



Infectious Encephalitis in the Neurocritical Care Unit

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Abstract

Purpose of review Infectious encephalitis is a rapidly progressive encephalopathy caused by a variety of pathogens, most commonly viruses. It is associated with significant mortality and morbidity, often requiring evaluation and treatment in the intensive care unit. This review article discusses the diagnosis of the infectious etiologies, the assessment for differential diagnoses, and the initiation of therapies, and most importantly, it entails the rapid and efficient management of the associated complications.

Recent findings Novel emerging technologies (e.g., metagenomic next-generation sequencing) have the potential to assist in the diagnosis, etiology identification, and treatment of encephalitis. Interventions such as ketogenic diet therapies have been promising in their potential to treat patients with refractory status epilepticus in the setting of infectious encephalitides.

Summary Early recognition of encephalitis and appropriate treatment of the primary infection and its complications are essential to increase survival and reduce sequelae. Intensivists are crucial given the high mortality rate of infectious encephalitis in the ICU setting, and their role may significantly impact patients' outcomes.

Introduction

Infectious encephalitis frequently evolves as an acute inflammation of the brain parenchyma due to a viral, bacterial, fungal, or parasitic infection. [1] Acute infectious encephalitis often requires assessment in the intensive care unit (ICU) due to the magnitude of the

neuroinflammatory process and associated complications. Mortality, morbidity, and prognosis are influenced not only by specific etiologies, but also the complications that emerge during the disease process. In this review article, we will discuss the epidemiology,

etiology, clinical manifestations, diagnostic assessment, treatment options, and complications for common infectious encephalitides encountered in the critical care setting, as well as the management of these complications.

Definition

Acute infectious encephalitis emerges as an inflammation of the brain parenchyma, clinically manifested by altered mental status for more than 24 h and at least two of the following criteria: fever up to 38 °C before or after presentation, new onset of seizures, focal neurologic deficits, cerebrospinal fluid (CSF) pleocytosis, and electroencephalogram or neuroimaging abnormalities consistent with the diagnosis of encephalitis. [2•, 3]

Encephalitis can be classified by etiology, namely infectious, post-infectious, or autoimmune. Although infectious encephalitides have been historically considered as the most frequent type, particularly viral; there is increased recognition of autoimmune etiologies. [4] Of note, some infections may trigger post-infectious encephalitides, such as acute disseminated encephalomyelitis (ADEM), autoimmune encephalitides including anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis or autoimmune responses such as myelin oligodendrocyte (MOG)-associated disorders. [5–7]

Epidemiology

The incidence of infectious encephalitis varies according to geography and affected populations (e.g., immunocompromised and vulnerable persons [children and the elderly]). The annual incidence of infectious encephalitis is an estimated 1 per 100,000 person-years, with 60% of cases being viral, particularly among children. [4] More than 50% of cases remain without an identified pathogen; nevertheless, the development of new molecular techniques for pathogen discovery has improved the rate etiological diagnosis. [8, 9••]

Viral encephalitis may be due to either DNA or RNA viruses, which have various modes of transmission, including bloodborne, airborne, or mosquito-borne. Ecological, environmental, and host-dependent factors are critical in the epidemiology of viral encephalitis. A patient's travel history and geographic location may suggest the etiology such as West Nile Virus in the USA or Dengue in South America. [10, 11] In addition, the presence of an immunosuppressive state can predispose to opportunistic infections, particularly those produced by DNA viruses. [12]

Etiology

Viruses

DNA Viruses

Among the DNA viruses, herpesviruses are the most frequently identified pathogen of viral encephalitis. [13] There are more than 100 known

herpesviruses, but only seven may produce encephalitis, namely herpes simplex virus, varicella zoster virus, Epstein-Barr virus, cytomegalovirus, human herpesvirus 6, and, rarely, human herpesvirus 7 and human herpesvirus 8.

Herpes simplex virus

HSV is the most recognized cause of infectious encephalitis worldwide. HSV encephalitis is almost exclusively caused by HSV-1, except in newborns, among whom HSV-2 is more prevalent. This virus has a bimodal pattern of presentation, one in early childhood and another among those older than 50 years of age. [14]

Patients develop an acute course of fever, confusion, altered behavior, headaches, dysphasia, and cranial neuropathies. Seizures affect 85% of patients, particularly younger patients, and 33% of people may become comatose. [15] Magnetic resonance imaging (MRI) of the brain is abnormal in 90% of cases, demonstrating cytotoxic and vasogenic edema in the medial and inferior temporal lobes (Fig. 1). Therapy should be initiated with acyclovir and its discontinuation requires a second CSF study to reevaluate HSV DNA presence. [16, 17, 18•]

Varicella zoster virus

VZV is the second most significant cause of viral encephalitis after HSV. [3] VZV encephalitis may affect children 1 week after primary varicella infection, as well as immunosuppressed and older adult patients. [19] A portion of patients develops VZV encephalitis in the setting of acute varicella, while others have neurological symptoms in the absence of the rash. Neurological symptoms include altered consciousness, focal neurological signs, cranial neuropathies, and convulsions. [19]

Brain MRI demonstrates areas of T2 hyperintensities and areas of restricted diffusion in the basal ganglia, thalami, cerebellum, temporal lobes, and

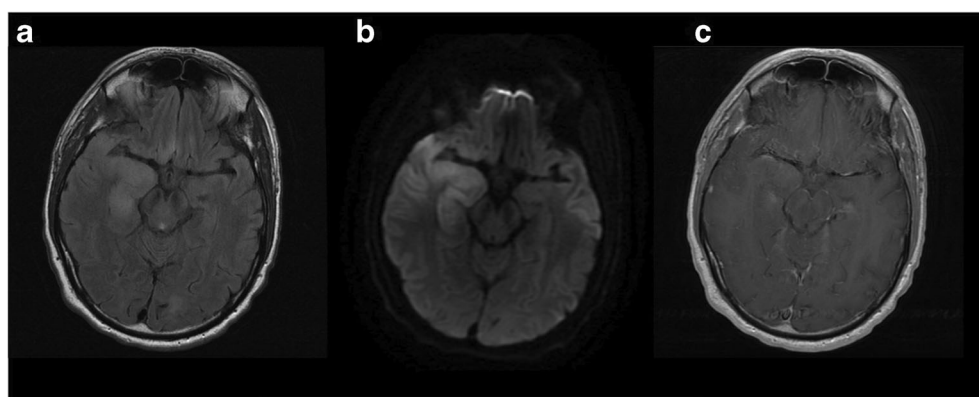


Fig. 1. Brain MRI of a patient with HSV-1 encephalitis. **a** FLAIR sequence demonstrates T2 hyperintensities of the right mesial temporal lobe including the hippocampus, amygdala, and anteroinferior temporal lobe with associated gyriform swelling. **b** Diffusion-weighted imaging sequence demonstrates restricted diffusion in the same structures as well as within the left anterior temporal lobe. **c** T1-post-gadolinium sequence demonstrates leptomeningeal enhancement as well as subtle enhancement of the right hippocampus.

cerebral cortex. In addition, hemorrhages, ischemia, and vasculopathy may be present. [20] Therapy includes acyclovir; however, clinical trial data do not exist to support this approach. [18•, 21, 22] Ganciclovir can be considered as an alternative. [18•, 23]

RNA viruses

RNA viruses have a rapid rate of mutagenesis and genomic variation, properties that have played an important evolutionary role. [24] Among the most frequent RNA viruses that produce encephalitis are enteroviruses; influenza; arboviruses; HIV; and more recently emerging and re-emerging viruses such as rabies, mumps, measles, and ebola.

