Encephalitis is a syndrome characterized by altered mental status and various combinations of acute fever, seizures, neurologic deficits, cerebrospinal fluid (CSF) pleocytosis, and neuroimaging and electroencephalographic (EEG) abnormalities. The syndrome has many causes; the most commonly identified causes are neurotropic viruses. The general principles of diagnosis and treatment of viral encephalitis are presented in this review.

Epidemiologic Features

Each year in the United States, approximately 7 patients are hospitalized for encephalitis per 100,000 population. The cause is unknown in approximately half these cases. Of the cases with a known cause, 20 to 50% are attributed to viruses. Herpes simplex virus (HSV) accounts for 50 to 75% of identified viral cases, with varicella–zoster virus (VZV), enteroviruses, and arboviruses accounting for the majority of the remainder. HSV encephalitis occurs in all age groups and does not have a characteristic seasonal or geographic pattern, whereas arbovirus encephalitis has considerable year-to-year variation in case counts, occurs seasonally, and varies in incidence according to geographic region, reflecting the ecology of arboviral transmission. The characteristics of arboviruses with regional occurrence in the United States are summarized in Table 1.

The estimated median hospitalization charge for a patient with viral encephalitis is $89,600 for West Nile virus encephalitis and $58,000 for HSV encephalitis. There are approximately 6000 hospitalizations for acute viral encephalitis per year in the United States; the total annual cost is approximately $350 million to $540 million, not including the cost of care after discharge, costs for family caregivers, and lost earnings.

Host Factors

The factors that affect susceptibility to encephalitis are poorly understood. Certain viruses, such as La Crosse virus, cause central nervous system disease predominantly in children, and other viruses, such as West Nile virus, tend to cause severe central nervous system disease in the elderly, whereas HSV causes encephalitis in persons at both ends of the age spectrum. Age-related declines in innate and adaptive immunity, including reduced expression of toll-like receptors (TLRs) and retinoic acid–inducible gene 1 (RIG-I)–like receptors, decreased phagocytic function, and reduced natural killer and cytotoxic T-cell activity, may contribute to susceptibility in older persons. Conversely, children may have decreased type I interferon signaling, as compared with adults, a feature that has been linked to susceptibility to La Crosse virus in mice.
### Table 1. Arboviruses That Cause Encephalitis in the United States.*

<table>
<thead>
<tr>
<th>Virus</th>
<th>Region of the U.S.</th>
<th>Reservoir</th>
<th>Vector</th>
<th>Susceptible Group</th>
<th>Mortality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alphaviruses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eastern equine encephalitis virus</td>
<td>East and Gulf Coasts</td>
<td>Birds</td>
<td><em>Culicoides melanura</em>, <em>aedes species</em></td>
<td>Children, elderly persons</td>
<td>50–70</td>
<td>Severe encephalitis</td>
</tr>
<tr>
<td>Western equine encephalitis virus</td>
<td>West, Midwest</td>
<td>Birds, jackrabbits</td>
<td><em>Culex tarsalis</em></td>
<td>Infants, elderly persons</td>
<td>5–10</td>
<td>No cases in the U.S. since 1994</td>
</tr>
<tr>
<td>Venezuelan equine encephalitis</td>
<td>Florida, Texas, and Gulf</td>
<td>Horses, birds, rodents</td>
<td>*Culex species, aedes species, others</td>
<td>Children, elderly persons</td>
<td>10–20</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>virus</td>
<td>Coast</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Flaviviruses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>West Nile virus</td>
<td>All regions</td>
<td>Birds</td>
<td><em>Culex species</em></td>
<td>Elderly persons</td>
<td>10–15</td>
<td>Encephalitis, meningitis, anterior horn-cell paralysis</td>
</tr>
<tr>
<td>St. Louis encephalitis virus</td>
<td>All regions</td>
<td>Birds</td>
<td><em>Culex species</em></td>
<td>Elderly persons</td>
<td>5–25</td>
<td>Encephalitis, meningitis, anterior horn-cell paralysis</td>
</tr>
<tr>
<td>Zika virus</td>
<td>Texas, Florida, Puerto Rico</td>
<td>Humans, nonhuman primates</td>
<td><em>Aedes species</em></td>
<td>Fetus</td>
<td></td>
<td>Congenital Zika microcephaly syndrome, Guillain–Barré syndrome; encephalitis is rare</td>
</tr>
<tr>
<td>Powassan virus</td>
<td>Northeast</td>
<td>Squirrels, mice, small mammals</td>
<td><em>Ixodes species</em></td>
<td></td>
<td>10–15</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Dengue virus</td>
<td>Florida, Texas, Hawaii, and Puerto Rico</td>
<td>Humans, nonhuman primates</td>
<td><em>Aedes aegypti, A. albopictus</em></td>
<td></td>
<td>&lt;1</td>
<td>Guillain–Barré syndrome; encephalitis is rare</td>
</tr>
<tr>
<td><strong>Bunyaviruses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>La Crosse virus</td>
<td>East and Midwest</td>
<td>Squirrels, chipmunks</td>
<td><em>A. albopictus, A. triseriatus</em></td>
<td>Children</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>Jamestown Canyon virus</td>
<td>Various regions</td>
<td>White-tailed deer</td>
<td><em>Aedes species, C. inornata</em></td>
<td>Adults</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>California encephalitis virus</td>
<td>West</td>
<td>Rabbits, rodents</td>
<td><em>A. melanimon, A. dorsalis</em></td>
<td>Children</td>
<td>&lt;1</td>
<td>Rare</td>
</tr>
<tr>
<td>Coltivirus</td>
<td>West</td>
<td>Squirrels, chipmunks, small mammals</td>
<td><em>Dermacentor andersoni</em></td>
<td></td>
<td>&lt;1</td>
<td>Meningitis; encephalitis is rare</td>
</tr>
</tbody>
</table>

