Infectious Encephalitis
A Persistent Clinical Challenge

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KEYWORDS

• Encephalitis review • HSV encephalitis • West Nile virus • Acyclovir
• Next-generation sequencing • Lumbar puncture

KEY POINTS

- Encephalitis is characterized by altered mental status, fever, seizures, and abnormal MRI or electroencephalogram findings, and needs cerebrospinal fluid (CSF) analysis for diagnosis.
- Infectious encephalitis is often viral, commonly caused by herpes simplex virus, varicella-zoster virus, enteroviruses, or West Nile virus, though 50% of cases remain undiagnosed.
- Initial management involves empiric therapy for bacterial meningitis and timely high-dose IV acyclovir for viral causes, with doxycycline added if tick-borne pathogens are suspected.
- If standard testing is inconclusive, metagenomic next-generation sequencing of CSF or brain biopsy may be considered.

INTRODUCTION

Encephalitis can be defined as an inflammatory process within the brain parenchyma that leads to altered mental status.[1] The term is sometimes incorrectly interchanged with "encephalopathy," which is primarily noninflammatory dysfunction of the cerebrum (usually metabolic, toxic, or ischemic), and "meningoencephalitis," in which meningeal irritation predominates or coexists with altered mental status.[2] Encephalitis is either a consequence of direct infection of brain parenchyma or subsequent inflammatory process, or may be from autoimmune phenomena such as anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis.[3,4] The focus of this review will be on infectious encephalitis.

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Abbreviations	
AIE	autoimmune encephalitis
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computed tomography
EEG	electroencephalogram
EVE	enterovirus encephalitis
HIV	human immunodeficiency virus
HSV	herpes simplex virus
HSV-1	herpes simplex virus-1
HSVE	HSV encephalitis
ICH	immunocompromised host
ICU	intensive care unit
IgG	immunoglobulin G
IgM	immunoglobulin M
IVIG	intravenous immunoglobulin
JEV	Japanese encephalitis virus
LCMV	lymphocytic choriomeningitis virus
LFT	liver function tests
LP	lumbar puncture
mNGS	metagenomic next-generation sequencing
NAAT	nucleic acid amplification techniques
NMDAR	N-methyl-D-aspartate receptor
OP	Opening pressure
PCR	polymerase chain reaction
RBCs	red blood cells
SOT	solid organ transplant
TBE	tick-borne encephalitis
VZV	varicella zoster virus
WBC	white blood cell
WNV	West Nile virus

EPIDEMIOLOGY AND BURDEN OF DISEASE

Encephalitis affects individuals of all ages and has high rates of morbidity and mortality. Due to inaccurate reporting systems, the true incidence is likely unknown.[5] However, recent international reports have estimated approximately 1.4 million incident cases of encephalitis with 89,000 associated deaths per year.[6] Meanwhile, in the United States, there are an estimated 20,000 encephalitis-associated hospitalizations per year. These hospitalizations are costly; in 2010, they cost an estimated US$2 billion with an average 11.2 day length of stay.[7] Mortality from encephalitis varies widely by pathogen but estimates range from 5.8% to 17% in those requiring intensive care unit (ICU) level of care.[7,8] Recovery following encephalitis often takes months to years, and it is estimated that 26% to 62% of adult survivors struggle with neurologic sequelae including neurocognitive disabilities, epilepsy, and inability to perform tasks of daily living.[5]

CLINICAL PRESENTATION

Per the International Encephalitis Consortium, the clinical definition of encephalitis requires the major criterion of altered consciousness, with either 2 (for possible) or 3 (for confirmed) minor criteria, including fever greater than 38°C, seizures, neurologic deficits, cerebrospinal fluid (CSF) white blood cell (WBC) greater than 5 and abnormal brain imaging/electroencephalogram (EEG; **Box 1**).[9]

Box 1
Clinical criteria for the diagnosis of encephalitis

Major criterion (required):
- Altered mental status for ≥24 h with no alternative cause identified (eg, decreased level of consciousness, personality change, or psychiatric manifestations)

Minor criteria (2 for possible encephalitis; ≥3 for probable or confirmed encephalitis):
- Fever ≥38°C (100.4°F)
- Seizures without a preexisting seizure disorder
- New onset focal neurologic deficit
- CSF WBC count ≥5/mm^3
- New abnormality of brain parenchyma on neuroimaging
- Abnormal EEG

