Viral Encephalitis in the ICU

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BACKGROUND

Several viruses may infect the central nervous system (CNS) and cause inflammation of the meninges and brain parenchyma. The term “aseptic meningitis” is used when there is clinical evidence of meningeal irritation, including a characteristic headache or nuchal rigidity, in combination with an elevated cerebrospinal fluid (CSF) white blood cell (WBC) count, occurring in the absence of bacterial growth. The term “encephalitis” is used when there are features of cerebral dysfunction, which may include an altered level of consciousness or focal neurologic deficits, such as hemiparesis, aphasia, hemispatial neglect, or movement disorders. Seizures can occur with both meningitis and encephalitis, but are far more common and difficult to treat with encephalitis. Coma occurs in a subgroup of patients and is the main reason patients may require mechanical ventilation and admission to an intensive care unit (ICU). In recognition of the fact that meningitis and encephalitis frequently coexist in individual patients, the term “meningoencephalitis” is sometimes used.1,2

Because isolated aseptic meningitis is rarely life-threatening, this review focuses primarily on encephalitis. In recent years, there has been increasing recognition of various
noninfectious, usually autoimmune, forms of encephalitis. In addition, systemic viral infections may precede the development of postinfectious encephalitis, which is largely due to the effects of the host immune response rather than the virus itself.

A clinical case definition for encephalitis was recently proposed by a group in the United Kingdom. To be diagnosed, a patient should have evidence of “encephalopathy” (altered level of consciousness persisting for more than 24 hours) and at least 2 of the following criteria: fever or history of fever; seizures and/or focal neurologic deficits; CSF pleocytosis; electroencephalogram characteristics consistent with encephalitis; or neuroimaging abnormalities consistent with encephalitis.3

**EPIDEMIOLOGY**

The reported incidence of encephalitis varies widely across studies and geographic regions. In the absence of an outbreak, the annual incidence is estimated to be in the range of 3.5 to 7.5 cases per 100,000 persons. Although viral encephalitis affects all age groups, the overall incidence is significantly higher in children.4–7

In many patients thought to have encephalitis, no specific pathogen or cause can be detected. With advances in molecular techniques, especially the use of polymerase chain reaction (PCR), the relative proportion of idiopathic cases may be decreasing. Still, even with systematic testing for known infectious and noninfectious causes, a specific cause is found in less than half of the cases. It is likely that emerging infections and still unrecognized immune-mediated encephalitis are responsible for many of these cases.8

There are dozens of viruses and bacteria that may cause encephalitis (Table 1), including some pathogens that occur worldwide and others that are clustered in certain regions.4

*Herpes Simplex Virus*

In recent multicenter studies performed in Europe, North America, Australia, and New Zealand, the most common pathogen to be implicated continues to be herpes simplex virus (HSV), consistently accounting for more than 40% to 50% of cases where a cause is determined, and 10% to 20% overall.9–14 HSV-1 accounts for most cases; HSV-2 is a frequent cause of aseptic meningitis, but not encephalitis. A large proportion of the population has previously been exposed to HSV, as reflected by an 80% to 90% rate of seropositivity.15 A nationwide study from Sweden revealed an annual incidence of HSV encephalitis of 2.2 cases per million persons.16 HSV occurs across all age categories and the incidence does not differ based on gender.15–17

*Varicella-Zoster Virus and Other Herpes Viruses*

Varicella zoster virus (VZV) is now recognized as the most common cause of encephalitis among immunocompromised patients, occurring as a complication of human immunodeficiency virus (HIV)/AIDS, hematopoietic stem cell transplantation, and the use of corticosteroids or other immunosuppressive drugs.18–21 However, it also develops in the immunocompetent and is the second most common viral cause of sporadic encephalitis not occurring during an outbreak.7–15 Encephalitis may develop with acute varicella (chickenpox; primarily in children) or during herpes zoster infections (shingles). It is one of numerous neurologic conditions that may complicate VZV infections; others include myelitis, polyradiculo-neuropathy, and postherpetic neuralgia.

Other herpes viruses account for only a small proportion of cases. CMV encephalitis is almost exclusively a disease of immunosuppressed patients.22 In contrast, Epstein-Barr virus (EBV) and human herpesvirus (HHV)-6 may cause encephalitis in both immunocompetent and immunosuppressed patients and can sometimes also trigger
postinfectious encephalitis.\textsuperscript{23–25} HHV-6 may be an underdiagnosed cause of encephalitis, accounting for some of the patients in whom no pathogen is identified.\textsuperscript{26,27} HHV-6 has also been isolated from surgical specimens of patients with mesial temporal lobe epilepsy, suggesting that it may have a pathogenic role in some cases of “idiopathic” epilepsy.\textsuperscript{28} Both EBV and HHV-6 can reactivate in the context of immunosuppression, especially among patients undergoing hematopoietic stem cell transplantation.\textsuperscript{29}

**Enterovirus**

Enteroviruses are the most common cause of aseptic meningitis, but may also occasionally cause encephalitis. As a group, enteroviruses (coxsackievirus A and B,
echovirus, and enterovirus) are collectively the third most common cause of sporadic viral encephalitis, with most cases occurring in children. Enterovirus 71 is a particularly virulent strain that has produced major outbreaks in Southeast Asia. This strain is associated with a high rate of cardiopulmonary complications and death.