Enteroviruses

Enteroviruses are a group of viruses that produce several mild infectious diseases and frequently affect children. Strains associated with central nervous system (CNS) impairment include EV-A71, A75, A76, A89, and D68; coxsackievirus A9 and A10; echovirus 4, 5, 9, 11, 19, 30; and human parechovirus 3. [25] Encephalitis is typically rare and mild compared with other etiologies. Approximately 25% of patients present with focal neurological deficits, while less than 10% of patients have severe deterioration of mental status and seizures. [26]

Enterovirus A71 (EV-A71) is exceptional in that it may cause rhombencephalitis with a more fulminant course. [27, 28] EV-A71 is a frequent pathogen in Southeast Asia, but clusters of EV-A71 have been reported recently in the USA. [29] EV-A71 encephalitis manifests with cranial neuropathies, respiratory failure, movement disorders and ataxia. [30] Brain MRI is abnormal in approximately 50% of cases, typically involving the temporal lobes. [3, 31] There is no specific treatment for enterovirus encephalitis, but there are anecdotal reports of some antiviral treatments such as pleconaril and ribavirin. [18•, 25]

Arboviruses

Arboviruses are a family of viruses transmitted to humans through a mosquito or tick bite. [32] Outbreaks depend on vector presence and geographic distribution. The infection may be completely asymptomatic, produce systemic manifestations or neurological syndromes. Among the most frequent neurological syndromes are meningitis, encephalitis, and less frequently, peripheral neuropathy or myelopathy with a preference for the anterior horn cells (e.g., acute flaccid paralysis). [33]

West Nile virus

WNV is a mosquito-borne flavivirus that represents a frequent cause of viral encephalitis in the USA, Europe, and North Africa, affecting primarily elderly and immunocompromised patients. [11, 34]. Encephalitis is the most common neurologic presentation of WNV, accounting for 60% of neuroinvasive WNV infection. Common manifestations include

movement disorders and cranial neuropathies. [11] Mild lower motor neuron symptoms may also occur, even in the absence of acute flaccid paralysis. [3, 33] This condition commonly shows a neutrophilic CSF pleocytosis during the first week. MRI is abnormal in 66% of cases, typically demonstrating lesions in the basal ganglia, thalami, temporal lobes, cerebellum, leptomeninges, and ventricles. [35] Specific treatment is not available, and management is mainly supportive. [18•]

Human immunodeficiency virus

HIV infection and AIDS may be associated with acute neurological emergencies presenting as HIV encephalitis, opportunistic infections, or other forms of acute immune-mediated manifestations as the result of immune reconstitution after antiretroviral therapy (ART). The epidemiology of these HIV-associated complications has changed dramatically with the introduction of ART at the end of the twentieth century. While the epidemiology of HIV-associated neurological complications is influenced by socioeconomic and environmental factors in different areas of the world, HIV-related opportunistic infections, HIV-associated CNS neoplasms and immune reconstitution syndrome (IRIS) are the most frequent HIV-related disorders in the critical care setting regardless of such factors. [36, 37]

a) Intracranial opportunistic infections associated with HIV

During the early stage of AIDS and/or stages of immunosuppression due to the marked decrease of CD4⁺ lymphocytes and increased HIV viral load, several opportunistic infections have the potential to affect the CNS. Most of these infections include DNA viruses such as JCV, VZV, CMV, and EBV as well as bacteria (e.g., *Mycobacterium tuberculosis*), fungi (e.g., *Cryptococcus neoformans*, *Candida albicans*, *Aspergillus*, *Histoplasma*, and *Coccidioides*), and parasites (e.g., *Toxoplasma gondii*).

b) Immune reconstitution syndrome (IRIS) as an encephalitic manifestation in HIV infection

IRIS is a group of inflammatory disorders associated with a paradoxical worsening of neuroinflammatory responses after treatment with ART and control of preexisting opportunistic infections. [38, 39] Retrospective case series suggest that up to 30% of HIV patients treated with ART develop one or more inflammatory syndromes. [40–42] Clinical manifestations follow a subacute or chronic course succeeding the initiation of ART and depend on the type of preexisting opportunistic infection. [43] For instance, patients with a previous cryptococcal infection could develop fever, gastrointestinal symptoms, eye pain, and meningismus, while patients with *M. avium complex* may experience expansion of preexisting intracranial tuberculomas. [44, 45]

Although there are no well-established diagnostic criteria of IRIS, the diagnosis could be made if patients satisfy the following features: the presence of AIDS with a CD4 count of less than 100 cells/ μ L; viral or immune response to ART; absence of drug-resistant infection, bacterial infection, or drug allergy; the presence of clinical features compatible with an inflammatory disorder; and timeframe consistent with IRIS. [40, 46] Management requires the continuation of ART and urgent treatment of the underlying

opportunistic infection whether it is still present.

Bacteria

Mycobacterium tuberculosis

Mycobacterium tuberculosis is one of the most serious opportunistic infections in HIV patients and transplants. In 2018, approximately 10 million people had tuberculosis (TB) and about 17% of these patients presented with extrapulmonary disease. [47, 48] In HIV-positive patients, this figure reaches 40% due to their risk of CNS involvement is five times higher than in HIV-negative individuals. [49, 50] The clinical presentation is usually mild at the beginning of the infection and includes severe headache, fever, unbalance, altered consciousness, and cognitive impairment. [47, 51]

CSF analyses typically demonstrate hyperproteinorachie, lymphocytic pleocytosis, and hypoglycorrhachia. [47, 52] The use of PCR based techniques and Quantitative Xpert MTB/RIF PCR as a diagnostic tool have been preferred above CSF cultures, despite a relatively low yield of diagnosis. [53–56] Brain MRI is commonly normal, but cases of granulomas and brain abscess have been described. [47] Treatment consists of 6-month therapy with isoniazid, rifampicin, pyrazinamide, and ethambutol. [18•] Corticosteroids may improve outcomes related to brain edema and vasculitis in patients with meningitis. [57, 58]

Fungi

Cryptococcus

Cryptococcus is an encapsulated yeast that causes one million cases of the *Cryptococcus*-associated neurological complications per year, resulting in about 600.000 deaths. [59, 60] Meningitis, encephalitis, or meningoencephalitis are considered the most common causes of life-threatening fungal infection. The majority of cases of cryptococcal encephalitis are seen among severely immunocompromised patients with AIDS and CD4 count of less than 100 cells/ μ l, or HIV patients with antiretroviral-drug resistance or poor adherence.

Patients may present with an acute or chronic course of headaches, behavioral changes, cognitive impairment, and lethargy. Approximately 30% of patients may have normal CSF findings, but elevated opening pressure is present in more than 50% of cases. [61–63] Cryptococcal antigen testing in serum and CSF confirms the diagnosis and is sufficient for treatment initiation, but a confirmatory cryptococcal culture should be performed. Brain MRI may show lesions in the basal ganglia suggesting cysts, nodules, and leptomeningeal enhancement. Imaging may suggest intracranial hypertension with or without space-occupying lesions and hydrocephalus.

The treatment regimen consists of the aggressive administration of antifungal agents with therapeutic relief of elevated intracranial pressure by serial lumbar punctures or ventricular drainage. The treatment includes the use of amphotericin B, flucytosine, and fluconazole in three different stages of therapy (induction, consolidation, and maintenance). The use of corticosteroid treatment during the *Cryptococcus*-associated complications may prevent vasculitic or inflammatory processes. [64]

Parasites

Toxoplasma gondii

Toxoplasma gondii is a parasite that potentially affects the brain of AIDS patients as the by-product of a reactivation of a chronic infection. Of note, 10–40% of HIV-infected patients who have antibodies against *T. gondii* are susceptible to toxoplasmic encephalitis. [65] The epidemiology of *T. gondii* in patients with HIV/AIDS has changed from 10,000 hospitalization per year in 1995 to 2985 in 2008 due to the introduction of prophylaxis treatment and ART. [66, 67] Clinical manifestations include a subacute onset of language dysfunction, weakness, headache, altered consciousness and fever.