Data from IEC Guidelines.[9]

A thorough history can provide important clues in the diagnosis of infectious encephalitis. Fever, though common, may be absent due to antipyretic drug intake. Other important details that point toward specific pathogens include season, geographic location, travel, sick contacts, animal exposures, occupation, and recreational hobbies. For instance, outdoor activities like hiking and gardening increases the risk of arthropod-borne infections. Such risk can be further subdivided by geographic location, with Lyme most prevalent in the Northeast United States, *Ehrlichia* in the Mid-Atlantic, and eastern equine encephalitis seen in these areas as well as the Gulf Coast. Other specific exposures include freshwater as a risk factor for *Naegleria fowleri* amebic encephalitis and unpasteurized dairy products as a source for *Listeria monocytogenes*. In addition to fever and neurologic deficits, certain physical examination findings can point to a diagnosis of infectious encephalitis. For example, vesicular skin eruptions can be seen in encephalitis secondary to varicella-zoster virus (VZV), regional lymphadenopathy is typically seen in those with *Bartonella*, and a diffuse petechial rash is characteristic of infections with *Rickettsia* spp.[1,9,10] These epidemiologic associations and clinical findings are further summarized in **Table 1**.

PATHOGENESIS

The proposed pathophysiology of infectious encephalitis is via direct invasion of neurotropic microbes into the central nervous system (CNS), which causes cytokine release and localized inflammation. This, in turn, increases permeability of the blood–brain barrier (BBB) and allows for perivascular lymphocytic infiltration.[11] In a study analyzing 38 host inflammatory mediators in serum and CSF specimens from patients with encephalitis, a proinflammatory cytokine response was associated with greater BBB permeability, more significant imaging findings, and more severe symptoms, suggesting that host inflammatory response is directly correlated to disease course.

The pathogenesis of herpes simplex virus (HSV) encephalitis (HSVE) is of particular interest due to its large burden of disease. Classically, HSVE is associated with hemorrhagic necrosis with tropism to the temporal lobe.[12] Although antivirals are effective at achieving viral clearance from the CNS, patients with HSVE often still suffer significant morbidity from marked cerebral edema related to the host inflammatory response. Studies have shown that specific leukocyte subsets, namely CXCL1-CXCR2 (Chemokine (C-X-C motif) ligand 1 and Chemokine (C-X-C motif) ligand 2) play a role in neutrophils crossing the BBB, thereby representing another potential therapeutic target to limit neutrophil-mediated morbidity in HSV encephalitis.[13]

Table 1
Epidemiologic and clinical clues for the diagnosis of encephalitis

Epidemiology or Risk Factor	Possible Infectious Etiology
Animals	
Bats	Nipah virus and rabies virus
Birds	Eastern equine encephalitis virus, Western equine encephalitis virus, and *Cryptococcus neoformans*
Cats	*Bartonella henselae*, *Coxiella burnetii*, and *T gondii*
Animal urine	*Leptospira* spp
Rodents	LCMV
Mosquitos/ticks	
Northeastern United States, mid-Atlantic	*A phagocytophilum*, *B burgdorferi*, and Powassan virus
Coastal Northeastern, Gulf Coast, and Great Lakes	*Eastern equine encephalitis virus*
Eastern and Central States	*St Louis encephalitis virus*
Southeastern, East South-central regions	*E chaffeensis* and *R rickettsii*
Outdoor Exposure	
Freshwater	*Leptospira* spp and *N fowleri*
Soil	*Acanthamoeba* spp and *Balamuthia mandrillaris*
Ingestions	
Undercooked meat	*T gondii*
Unpasteurized milk	*Coxiella burnetii*, *L monocytogenes*, and TBE virus
International Travel	
South America	*Bartonella bacilliformis*, *R rickettsii*, rabies virus, Venezuelan equine encephalitis virus, Western equine encephalitis virus, *Plasmodium falciparum*, and *Taenia solium*
Africa	Rabies virus, West Nile virus, *P falciparum*, and *Trypanosoma brucei gambiense*
Europe	*A phagocytophilum*, *B burgdorferi*, TBE virus, and West Nile virus
India and Nepal	Japanese encephalitis virus, rabies virus, and *P falciparum*
China, Pacific Rim, and Southeast Asia	Japanese encephalitis virus, Nipah virus, TBE virus, *Gnathostoma* spp, *P falciparum*, and *Taenia solium*
Unvaccinated	Measles virus, mumps virus, rubella virus, poliovirus, Varicella Zoster virus
Clinical Findings	**Possible Infectious Etiology**
Acute flaccid paralysis	Enteroviruses, Rabies virus, and West Nile virus
Cranial nerve abnormalities	*B burgdorferi*, *L monocytogenes*, *Mycobacterium tuberculosis*, *T pallidum*, *Tropheryma whipplei*, Epstein-Barr virus, Herpes Simplex virus, *C neoformans*, *Histoplasma capsulatum*
Hepatitis	*Coxiella burnetii*
Lymphadenopathy	*Bartonella henselae*, *T pallidum*, CMV, Epstein–Barr virus, Measles virus, rubella virus, and West Nile virus