Arboviruses

Arboviruses, which are transmitted by insects or ticks, are the most common pathogens to cause encephalitis that is restricted to certain geographic regions. Several of these pathogens are genetically related and belong to the Flavivirus genus, including Japanese (JEV), West Nile (WNV), tick-borne (TBEV), Murray Valley (MVEV), and St. Louis (SLEV) encephalitis viruses. Each pathogen is “zoonotic,” in that it is primarily transmitted among animals, which serve to “amplify” the virus, but can also infect humans. Most flaviviruses are transmitted by mosquitoes (Culex sp.), principally among birds. Thus, in less temperate climates like North America, encephalitis occurs only during certain times of the year. TBEV is transmitted by hard ticks (Ixodes sp.), primarily among small rodents. Other flaviviruses, such as dengue or yellow fever, may cause significant systemic illness, but almost never encephalitis.

JEV is prevalent in China and Southeast Asia, where it is spread by mosquitoes. It is primarily a pediatric condition and is numerically the most common global cause of encephalitis. Almost the entire population in some regions becomes exposed to JEV during childhood. Infections generally do not recur after natural immunity has been acquired, but JEV is a potential cause of encephalitis in travelers to these regions. Modest reductions in JEV incidence have been observed in countries that have introduced vaccination programs.

WNV is prevalent in Africa, the Middle East, and southeastern Europe. Beginning in 1999, it spread rapidly across North America from east to west, with epidemics occurring especially in the summers of 2002 and 2003. During the winter, the virus resides in hibernating female mosquitoes, as well as some birds. In the spring, a mosquito–bird–mosquito amplification cycle begins, which continues until autumn. Most of the population remains asymptomatic when infected with WNV. About 1 in 5 infected persons develop “West Nile fever,” characterized by the presence of systemic symptoms, but no neurologic manifestations. West Nile fever is, in turn, estimated to be greater than 100-fold more common than neuroinvasive disease. Encephalitis is more frequent in the elderly and immunosuppressed. WNV accounted for more than 80% of human arbovirus infections reported to the Centers for Disease Control and Prevention in 2011. Transmission has also been reported to occur vertically (mother to fetus) and via blood transfusions and organ transplants. The risk of neuroinvasive disease seems to be much higher when WNV is transmitted in this fashion. Nucleic acid amplification testing is now used routinely to screen the blood supply and potential organ donors.

TBEV is endemic to much of Europe, Russia, and northern Asia. Transmission occurs via the saliva of infected ticks. Cases generally occur between spring and late autumn, with a peak incidence in midsummer. TBEV has also been reported to be transmitted by oral consumption of milk products from infected animals such as goats. As with other arboviruses, most infections are asymptomatic. Similar tick-borne viruses that may cause encephalitis in northern US states and Canada include Powassan virus encephalitis and the closely related deer tick virus. The highest rates in recent years have been reported in Minnesota, North Dakota, and Wisconsin.

MVEV and SLEV have similar characteristics to JEV and WNV. MVEV is endemic to northern Australia and Papua New Guinea, with occasional outbreaks in southeastern Australia. An increment in the usual number of animal and human cases was reported.
in 2011 following regional flooding and an uncommonly large burden of mosquitoes.\textsuperscript{46}

There have been occasional outbreaks of SLEV in the United States every 3 to 10 years, with the largest occurring in 1975. There is evidence that WNV is displacing SLEV in some regions of North America.\textsuperscript{47} Apart from WNV, by far the next most common arbovirus to cause neuroinvasive disease in the United States is La Crosse virus. The highest rates are reported in West Virginia, with most occurring in children.\textsuperscript{48}

**Influenza**

Encephalitis is a very uncommon complication of seasonal influenza infections. However, because influenza itself is common, intensivists may encounter neurologic complications, especially during outbreaks. In one case series involving 571 hospitalized patients with influenza A, 21 were found to develop significant neurologic sequelae.\textsuperscript{49} The nonspecific term “influenza-associated acute encephalopathy/encephalitis” (IAE) is used in the literature in recognition of the uncertain pathogenesis of the neurologic manifestations, which may not involve direct viral invasion of the CNS.\textsuperscript{50} Using highly sensitive PCR assays, some investigators have been able to detect influenza RNA in the CSF.\textsuperscript{51} However, in most cases, features of IAE are more likely to be attributable to the host immune response. Neurologic complications were more common and severe than usual during the 2009 influenza A (H1N1) pandemic.\textsuperscript{52} Studies in various parts of the world reported that neurologic complications (not necessarily IAE) developed in 4% to 19% of patients with severe or fatal H1N1.\textsuperscript{53–56}

**Other Pathogens**

Unvaccinated persons are vulnerable to mumps, measles, and rubella, all of which may rarely cause encephalitis. Acute HIV seroconversion is associated with a mononucleosis-like syndrome, which may in turn be accompanied by aseptic meningitis and an encephalopathy, which is usually self-limited.\textsuperscript{57} Rabies, transmitted by the bite of an infected animal, remains a significant problem in some parts of the world. Progressive multifocal leukoencephalopathy attributable to John Cunningham (JC) virus is an important consideration in patients with impaired cell-mediated immunity, especially those with advanced HIV infection or use of certain drugs, such as natalizumab, which is used to treat multiple sclerosis.\textsuperscript{58} Intensivists must be particularly aware that certain bacterial or fungal pathogens may produce clinical manifestations consistent with encephalitis. In fact, in recent cohort studies using typical case definitions for encephalitis, *Mycobacterium tuberculosis* and *Listeria monocytogenes* were among the most common organisms.\textsuperscript{13,14} If the clinical suspicion justifies the possibility of these pathogens, empiric therapy should be implemented until the results of diagnostic testing become available.

