Sindbis Virus Infection Sindbis virus is transmitted among birds by infected mosquitoes. Infections with northern European or southern African variants are particularly likely in rural environments. After an incubation period of <1 week, Sindbis virus infection begins with rash and arthralgia. Constitutional clinical signs are not marked, and fever is modest or lacking altogether. The rash, which lasts ~1 week, begins on the trunk, spreads to the extremities, and evolves from macules to papules that often vesiculate. The arthritis is multiarticular, migratory, and incapacitating, with resolution of the acute phase in a few days; the ankles, elbows, knees, phalangeal joints, wrists, and—to a much lesser extent—proximal and axial joints are involved. Persistence of joint pain and occasionally of arthritis is a major problem and may continue for months or even years despite lack of deformities.

Zika Virus Infection Zika virus is an emerging pathogen that is transmitted among nonhuman primates and humans by *Aedes* mosquitoes. Human infections are usually benign and are most likely misdiagnosed as dengue or influenza. Zika virus infection is characterized by influenza-like clinical signs, including fever, headaches, and malaise. A maculopapular rash, conjunctivitis, myalgia, and arthralgia usually accompany or follow those manifestations. Zika virus infection was first documented in Africa in 1947 and was later recognized in southeastern and southern Asia. In recent years, the number of Zika virus infections reported from Micronesia and Polynesia has increased steadily.

ENCEPHALITIS

The major encephalitis viruses are found in the families Bunyaviridae, Flaviviridae, Rhabdoviridae, and Togaviridae. However, individual agents of other families, including Dhori virus and thogotovirus (Orthomyxoviridae) as well as Banna virus (Reoviridae), have been known to cause isolated cases of encephalitis as well. Arboviral encephalitides are seasonal diseases, commonly occurring in the warmer months. Their incidence varies markedly with time and place, depending on ecologic factors. The causative viruses differ substantially in terms of case–infection ratio (i.e., the ratio of clinical to subclinical infections), lethality rate, and residual disease. Humans are not important amplifiers of these viruses.

All the viral encephalitides discussed in this section have a similar pathogenesis. An infected arthropod ingests blood from a human and thereby initiates infection. The initial viremia is thought to originate from the lymphoid system. Viremia leads to multifocal entry into the CNS, presumably through infection of olfactory neuroepithelium, with passage through the cribriform plate; "Trojan horse" entry with infected macrophages; or infection of brain capillaries. During the viremic phase, there may be little or no recognizable disease except in tick-borne flavivirus encephalitides, which may manifest with clearly delineated phases of fever and systemic illness.

CNS lesions arise partly from direct neuronal infection and subsequent damage and partly from edema, inflammation, and other indirect effects. The usual pathologic features of arboviral encephalitides are focal necroses of neurons, inflammatory glial nodules, and perivascular lymphoid cuffing. Involved areas display the "luxury perfusion" phenomenon, with normal or increased total blood flow and low oxygen extraction. The typical patient presents with a prodrome of nonspecific constitutional signs and symptoms, including fever, abdominal pain, sore throat, and respiratory signs. Headache, meningeal signs, photophobia, and vomiting follow quickly. The severity of human infection varies from an absence of signs/symptoms to febrile headache, aseptic meningitis, and full-blown encephalitis. The proportions and severity of these manifestations vary with the infecting virus. Involvement of deeper brain structures in less severe cases may be signaled by lethargy, somnolence, and intellectual deficit (as disclosed by the mental status examination). More severely affected patients are obviously disoriented and may become comatose. Tremors, loss of abdominal reflexes, cranial nerve palsies, hemiparesis, monoparesis, difficulty swallowing, limb-girdle syndrome, and frontal lobe signs are all common. Spinal and motor neuron diseases are documented after West Nile and Japanese encephalitis virus infections. Seizures and focal signs may be evident early or may appear during the course of the disease. Some patients present with an abrupt onset of fever, convulsions, and other signs of CNS involvement. The acute encephalitis usually lasts from a few days to as long as 2–3 weeks. The infections may be fatal, or recovery may be slow, with weeks or months required for the return of maximal recoupable function, or incomplete, with persisting long-term deficits. Difficulty concentrating, fatigability, tremors, and personality changes are common during recovery.

The diagnosis of arboviral encephalitides depends on the careful evaluation of a febrile patient with CNS disease and the performance of laboratory studies to determine etiology. Clinicians should (1) consider empirical acyclovir treatment for herpesvirus meningoencephalitis and antibiotic treatment for bacterial meningitis until test results are received; (2) exclude intoxination and metabolic or oncologic causes, including paraneoplastic syndromes, hyperammonemia, liver failure, and anti-NMDA receptor encephalitis; and (3) rule out a brain abscess or a stroke. Leptospirosis, neurosyphilis, Lyme disease, cat-scratch disease, and more recently described viral encephalitides (e.g., Nipah virus infection) should be considered if epidemiologically relevant. CSF examination usually shows a modest increase in leukocyte counts—in the tens or hundreds or perhaps a few thousand. Early in the process, a significant proportion of these leukocytes may be polymorphonuclear, but mononuclear cells are usually predominant later. CSF glucose concentrations are generally normal. There are exceptions to this pattern of findings: in eastern equine encephalitis, for example, polymorphonuclear leukocytes may predominate during the first 72 h of disease and hypoglycorrhachia may be detected. In lymphocytic choriomeningitis/meningoencephalitis, lymphocyte counts may be in the thousands, and the glucose concentration may be diminished. A humoral immune response is usually detectable at or near the onset of disease. Both serum (acute- or convalescent-phase) and CSF should be examined for IgM antibodies and viruses by plaque-reduction neutralization assay and/or (RT)-PCR. Virus generally cannot be isolated from blood or CSF, although Japanese encephalitis virus has been recovered from CSF of patients with severe disease. RT-PCR analysis of CSF may yield positive results. Viral antigen is present in brain tissue, although its distribution may be focal. Electroencephalography usually shows diffuse abnormalities and is not directly helpful.

Experience with medical imaging is still evolving. Both computed tomography (CT) and magnetic resonance imaging (MRI) scans may be normal except for evidence of preexisting conditions or occasional diffuse edema. Imaging is generally nonspecific in that most patients do not present with pathognomonic lesions, but it can be used to rule out other suspected causes of disease. It is important to remember that imaging may yield negative results if done early in the disease course but later may detect lesions. For example, eastern equine encephalitis (focal abnormalities) and severe Japanese encephalitis (hemorrhagic bilateral thalamic lesions) have caused lesions detectable by medical imaging.

Comatose patients may require management of intracranial pressure elevations, inappropriate secretion of antidiuretic hormone, respiratory failure, or seizures. Specific therapies for these viral encephalitides are not available. The only practical preventive measures are vector management and personal protection against the arthropod transmitting the virus. For Japanese encephalitis or tick-borne viral encephalitis, vaccination should be considered in certain circumstances (see relevant sections below).

Bunyaviruses: California (Meningo)encephalitis The isolation of California encephalitis virus established California serogroup orthobunyaviruses as causes of encephalitides. However, California encephalitis virus has been implicated in only a very few cases of encephalitis, whereas its close relative, La Crosse virus, is the major cause of encephalitis in this serogroup (~70 cases per year in the United States). California (meningo)encephalitis due to La Crosse virus infection is most commonly reported from the upper Midwest of the United States but is also found in other areas of the central and eastern parts of the country, most often in West Virginia, Tennessee, North Carolina, and Georgia. The serogroup includes 13 other viruses, some of which (e.g., Inkoo, Jamestown Canyon, Lumbo, snowshoe hare, and Tahyña