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Table 1
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Clinical Findings	Possible Infectious Etiology
Parkinsonism	Japanese encephalitis virus, Nipah virus, St Louis encephalitis virus, West Nile virus, and *T gondii*
Petechial rash	*R rickettsia*
Vesicular rash	Varicella-zoster virus

Data from IDSA guidelines.[1]

Etiologies

A review of encephalitis publications found that a high proportion of cases (21%–72%) remain undiagnosed.[14]

The most reported organisms from diagnosed cases in the United States include HSV, VZV, enteroviruses, and West Nile virus (WNV), which will be reviewed in later discussion.

Herpes simplex virus

Herpes simplex virus-1 (HSV-1) is the single most common cause of sporadic encephalitis worldwide, accounting for approximately 20% of annual viral encephalitis cases.[15] HSV-1 is nonseasonal; most cases occur in those aged over 50 years, with both sexes equally affected.[16] HSVE usually results from the reactivation of latent virus from the trigeminal ganglion with spread to the olfactory bulb.[17]

Immunocompetent patients with HSVE often present with prodromal symptoms of upper respiratory tract, nonspecific fever, or headache. Without treatment, these symptoms can progress to encephalopathy, seizures, and focal neurologic deficits over several days.[12] CSF analysis in HSVE typically shows a lymphocytic pleocytosis with white blood count ranging from 10 to 400 cells/μL, an elevated protein, and a normal glucose.[18] Common findings on MRI include asymmetric hyperintense lesions on T2-weighted sequences corresponding to areas of edema and hemorrhagic necrosis in the mesiotemporal/orbitofrontal lobes and the insular cortex.[19] It should be noted that recent data has shown that up to 22% of HSVE cases may have no CSF pleocytosis.[20]

HSVE should be distinguished from HSV meningitis with the latter marked by signs of meningeal irritation (eg, headache, nausea, vomiting, fever, and neck stiffness) without significant change in mental status or focal findings on head imaging. In contrast to encephalitis, most patients with HSV meningitis do not need antiviral treatment, unless immunocompromised.[21]

To diagnose HSVE, polymerase chain reaction (PCR) for HSV-1 and HSV-2 obtained from the CSF has a high sensitivity and specificity (~99%). Nevertheless, false-negative PCR can occur early in the illness, and if clinical suspicion is high, repeat CSF HSV PCR should be obtained within 3 to 7 days while continuing antiviral treatment.[22] The first-line treatment of HSVE is high-dose intravenous acyclovir.[23]

Poor prognostic features in HSVE include age greater than 30 years, a Glasgow Coma Score less than 10, extensive brain involvement on MRI, and delay in initiation of acyclovir.[24,25] Potential reasons for delayed acyclovir initiation include severe underlying comorbidities, alcohol use disorder, delay in brain imaging, and absence of CSF pleocytosis.[26] Despite treatment, neurologic or cognitive deficits persist in more than 70% of survivors.[12]

The incidence and significant morbidity of HSVE highlight the need to maintain a high index of suspicion for HSVE in patients presenting with signs and symptoms of

encephalitis. Empiric and early initiation of intravenous acyclovir is recommended and should only be discontinued once the diagnosis of HSVE has been definitively excluded.