**Postinfectious Encephalitis**

Most pathogens discussed above have (rarely) been associated with the development of postinfectious encephalitis. The most common pattern of CNS involvement is acute disseminated encephalomyelitis (ADEM). ADEM is defined as an inflammatory demyelinating condition that occurs within days to as much as 3 to 4 weeks after a viral infection. Idiopathic cases also occur, and ADEM has very rarely been linked with certain vaccinations. Although ADEM is mainly a pediatric condition, it also occurs in adults, most often younger than 50 years of age. Unlike other demyelinating conditions, especially multiple sclerosis, ADEM is a “monophasic” disorder.\textsuperscript{59–61} Variants of ADEM have been described: acute hemorrhagic leukencephalitis (AHLE) is a more hyperacute and fulminant subtype than ADEM, with evidence of hemorrhage and a greater degree of cerebral edema; Bickerstaff’s encephalitis is characterized by
prominent brainstem involvement; these patients sometimes have anti-GQ1b antibodies that also occur in patients with Guillain-Barre syndrome.59,62

Noninfectious Encephalitis

A detailed discussion of autoimmune and paraneoplastic encephalitis is beyond the scope of this review. However, clinicians should be aware that these conditions are just as or more common than most infectious causes of encephalitis and may have a very similar presentation.10 Thus, earlier diagnostic testing and consideration of empiric immunomodulatory therapy is appropriate once an infectious pathogen has been excluded. The most common of these syndromes is anti-NMDA receptor encephalitis, which accounts for 4% of all encephalitis in the United Kingdom.13,63,64 It is more frequent in women and is associated with a tumor in more than half of cases, most often ovarian teratomas. It usually occurs in young adults, with a median age of 21 years. The next most common subtype is anti-LGI1 limbic encephalitis, previously thought to involve voltage-gated potassium channels.65 Intensivists may also encounter paraneoplastic encephalitis, especially when it affects the hippocampus (limbic encephalitis; a frequent cause of seizures) and the brainstem (rhombencephalitis). A variety of tumors (breast, lung, testicular, ovary, neuroendocrine) can produce the related antibodies.65

CLINICAL MANIFESTATIONS

The predominant reasons patients with encephalitis sometimes require admission to an ICU include the following: (1) stupor or coma, with resultant impairment in patients’ airway protective capabilities; (2) seizures, which may impair consciousness and necessitate the use of sedating medications; and (3) respiratory failure, which may be a consequence of the aspiration of gastrointestinal contents or may develop because of neuromuscular weakness and increasing atelectasis due to poliomyelitis-like paralysis.66

Stupor and Coma

Although essentially all patients with encephalitis have an altered level of consciousness, only about 10% to 25% develop coma (Table 2). For coma to occur there must be a bihemispheric process or, if there is focal involvement, there must be disruption of the ascending reticular activating system (RAS).67 Encephalitis may sometimes affect the brain in a diffuse fashion. In addition, there may be the development of global cerebral edema, which in turn raises intracranial pressure (ICP) and interferes with cerebral perfusion.68 Some pathogens may selectively target the brainstem and diencephalon, thereby interfering with the normal functions of the RAS (Fig. 1). If encephalitis localizes to the cerebral cortex, then increasing edema may cause midline shift or downward herniation, which may in turn distort or compress the RAS, which may be especially common with temporal lobe involvement (Fig. 2).

Seizures and Status Epilepticus

The proportion of patients with encephalitis that develops seizures varies greatly, ranging from about 10% among those with WNV to as high as 85% with JEV or MVEV (see Table 2).69 Of more than 1000 consecutive patients in the California Encephalitis Project, 44% had seizures. Refractory status epilepticus (SE), with the need to use deeply sedating drugs, is more common with encephalitis than with other neurologic conditions and is associated with a relatively high rate of mortality and disability among survivors.70,71 Even among patients who do not have overt seizures,
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Abbreviations: +, <25%; ++, 25%–50%; ++++, 50%–75%; ++++, >75%; EV, enterovirus; PMNs, polymorphonuclear cells.
Fig. 1. CT scan of a 19-year-old patient who acquired Murray Valley encephalitis while traveling in Australia and New Zealand. Her level of consciousness declined quickly, and the CT scan demonstrates profound hypodensity of both thalami and the midbrain. There is also global cerebral edema and obstructive hydrocephalus, which developed because of compression of the third ventricle and cerebral aqueduct.

Fig. 2. MRI (FLAIR sequence) of a 21-year-old woman with HSV-1 encephalitis. There is increased T2 signal due to edema especially in the medial right temporal lobe, with early uncal herniation. (Courtesy of Thomas Bleck, MD.)
encephalitis is among the most common causes of nonconvulsive SE.\textsuperscript{72,73} This condition can only be reliably diagnosed with electroencephalography, preferably continuously for 24 to 48 hours (Fig. 3). The presence of frequent or periodic (interictal) epileptiform discharges should be regarded as indicating a high risk of subsequent electrographic seizures (Fig. 4).\textsuperscript{72–74}

**Weakness**

Some viruses may also affect the spinal cord or peripheral nervous system. Quadriplegia is particularly common with WNV, which may damage anterior horn cells, producing poliomyelitis-like weakness. With involvement of dorsal root ganglia or peripheral nerves, there is both paraparesis and sensory loss.\textsuperscript{75,76} Weakness of the muscles involved in respiration and coughing leads to atelectasis and inability to clear secretions. Cranial neuropathies may interfere with swallowing and laryngeal function, thereby further predisposing to aspiration. Thus, the need for mechanical ventilation is not uncommon. Recovery is typically slow over a period of weeks.