* Data are from Tunkel et al.4 and Salimi et al.3
Variations in HLA regions, potentially affecting the efficiency of adaptive immune responses, have been associated with susceptibility to infection with herpesviruses and arboviruses. Other host genetic factors involved in susceptibility to neurotropic viruses have been proposed to be due to polymorphic sets of genes that influence both innate and adaptive immunity. For example, a loss-of-function deletion in chemokine receptor 5 impairs lymphocyte trafficking into the central nervous system, which results in enhanced susceptibility to both tick-borne encephalitis virus and West Nile virus. Mutations or polymorphisms in genes encoding components of innate immune pathways — notably, TLR3 and interferon signaling — have been linked to encephalitis caused by HSV in children, VZV-associated encephalitis, the measles–subacute sclerosing panencephalitis complex, Japanese encephalitis virus, enterovirus 71, and influenza A virus–associated encephalopathy. Genomewide association studies have also linked polymorphisms in interferon signaling with an increased association with HSV–associated encephalopathy. Genomewide association studies have also linked polymorphisms in interferon signaling with an increased association with HSV–associated encephalopathy. 

**Clinical Profiles of Viral Encephalitides**

The history taking in cases of encephalitis should include consideration of the season during which the patient became ill, geographic location, travel and exposure history, contact with animals, health of relatives, contact with sick persons, and known cases of encephalitis in the area. The clinician should inquire about the patient’s occupation, hobbies, recreational activities, diet, sexual practices, drug use, and health status (vaccinations, medical conditions and medications, and possible immunosuppression due to human immunodeficiency virus (HIV), medications, or other factors). The physical and neurologic examinations may provide clues to potential causes and may guide testing. The presence of exanthem or enanthem is helpful in identifying some forms of viral encephalitis but does not have high specificity. Several systems that incorporate these features have been developed to aid in identifying the infecting agent in cases of encephalitis. Initial diagnostic efforts focus on distinguishing viral from autoimmune encephalitis and on differentiating HSV encephalitis from other viral causes. Early reports comparing HSV encephalitis and non-HSV encephalitis noted that they did not differ substantially with respect to clinical features but that HSV encephalitis was characterized by more pronounced CSF pleocytosis and more frequent focal abnormalities on EEG and neuroimaging.

In a review of cases of adult encephalitis that were characterized by abnormalities in the temporal lobes on magnetic resonance imaging (MRI), features favoring HSV over other causes included older age, acute clinical presentation (in 88% of patients with HSV encephalitis vs. 64% of patients with encephalitis from other causes), fever (80% vs. 49%), gastrointestinal symptoms (37% vs. 19%), and lower incidences of ataxia (18% vs. 33%) and rash (2% vs. 15%). Patients with HSV encephalitis were more likely than those with autoimmune encephalitis to be men (50% vs. 14%) and were less likely to have psychosis (5% vs. 20%) or rash (2% vs. 21%). Most neurologic symptoms, including impaired consciousness, confusion, aphasia, hallucinations, and movement disorders, did not differ among the various types of encephalitis. On MRI, findings of hemorrhage, enhancement, and restricted diffusion also did not differ across the types, although patients with non-HSV encephalitis more frequently had bilateral temporal lesions, as well as lesions outside the temporal lobe and the cingulate and insula areas.