Varicella-zoster virus

VZV is the second most common cause of encephalitis in adults.[27,28] After primary infection with VZV, the virus becomes latent in the dorsal root ganglion. It can then reactivate in immunocompromised individuals and spread along neurons to cause a wide spectrum of CNS disease including encephalitis, meningitis, and vasculopathy via infection of intracranial arteries. Though rates of encephalitis from VZV reactivation are low, the burden of VZV encephalitis remains significant given VZV ubiquity.[29] Greater than 90% of the world's population harbors latent VZV and greater than 50% will reactivate by the age of 85 years and develop some form of disease.[30]

VZV encephalitis is frequently thought of as a complication of the more common shingles rash. However, VZV encephalitis can occur before, during, or after dermatomal zoster lesions erupt, with up to one-third of cases having no abnormal skin findings.[31] VZV vasculopathy, a related syndrome, can present as strokes, aneurysm, dissection, or other vascular abnormalities. As with VZV encephalitis, one-third of patients with VZV vasculopathy do not have a zoster rash prior to presentation and in those with a rash, the average time from rash onset to neurologic symptoms is 4 months.[32]

Diagnosis of VZV CNS disease is supported by a positive CSF VZV PCR. Due to the low sensitivity of CSF VZV PCR, CSF VZV immunoglobulin G (IgG) is an additional diagnostic tool, which increases sensitivity to greater than 90%.[33] In contrast to VZV encephalitis, a diagnosis of VZV vasculopathy is supported by evidence of ischemic lesions on brain imaging.[34]

As with HSVE, VZV CNS disease is treated with intravenous acyclovir. Prognosis of VZV encephalitis, however, remains poor. In a multicenter cohort study of patients admitted to ICUs with VZV encephalitis, only one-third of patients had a favorable neurologic outcome at 1 year, and ICU mortality was 25%.[35] It is, therefore, imperative to start empiric intravenous acyclovir treatment when VZV CNS disease is suspected and only definitively rule it out if both CSF VZV PCR and IgG are negative.

West Nile virus

WNV is an arbovirus, maintained in nature by a mosquito–bird–mosquito transmission cycle, which was first detected in 1999 after a cluster of encephalitis cases in New York City.[36] Between 2009 and 2018, a total of 1328 cases were reported annually in the United States, with the majority of cases occurring in the mosquito active season between July and September. This makes WNV the leading cause of domestically acquired arboviral disease in the United States.[37]

The majority (70%–80%) of WNV infections are asymptomatic.[37] Symptomatic patients typically develop an acute systemic febrile illness; fewer than 1% of those infected develop neuroinvasive disease, which can present as encephalitis (53%), meningitis (37%), or acute flaccid paralysis (7%).[37] Risk factors for developing neuroinvasive disease secondary to WNV are age greater than 70 years, male sex, and an immunocompromised state, especially solid organ transplant receipt.[38]

In encephalitis secondary to WNV, detection of WNV immunoglobulin M (IgM) antibody in serum or CSF forms the cornerstone of diagnosis.[39] However, WNV IgM can persist in the serum for greater than 1 year after initial infection, so serologic results should be interpreted cautiously.[40] Patients with humoral immune defects may benefit from checking serum WNV PCR in lieu of IgM, as antibody production may

be impaired.[41] The CSF profile in WNV encephalitis typically demonstrates an elevated protein (<150 mg/dL) with a moderate lymphocyte-predominant pleocytosis (<500 cells/μL). These are not exclusive criteria; however, in a study of 250 patients with confirmed WNV neuroinvasive disease, a significant proportion of patients (~37%) had neutrophil-predominant pleocytosis, and a few (~5%) had zero WBCs in CSF.[42]

Unfortunately, no effective antiviral treatment or vaccine is available for WNV encephalitis, and the mortality rate remains significant, at 10% to 14%.[37] Immunologic therapies including intravenous immunoglobulin (IVIG) have been studied, but the data are mixed. In animal models, IVIG has demonstrated anti-inflammatory activity against WNV.[43] In contrast, a subsequent randomized placebo-controlled trial of IVIG for WNV encephalitis did not show a morbidity or mortality benefit, with the caveat that the trial was designed to determine the safety of IVIG (which was demonstrated) as opposed to efficacy.[44] It may, therefore, be safe and reasonable to consider IVIG in select patients with WNV neuroinvasive disease who are not improving.

