by "bridging vectors" (nonenzootic mosquitoes that feed on both birds and mammals) (see figure). EEEV is not transmitted between dead-end hosts such as horses and humans. Determinants of spillover most likely include complex interactions among human behaviors, weather, environmental perturbation, movement of birds, and other variables. EEEV is also a potential bioweapon, since it is transmissible by aerosol. Although it has been found in most of the eastern United States, major persistent enzootic sites are relatively few and geographically focal; they can, however, be the source of seeding of additional EEEV foci.

Many other mosquito-borne or tickborne diseases of mammals and humans occur throughout the United States and globally.



Transmission Cycle of Eastern Equine Encephalitis Virus (EEEV).

Multiple bird and mosquito species and environmental variables are associated with human EEEV infection. There are numerous other arboviruses in the continental United States, including the mosquito-borne alphavirus disease western equine encephalitis, the California group bunyavirus diseases such as La Crosse encephalitis, and the flavivirus diseases St. Louis encephalitis and West Nile, the latter two prevailing over most of the continental United States. Tickborne encephalitis viruses include Powassan (a flavivirus) and Colorado tick fever (an orbivirus). These six viruses also extend northward into Canada, and some are found in Central and South America. In addition, the four *Aedes aegypti*–borne viruses (yellow fever, dengue, chikungunya, and Zika) circulate globally and present ongoing threats, from endemic circulation or importation, to the continental United States and especially to U.S. tropical jurisdictions. Adapted from the U.S. Centers for Disease Control and Prevention.

The types of arthropods and other vectors vary geographically, and complex interactions between humans and the environment may be unique in each situation and location. Variables influencing disease emergence in one Massachusetts EEE focus exemplify the ecologic complexity of arboviruses.[2] After Atlantic white cedar trees were harvested for use in houses and carpentry products and the resulting swamps were drained in the early 1800s, wetland forests were reestablished over the next century; these forests included red maple trees, whose roots — lying just below bird-roosting sites — provide excellent oviposition (egg-laying) sites for *C. melanura* mosquitoes. As passerine birds such as American robins foraged from these trees in burgeoning suburbs, growth and movement of the human population facilitated spillovers of EEEV to humans, leading to cases of encephalitis.

More than 130 human and 50 animal arboviral diseases occur around the world. Most are transmitted by mosquitoes or ticks. Symptomatic human arboviral disease falls into three distinct syndromes: febrile systemic illness (e.g., uncomplicated dengue), hemorrhagic fever (e.g., dengue hemorrhagic fever and yellow fever), and encephalitis (e.g., EEE, Venezuelan equine encephalitis, Japanese encephalitis, and La Crosse encephalitis). Each of these syndromes may be caused by multiple arboviruses from multiple unrelated taxonomic groups. Four of the human-infecting arboviruses — the flaviviruses dengue, yellow fever, and Zika, and the alphavirus chikungunya — have evolved to infect a mosquito that is uniquely anthropophilic (feeding almost exclusively on humans): *Aedes aegypti*. Humans serve not only as the

reservoir for these four viruses, but also as an amplification host that up-regulates viral cycling. Any virus that can efficiently infect *A. aegypti* also has potential access to billions of humans, which explains why the four viruses that have done so have spread pandemically. We cannot discount the possibility that other arboviruses will adapt to *A. aegypti* in the future — a sobering thought, given the high case-fatality rate of diseases such as EEE.

After inoculation of virus-infected mosquito saliva into perivascular dermal tissue, EEEV infects Langerhans and dendritic cells, which migrate to regional lymphoid tissue, where virus replication leads to systemic viremic seeding. After an incubation period of approximately a week (range, 3 to 10 days), EEEV infection presents nonspecifically with fever, malaise, intense headache, muscle aches, and nausea and vomiting — a sign and symptom complex not easily distinguishable from those of most other arboviral infections or from influenza and a host of other diseases.

At the onset of symptoms, specific diagnostic tests may be unrevealing: viral isolation and polymerase-chain-reaction analysis from blood and spinal fluid, as well as testing for EEEV-specific IgM, may be negative. Neurologic signs appearing soon (0 to 5 days) after onset are initially nonspecific and are indistinguishable from those associated with enteroviral meningoencephalitis, which is also prevalent in late summer. However, rapid clinical progression ensues. By the time definitive serologic diagnosis is possible, within a week after infection, neurologic damage may already have occurred. Neuroimaging typically shows involvement of the basal ganglia and thalami.

An estimated 96% of people infected with EEEV remain asymptomatic; however, of those who have symptoms, 33% or more die and most of the rest sustain permanent, often severe, neurologic damage.