Diagnosis requires the identification of *Toxoplasma* IgG and IgM antibodies, parasite isolation from body fluids or tissues or amplification through RT-PCR. Although there are no pathognomonic findings in imaging, CT scan may demonstrate lesions in the basal ganglia and subcortical regions with associated enhancement in 80% of patients. [68–70] Treatment includes the use of pyrimethamine and sulfadiazine. [18•] Corticosteroids in the setting of cerebral edema and intracranial hypertension are recommended for no more than 2 weeks.

Diagnosis and laboratory approach in the ICU

Encephalitis should be a consideration in a patient who presents with altered consciousness, fever, cranial neuropathies, movement disorders, meningismus, seizures, and/or new focal neurological deficits. In addition to a comprehensive clinical examination, the intensivist should assess for complications such as seizures or status epilepticus, brain edema, hydrocephalus, systemic metabolic disturbances, or infections when managing patients with encephalitis in the ICU. Several diagnostic modalities are available for a comprehensive evaluation of patients with concern for encephalitis, including infectious encephalitis. Diverse techniques include imaging techniques (e.g., CT and brain MRI, FDG-PET scan), neurophysiological methods (e.g., electroencephalography [EEG] monitoring, nerve conduction studies [NCS] and electromyography [EMG]), laboratory testing of blood, CSF, and other biological samples to establish an etiology, treatment, and monitoring for potential complications.

Neuroimaging in the ICU

Rapid brain imaging with CT scan is an important initial test to evaluate for brain edema, intracranial hypertension, hydrocephalus, and brain herniation. Brain MRI is always a helpful tool to support the diagnosis of encephalitis, assessing the burden of brain and brainstem involvement as well as providing clues for possible causes. The most pertinent MRI sequences in encephalitis are T2-weighted images, fluid-attenuated inversion recovery (FLAIR), gradient-echo or susceptibility-weighted imaging, and post-gadolinium sequences. [71] Despite limited logistic resources in the ICU, PET-based techniques such as FDG-PET/CT may be of value in evaluating etiologies (namely autoimmune encephalitides) or assessment of brain physiology; however, experience with FDG-PET/CT in infectious

encephalitides is largely restricted to tertiary centers and case reports. [72, 73•, 74–76] Future study is needed to determine the utility of FDG-PET/CT in the diagnosis and clinical monitoring of infectious encephalitides as well as the differentiation from autoimmune encephalitis and other causes of subacute cognitive decline. Empiric antimicrobial therapy should be started in those patients with suspected infectious encephalitis until laboratory tests are available to guide discontinuation. [33]

Laboratory analysis of CSF and blood

Lumbar puncture for evaluation of opening pressure and CSF analyses are critical tools in the ICU setting. The initial approach for CSF analysis should include a comprehensive assessment of potential etiologies and include the proper microbiological tests such as bacterial or fungal cultures as well as specific molecular and immunological studies used for specific pathogens (Table 1). Early and efficient detection of pathogens by PCR or immunological tests are influenced by different factors including the timing of the infection, duration of symptoms, and CSF sampling, thus negative results should be interpreted carefully and account for such factors. [3] CSF markers including oligoclonal bands and IgG index are valuable in the assessment for neuroinflammation and always should be included during the initial assessment. In the setting of preceding respiratory tract infections, cultures or molecular assays (e.g., PCR) of nasopharyngeal swabs or aspirates should be always part of the evaluation.

Blood tests to consider include HIV serologies to assess for HIV infection and immune status, complete blood cell counts with differential analyses of cells, complete metabolic panels to evaluate for renal and hepatic involvement, and bacterial blood cultures. Serum electrolyte levels to identify electrolyte disorders (e.g., 25% of patients with St. Louis encephalitis develop inappropriate secretion of antidiuretic hormone). Blood urea nitrogen and creatinine levels are useful to assess hydration status and adjust antimicrobial therapy. [163] Urine or serum toxicology testing may be helpful in patients with toxic delirium or confusional state. [164]

If CSF and imaging suggest encephalitis, and microbiology tests are non-revealing, paraneoplastic and autoimmune causes should be considered. When autoimmune or paraneoplastic encephalitis is a consideration, both serum and CSF evaluation for anti-neuronal autoantibodies should be included (e.g., anti-NMDAR, anti-LGI1, anti-AMPA, GAD65, GABA-A, and GABA-B). Absence of antibodies does not rule out the disease. CT of the chest, abdomen, pelvis; tumor markers; gonadal ultrasound; and FDG-PET studies should be considered to rule out occult malignancy or other systemic sources of infection. [165]

Novel emerging technologies include molecular-based assays such as BioFire FilmArray® Panels (BioFire/bioMérieux, Salt Lake City, USA) and metagenomic next-generation sequencing (mNGs). The FilmArray® panels are focused PCR-multiplexed assays which include a meningitis/encephalitis panel for testing fourteen frequent microorganisms and viruses that cause meningitis and encephalitis. [166] Although the panel's sensitivity and specificity are high, its availability is still limited and many pathogens are not included in the panel. [167, 168, 169••]

Table 1. Infectious encephalitis by etiology

Pathogen	Population at risk	Geographic areas	Clinical presentation	Neuroimaging
DNA viruses				
Herpes simplex virus (HSV) [16, 17, 18, 71, 72, 73, 77–80]	Immunocompromised, elderly, and newborns	Worldwide	Fever, confusion, altered behavior, headaches, dysphasia, seizures, and cranial neuropathies	Temporal lobe abnormalities, unilateral lesions may produce mass effect
Vaccinia zoster virus (VZV) [18, 21, 81, 82]	Immunocompromised, children with acute varicella	Worldwide	Altered consciousness, focal neurological signs, cranial neuropathies, and seizures	Cortical, deep gray and white matter; ischemic lesions on MRI with diffusion sequences
Cytomegalovirus (CMV) [18, 83, 84]	Immunocompromised	Worldwide	Confusion, lethargy, cranial palsies, focal neurological deficits	Periventricular inflammation or meningeal enhancement (not specific)
Epstein-Barr virus (EBV) [18, 85–89, 83]	Immunosuppressed and immunocompetent (children and young adults)	Worldwide	Altered mental status, Alice in Wonderland syndrome, Foix-Chavany-Marie syndrome, seizures, and hemorrhagic meningoencephalitis	Basal ganglia, cerebral cortex, basal ganglia, brainstem, and thalamic lesions.
Human herpesvirus 6 (HHV-6) [18, 90–92]	Immunosuppressed and immunocompetent (children)	Worldwide	Behavior changes; altered mental status, and brainstem manifestations	Mesial temporal lobes
RNA viruses				
Enterovirus [3, 18, 31, 93]	Children	Worldwide	Usually mild, may produce focal neurological deficits, <10% of cases develop severe deterioration of mental status EV-A71 may cause rhombencephalitis (cranial neuropathies, respiratory failure, myoclonus, tremors, ataxia) EV-D68: Brainstem encephalitis	Brain MRI abnormal in 50% of cases, temporal lobes EV-71: midbrain, pons and medulla
Influenza [18, 94, 95]	Children, elderly	Worldwide	Fever, altered mental status, seizures, vomiting, ataxia and focal neurological deficits Acute necrotizing encephalopathy: rare and severe encephalitis. The presence of RANBP2 gene mutation is a predisposing genetic factor	Brain MRI may be normal, in some cases it shows abnormalities of the subcortical white matter and deep gray nuclei or hemorrhages in the thalamus and the pons
Human immunodeficiency virus (acute HIV encephalitis) [18, 96, 97]	Risk factors for HIV: sexual transmission, injection drug use, mother to child transmission	Worldwide	Headache, fever, altered mental status, seizures, agitation, photophobia, focal neurological deficits	Brain MRI: Lesion in cortical sulci, cerebellum, caudate nucleus, splenium, genu of the corpus callosum, pons and thalami
West Nile virus [18, 98, 99]	Elderly, immunosuppressed	USA, Canada, Southeastern Europe, North Africa, Caribbean Islands	Mental status changes, fever, seizures, headaches, meningitis, myelopathic syndromes, polio-like myelitis	Thalamic, temporal lobes, cerebellum, brainstem, basal ganglia lesions
Eastern equine virus [18, 32, 100]	Children <15 years and adults >50 years	Eastern regions of the US	Systemic infection: fever, chills, malaise, arthralgia, myalgia. Encephalitis: fever, headache, behavioral changes (irritability), fatigue, gastrointestinal	Basal ganglia and thalamic lesions