Enteroviruses

Enteroviruses cause approximately 5% of all cases of acute encephalitis. Although the majority of confirmed enterovirus encephalitis (EVE) cases occur in children, adults constitute up to one-third of cases.[45] The most reported EVE serotypes are Coxsackie and Echovirus subtypes. Other serotypes, specifically Enterovirus A71 and D68, can directly affect the brainstem and have been implicated in cases of acute flaccid myelitis.[46,47]

Clinical features of EVE are usually indistinguishable from other causes of encephalitis. EVE is characterized by less severe disease and better outcomes compared to encephalitis from other viruses. Diagnosis can be challenging, as EVE CSF viremia is exceedingly brief, leading to limited sensitivity even on modern PCR assays. Moreover, the presence of enterovirus in non-CNS sites, such as respiratory or stool specimens, or serologic evidence (eg, a positive serum IgM) should be interpreted cautiously, as viral shedding persists for months after initial infection and does not prove causation.[45]

No optimal treatment of EVE exists, although some studies suggest that IVIG may have benefit due to the potential association of immunoglobulin deficiencies with EVE. Optimal dosing of IVIG remains debated.[48]

ENCEPHALITIS IN THE RETURNING TRAVELER

For international travelers returning to the United States with signs and symptoms of encephalitis, additional pathogens must be considered.

Japanese encephalitis virus (JEV) is endemic throughout Asia and parts of the Western Pacific region, with recent emergence in Australia.[49] JEV is a mosquito-borne flavivirus with an incubation period of 5 to 15 days that can lead to severe symptomatic neuroinvasive disease; it is diagnosed by the detection of JEV-specific IgM in CSF or serum. Corticosteroids and interferon alfa-2a have been studied as potential therapeutics, but in randomized controlled trials, neither demonstrated a mortality benefit.[50,51] IVIG has been shown to be safe in the treatment of JEV, but large trials to assess for efficacy are pending.[52] Most importantly, the JEV vaccine provides greater than 90% protection and is recommended for travelers to endemic regions staying for greater than 1 month.[53]

Those returning from Eastern Europe and western Asia are potentially susceptible to tick-borne encephalitis (TBE) virus, a flavivirus transmitted by the *Ixodes ricinus* tick.

TBE is characterized by a biphasic disease with an initial nonspecific febrile illness followed by signs of encephalitis approximately 1 week later. TBE vaccination can be considered in select individuals traveling to affected areas who anticipate prolonged tick exposure. Treatment is mainly supportive.[54]

Travelers with exposures to undomesticated animals (such as dogs and bats) are susceptible to encephalitis secondary to rabies virus, a lyssavirus transmitted via animal saliva.[55] Rabies encephalitis may present with additional symptoms like hypersalivation and hydrophobia caused by autonomic stimulation. Unlike other infectious etiologies, the incubation period can range from a few months to years following exposure, highlighting the importance of postexposure prophylaxis with rabies immune globulin and vaccination when indicated.[56]

Finally, other emerging international pathogens linked to encephalitis include mosquito-borne Chikungunya virus in Central and South America, and mite-born scrub typhus (*Orientia tsutsugamushi*) in South Asia.[57]

IMMUNOCOMPROMISED HOST

Infectious encephalitis in the immunocompromised host (ICH) can be associated with atypical clinical presentations and laboratory results, leading to delayed diagnosis. For instance, ICH with HSVE may have fewer prodromal symptoms, a lack of CSF pleocytosis, and significant extratemporal involvement on imaging.[58] Similarly, in VZV encephalitis in ICH, CSF pleocytosis may be absent, and vasculopathy is typically confined to the small vessels.[32] As well, a large comparative study found significantly higher rates of infectious encephalitis in ICH as compared to the general population, including both common causes (eg, HSV-1), but also rarer etiologies including cytomegalovirus (CMV) and *Cryptococcus*.[59]