Point-of-care differential diagnostics for the many arboviral and nonarboviral causes of encephalitis are currently lacking and would be of limited value without effective treatments. Although antiviral drug screening efforts have been undertaken in vitro and in vivo, no antiviral drug has thus far been demonstrated to have efficacy against EEEV. An important requirement of such a drug, were it available, would be the ability to cross the blood–brain barrier. EEE-specific monoclonal antibodies have been effective in an experimental animal model only when given before infection, and data from experiments with Venezuelan equine encephalitis virus (a related alphavirus) suggest that immunopathogenic mechanisms could be involved. Supportive care, often including admission to an intensive care unit with ventilatory support, is the mainstay of treatment. Patients need not be isolated, since they are not infectious. Given the seriousness of the disease, social support and counseling of the patient and family are critically important.

Several EEEV vaccines are in development; however, there may not be strong incentives to proceed to advanced development and licensure because of the nature of the disease: outbreaks are rare, brief, and focal, and they occur sporadically in unpredictable locations, making it difficult to identify an appropriate target population for vaccination. Such vaccines, however, might have utility for persons at high occupational risk — laboratory workers, for instance — as is the case for an early-generation experimental EEEV vaccine now available under a U.S. Army Investigational New Drug program. Efforts to develop mosquito saliva vaccines that would be effective against multiple mosquito-borne diseases are in early stages.[3] A theoretical advantage of such vaccines is the inclusion of various salivary proteins from selected mosquitoes that transmit multiple arboviruses that infect humans.

In the absence of vaccines or specific treatments, state and local health departments can provide early warning of imminent human infections by surveilling equids, birds, and mosquitoes; however, even these blunt prevention tools are continuously threatened by underfunding of public health efforts. Sadly, the United States' ability to control arboviral diseases is little better in 2019 than it was more than a century ago, when William Crawford Gorgas eliminated *A. aegypti* from Havana and the Panama Canal Zone. Recently, several American public health experts have called for a national defense strategy for arboviruses and other vectorborne diseases,[4] an idea also supported by international experts.[5] We strongly agree. Arbovirus threats are not easily thwarted by piecemeal efforts. Multiple potentially deadly viruses are constantly present in virologically occult enzootic foci throughout the United States and globally. Effects of climate and weather, such as changes in heat and

rainfall and their impact on variables associated with viruses, vectors, and vertebrates, are cause for additional concern, since they may affect the life cycles and geographic distribution of arthropod vectors and viral transmission patterns. Given the near certainty of future emergences, arboviruses constitute a real and present danger. Although EEE is not yet a disease of major national importance, this year's spike in cases exposed our inadequate preparation for emergent disease threats. Though the best way to respond to these threats is not entirely clear, to ignore them completely and do nothing would be irresponsible.

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The Den

Sauarbh Jha, M.B., B.S.

When I recall my house job (internship), I remember fatigue and camaraderie. I also remember the hospital pub. Nestled in the hospital complex, a stone's throw from the main entrance, the pub was unassuming, unmarked, and innominate. I called it "the den."

On first approach, the den could have been mistaken for the ICU, with white coats hung at its entrance as if they were prohibited from entering. Indistinguishable from one another, the coats all held a folded stethoscope in one pocket and the yellow *Oxford Handbook of Clinical Medicine* in the other. If you took someone else's coat by mistake, it scarcely mattered; we were all cut from the same cloth. In a sense, the den *was* an ICU — a site of intensive care for the hospital staff, a place to unload after another intense day of work. It was also a place where ranks were temporarily forgotten and gradients were abolished — it was egalitarianism in practice. We knew each other by name and by our preferred drinks. Mine was vodka and Red Bull.

The den was empty at 5 p.m., but by 7, it was buzzing with doctors, nurses, pharmacists, porters, administrative assistants, technologists, and even hospital managers. In the small, stuffy, utterly undecorated room, clusters of people formed for no particular reason. The den wasn't divided into doctors and nurses or residents and attendings or surgeons and internists. Everyone spoke with everyone. When you joined a group, it was good manners to buy everyone a round of drinks, though this etiquette was waived for radiologists, who, as the most important people in the hospital, never bought drinks.

By all objective indicators, I should have been unhappy in those grueling months I spent as a medical house officer. The town was dreary, even by British standards, and had a limited range of restaurants. I was distant from my friends in London, where I went to medical school, and I found myself suddenly laden with responsibility, working hours I'd never imagined I was capable of working. Like most junior doctors, I lived on the hospital campus in free housing that pushed minimalism to its limits. One of our many hardships was the difficulty of maintaining a comfortable room temperature during the winter nights. The rooms were warmed by centrally controlled radiators that emitted far too much heat; I had to keep my room window open precisely 6 inches — at 8 inches I'd shiver, at 4 I'd sweat.

The den was an escape, a redoubt where we reflected and planned and spoke about our patients — what else, after all, was there to talk about? Education was delivered informally over banter and beer. I learned more medicine in the den than in all the grand rounds I've ever attended.