Retrospective studies of patients with encephalitis have used clusters of clinical and MRI characteristics to construct “focal” and “generalized” disease profiles (Table 2). Certain viruses tend to cause regional MRI abnormalities and can sometimes be suspected on the basis of these patterns (Fig. 1). Focal profiles comprise signs and symptoms attributable to specific brain regions, and generalized profiles involve diffuse cerebral dysfunction, including diffuse cerebral edema, generalized seizures, and psychosis. This approach can help prioritize diagnostic testing and evaluation for specific viruses or point to nonviral causes.

**Diagnostic Strategies**

Routine virologic testing for acute encephalitis includes polymerase-chain-reaction (PCR) and reverse-transcriptase PCR (RT-PCR) assays of a CSF specimen. PCR is for detection of DNA...
Table 2. Focal and Generalized Profiles of Encephalitis and Their Causes.\textsuperscript{*}

<table>
<thead>
<tr>
<th>Profile</th>
<th>Unknown Cause</th>
<th>Viral Cause</th>
<th>Infectious Nonviral Cause</th>
<th>Noninfectious Cause</th>
<th>Possible Viral Cause</th>
<th>Possible Nonviral Cause</th>
<th>Selected Other Noninfectious Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal (% of total focal syndromes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal lobe (53%)</td>
<td>52</td>
<td>34</td>
<td>10</td>
<td>4</td>
<td>HSV, VZV, enterovirus, EBV, HHV-6, influenza A or B virus</td>
<td>TB, mycoplasma, balamuthia, prion, RMSF, syphilis, fungal infection</td>
<td>Tumor, vasculitis or other vascular cause, autoimmune cause, paraneoplastic syndrome</td>
</tr>
<tr>
<td>Cerebellar (25%)</td>
<td>72</td>
<td>8</td>
<td>7</td>
<td>13</td>
<td>EBV, enterovirus, rotavirus, adenovirus, HCV</td>
<td>Mycoplasma</td>
<td>Paraneoplastic syndrome, autoimmune cause, vascular cause, neoplasm</td>
</tr>
<tr>
<td>Extrapyramidal or movement disorders due to thalamic or basal ganglia lesions (13%)</td>
<td>66</td>
<td>17</td>
<td>6</td>
<td>11</td>
<td>Respiratory viruses, EBV, WNV, enterovirus, HSV, VZV, HHV-6, SSPE</td>
<td>TB, \textit{Streptococcus pneumoniae}, mycoplasma, prion</td>
<td>Autoimmune cause, paraneoplastic syndrome, neoplasm, metabolic or toxic cause, vascular cause</td>
</tr>
<tr>
<td>Hydrocephalus (9%)</td>
<td>25</td>
<td>16</td>
<td>50</td>
<td>9</td>
<td>Enterovirus, parainfluenza virus, adenovirus</td>
<td>TB, fungal infection, bacterial infection</td>
<td>Sinus thrombosis</td>
</tr>
<tr>
<td>Generalized (% of total generalized syndromes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multifocal white-matter lesions (36%)</td>
<td>63</td>
<td>19</td>
<td>12</td>
<td>6</td>
<td>Enterovirus, adenovirus, influenza A virus, WNV, HIV, EBV, VZV, HSV, SSPE, HMPV, rotavirus</td>
<td>\textit{Balamuthia mandrillaris}, bartonella, mycoplasma</td>
<td>MS, NMO, ADEM, CNS lymphoma</td>
</tr>
<tr>
<td>Intractable seizures (19%)</td>
<td>72</td>
<td>15</td>
<td>10</td>
<td>3</td>
<td>Enterovirus, EBV, rotavirus, adenovirus, HSV, HHV-6</td>
<td>Mycoplasma</td>
<td>Metabolic or toxic cause</td>
</tr>
<tr>
<td>New-onset psychosis (15%)</td>
<td>59</td>
<td>16</td>
<td>6</td>
<td>19</td>
<td>HCV, HSV, VZV, rotavirus, rabies virus, influenza A virus</td>
<td>Bartonella, prion</td>
<td>Psychiatric cause, autoimmune cause, SLE</td>
</tr>
<tr>
<td>Diffuse cerebral edema (14%)</td>
<td>68</td>
<td>21</td>
<td>11</td>
<td>0</td>
<td>Influenza A or B virus, VZV, enterovirus, HSV, HMPV</td>
<td>Mycoplasma</td>
<td></td>
</tr>
<tr>
<td>Recurrent or chronic inflammatory CNS disease (9%)</td>
<td>55</td>
<td>7</td>
<td>10</td>
<td>28</td>
<td>EBV, enterovirus, adenovirus, influenza A or B virus</td>
<td>Mycoplasma</td>
<td>MS, vasculitis, autoimmune cause</td>
</tr>
<tr>
<td>Seizures with rapid recovery (7%)</td>
<td>36</td>
<td>28</td>
<td>32</td>
<td>4</td>
<td>EBV, enterovirus, adenovirus, influenza A or B virus</td>
<td>Bartonella, mycoplasma</td>
<td>Metabolic or toxic cause, epilepsy</td>
</tr>
</tbody>
</table>