Of special consideration are solid organ transplant (SOT) recipients, whose risk for encephalitis includes donor-derived infections. A US survey from 2002 to 2013 identified multiple clusters of donor-derived WNV encephalitis and rabies encephalitis, as well as more esoteric diagnoses including lymphocytic choriomeningitis virus (LCMV) and *Balamuthia* granulomatous amebic encephalitis.[60] Morbidity and mortality rates are also higher in SOT recipients; for instance, a cohort of kidney and pancreas SOT recipients exhibited a WNV encephalitis mortality rate of approximately 25%, as opposed to 4% in immunocompetent individuals.[61] As such, it is generally recommended to proceed with caution or reject organs from deceased donors with concern for infectious encephalitis, especially if the etiology is incurable or otherwise unknown.[62]

Assessment of encephalitis in ICH, therefore, requires a thorough screen for subtle signs and symptoms, a broad infectious differential, and a low threshold to start empiric therapy.

AUTOIMMUNE ENCEPHALITIS

Though infectious etiologies are more common, physicians should also consider the possibility of autoimmune encephalitis (AIE). AIE encompasses multiple syndromes and includes anti-NMDAR encephalitis, autoimmune limbic encephalitis, postinfectious autoimmune encephalitis, and demyelinating conditions such as acute disseminated encephalomyelitis.[63]

Suggested diagnostic criteria for AIE include (1) subacute onset (<3 months) of memory deficits, altered mental status, or psychiatric symptoms with some combination of new focal CNS findings, (2) seizures not explained by a previously known seizure disorder, CSF pleocytosis, and MRI features suggestive of encephalitis; and

(3) reasonable exclusion of alternative causes including infection.[64] In cases of suspected AIE, immunomodulatory therapies should be considered expeditiously, as delayed initiation is associated with poor clinical outcomes.[65]

Autoimmune sequelae following infectious encephalitis has been well documented, most notably anti-NMDAR following HSVE. Up to approximately 25% of patients with HSVE develop antineuronal antibodies, usually within 2 months of initial infection, and typically respond to immunotherapy such as high-dose corticosteroids, IVIG, and plasma exchange.[66]

Diagnostics

When infectious encephalitis is suspected, crucial initial testing includes CSF sampling (ie, lumbar puncture) with analysis, CNS imaging, and EEG. It is essential not to delay lumbar puncture (LP) unnecessarily. The principal reason for considering CNS imaging prior to LP is to rule out an intracranial abnormality with elevated intracranial pressure that could increase the risk for brain herniation.

Current Infectious Diseases Society of America (IDSA) guidelines for meningitis (which have been interpolated in clinical practice to encephalitis) recommend head computed tomography (CT) prior to LP if (1) immunocompromised state (ie, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome and SOT), (2) history of CNS disease (known mass lesion and stroke), (3) new-onset seizure, (4) papilledema, (5) abnormal level of consciousness, or (6) focal neurologic deficit[67] (**Fig. 1**). On the other hand, a Swedish study challenging these guidelines found that early LP in patients with meningitis presenting with altered mental status, seizures, and/or an immunocompromised state was associated with decreased mortality.[68]

We recommend a balanced approach of these conflicting recommendations; that is, in suspected encephalitis, CT head should precede LP only if there is clear suspicion for a cerebral mass, clinical signs of herniation, or profound immunosuppression, so as not to delay diagnostics.

The following approach to diagnostic testing is recommended by the IDSA guidelines on encephalitis management.[1]

CEREBROSPINAL FLUID ANALYSIS IN ENCEPHALITIS

- Opening pressure (OP)
  - OP greater than 25 mm Hg suggests increased intracranial pressure and need for ICU level of care
- Cell count and differential, protein, and glucose
  - An abnormal CSF cell count is defined as greater than 4 nucleated cells/mm^3.
  - Viral encephalitis is typically lymphocyte predominant but can be neutrophil predominant early in the course. Persistent neutrophilic pleocytosis has been observed in patients with WNV encephalitis.[42]
  - HSVE can be characterized by elevated red blood cells (RBCs) in the CSF. If significant RBCs are seen, it is recommended to apply the following correction formula:
- Corrected WBC = Reported CSF WBC − [(WBC in peripheral blood × RBC in CSF)/(RBC in peripheral blood)][69]
  - The presence of CSF eosinophils may suggest certain etiologic agents (ie, helminths, *Treponema pallidum*, *Mycoplasma pneumoniae*, *Rickettsia rickettsii*, *Coccidioides immitis*, and *Toxoplasma gondii*).
  - CSF protein is abnormal when greater than 30 mg/dL. It is generally mildly or moderately elevated in infectious encephalitis.