Other clinical manifestations may include fever, headache, movement disorders, or ataxia. No one finding has sufficient negative predictive value to completely exclude the possibility of encephalitis.

**Herpes Simplex Virus**

HSV encephalitis is most often localized to the medial and inferior temporal lobes, with possible spread to the subfrontal, insular, and cingulate regions (see Figs. 2 and 4). The interplay between the viral infection and the host immune response produces tissue damage and necrosis. The binding of viral particles to toll-like receptors stimulates pro-inflammatory cytokines and chemokines, as well as the recruitment of cytotoxic T cells, which in turn contribute to the destruction of infected cells. Interferon production induces expression of proteins that degrade intracellular mRNA and interrupt translation. Not only does this decrease viral replication, but it also induces neuronal apoptosis.\textsuperscript{77,78}

Numerous cohort studies have described the clinical characteristics of patients with HSV encephalitis.\textsuperscript{13,14,79–82} The median Glasgow Coma Scale at presentation is approximately 12 to 14, but the range is much wider. Seizures have been reported in as many as two-thirds of cases and are more common in younger patients. Possible reasons for the high rate of seizures may include the predilection of HSV for “epileptogenic” regions of the brain (mesial temporal lobes), involvement of the cortex, and the characteristically intense inflammation and necrosis. Seizures are an independent predictor of worse outcomes. Chronic epilepsy is a common complication after recovery.\textsuperscript{83,84}

Computed tomography (CT) scans are abnormal in more than half of the cases, but this is dependent on the timing of presentation and the rate at which therapy is implemented. Magnetic resonance imaging (MRI) scans are abnormal in about 90%. Diffusion-weighted imaging reveals that some degree of cytotoxic edema is usually present; these changes are frequently reversible.\textsuperscript{85,86} There is usually some surrounding vasogenic edema. Uncommon locations (eg, rhombencephalitis) or patterns (eg, concomitant ADEM) are described in the literature (Fig. 5).\textsuperscript{87–89} More widespread involvement may occur in patients who are immunosuppressed.\textsuperscript{90}

The median CSF WBC in cohort studies ranges from about 40 to 150 cells/μL, with a range of 0 to 1420 cells/μL (see Table 2). The proportion of WBCs that are lymphocytes usually exceeds 80%. The absence of CSF WBCs is unusual, but does not definitively exclude the possibility of HSV encephalitis, especially in immunosuppressed patients or patients with cancer.\textsuperscript{90,91} The protein count is typically in the range of 0.6 to 0.8 g/L.
Fig. 3. Continuous EEG monitoring in a 19-year-old woman with Murray Valley encephalitis (same patient as in Fig. 1). At the bottom of the screen is a 4-hour compressed density spectral array tracing demonstrating innumerable electrographic seizures. At the top of the screen is a 10-second EEG epoch corresponding to one of the seizures. Rhythmic sharp waves are seen arising in the right fronto-temporal region.
Fig. 4. DWI-MRI and EEG from an 81-year-old woman with HSV-1 encephalitis and status epilepticus. The DWI images demonstrate restricted diffusion in the left temporal lobe. The corresponding EEG shows lateralized periodic epileptiform discharges with additional faster activity (LPEDs+), indicating a very high risk of subsequent electrographic seizures.
Varicella Zoster Virus

Following acute VZV infections (chickenpox), the virus remains latent in ganglia throughout the nervous system. With the natural decline in cell-mediated immunity that occurs with aging, or with acquired immunosuppression, VZV reactivation may occur, resulting in zoster eruptions (shingles). By the age of 85, about 50% of the population will have experienced episodes of zoster.92,93 Most VZV encephalitis, especially in older adults, occurs following zoster. However, a sizable proportion, especially in children or young adults, is associated with acute varicella. It is not uncommon for encephalitis to occur in the absence of a detectable rash.94,95 Even without significant neurologic manifestations, a proportion of patients with zoster can be demonstrated to have abnormal CSF and MRI scans.96

The histopathologic findings with cerebral VZV infections consistently involve the presence of a vasculopathy.97 Early in the disease, VZV antigens can be detected in the outermost layer (tunica adventitia), together with prominent neutrophilic infiltration. Later in the course, the virus migrates into the tunica media and intima. At this stage, there is a paucity of smooth muscle cells in the tunica media and the gradual appearance of myofibroblasts in the tunica intima.98,99

Some patients develop a large-vessel vasculopathy, referred to as granulomatous arteritis, which may result in ischemic strokes, the formation of aneurysms, or arterial dissection.100 VZV vasculopathy is a leading cause of ischemic strokes in children.101,102 More commonly, there is small-vessel involvement.103 Some investigators have argued that most VZV CNS involvement should be considered to represent a vasculopathy rather than encephalitis.100 However, MRI scans usually reveal areas of increased T2 signal without restricted diffusion, indicating that there is no infarction.18

The incidence of fever and seizures may be lower with VZV encephalitis compared with other pathogens, but focal neurologic deficits are common. MRI scans are abnormal in about half of the cases, with signal change in a variety of locations.13,14,18,79,104

Enterovirus

In general, encephalitis due to enterovirus is less severe compared with other causes. Less than 10% of patients present with coma.30 MRI scans are abnormal in about 50% of cases (Fig. 6). There are insufficient data to determine which parts of the brain are
most likely to be involved. Cases mimicking HSV, with significant temporal lobe inflammation, have been reported. Enterovirus 71 is unique in that it causes rhombencephalitis and has a more fulminant course.