\textsuperscript{*} Data are from Chow et al.,\textsuperscript{23} Glaser et al.,\textsuperscript{24} and Beattie et al.\textsuperscript{25} Focal profiles comprise signs and symptoms attributable to specific brain regions, and generalized profiles involve diffuse cerebral dysfunction, including diffuse cerebral edema, generalized seizures, and psychosis. ADEM denotes acute disseminated encephalomyelitis, CNS central nervous system, EBV Epstein–Barr virus, HCV hepatitis C virus, HHV human herpesvirus, HSV herpes simplex virus, HIV human immunodeficiency virus, HMPV human metapneumovirus, MS multiple sclerosis, NMO neuromyelitis optica, RMSF Rocky Mountain spotted fever, SLE systemic lupus erythematosus, SSPE subacute sclerosing panencephalitis (measles), TB tuberculosis, VZV varicella–zoster virus, and WNV West Nile virus.
viruses, and RT-PCR for detection of RNA viruses. Initial testing in immunocompetent hosts includes PCR and RT-PCR tests on CSF for HSV-1, HSV-2, VZV, enteroviruses, and in children younger than 3 years of age, human parechoviruses. If these initial tests (tier 1 tests) fail to establish a diagnosis, additional testing (tier 2 and 3 tests) can be undertaken (Table 3). Tier 2 tests often include CSF PCR tests for cytomegalovirus (CMV), human herpesviruses 6 and 7 (HHV-6 and HHV-7), Epstein–Barr virus (EBV), and HIV. These tier 2 tests are typically part of the initial evaluation in immunocompromised patients. Serologic tests, including tests of serum specimens obtained during the acute and convalescent phases of illness and CSF specimens, are also essential parts of the diagnostic evaluation for arboviruses, with the specific viruses tested for determined by factors such as geographic region, season, and exposure history. Serologic testing of CSF IgM may help diagnose encephalitis due to arboviruses, VZV, EBV, measles virus, mumps virus, rubella virus, rabies virus, or other causes. Viral PCR or RT-PCR of specimens from the throat and nasopharynx may help establish a diagnosis of adenoviral infection, influenza, or measles; testing of saliva may help diagnose mumps or rabies; and testing of stool specimens may help diagnose enteroviral infections. Diagnosis of rabies involves serologic testing of CSF and serum specimens, RT-PCR testing of CSF and salivary specimens, and electron-microscopic and immunohistochemical examination of a full-thickness, hair-follicle-containing skin-biopsy specimen from the back of the neck.

Most available viral diagnostic methods test for a single organism and are ordered individually from diagnostic laboratories. It is possible to perform a comprehensive analysis of a large panel of antiviral antibodies against all known human viruses, known as systemic viral epitope scanning, although this procedure is not yet commercially available.26 Simpler and less sophisticated multiplex diagnostic panels are entering clinical practice. For example, the Food and Drug Administration has approved a multiplex diagnostic panel that allows for rapid PCR-based detection of multiple pathogens associated with meningitis and encephalitis in CSF specimens, including seven viruses (HSV-1, HSV-2, VZV, enterovirus, CMV, HHV-6, and human parechovirus). Arboviruses are not included in the panel, despite their clinical importance. Available multiplex assays have an overall sensitivity of 86 to 100% and a specificity of more than 99.5%.27 However, additional studies in broad populations and various settings are needed to confirm their sensitivity and specificity.