Table 1. (Continued)

Pathogen	Population at risk	Geographic areas	Clinical presentation	Neuroimaging
St. Louis virus [18•, 100–104]	Immunocompromised	Widely distributed throughout North America Southern and eastern Asia	symptoms, convulsions, and altered mental status. Most are asymptomatic, altered mental status and fever.	Substantia nigra lesions
Japanese encephalitis virus [18•, 105, 106]	Children, young adults	Midwestern and mid-Atlantic US	Seizures, extrapyramidal symptoms (choreoathetoid movements, tremor, dystonia and rigidity)	Hippocampus, midbrain, basal ganglia, cerebral cortex lesions
La Crosse virus [18•, 107–109]	Children	Northeastern and Midwest states	Altered mental status, seizures, and coma in rare cases	Adults: no focal cortical inflammation, cerebral edema. Children: focal areas of gadolinium enhancement in cortical areas.
Powassan virus [18•, 110–112]	Elderly	Widely distributed throughout North America United States, Europe, Asia	Prodrome: sore throat, drowsiness, headache, disorientation. Neurological symptoms: loss of coordination, speech difficulties, paralysis, and seizures. Neurologic sequelae: hemiplegia, muscle wasting, severe headaches, memory issues.	Cerebellum, vermis, brainstem, basal ganglia, thalamic lesions
Jamestown Canyon virus [18•, 113]	All age groups	Central and South America, Africa, South Asia	Non-specific febrile illness, mild encephalitis, myelitis and meningitis.	Non-specific
Tick-borne virus [18•, 114–117]	People with recreational or occupational exposure to outdoor settings	Central and South America, Africa, South Asia	The vast majority of cases develop meningitis, rarely meningoencephalitis.	Non-specific T1-weighted contrast enhancement of cerebellar folia, cerebral peduncles, middle cerebral arteries, meninges; T2/FLAIR hyperintensity in thalami, internal capsule, caudate nucleus, basal ganglia.
Dengue [18•, 118, 119]	All age groups within and travelers to endemic areas	Central and South America, Africa, South Asia	Neurological symptoms <10% of people affected. Seizures, cognitive and psychiatric disorders.	Non-specific T2/FLAIR abnormal hyperintensities in cerebellum, thalami, medial temporal lobes, corpus callosum
Chikungunya [18•, 113, 120–123]	All age groups within and travelers to endemic areas	Central and South America, Africa, South Asia	Cases of CNS involvement are rare. Cases reported of encephalitis, optic neuropathy meningitis, myelitis, Guillain-Barre syndrome.	Non-specific Edema or non-specific hemorrhage on CT scan T2/FLAIR hyperintensities or restricted diffusion signal in several areas of the brain Some cases normal brain MRIs
Zika [18•, 113, 124, 125]	All age groups within and travelers to endemic areas	Central and South America, Africa, South Asia	Altered mental status, personality changes, seizures, irritability associated with systemic symptoms (rash, myalgia, arthralgia, fever)	T1 postcontrast with leptomeningeal enhancement, T2/FLAIR extensive superficial gray matter thickening
Other rare RNA viruses Rabies [18•, 126–131]	All age groups	Africa, Asia and South America	Prodromal symptoms: dysautonomia, agitation, fluctuating levels of	Medulla extending to the cervical cord with associated cord expansion,

Table 1. (Continued)

Pathogen	Population at risk	Geographic areas	Clinical presentation	Neuroimaging
Lymphocytic choriomeningitis virus (LCMV) [18•, 132, 133]	All age groups	Worldwide	consciousness, inspiratory muscle spasms, hydrophobia, and aerophobia. Lymphic encephalitis: memory impairment, seizures, sleep disturbances, psychiatric symptoms. Paralytic rabies: coma and flaccid paralysis	hypothalamus, brainstem, gray matter of the spinal cord
Mumps [18•, 134–137]	Children, young adults	Worldwide	First phase: fever, myalgia, GI symptoms, headache. Second phase: symptoms of meningitis or encephalitis	Non-characteristic
Measles [18•, 134, 138]	Children	Worldwide	Altered mental status, cranial neuropathies, movement disorders, language impairment	Lateral, 3rd ventricles and periventricular edema, brainstem, hippocampus
Ebola [139, 140]	All age groups	West Africa	Convulsions, altered mental status, intracranial hypertension, edema and focal neurological symptoms	Cortex, putamen, caudate nucleus
Bacteria			Behavioral changes, altered consciousness, headaches, convulsions, meningeal irritation, hearing impairment, sightlessness.	Microvascular lesions in the white matter
<i>Mycobacterium tuberculosis</i> [18•, 51, 141, 142]	All age groups, immunosuppressed	Worldwide Common in Southeast Asia and South Africa	Severe headache, fever, balance issues, altered mental status and cognitive impairment	Brain MRI commonly normal, but may show granulomas and brain abscess
<i>Listeria monocytogenes</i> [143–146]	Children, elderly, pregnant women, immunosuppressed, diabetes; soil and flowing bodies of water	Worldwide	Rhombencephalitis: cranial neuropathies, nystagmus, ataxia	Brain MRI shows signal abnormalities in T2-weighted and FLAIR located in the brainstem and cerebellum
Fungus				
<i>Cryptococcus</i> [60, 147, 148]	Immunosuppressed, particularly HIV/AIDS; bird droppings	Worldwide	Headache, behavioral changes, cognitive impairment such as memory loss, and lethargy	Brain MRI: Lesions in basal ganglia suggesting cysts, or nodules and leptomeningeal enhancement
<i>Aspergillus</i> [18•, 149–151]	Immunosuppressed	Worldwide	Headache, seizures, altered consciousness, paresthesia and cranial neuropathies	Lesions in the internal capsule, corpus callosum, substantia nigra, mesencephalic lesions, basal nuclei, thalami, brain stem
<i>Histoplasma</i> [18•, 152, 153]	Immunosuppressed	Ohio and Mississippi River valleys America, Africa, Eastern Asia, Australia Southwestern United States,	Headache, confusion, neck stiffness, ataxia, weakness, altered mental status, seizures	Diffuse white matter changes, areas of restricted diffusion, low-density lesions in the cerebellum, subdural hematoma and focal mass lesion.
<i>Coccidioides</i> species [18•, 154]			Disorientation, lethargy, altered mental status, memory impairment	Leptomeningeal enhancement, enhancement in the middle cerebral