Arboviruses

After transmission to humans through a mosquito or tick bite, viruses replicate in cutaneous Langerhans cells before spreading to regional lymph nodes. Further replication eventually leads to viremia. The mechanisms whereby viruses interact with and cross the blood-brain barrier in more severely affect patients are not well understood. After gaining access to the CNS, flaviviruses induce pronounced perivascular inflammation.

Following outbreaks of WNV in North America, several cohort studies described the usual characteristics. Another study described an outbreak in Romania in the 1990s. Almost all patients have a history of fever. Coma and seizures develop substantially less often than with HSV encephalitis. Mechanical ventilation is required in about a quarter of patients, often because of progressive weakness. It is rare for patients to develop flaccid paralysis without also having had meningoencephalitis. The most common pattern is one of flaccid, areflexic paresis that is greater in the proximal musculature. Electrophysiologic testing typically demonstrates motor responses that have reduced amplitude, but normal conduction velocity, consistent with an anterior horn cell process. However, variants are not uncommon, with demyelinating

Fig. 6. FLAIR MRI from a 19-year-old woman who presented with an altered level of consciousness and status epilepticus. There is intensely increased T2 signal in the thalamus bilaterally. CSF demonstrated a WBC count of 17 (predominantly lymphocytes) and a protein concentration of 0.80 g/L. PCR testing was positive for enteroviral DNA. More subtle T2 signal change was observed in the temporal and occipital horns bilaterally. She improved rapidly during her hospitalization and was discharged home. Follow-up MRI revealed complete resolution of the MRI findings.
(Guillain-Barre-like) and sensorimotor axonal neuropathy having also been reported.\textsuperscript{76,114} MRI scans are abnormal in about one-third of cases and may show leptomeningeal enhancement, periventricular hyperdensities, and involvement of basal ganglia, thalamus, cerebellum, and brainstem.\textsuperscript{115,117,118} The median CSF WBC count is relatively high, in the range of about 100 to 150 cell/μL. Clinicians may easily initially mistake WNV meningoencephalitis for bacterial meningitis, because there is usually a predominance of neutrophils during the first week.\textsuperscript{76}

**Influenza**

The term IAE describes a spectrum of neurologic manifestations. On the mild end of the spectrum are patients who have an altered level of consciousness with normal CSF and neuroimaging. In some of these cases, the encephalopathy is simply metabolic in origin and the prognosis is favorable. In more severe cases, there is evidence of lymphocytic pleocytosis.

When MRI abnormalities develop, they have a predilection for subcortical white matter and deep gray nuclei. Mild contrast enhancement is common.\textsuperscript{119} Various terms have been used to describe these changes, with some clinicians preferring to cluster them together under the heading of ADEM. However, unique characteristic patterns have been reported; for example, some patients have been found to have isolated involvement of the corpus callosum. Others have been characterized as having posterior reversible leukoencephalopathy syndrome, although it is not always clear how, apart from location, this entity was distinguished from ADEM. Cases of AHLE and malignant cerebral edema have also been described.\textsuperscript{120,121} In patients with prominent thalamic and brainstem pathologic abnormality, the term acute necrotizing encephalopathy has been used.\textsuperscript{50,121,122}

**Postinfectious Encephalitis**

The pathogenesis of ADEM and AHLE is thought to involve the following 2 mechanisms: first, structural similarities between microbial antigens and myelin proteins lead to an immune response, which targets the brain and spinal cord. This phenomenon is referred to as “molecular mimicry.” Second, infection of the CNS may compromise the blood-brain barrier and lead to the expression of unique myelin antigens that illicit an immune response.

In a large clinical series involving adult patients with ADEM admitted to an ICU, clinical manifestations were not dissimilar to viral encephalitis. Most were febrile at presentation (median temperature 39°C) and had a depressed level of consciousness (median Glasgow Coma Scale 7). Seizures occurred in 30% and were more common among patients who ultimately had a poor outcome. Other neurologic findings included focal deficits (85%) and cranial neuropathies (40%). The CSF WBC count was elevated in most patients, with a median of 90 cells/μL, a range of 60 to 378 cells/μL, and a predominance of lymphocytes. CSF protein counts were quite elevated (median 1.3 g/L).\textsuperscript{60}

Most patients had multifocal or diffuse areas of increased MRI T2 signal, primarily in the supratentorial white matter (90%). Involvement of infratentorial white matter was less common (40%), as was involvement of the cortex (35%) and deep nuclei (15%). Just over half of the patients had spinal cord involvement.\textsuperscript{60}

**Noninfectious Encephalitis**

Of patients with anti-NMDA receptor encephalitis involved in the California Encephalitis Project, 13% were comatose, 53% were admitted to an ICU, and 41% were mechanically ventilated.\textsuperscript{10} More than 90% of patients have altered mental status.
Seizures develop in 60% to 70%. Hemiparesis is relatively uncommon, occurring in less than 10%. MRI is abnormal in about one-third to one-half of patients. The CSF WBC count is usually somewhat lower than with viral encephalitis.

In a series of 57 patients with anti-LGI1 encephalitis, the average age was 60 years, with a slight preponderance of men. Essentially all patients had an altered mental status and seizures were reported in more than 80%. MRI revealed abnormalities in the medial temporal lobes in more than 80%, whereas CSF was abnormal less often (41%).