Next-generation sequencing (tier 3 tests) to identify pathogens in CSF or brain tissue28,29 has recently become commercially available. This is an unbiased technique, in which nucleic acid from the host, or from any pathogen that is present, is extracted from CSF or brain tissue, purified, and sequenced. DNA libraries are prepared from the purified DNA and from RNA converted to complementary DNA and are subjected to next-generation sequencing. Computa-
### Table 3. Initial and Subsequent Virologic Evaluation for Encephalitis According to Immune Status.*

<table>
<thead>
<tr>
<th>Tier</th>
<th>Virologic Testing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CSF Serologic Tests</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serum Serologic Tests</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunocompetent patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tier 1 (initial testing)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSV-1, HSV-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VZV</td>
<td>VZV IgM</td>
<td></td>
</tr>
<tr>
<td>Enterovirus</td>
<td></td>
<td>Nasopharyngeal and stool RT-PCR for enterovirus</td>
</tr>
<tr>
<td>HPeV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>WNV, arbovirus IgM</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>WNV, arbovirus IgG, IgM</td>
<td></td>
</tr>
<tr>
<td>Tier 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>HIV</td>
<td>HIV viral load</td>
</tr>
<tr>
<td>Adenovirus</td>
<td></td>
<td>Nasopharyngeal PCR for adenovirus</td>
</tr>
<tr>
<td>EBV</td>
<td>EBV</td>
<td></td>
</tr>
<tr>
<td>Measles virus</td>
<td>Measles virus</td>
<td>Measles virus</td>
</tr>
<tr>
<td>—</td>
<td>—</td>
<td>Nasopharyngeal and urine RT-PCR for measles virus</td>
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<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Mumps virus</td>
<td>Mumps virus</td>
<td>Mumps virus</td>
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<tr>
<td>—</td>
<td>—</td>
<td>Salivary PCR for mumps virus</td>
</tr>
<tr>
<td>—</td>
<td>—</td>
<td>In unvaccinated patients</td>
</tr>
<tr>
<td>—</td>
<td>—</td>
<td>In children</td>
</tr>
<tr>
<td>HHV-6, HHV-7</td>
<td>HHV-6, HHV-7</td>
<td></td>
</tr>
<tr>
<td>B19</td>
<td>B19</td>
<td></td>
</tr>
<tr>
<td>Tier 3</td>
<td></td>
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</tr>
<tr>
<td>—</td>
<td>—</td>
<td>NGS</td>
</tr>
<tr>
<td>Immunocompromised patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tier 1 (in addition to tier 1 above)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td></td>
<td>Serum CMV viral load</td>
</tr>
<tr>
<td>HHV-6, HHV-7</td>
<td>HHV-6, HHV-7</td>
<td></td>
</tr>
<tr>
<td>JC virus</td>
<td>JC virus</td>
<td></td>
</tr>
<tr>
<td>LCMV</td>
<td>LCMV</td>
<td>LCMV</td>
</tr>
<tr>
<td>WNV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tier 2 (in addition to tier 2 above)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>—</td>
<td>NGS</td>
</tr>
</tbody>
</table>

* Data are from Venkatesan et al.,1 Tunkel et al.,4 Steiner et al.,20 and Solomon et al.21 B19 denotes parvovirus B19, CMV cytomegalovirus, CSF cerebrospinal fluid, HPeV human parechovirus, LCMV lymphocytic choriomeningitis virus, NGS next-generation sequencing, PCR polymerase chain reaction, and RT reverse transcriptase.

† For arbovirus testing in the United States, Eastern equine, La Crosse, Powassan, St. Louis, and West Nile viruses should be considered, with tests for other viruses added according to the patient’s exposure and travel history or known epidemics or regional cases.
tional techniques are used to filter out redundant sequences and assemble overlapping sequences. With the use of bioinformatic approaches, the millions of reads obtained are compared with those in reference databases to filter out host sequences and identify potential pathogen sequences. In clinical specimens such as CSF and brain tissue, only a tiny fraction (<1%) of sequence reads map to pathogens, since most are of host origin. The promise of next-generation sequencing has been demonstrated by pathogen identification in otherwise undiagnosed cases of encephalitis due to leptospira, Cache Valley virus, astrovirus, variegated squirrel bornavirus, parvovirus 4, St. Louis encephalitis virus, Powassan virus, and hepatitis E virus, as well as other infectious causes. Next-generation sequencing also identifies nucleic acid contaminants from specimen-collection procedures (e.g., skin flora), in collection tubes, or in nucleic acid purification columns or other assay components, requiring knowledge of laboratory-specific contaminants that appear in many specimens and careful interpretation of results. Understanding the sensitivity and specificity of next-generation sequencing, the effect on outcomes, and situations in which it could replace conventional diagnostic testing requires additional studies involving unselected populations with suspected viral encephalitis and other neuroinfectious diseases.