Table 1. (Continued)

Pathogen	Population at risk	Geographic areas	Clinical presentation	Neuroimaging
Parasites				
<i>Toxoplasma gondii</i> [18•, 68, 69]	Immunosuppressed, elderly, children, males, pregnancy	Mexico, South America	Language dysfunction, weakness, headache, altered consciousness, and fever	artery, hydrocephalus, infarcts in the left cerebellum, thalami and pons
<i>Acanthamoeba histolytica</i> and <i>Balamuthia mandrillaris</i> (granulomatous amoebic encephalitis) [18•, 155, 156]	Immunosuppressed	Worldwide	Language dysfunction, weakness, headache, altered consciousness, and fever	Brain MRI abnormalities in the basal ganglia, periventricular regions, subcortical regions
<i>Naegleria fowleri</i> (primary amoebic meningoencephalitis) [3, 18•, 156–158]	<i>A. histolytica</i> : immunosuppressed. <i>B. mandrillaris</i> : immunosuppressed and immunocompetent. Freshwater and soil.	Worldwide	<i>A. histolytica</i> : altered mental status, focal neurological deficits, seizures, fever. <i>B. mandrillaris</i> : fever, headaches, GI symptoms, cranial neuropathies, ataxia	CT scan: ring-enhancing lesions Brain MRI: cerebral edema and areas of diffusion restriction suggesting abscess.
<i>Gnathostoma spingereum</i> [18•, 159]	Children and young adults. Freshwater.	Worldwide	Severe throbbing headache, nausea, vomiting, fever, meningismus, seizures and coma in association with a history of swimming or bathing	CT scan: obliteration of the subarachnoid cisterns and the subarachnoid space associated with diffuse enhancement
<i>Baylisascaris procyonis</i> [18•, 160]	All age groups. Exposure to undercooked fish, frogs, snakes, and fowl.	Southeast Asia, particularly in Thailand, Central, and South America	Systemic: vomiting, malaise, diarrhea, anorexia, and fever. Neurological symptoms: headache, weakness, altered mental status.	MRI: hemorrhage and hydrocephalus.
<i>Taenia solium</i> (cysticercosis) [18•, 161]	Children. Raccoon exposure.	North America and Europe	Asymptomatic or severe symptoms: lethargy, ataxia, paralysis, seizures, cranial nerve involvement, spasticity	MRI: deep white matter disease
	All age groups. Acquired by egg ingestion.	Africa, Asia, and Central and South America	Principal symptom: epilepsy and convulsion. Headache, vomiting, sensory deficits, cerebellar ataxia, involuntary movements, dementia, seizures	CT scan and MRI may help to identify cysts with scolex.
Pathogen	Diagnostic tests	Treatment and prevention (IDSA recommendation level) ^a	Typical reasons for admission to the ICU/prognosis	
DNA viruses				
Herpes simplex virus (HSV) [16, 17, 18•, 71, 72, 73•, 77–80]	CSF HSV PCR (sensitivity 98% and specificity 94%) (A-III). If PCR result is negative, the test should be repeated 3–7 days later in patients with a suspicion of HSV encephalitis (B-III).	IV acyclovir 10 mg/kg every 8 h for 14 (A-I) ^a	Altered mental status, respiratory failure, seizures, cerebral edema, intracranial hypertension, stroke. Acyclovir-associated nephrotoxicity. Mortality: 20–30%.	
Varicella zoster virus (VZV) [18•, 21, 81, 82]	Direct fluorescent antibody (DFA) of skin lesions; Serum and CSF VZV IgM CSF VZV PCR (A-III); Brain biopsy (B-III)	IV acyclovir 10 mg/kg every 8 h for 14–21 days (B-III); Ganciclovir (alternative in case acyclovir is not available: C-III). Preventive measures: VZV vaccination with live attenuated varicella vaccine for children: 2 doses, 12 months and 5 years; recombinant zoster vaccine	Coma, respiratory failure. Mortality: >20%.	

Table 1. (Continued)

Pathogen	Diagnostic tests	Treatment and prevention (IDSA recommendation level) ^a	Typical reasons for admission to the ICU/prognosis
Cytomegalovirus (CMV) [18•, 83, 84]	CSF CMV PCR (A-III).	for adults >50 years: 2 doses separated by 2–6 months. Ganciclovir 5 mg/kg every 12 h and Foscarnet 90 mg/kg per day until symptomatic improvement in immunocompromised (B-III). Immunocompetent: same medications (C-III). No specific IDSA recommendation. Supportive. Corticosteroids (C-III). Acyclovir not recommended.	Altered mental status, respiratory failure, weakness. Mortality: without treatment, close to 100%; with treatment, 50%.
Epstein-Barr virus (EBV) [18•, 85–89, 83]	CSF EBV PCR (A-III). Serum antiviral capsid antigen (VCA) IgG and IgM EBV nuclear antigen (EBNA). Serum heterophile antibodies		Status epilepticus, coma, brain edema. Good prognosis in 85% of patients Only few fatal cases
Human herpesvirus 6 (HHV-6) [18•, 90–92]	CSF HHV-6 PCR (sensitivity >95%) (A-III); Serum anti-HHV-6 IgG and IgM; and culture	Ganciclovir 5 mg/kg every 8 h and foscarnet 60 mg/kg every 12 h in immunocompromised persons (B-III) and immunocompetent persons (C-III)	Status epilepticus, coma. Mortality: 50%
RNA viruses			
Enterovirus [3, 18•, 31, 93]	CSF RT-PCR, CSF culture (less sensitive); Nasal swab or stool PCRs may provide diagnosis support.	Supportive; Plecorani and ribavirin under study.	EV-71: cardiac failure, respiratory failure, dysphagia. Mortality EV-71: 14%.
Influenza [18•, 94, 95]	CSF: normal or lymphocytic pleocytosis; Antigen detection, viral culture, and PCR of body fluids (e.g., respiratory tract, nasal swabs).	Oseltamivir 75 mg twice per day for 5 days or more (C-III).	Cerebral edema, respiratory failure, AHLE. Mortality: 9–37%.
Human immunodeficiency virus (acute HIV encephalitis) [18•, 96, 97]	CSF: Lymphocytic pleocytosis, hyperproteinorachie, CSF HIV PCR (CSF viral load); HIV serologic testing.	ART (A-II) Nucleoside reverse transcriptase inhibitors: abacavir, lamivudine, zidovudine. Integrase strand transfer inhibitors: raltegravir and dolutegravir.	Respiratory and cardiovascular dysfunction, stroke, metabolic encephalopathy
West Nile virus [18•, 98, 99]	CSF or serum anti-WNV IgM. Other testing: Viral cultures and CSF RT-PCR, serum and tissue specimens.	No specific IDSA recommendation. Supportive.	Altered mental status/coma, seizures, respiratory failure, generalized weakness, flaccid paralysis. Mortality: 15%, prognosis is poor in elderly patients.
Eastern equine virus [18•, 32, 100]	CSF or serum anti-EEE IgM	No specific IDSA recommendation. Supportive.	Coma, respiratory failure. Mortality: 40%. Morbidity: cognitive impairment, behavioral disorders, seizures, paralysis.
St. Louis virus [18•, 100–104]	CSF or serum anti-St Louis virus IgM	No specific IDSA recommendation. Supportive. Interferon-alpha has been previously used (C-III).	Altered mental status, coma, respiratory failure, status epilepticus, brain edema. Mortality: 5–15%.
Japanese encephalitis virus [18•, 105, 106]	CSF or serum anti-JEV IgM	No specific IDSA recommendation. Supportive. Vaccine available.	Altered mental status, coma, respiratory failure. Mortality: 25%. 40% have sequelae (neurologic, cognitive and psychiatric symptoms).
La Crosse virus [18•, 107–109]	CSF and serum anti-La Crosse virus IgM	No specific IDSA recommendation. Supportive.	Altered mental status, coma, respiratory failure, status epilepticus, intracranial