**DIAGNOSIS**

The diagnosis of encephalitis should be considered in any patient presenting with an altered level of consciousness, especially when this is accompanied by otherwise unexplained fever, seizures, or new focal neurologic deficits. A lumbar puncture is a crucial diagnostic test, but should be preceded by a CT scan to ensure that there is no radiographic contraindication. Lumbar puncture should not be performed if there is significant brain tissue shift, evidence of transtentorial or tonsillar herniation, or effacement of basal cisterns or the fourth ventricle (see Figs. 1 and 2). Empirc antiviral therapy should be initiated before obtaining CSF results if there is more than a low pre-test probability of encephalitis. CSF should be sent for standard tests, including WBC count and differential, as well as protein and glucose concentrations. CSF should also undergo appropriate molecular testing for relevant viruses. In most cases, this will include PCR testing for the DNA of HSV-1, HSV-2, VZV, and enterovirus, because these pathogens account for about 90% of viral encephalitis. HSV PCR has a particularly high sensitivity, approaching 100%, but may decrease after a few days of therapy. Antibody testing of the CSF and serum can be helpful for cases where CSF was not immediately obtained or when the diagnosis is still deemed possible even after the PCR is negative. The utility of performing viral cultures is questionable, but it can still be considered when a diagnosis remains elusive.

Further testing should be guided by historical and clinical features. In patients who reside in, or have traveled to, areas where certain viruses are endemic, the corresponding test should be performed (eg, PCR for WNV or TBEV; IgM and IgG antibodies from CSF and serum). In patients who are immunosuppressed, testing should be directed at other herpes viruses (eg, PCR for EBV, CMV, HHV 6 and 7) and JC virus. For patients with recent respiratory tract infections, PCR of CSF and nasopharyngeal aspirates can be performed to assess for influenza (A and B) and adenovirus. HIV testing should be considered, because the spectrum of CNS pathogens will be broader compared with an immunocompetent patient.

An MRI scan is helpful in confirming the diagnosis of encephalitis, clarifying the possible causes, and assessing the burden of cerebral involvement (see Table 2). The most relevant MR sequences include T2-weighted images, fluid attenuated inversion recovery (FLAIR), and gradient echo or susceptibility weighted imaging. Temporal lobe involvement is consistent with HSV, although other viruses and autoimmune encephalitis may sometimes produce a similar pattern (see Figs. 2, 4, and 6). Flaviviruses frequently target the basal ganglia and thalamus. MRI is also the crucial test in diagnosing ADEM and other forms of postinfectious encephalitis. In patients with a persistently altered level of consciousness, continuous electroencephalography (EEG) monitoring for 24 to 48 hours is ideal to exclude intermittent nonconvulsive seizures (see Fig. 3).

For patients in whom the combination of clinical manifestations, neuroimaging, and CSF characteristics are suggestive of encephalitis, but the microbiological studies are
normal, early assessment for autoimmune or paraneoplastic causes should be performed. This assessment should include assessment of antibodies directed against intraneuronal antigens and neuronal receptor proteins (see Table 2). Testing CSF is not routine, although there is some evidence that anti-NMDA receptor antibodies can be detected more often than in serum.63 Clearly, there are still antigens that have not been characterized, such that the absence of these markers does not exclude an autoimmune or paraneoplastic syndrome. Evaluation for undiagnosed malignancies (measurement of tumor markers; CT scans of the chest, abdomen, and pelvis; use of positron emission tomography scans) may be appropriate.1,65

ANTIMICROBIAL MANAGEMENT

**Herpes Simplex Virus**

The drug of choice for the treatment of HSV encephalitis is high-dose intravenous acyclovir. Two large clinical trials in the 1980s demonstrated that acyclovir, at a dose of 10 mg/kg every 8 hours, dramatically reduced mortality in comparison with vada-rabine, which was the previous standard of care.129,130 Acyclovir prevents viral replication and should be administered as early as possible. Delays in therapy seem to be relatively common and are predicted by more severe comorbidities, alcohol abuse, and delays in brain imaging.131 Later treatment is associated with worse outcomes.81

Although the definitive clinical trials used a treatment duration of 10 days, neurologic deterioration has been described after cessation of therapy.132,133 Consequently, international guidelines recommend treatment for 14 to 21 days.1,2,58 A recent review of HSV encephalitis treatment in France revealed that 76% of patients received a 21-day course of treatment.134,135 Some experts recommend performing a second lumbar puncture near the end of therapy, with treatment continued if there is still HSV DNA present; however, there are little data to support this practice.1,2 A clinical trial is currently assessing longer courses of therapy using oral valacyclovir.

Acyclovir can cause acute kidney injury at high doses. The mechanism is thought to involve precipitation of acyclovir crystals in renal tubules with resultant obstructive uropathy, which may be preventable with hydration and slow drug administration.136 Clinicians should also be aware that at very high doses, acyclovir may cause neurotoxicity, which could be mistaken for ongoing manifestations of encephalitis and may even produce MRI changes.137 Appropriate renal dose adjustment is required.138

Because HSV PCR can theoretically be negative very early in the course of disease, some experts recommend repeating a lumbar puncture if the first PCR is negative, but was performed within 72 hours of symptom onset.1,2,139

**Varicella-Zoster Virus**

There are no clinical trials to support the use of antiviral therapy for VZV encephalitis. However, use of acyclovir does accelerate recovery from both acute varicella and zoster infections and is therefore recommended for severe infections like encephalitis.140,141 The recommended dose is 10 to 15 mg/kg of intravenous acyclovir 3 times per day for up to 14 days.1,2,58 The higher dose is listed as an option because VZV is somewhat less sensitive to acyclovir than HSV. A course of 3 weeks is recommended by the European Guidelines.2 A longer duration of therapy should be considered for patients who are immunosuppressed.

