majority of cases of acute encephalitis of suspected viral etiology remain of unknown cause. Hundreds of viruses are capable of causing encephalitis, although only a limited subset is responsible for most cases in which a specific cause is identified (Table 164-4). The most commonly identified viruses causing sporadic cases of acute encephalitis in immunocompetent adults are herpesviruses (HSV, VZV, EBV). Epidemics of encephalitis are caused by arboviruses, which belong to several different viral taxonomic groups including *Alphaviruses* (e.g., EEE virus, western equine encephalitis virus), *Flaviviruses* (e.g., WNV, St. Louis encephalitis virus, Japanese encephalitis virus, Powassan virus), and *Bunyaviruses* (e.g., California encephalitis virus serogroup, La Crosse virus). Historically, the largest number of cases of arbovirus encephalitis in the United States has been due to St. Louis encephalitis virus and the California encephalitis virus serogroup. However, since 2002, WNV has been responsible for the majority of arbovirus meningitis and encephalitis cases in the United States. WNV caused 2873 confirmed cases of neuroinvasive disease (encephalitis, meningitis, or myelitis) in 2012 with 286 deaths. States reporting >200 cases included Texas (1868 cases), California (479), Louisiana (335), Illinois (290), Mississippi (249), South Dakota (203), and Michigan (202). In 2013, there were 1140 neuroinvasive cases with 100 deaths. States reporting >100 cases included California (357 cases), Colorado (315), Nebraska (213), Texas (157), South Dakota (148), North Dakota (123), and Illinois (106). It is important to recognize that WNV epidemics are unpredictable and that cases have occurred in every state in the continental United States. New causes of viral CNS infections are constantly appearing, as evidenced by the outbreak of cases of encephalitis in Southeast Asia caused by Nipah virus, a newly identified member of the Paramyxoviridae family; of meningitis in Europe caused by Toscana virus, an arbovirus belonging to the Bunyavirus family; and of neurologic disorders associated with major epidemics of Chikungunya virus, a togavirus, in Africa, India, and Southeast Asia. Parechoviruses including human parechovirus 3 (HPeV3), members of the Picornavirus family, have recently been reported as causes of fever, sepsis, and meningitis in infants (age <3 months) in the United States and abroad.

LABORATORY DIAGNOSIS

CSF Examination CSF examination should be performed in all patients with suspected viral encephalitis unless contraindicated by the presence of severely increased ICP. Ideally at least 20 mL should be collected with 5–10 mL stored frozen for later studies as needed. The characteristic CSF profile is indistinguishable from that of viral meningitis and typically consists of a lymphocytic pleocytosis, a mildly elevated protein concentration, and a normal glucose concentration. A CSF pleocytosis (>5 cells/μL) occurs in >95% of immunocompetent patients with documented viral encephalitis. In rare cases, a pleocytosis may be absent on the initial LP but present on subsequent LPs. Patients who are severely immunocompromised by HIV infection, glucocorticoid or other immunosuppressant drugs, chemotherapy, or lymphoreticular malignancies may fail to mount a CSF inflammatory response. CSF cell counts exceed 500/μL in only about 10% of patients with encephalitis. Infections with certain arboviruses (e.g., EEE virus or California encephalitis virus), mumps, and LCMV may occasionally result in cell counts >1000/μL, but this degree of pleocytosis should suggest the possibility of nonviral infections or other inflammatory processes. Atypical lymphocytes in the CSF may be seen in EBV infection and less commonly with other viruses, including CMV, HSV, and enteroviruses. Increased numbers of plasmacytoid or Mollaret-like large mononuclear cells have been reported in WNV encephalitis. Polymorphonuclear pleocytosis occurs in ~45% of patients with WNV encephalitis and is also a common feature in CMV myeloradiculitis in immunocompromised patients. Large numbers of CSF PMNs may be present in patients with encephalitis due to EEE virus, echovirus 9, and, more rarely, other enteroviruses. However, persisting CSF neutrophilia should prompt consideration of bacterial infection, leptospirosis, amebic infection, and noninfectious processes such as acute hemorrhagic leukoencephalitis. About 20% of patients with encephalitis will have a significant number of red blood cells (>500/μL) in the CSF in a nontraumatic tap. The pathologic correlate of this finding may be a hemorrhagic encephalitis of the type seen with HSV; however, CSF red blood cells occur with similar frequency and in similar numbers in patients with nonherpetic focal encephalitides. A decreased CSF glucose concentration is distinctly unusual in viral encephalitis and should suggest the possibility of bacterial, fungal, tuberculous, parasitic, leptospiral, syphilitic, sarcoid, or neoplastic meningitis. Rare patients with mumps, LCMV, or advanced HSV encephalitis and many patients with CMV myeloradiculitis have low CSF glucose concentrations.