Table 1. (Continued)

Pathogen	Diagnostic tests	Treatment and prevention (IDSA recommendation level) ^a	Typical reasons for admission to the ICU/prognosis
Powassan virus [18•, 110–112]	CSF or serum anti-Powassan virus IgM (a positive result should be confirmed by neutralizing antibody testing—plaque-reduction neutralization test (PRNT) of serum specimens). Other testing: RT-PCR in serum, CSF, tissue specimens. PRNTs or RT-PCR	No specific IDSA recommendation. Supportive. Some patients have been treated with steroids and IVIg.	hypertension, cerebral herniation. Low mortality. Respiratory failure, cerebellar edema, hydrocephalus, cerebral herniation. Low mortality.
Jamestown Canyon virus [18•, 113]	PCR of whole blood. Serum anti-Tick-borne virus IgG. Immunohistochemistry of organisms in skin or bone marrow.	No specific IDSA recommendation. Supportive.	Intracranial hypertension. Low mortality.
Tick-borne virus [18•, 114–117]	Nucleic acid amplification tests (NAATs). Others: Anti-dengue IgM PRNTs.	No specific IDSA recommendation. Supportive. Vaccine available.	Altered mental status, coma, generalized weakness, stroke.
Dengue [18•, 118, 119]	Serum or CSF anti-Chikungunya virus IgM or RT-PCR	No specific IDSA recommendation. Supportive.	Altered mental status, coma, respiratory failure. High morbidity and mortality.
Chikungunya [18•, 113, 120–123]	Blood or urine Zika virus RT-PCR, IgM serum (ELISA)	No specific IDSA recommendation. Supportive.	Respiratory failure, cerebral edema. Mortality: <1%.
Zika [18•, 113, 124, 125]	Humans: Virus isolation in saliva or reverse transcription followed by RT-PCR, Rabies antibodies in serum and CSF	No specific IDSA recommendation. Supportive.	Cerebral edema, altered mental status, coma, hemodynamic instability. Low mortality.
Other rare RNA viruses			
Rabies [18•, 126–131]	CSF anti-LCMV IgM and IgG CSF LCMV PCR or viral isolation	No specific IDSA recommendation. Supportive. Pre-exposure vaccination schedule: 3 doses over 21 or 28 days. Post-exposure vaccination schedule: If no prior vaccination: 4 doses, first dose should be administered followed by other doses on day 3rd, 7th and 14th. Patient should get a single dose of human rabies Ig. If previously vaccinated: only two doses, first dose should be administered immediately and second on the 3rd day.	Altered mental status, coma, respiratory failure, diabetes insipidus, hemodynamic instability. Mortality rate was close to 100%, but a few cases of survival have been described with therapeutic brain hypothermia (cooling helmet or intranasal cooling), or ketamine.
Lymphocytic choriomeningitis virus (LCMV) [18•, 132, 133]	Serum anti-mumps IgM CSF PCR, IgM, and IgG. Viral isolation from saliva, CSF and urine.	No specific IDSA recommendation. Supportive.	Hydrocephalus, intracranial hypertension.
Mumps [18•, 134–137]	Serum anti-measles IgM. CSF PCR. PCR of nasopharyngeal, throat, or urine	No specific IDSA recommendation. Supportive. MMR Vaccine: 1st dose at 9–15 months of age, 2nd dose at 15 months–6 years of age and should consider one dose in young adults.	Hydrocephalus, increased intracranial pressure, cerebral edema. Mortality: <5%.
Measles [18•, 134, 138]		No specific IDSA recommendation. Supportive. MMR Vaccine: 1st dose at 9–15 months of age, 2nd dose at 15 months–6 years of age and should consider one dose in young adults.	Altered mental status, coma, respiratory failure. Mortality: 15–25%. Sequelae: Seizures and developmental delay, subacute sclerosing panencephalitis (chronic measles infection).

Table 1. (Continued)

Pathogen	Diagnostic tests	Treatment and prevention (IDSA recommendation level) ^a	Typical reasons for admission to the ICU/prognosis
Ebola [139, 140]	CSF and serum viral PCR	Post-measles encephalitis: corticosteroids and IVIg. No specific IDSA recommendation. Supportive. Emerging medications: nucleoside and nucleotide analogs, nucleic acid-based drugs and immunotherapeutic drugs. Available vaccines, look promising	Altered mental status, hypoventilation. Mortality: >90%.
Bacteria			
<i>Mycobacterium tuberculosis</i> [18•, 51, 141, 142]	Gen-Probe Amplified Mycobacterium Tuberculosis Direct test (sensitivity 94%). Quantitative Xpert MTB/RIF PCR CSF culture. Microorganism isolation from other body fluids	Isoniazid, rifampicin, pyrazinamide, and ethambutol for 2 months, followed by a combination of 2 medications for 9–12 months (A-III). Isoniazid 4–6 mg/kg/day + pyridoxine 10–25 mg/day Rifampicin 10 mg/kg/day Pyrazinamide 20–40 mg/kg/day (without exceeding 2 g/day) Ethambutol 15 mg/kg/day Alternative: fluoroquinolones (moxifloxacin) Dexamethasone in meningitis (B-I). Amoxicillin 200 mg/kg/day divided into 4 to 6 infusions and gentamicin 5–6 mg/kg/day as one infusion for 5 days (A-III). Alternative: trimethoprim-sulfamethoxazole (A-III).	Stroke, hydrocephalus, brain abscesses, brain edema. Mortality: 30%. Sequelae in 70% of cases (cranial neuropathies, cognitive and motor deficits).
<i>Listeria monocytogenes</i> [143–146]	CSF or blood cultures CSF PCR		Hydrocephalus, intracranial hemorrhage. Mortality: 51% but may be 20–30 if treatment is promptly started. Sequelae in 61% of cases (tetraparesis, seizures and cognitive dysfunction).
Fungus			
<i>Cryptococcus</i> [60, 147, 148]	Cryptococcal antigen in serum or CSF. Cryptococcal culture. Alternatives: India ink, cryptococcal PCR.	Induction: IV amphotericin B 3–4 mg/kg/day + oral flucytosine 100 mg/kg/day in four divided doses for 2 weeks (A-I). Consolidation: oral fluconazole 6–12 mg/kg/day for 8 weeks. Maintenance: oral fluconazole 200–400 mg/day for 1 year. Lumbar punctures to release intracranial pressure (A-II). Corticosteroids may prevent inflammatory complications. Voriconazole (B-I). Alternatives: liposomal amphotericin B (B-I).	Intracranial hypertension
<i>Aspergillus</i> [18•, 149–151]	Immunodiffusion assays in blood and CSF, CSF culture or direct visualization by Indian ink or others.		Acute respiratory distress syndrome, respiratory failure, sepsis.
<i>Histoplasma</i> [18•, 152, 153]	Visualization of the yeast in CSF. Histoplasma antigen and Histoplasma antibody in CSF. Urine for Histoplasma antigen, yeast in sputum or blood. Complement fixing or immunodiffusion antibodies tests in serum or CSF, CSF culture isolation.	Liposomal amphotericin B for a period of 4–8 weeks followed by itraconazole for at least 1 year or until CSF normalization (B-III). Fluconazole (A-II). Alternatives: Itraconazole (B-II), Voriconazole (B-III), Amphotericin B (C-III).	Respiratory failure, hydrocephalus, stroke
<i>Coccidioides</i> species [18•, 154]			Hydrocephalus, subarachnoid hemorrhage