It would be useful to determine whether there are genetic or protein biomarkers in CSF that are specific for infectious encephalitis. One such approach is to examine CSF with the use of multiplex techniques that allow simultaneous detection of cytokines and chemokines. However, most studies suggest that proinflammatory cytokine and chemokine levels are elevated in patients with encephalitis, regardless of the cause, and no unique cytokine signature differentiates viral from nonviral encephalitis.

TREATMENT AND PREVENTION

APPROACHES TO TREATMENT

Patients with encephalitis often require intensive monitoring and supportive care to ensure oxygenation, airway protection, circulatory support, and treatment of pyrexia, cardiac arrhythmias, and autonomic instability. Monitoring and therapy are also required for the direct effects of cerebral inflammation — mainly, cerebral edema, increased intracranial pressure, and focal or generalized seizures.

There are several guidelines for empirical and specific antiviral treatment of patients with encephalitis. However, few currently available treatments have been subjects of randomized, controlled clinical trials. For example, in the Infectious Diseases Society of America (IDSA) guidelines, only the use of acyclovir for the treatment of HSV encephalitis is ranked as having an A-level strength of recommendation (good evidence to support a recommendation for use) and an I-level quality of evidence (evidence from one or more randomized, controlled trials). Recommendations from other organizations are similar. Another IDSA A-level recommendation is to start empirical acyclovir therapy in all patients with suspected encephalitis. British guidelines also recommend empirical acyclovir therapy but, like the IDSA guidelines, acknowledge that this recommendation is based on evidence of lower quality than data from randomized, controlled trials. IDSA guidelines provide A-level recommendations for reversal of immunosuppression in patients with JC virus infection and initiation of highly active antiretroviral therapy in HIV-infected persons, again noting that the evidence is of lower quality than evidence derived from randomized, controlled trials. Two sets of guidelines suggest ganciclovir or foscarnet for encephalitis related to CMV and HHV-6 and acyclovir for VZV-related encephalitis, but these recommendations are based on moderate levels of evidence derived from expert opinions and descriptive studies; another set of guidelines makes no specific treatment recommendation for CMV, HHV-6, and VZV-related encephalitis because of the poor quality of available evidence.

Initial trials of acyclovir in adults with HSV encephalitis used a regimen of 10 days of intravenous therapy (10 mg per kilogram of body weight every 8 hours for patients with normal renal function), although concern about the risk of relapse led to an increase in the recommended duration of treatment, from 10 days to 14 to 21 days. Neither a higher dose of acyclovir (15 mg per kilogram every 8 hours) in adults nor long-term therapy with valacyclovir (2 mg three times daily for 90 days) improves outcomes in adults. In children (3 months to 12 years of age) with HSV encephalitis, a higher
dose of acyclovir (20 mg per kilogram every 8 hours for 21 days) has been recommended, since this results in better outcomes and fewer relapses than lower doses.35

Immunomodulatory agents have been used in the treatment of encephalitis as either an adjunct to antiviral drugs or as monotherapy when no effective antimicrobial agents are available. Perhaps the most widely used agents are glucocorticoids, which are of uncertain benefit.36,37 In the IDSA guidelines, adjunctive glucocorticoids are listed as having poor-quality evidence to support a recommendation for use in patients with encephalitis due to HSV, EBV, or VZV.4 Clearer information on the potential role of glucocorticoids in the treatment of encephalitis may come from the results of a randomized trial testing dexamethasone (10 mg given intravenously every 6 hours for 4 days) as compared with no intervention, which is scheduled to begin this year (ClinicalTrials.gov number, NCT03084783). In a randomized, controlled trial, oral minocycline, which can inhibit inflammation in the nervous system, did not significantly reduce mortality or improve outcomes in patients with encephalitis38; however, a larger study may be warranted, since there was a trend toward better outcomes in some subgroups.