CSF PCR

CSF PCR has become the primary diagnostic test for CNS infections caused by CMV, EBV, HHV-6, and enteroviruses (see "Viral Meningitis," above). In the case of VZV CNS infection, CSF PCR and detection of virus-specific IgM or intrathecal antibody synthesis both provide important aids to diagnosis. The sensitivity and specificity of CSF PCRs vary with the virus being tested. The sensitivity (~96%) and specificity (~99%) of HSV CSF PCR are equivalent to or exceed those of brain biopsy. It is important to recognize that HSV CSF PCR results need to be interpreted after considering the likelihood of disease in the patient being tested, the timing of the test in relationship to onset of symptoms, and the prior use of antiviral therapy. A negative HSV CSF PCR test performed by a qualified laboratory at the appropriate time during illness in a patient with a high likelihood of HSV encephalitis based on clinical and laboratory abnormalities significantly reduces the likelihood of HSV encephalitis but does not exclude it. For example, in a patient with a pretest probability of 35% of having HSV encephalitis, a negative HSV CSF PCR reduces the posttest probability to ~2%, and for a patient with a pretest probability of 60%, a negative test reduces the posttest probability to ~6%. In both situations, a positive test makes the diagnosis almost certain (98–99%). There have been several recent reports of initially negative HSV CSF PCR tests that were obtained early (≤72 h) following symptom onset and that became positive when repeated 1–3 days later. The frequency of positive HSV CSF PCRs in patients with herpes encephalitis also decreases as a function of the duration of illness, with only ~20% of cases remaining positive after ≥14 days. PCR results are generally not affected by ≤1 week of antiviral therapy. In one study, 98% of CSF specimens remained PCR-positive during the first week of initiation of antiviral therapy, but the numbers fell to ~50% by 8–14 days and to ~21% by >15 days after initiation of antiviral therapy.

The sensitivity and specificity of CSF PCR tests for viruses other than HSV have not been definitively characterized. Enteroviral (EV) CSF PCR appears to have a sensitivity and specificity of >95%. EV PCR sensitivity for EV71 may be considerably lower (~30% in some reports). Parechoviruses are also not detected by standard EV RT-PCRs. The specificity of EBV CSF PCR has not been established. Positive EBV CSF PCRs associated with positive tests for other pathogens have been reported and may reflect reactivation of EBV latent in lymphocytes that enter the CNS as a result of an unrelated infectious or inflammatory process. In patients with CNS infection due to VZV, CSF antibody and PCR studies should be considered complementary, because patients may have evidence of intrathecal synthesis of VZV-specific antibodies and negative CSF PCRs. In the case of WNV infection, CSF PCR appears to be less sensitive (~70% sensitivity) than detection of WNV-specific CSF IgM, although PCR testing remains useful in immunocompromised patients who may not mount an effective anti-WNV antibody response.

CSF Culture CSF culture is generally of limited utility in the diagnosis of acute viral encephalitis. Culture may be insensitive (e.g., >95% of patients with HSV encephalitis have negative CSF cultures as do virtually all patients with EBV-associated CNS disease) and often takes too long to significantly affect immediate therapy.

Serologic Studies and Antigen Detection The basic approach to the serodiagnosis of viral encephalitis is identical to that discussed earlier for viral meningitis. Demonstration of WNV IgM antibodies is diagnostic of WNV encephalitis because IgM antibodies do not cross the