Table 1. (Continued)

Pathogen	Diagnostic tests	Treatment and prevention (IDSA recommendation level) ^a	Typical reasons for admission to the ICU/prognosis
Parasites			
<i>Toxoplasma gondii</i> [18•, 68, 69]	IgG and IgM antibodies against <i>T. gondii</i> . Parasite isolation from body fluids or tissues RT-PCR.	Pyrimethamine 200 mg loadings followed by 50–75 mg every 24 h PO with sulfadiazine 1–1.5 g every 6 h PO or clindamycin 600–1200 mg q6 hours IV or PO for 3–6 weeks (A-I). A. <i>histolytica</i> : trimethoprim-sulfamethoxazole, ketoconazole and rifampin (C-III). Alternative: fluconazole, sulfadiazine, and pyrimethamine (C-III). B. <i>mandrillaris</i> : macrolide, fluconazole, pentamidine, sulfadiazine, flucytosine, and a phenothiazine (C-III). Amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered (C-III).	Cerebral edema, intracranial hypertension Cerebral edema. Mortality: 98%.
<i>Acanthamoeba histolytica</i> and <i>Balamuthia mandrillaris</i> (granulomatous amoebic encephalitis) [18•, 155, 156]	A. <i>histolytica</i> : the visualization of trophozoites or cysts and biopsy. B. <i>mandrillaris</i> : The majority of cases postmortem. Serologic testing and analysis of brain biopsy.		
<i>Naegleria fowleri</i> (primary amoebic meningoencephalitis) [3, 18•, 156–158]	Isolation of trophozoites by PCR		Intracranial hypertension, cardiac arrhythmias, myocardial necrosis. Mortality: 95%, only 3 patients have survived.
<i>Gnathostoma spingegerum</i> [18•, 159]	CSF: Eosinophilia >10%, glucose normal or slightly reduced. Presence of worms in tissues.	Albendazole (B-III) or ivermectin (B-III). Prognosis is unknown, but full recovery is seen in most cases. Mortality is low. Sequelae occur in 50% of patients.	Intracerebral hematoma, hydrocephalus
<i>Baylisascaris procyonis</i> [18•, 160]	CSF: eosinophilia Anti-Baylisascaris antibodies in CSF and serum by immunofluorescence, ELISA, and Western blotting. Brain biopsy may demonstrate the presence of the larva.	Albendazole + diethylcarbamazine (C-III). Adjunctive corticosteroids (B-III).	Hydrocephalus, cerebral edema, status epilepticus
<i>Taenia solium</i> (cysticercosis) [18•, 161]	Immunoblot against glycoprotein fraction of cyst fluid. CSF antibodies, cysts in brain MRI	Albendazole + corticosteroids (B-III). Praziquantel as an alternative (C-II).	Cerebral edema, Status epilepticus, hydrocephalus, intracranial hypertension, coma.

CSF cerebrospinal fluid, PCR: Polymerase chain reaction, ELISA enzyme-linked immunosorbent assay, IgM immunoglobulin M, IgG immunoglobulin G, FLAIR fluid-attenuated inversion recovery, Ig immunoglobulin, IDSA The Infectious Diseases Society of America, US United States, EV-71 enterovirus 71, AHLE acute hemorrhagic leukoencephalitis, ART antiretroviral treatment, GI gastrointestinal, RT-PCR reverse transcriptase polymerase chain reaction, PRNTs plaque-reduction neutralization tests, JEV Japanese encephalitis virus, EEE: eastern equine encephalitis virus, CT computed tomography, MRI magnetic resonance imaging, EITB enzyme-linked immunoelectrotransfer blot techniques, CFTs complement fixation tests, IHA indirect hemagglutination test a: Levels of recommendation for management of encephalitis according to IDSA clinical guideline. Strength of recommendation: A=Good evidence to support management, B=moderate evidence, C=poor evidence. Quality of evidence: I=more than one randomized, controlled clinical trial, II=more than 1 non-randomized clinical trial, multiple time-series analysis, observational studies (cohort and case-controlled studies), or significant results from uncontrolled experiments. III=Expert opinions of encephalitis authorities, descriptive studies. [18•, 162]

Metagenomic NGS offers a comprehensive evaluation of viral, bacterial, parasitic, and fungal infections by deep sequencing of the RNA or DNA of fluids or tissue samples. This method involves isolation and sequencing of RNA and DNA from CSF specimens, followed by computational analysis for identification of non-human pathogens based on the known sequences of viruses, bacteria or fungi available in genomic databases. [9••] Advantages of mNGS include its unbiased approach as it does not require prior assumptions regarding the type of pathogen and thus allows for the discovery of more potential and unusual pathogens (e.g. leptospirosis, dengue, toxoplasmosis, *Balamuthia mandrillaris*). [170–173] In a prospective study of over 200 patients (58 of whom had an infection of the nervous system), mNGS identified 32 (55%) patients with infection, 13 of whom (22%) were not diagnosed by hospital clinical testing. [9••] In addition, mNGS may complement conventional testing in ruling out co-infections and supporting clinical diagnoses, such as in autoimmune encephalitis, where providers may more readily initiate systemic immunosuppression in the setting of results excluding an occult infection.

Clinicians have adopted the “tumor board” concept from oncology to discuss mNGS results to guide their clinical decisions. Even though the usefulness of mNGS results is still under study, this novel technique provides more information than just “positive” and “negative” results from methods such as PCR, cultures or serologic testing. [9••] However, disadvantages of mNGS include the potential of false-positive results due to sample contamination either by normal body flora, environment, or laboratory procedures or misidentification errors in the computational bioinformatics approach. [174] In addition, mNGS interpretation remains challenging as a lack of standardized thresholds for reporting a positive test and the adoption of conservative clinical references have consequently resulted in a high percentage of false-negative results. [9••] In addition, this technique depends on the presence of nucleic acids in CSF, a factor that may limit diagnosis of pathogens that have a short-lived presence in the CNS or have a very low “pathogen-load” in the CSF such as WNV, VZV, or neurosyphilis. In fact, 26 (44%) of 58 infections described in the prospective study previously discussed, were not diagnosed with either mNGS or conventional testing, but through serologic testing only. [9••]

In terms of costs, the median length of hospitalization stay of an encephalitis patient ranges from 3 to 13 days, with average costs of care being \$ 60,000. [175, 176] Major contributing factors to costs of care and length of hospitalization are difficulty in the identification of culprit pathogens and the extensive evaluations employed to rule out infection. [177] mNGS may prove to be a useful diagnostic tool for rapid pathogen identification; however, current associated costs and availability of testing have delayed its widespread adoption. Recently, demographic and health care criteria have been explored in specific patient populations where mNGS may prove cost-effective in evaluating for infectious meningitis and encephalitis. These include those patients who had undergone a neurosurgical procedure, were admitted to the ICU, were co-infected with HIV-1 or had undergone a previous organ transplant, were less than 1 year of age, or had been hospitalized for at least 2 days. [175] Further study is needed to truly determine

the benefits and associated costs of mNGS to guide its broader adoption in the evaluation of patients with suspected infectious encephalitis.