Anecdotal reports and uncontrolled trials have suggested a possible benefit of interferon alfa treatment in arbovirus infections caused by West Nile virus or St. Louis encephalitis virus, but a placebo-controlled, randomized trial involving patients with Japanese encephalitis showed no effect of interferon alfa on outcomes.39 Intravenous immune globulin also did not have an effect on outcomes in a randomized, double-blind, placebo-controlled trial involving patients with Japanese encephalitis,40 nor did intravenous immune globulin containing high titers of virus-specific antibody alter outcomes in patients with West Nile virus encephalitis.41 A multicenter randomized trial of intravenous immune globulin in children with acute encephalitis has been initiated (NCT02308982). Another immunotherapeutic approach that has shown promise in early-stage clinical trials involves the adoptive transfer of histocompatible, virus-specific T cells to immunosuppressed persons with adenovirus, CMV, EBV, or JC virus infection, including those with progressive multifocal leukoencephalopathy.42,43

**APPROACHES TO PREVENTION**

The absence of treatments of proven efficacy for most neurotropic viral infections has led to a renewed emphasis on prevention.44 Effective vaccines are now available for many neurotropic viruses, including poliovirus, rabies virus, measles virus, mumps virus, rubella virus, influenza viruses, VZV, and several neurotropic flaviviruses, such as Japanese encephalitis virus and tickborne encephalitis virus. Candidate vaccines for several additional flaviviruses, including West Nile virus, dengue virus, and Zika virus, are being tested in clinical trials or, in the case of West Nile virus, are licensed for equine use. Several examples of the efficacy of newer vaccines in reducing cases of human encephalitis have been reported. A study of the effect of a 5-year vaccination campaign in Nepal for the prevention of Japanese encephalitis virus showed that cases of disease were reduced by 78%.45 A universal program of varicella virus vaccination for 1-year-old children in Germany in 2004 resulted in an estimated 60% decrease in varicella-associated neurologic complications.46 In the United States, rotavirus vaccination, recommended for infants by the Advisory Committee on Immunization Practices in 2006, has resulted in rates of seizure-associated hospitalizations of infected children younger than 5 years of age that are 4% lower overall and in some settings 16% lower than the rates in the period before vaccine licensure.47

**OUTCOMES**

The outcomes of acute viral encephalitis remain generally poor. Predictors of a poor outcome include the presence of an immunocompromised state, a Glasgow Coma Scale score of 8 or less (on a scale from 3 to 15, with lower scores indicating greater neurologic deficits), the need for admission to an intensive care unit, and an age of more than 65 years.48 In HSV encephalitis, the outcome of which has been more extensively studied than that of other viral encephalitides, factors negatively affecting the outcome 6 to 12 months after hospital discharge, in approximate order of importance, are coma, restricted diffusion on MRI, more than a 24-hour delay in the initiation of acyclovir therapy after admission, and older age. Other MRI or EEG features and CSF test results have not been predictive of out-
comes. Prognostic factors in arbovirus encephalitis have been identified with less certainty, but in West Nile virus disease, older age, membership in certain ethnic groups, female sex, and coma at presentation have been indicators of a poor prognosis. In Japanese encephalitis, rapid deterioration initially and midbrain involvement have predicted a poor recovery.51

Despite evidence that early initiation of acyclovir therapy improves outcomes in HSV encephalitis, delays in initiation of treatment are commonly reported. In a series from Canada, the mean time to initiation of acyclovir therapy was 21 hours for all patients with suspected HSV encephalitis and 11 hours (range, 3 to 118) for those subsequently confirmed to have HSV.54 In a study in the United States, only 29% of patients with suspected encephalitis received acyclovir in the emergency department.55 A European multicenter study showed that only 45% of patients with HSV encephalitis were treated within 48 hours after the onset of symptoms.50 Factors contributing to delays in drug administration included waiting for brain imaging, an absence of marked CSF pleocytosis, and the presence of confounding factors such as severe underlying disease and alcohol abuse.53 The initial dose of acyclovir has reportedly been incorrect in up to 75% of children56 and 24% of adults57 treated empirically for suspected viral encephalitis.

**Conclusions**

Viral encephalitis is a major cause of illness and death and imposes a heavy economic burden. Diagnostic strategies and technologies are being developed to allow identification of an expanding list of pathogens and to differentiate viral encephalitis from its mimics. Treatment remains largely empirical and, with the exception of acyclovir for HSV encephalitis, is not supported by high-quality evidence from clinical trials. New therapies to prevent infection and inhibit viral replication are needed.

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