**Other Viruses**

There is no pharmacotherapy that has been proven to be effective for enterovirus encephalitis. The drug pleconaril is an inhibitor of viral replication and has shown some
efficacy in alleviating symptoms among patients with aseptic meningitis.\textsuperscript{142} It is mentioned in the UK Guidelines as an option for patients with severe Enterovirus infections.\textsuperscript{1} There is also no specific treatment for arboviruses, including WNV. Foscarnet (60 mg/kg every 12 hours) is the preferred agent against HHV-6. Combination therapy with foscarnet and ganciclovir (5 mg/kg every 8 hours) is recommended as initial treatment of CMV encephalitis.\textsuperscript{1,2,58} Use of oseltamivir is appropriate for severe influenza.\textsuperscript{143} No pharmacotherapy is available for most other rare causes of encephalitis.

**SUPPORTIVE CARE**

**Corticosteroids**

The moderate degree of vasogenic edema that sometimes complicated HSV encephalitis provides a rationale for the adjunctive use of corticosteroids. Corticosteroids were commonly administered to patients before the availability of antiviral drugs and may have been associated with more favorable outcomes.\textsuperscript{144,145} In animal models, corticosteroids attenuate the development of MRI changes without amplifying the replication and dissemination of HSV.\textsuperscript{146,147} A retrospective study suggested that the concomitant use of acyclovir and corticosteroids was associated with superior outcomes compared with acyclovir alone.\textsuperscript{148} At present, corticosteroids should not be used routinely, but may be reasonable in selected cases where there is a large degree of vasogenic edema and mass effect. The use of dexamethasone, at a dose of 40 mg per day, is currently being evaluated in a European randomized controlled trial.\textsuperscript{149}

Because an inflammatory vasculopathy is thought to be important in the pathophysiology of VZV encephalitis, corticosteroids are widely recommended.\textsuperscript{1,2,58,100} In the setting of uncomplicated zoster, corticosteroids may confer a slight improvement in symptoms, but results have been variable.\textsuperscript{150,151} The optimal dosing regimen is unknown, but a relatively high dose (eg, 1 mg/kg prednisone) for a short period of time (eg, 3–5 days) is advocated.\textsuperscript{1}

**Prevention of Secondary Brain Injury and Treatment of Cerebral Edema**

Outcomes of critically ill patients with neurologic disorders seem to be best in dedicated neurocritical care units where there is an emphasis on the prevention of “secondary” brain injury.\textsuperscript{152} A variety of systemic and neurologic physiologic derangements have been implicated as potential contributors to worsened outcomes, including hypotension, hypoxemia, intracranial hypertension, hyperthermia, hypoglycemia, hyperglycemia, anemia, and seizures.\textsuperscript{152–156}

Given that ICP is unknown in many patients, a slightly higher than usual mean arterial pressure (eg, $\geq$80 mm Hg) is targeted than would be in other critically ill populations, especially if neuroimaging demonstrates evidence of significant edema, to minimize the chance that cerebral perfusion pressure decreases to less than 60 mm Hg. The usual goals of mechanical ventilation are to maintain an arterial $P_{O_2}$ between 80 and 120 mm Hg and $P_{CO_2}$ between 34 and 40 mm Hg, attempting to maintain core body temperature less than 38°C, initially with antipyretics and, if necessary, with active endovascular or surface cooling. In comatose patients with significant cerebral edema, hemoglobin concentration was targeted to greater than 80 to 90 g/dL (rather than 70 g/dL, as in other populations).\textsuperscript{153} Insulin is used as necessary to maintain serum glucose concentrations between 110 and 180 mg/dL.\textsuperscript{154}

**Treatment of Cerebral Edema and Intracranial Hypertension**

Cerebral edema, brain tissue shifts, and herniation are potential complications of encephalitis. No clinical trials have been performed in this particular population, such
that practice is largely guided by experience from other neurocritical care settings. Although ICP is not routinely monitored in patients with encephalitis, intracranial hypertension is not uncommon. Clinicians should rigorously avoid factors that may contribute to worsening cerebral edema. The head of the bed should remain elevated to at least 30°. The amount of time that patients are kept supine or in the Trendelenburg position for diagnostic imaging or various procedures should be minimized. Hyponatremia should be avoided, if necessary with the use of hypertonic saline. Intravenous medications and infusions should never be hypotonic. Insertion of an ICP monitor to help direct clinical care should be strongly considered when mass effect is observed on neuroimaging. Favorable outcomes have been reported even among patients with refractory intracranial hypertension who received aggressive care. This aggressive care may involve escalating therapy with deep sedation, osmotic agents (mannitol and hypertonic saline), mild induced hypothermia, and, in some cases, decompressive surgery. An ICP of less than 20 mm Hg is a reasonable initial treatment target, although recent clinical trials among patients with traumatic brain injury have solidified the notion that the clinical state of the patient and the degree of mass effect on serial CT scans are more critical than any specific ICP threshold.

Treatment of Seizures and Status Epilepticus

SE is defined as ongoing seizure activity for more than 5 minutes, or recurrent seizures without recovery of normal consciousness in between. Rapid control of seizures is crucial for several following reasons: (1) SE may produce numerous systemic complications, including rhabdomyolysis, lactic acidosis, or aspiration; (2) uncontrolled seizure activity may cause additional neurologic damage; and (3) seizures may become more difficult to treat over time.