Neurophysiological tools in the ICU

In cases of persistently altered consciousness, continuous EEG (cEEG) monitoring for at least 24 h is helpful to exclude intermittent seizures and status epilepticus. [71] Approximately 50% of patients with nonconvulsive seizures will be detected by conventional EEG. In contrast, cEEG detects about 95% of nonconvulsive seizures cases between 24 and 48 h of recording. [178] The American Clinical Neurophysiology Society recommends EEG if there is persistent altered mental status despite treatment; unknown etiology of altered consciousness; and evidence of generalized, lateralized, and bilateral independent periodic discharges. [179]

Complications of infectious encephalitis in the ICU

Critical care management in the setting of encephalitis is frequently driven by depressed mental status, seizures, respiratory failure, stroke, hydrocephalus and intracranial hypertension due to cerebral edema. Adequate management of these complications is critical to minimize both morbidity and mortality and ensure improved clinical outcomes.

Encephalopathy and decreased mental status

A great majority of patients with infectious encephalitis develop encephalopathy and decreased mental status; however, only 15% are unconscious and require intensive care management. [3] Encephalitis can involve the diencephalon and brainstem structures, affecting the reticular activating system (RAS), or may also produce cerebral edema and subsequent intracranial hypertension interfering with the normal cerebral blood perfusion, both leading to altered consciousness and coma.

Seizures and status epilepticus

Seizures are a frequent manifestation of infectious encephalitis, mostly as a result of cerebral cortex involvement. For instance, seizures affect about 85% of patients with JEV and 10% of patients with WNV infections. [180] Status epilepticus (SE) and refractory status epilepticus (RSE) are common complications of encephalitis, particularly nonconvulsive seizures.

SE is a continuing seizure activity for more than 5 minutes or repetitive seizures without recovery among episodes. Rapid seizure control is critical to decreasing the likelihood of additional neurologic damage or more systemic complications such as rhabdomyolysis, lactic acidosis, aspiration, and pulmonary problems. [181]

Acute treatment of seizures includes the initial standard of care with IV lorazepam administered 2 mg every 1–2 min (maximum dose 0.1 mg/kg). A second agent should be administered if lorazepam is inadequate to abort

seizures. These options include phenytoin, fosphenytoin, levetiracetam, valproate, and lacosamide. [181]

If convulsive seizure activity persists despite the use of two drugs, then the patient is likely in RSE. In this scenario, the patient should be sedated with an IV medication, for example, midazolam (1–2 mg/kg/h) or propofol (50–80 µg/kg/min), and intubated. [3] Quantitative EEG is useful for titrating therapy and evaluating seizure control. There is no consensus for an ideal level of EEG suppression; nevertheless, the recommendation is to reduce burst suppression pattern and decrease seizure recurrence through deep sedation for at least one day. [3]

Recent non-controlled clinical studies suggest that an alternative therapy for uncontrollable seizures with inadequate response to antiepileptic medications is the ketogenic diet (KD). It is a high-fat and low carbohydrate diet that induces ketone bodies and has been useful in drug-resistant epilepsy in children and adults. The KD has been used in patients with Rasmussen encephalitis, anti-NMDAR encephalitis, and post-infectious mycoplasma encephalitis with success, and it is a potential therapy option. [182] A recent study in a tertiary referral center demonstrated seizure control in 73% of patients with super RSE after two days of treatment with the diet. [183••]

Neuromuscular weakness

Neuromuscular weakness is a frequent sequela in critically ill patients, affecting more than 25% of patients in the ICU. It may be caused by a myopathy, polyneuropathy or a combination of both. The most common form of neuromuscular weakness is ICU-associated myopathy. This condition is characterized by the loss of myosin, myofibrillar disorganization, and necrosis. [184, 185] The use of glucocorticoids appears to be related to this process. [186] ICU-related polyneuropathy is the second most frequent cause of weakness and it is probably associated with microvascular compromise that produces ischemia and axonal degeneration. [187]

Clinical presentation includes flaccid quadriplegia typically affecting proximal more than distal muscles, weaning failure from mechanical ventilator, hyporeflexia, and impaired sensation. The presentation, examination, and electrodiagnostic tests (nerve conduction studies and electromyography; NCS and EMG) may help with the diagnosis. In the setting of myopathy, NCS and EMG demonstrate low motor amplitudes with a prolonged action potential, and decreased phrenic motor amplitudes, while sensory function is usually preserved. In contrast, neuropathy is frequently characterized by decreased motor and sensory amplitudes on NCS, fibrillation potentials on EMG, and reduced phrenic motor amplitudes. [188]

Management is centered on the treatment of the principal medical condition, physical therapy, decreasing sedation, and avoiding complications (e.g., pulmonary embolism and deep venous thrombosis). Despite the paucity of evidence related to the use of corticosteroids, the recommendation is to reduce these medications as soon as possible.

Cerebral edema and intracranial hypertension

Cerebral edema, intracranial hypertension, and herniation are potential complications of encephalitis, with a mortality rate of approximately 60%. [189,

190] Cerebral edema is defined as swelling of the brain that may become life-threatening when the intracranial pressure reaches levels above 25 cm water, leading to ischemia and herniation. Many infectious encephalitides, such as HSV and VZV encephalitis, can lead to vasogenic edema and intracranial hypertension. [3] In suspected cases, diagnostic imaging or intracranial pressure measurement may be considered.

Patients with cerebral edema and associated intracranial hypertension treated aggressively have better outcomes. [191, 192] Aggressive care includes the use of osmotic agents such as mannitol or hypertonic saline, sedation, induced hypothermia, hyperventilation, surgical brain decompression, control of fever, and management of seizures. Other general recommendations include reducing the period that the patient remains in a supine position, elevating the head at least 30°, and avoiding hyponatremia. [3]

Implementation of corticosteroids has been proposed as adjunctive therapy; however, clinical data is still limited to support their use. Despite this fact, combination therapy of acyclovir and corticosteroids may be considered in VZV and EBV encephalitis. [18•, 193, 194] In addition, consensus regarding corticosteroids dosage and duration in encephalitis does not exist, but prednisone at 1 mg/kg for 3–5 days has been described for VZV encephalitis. [195]

Stroke

Cerebrovascular disease occurs in a variety of CNS infections, including encephalitis, often requiring intensive care with a generally poor prognosis. [196] Strokes in the setting of infectious encephalitis may be associated with the primary infectious disease process and specific pathogen (e.g., HSV, VZV) or due to secondary factors such as increased brain edema and transtentorial herniations. Most of the infection associated cases of stroke have been reported with HSV, VZV, and CMV infections. The presence of a stroke may distract the medical team from the correct diagnosis and treatment. Thus, it is essential to consider other alternative diagnoses when the clinical picture is atypical. Treatment of the infection is the primary approach for this complication.

Hydrocephalus

Hydrocephalus is the result of an obstruction in the CSF pathway or alteration of CSF production that more frequently affects children and adolescents. [197] In infectious processes, the mechanism appears to be mediated by the desquamation of ependyma with a posterior mechanical obstruction or cross-linking between ependymal cells. [198] Also, the accumulation of particles in the aqueduct, the narrowest structure of the CSF system, stimulates this process. Numerous cases have been reported with HSV-2 infection. [199] Hydrocephalus may be life-threatening and should be treated with medical and surgical interventions. [200]

Conclusion

Infectious encephalitides include a diverse group of pathogens, including viruses, which together represent a frequent type of encephalitis. The prompt diagnosis and adequate treatment of the primary infection, as well as the management of associated complications, are crucial for better outcomes and

fewer neurological sequelae. Intensivists play a fundamental role in the management of patients with infectious encephalitis, particularly in the initial evaluation and treatment as well as the management of complications. ICU-level management is critical, given the high associated rate of mortality and the critical role of ICU-level intervention in outcomes and survival.

Compliance with Ethical Standards

Conflict of Interest

The authors report no conflicts of interest with this work.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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