Although the incidence of both convulsive and nonconvulsive seizures is high with encephalitis, there is no evidence to support the prophylactic use of antiepileptic drugs. The Neurocritical Care Society recently published consensus guidelines for the care of patients with SE. The initial drug of choice is intravenous lorazepam, which is administered in increments of 2 mg every 1 to 2 minutes to a maximum cumulative dose of 0.1 mg/kg. Unless there is an immediately correctable cause of SE (eg, hypoglycemia), a second agent is given, even if lorazepam was effective, to help prevent seizures from recurring. Because rapid administration is required, an intravenous preparation should be used. Options include phenytoin, fosphenytoin, valproate, levetiracetam, and lacosamide.

If there is ongoing convulsive seizure activity despite the use of 2 drugs, then patients are considered to have refractory SE. At this point, they should be intubated and receive an intravenous sedating drug, most often either midazolam or propofol. In patients with focal SE, it may be reasonable to persist for longer in trying to control seizures before resorting to the use of deep sedation, perhaps with the addition of a second nonsedating drug.

Many patients will have ongoing electrographic seizures even in the absence of visible convulsions. Thus, it is difficult to provide optimal care without the use of continuous EEG monitoring. Quantitative EEG tracings have been found to be useful in titrating therapy (see Fig. 3). Very large doses of midazolam, as high as 1 to 2 mg/kg/h, may be required. In the author’s experience, the combination of midazolam and propofol is very effective, while restricting the cumulative amount of either drug. The dose of propofol is limited to 50 to 80 μg/kg/min to minimize the risk of propofol infusion syndrome. The optimal degree of EEG suppression to target is a matter of controversy. Eradication of seizures should be the primary goal, but temporary
maintenance of a burst-suppression pattern may decrease the chance of seizure recurrence, which is usually maintained as deep sedation for at least 24 hours before attempting to wean anesthetic drugs. Given that the pathophysiology of SE involves increased expression of NMDA receptors, ketamine is used relatively early if patients fail to respond to conventional therapy.\textsuperscript{176}

There are no data to support the use of a particular preferred antiepileptic drug regimen among patients with encephalitis. SE that recurs repeatedly after cessation of deeply sedating drugs is sometimes referred to as “malignant” SE.\textsuperscript{177} There are multiple reports of favorable neurologic recovery even after many weeks of therapy for refractory SE. Thus, clinicians should be careful about concluding and communicating that the prognosis is poor, especially if there are no radiographic findings to support this contention.\textsuperscript{178–180}

**Postinfectious Encephalitis**

Although there are no published clinical trials, it is common practice to administer corticosteroids to patients with ADEM. A common regimen is to administer pulse dose methylprednisolone (20 mg/kg, maximum 1000 mg/d) for 3 to 5 days. Some clinicians also continue a daily dose of prednisone (1 mg/kg), which is tapered over 4 to 6 weeks. For patients who fail to respond to corticosteroids, there are case series suggesting that immunomodulatory therapy with either intravenous immune globulin or plasma exchange may be effective.\textsuperscript{181,182}

**Autoimmune and Paraneoplastic Encephalitis**

For autoimmune encephalitis, first-line therapy consists of pulse corticosteroids in combination with either intravenous immune globulin or plasma exchange. Second-line therapy involves additional immunosuppression with either cyclophosphamide or rituximab.\textsuperscript{63,183–185} For patients with paraneoplastic encephalitis, it is obviously crucial to identify the malignancy and remove it.

**OUTCOMES**

The prognosis of HSV encephalitis has improved dramatically with the use of acyclovir and the provision of modern critical care. Without treatment, the rate of case fatality was more than 70%. In more recent studies, this has decreased to about 5% to 20%.\textsuperscript{13–16,186} Nevertheless, a substantial proportion of survivors have persisting functional and cognitive limitations.\textsuperscript{186,187} Using the familiar Glasgow Outcome Scale system, slightly more than one-third have an unfavorable outcome.

The prognosis of VZV and WNV encephalitis is generally comparable to that of HSV encephalitis.\textsuperscript{13,14,95,100,111–116} With WNV, the prognosis is notably worse in elderly patients, especially if there is spinal cord involvement with flaccid paralysis. Outcomes are slightly better with enterovirus encephalitis, although this may be because affected patients are generally younger. Furthermore, this is not necessarily true for all serotypes.\textsuperscript{30–32}

The largest clinical series of adult patients with ADEM admitted to the ICU reported case-fatality and poor outcome rates of 25% and 30%, respectively.\textsuperscript{50} This study obviously assessed patients on the severe end of the spectrum. Outcomes are better when all patients are included.\textsuperscript{13} The prognosis is also better in children, with a rate of case fatality of less than 5% and favorable neurologic recovery in most.\textsuperscript{188} The prognosis is considerably worse with AHLE.

Autoimmune receptor encephalitis is usually responsive to immunomodulatory therapy, with about 75% of patients achieving a favorable outcome.\textsuperscript{63,64} The prognosis of
paraneoplastic encephalitis is, in part, dependent on the characteristics of the responsible tumor.

SUMMARY

Optimal critical care of patients with viral encephalitis requires a high index of suspicion, appropriate diagnostic testing, and timely initiation of antiviral therapy. Intensivists should also consider postinfectious, autoimmune, and paraneoplastic encephalitis, because the treatment of these entities is very different. To maximize the chance of a favorable neurologic recovery, efforts should be directed at identification and treatment of neurologic (eg, cerebral edema, high ICP, and seizures) and systemic (eg, hypoxemia, low cerebral perfusion pressure and fever) complications, which could potentially exacerbate brain damage.

REFERENCES