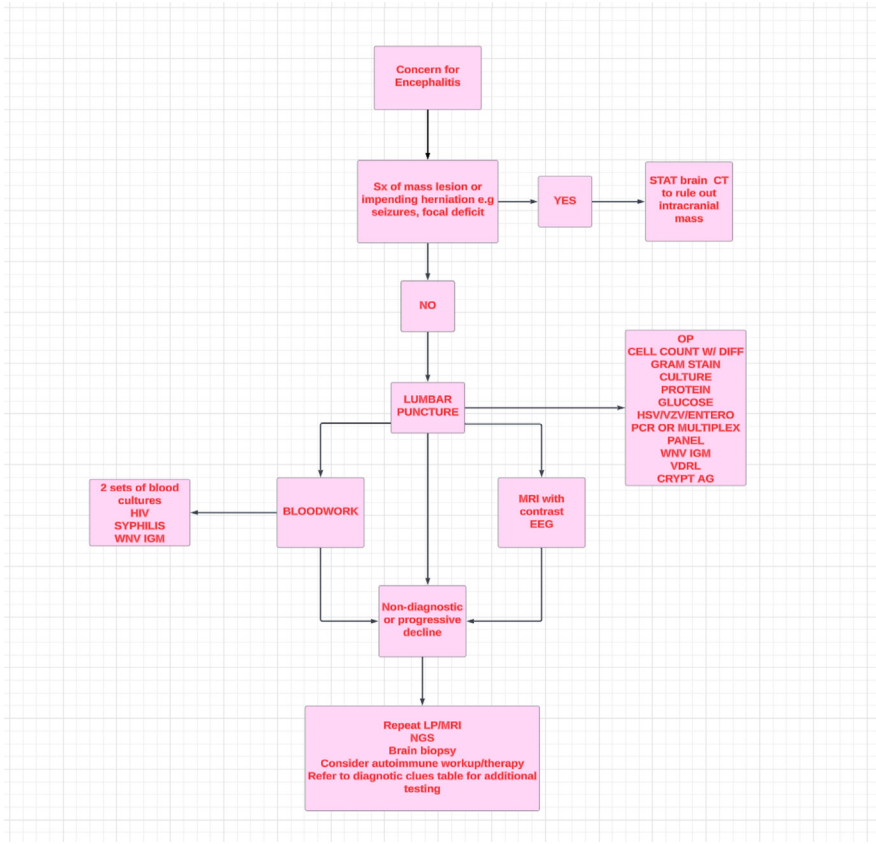

Fig. 1. Core diagnostic evaluation in infectious encephalitis.

- A CSF glucose level less than 40% of simultaneous blood glucose is considered low. Decreased CSF glucose is unusual in viral encephalitis and suggests disease caused by bacteria (eg, *L monocytogenes* and *M tuberculosis*), fungi, or protozoa (eg, *Naegleria* species).
- Up to 10% of patients with viral encephalitis have normal CSF findings.

- CSF culture
  - Culture may diagnose nonviral etiologies (eg, bacterial and fungal), though some species (eg, *Mycoplasma*, *Bartonella*, *Ehrlichia*, and *Rickettsiae* species and *T pallidum*) cannot be isolated in culture. Viral culture is of no benefit.
- Nucleic acid amplification techniques (NAAT)
  - NAAT testing, including PCR assays, can rapidly diagnose viral etiologies including HSV, VZV, and enteroviruses. Multiplex panels for multiple pathogens have been shown to decrease length of stay and improve patient outcomes.[70,71]
  - Limitations of NAAT testing include risk for false negatives in early HSVE (repeat testing in 3–7 days if suspicion is high) and risk for detection of less clinically relevant reactivation of Epstein-Barr virus and human herpes virus 6 in immunocompetent individuals.[72]
- Repeat LP or neurodiagnostic testing should be pursued when no cause is identified or for patients who experience progressive clinical decline.

BLOODWORK

- Obtaining a basic metabolic panel, complete blood count, liver function tests (LFT), coagulation profile, inflammatory markers (C-reactive protein and erythrocyte sedimentation rate), screening HIV and syphilis testing, and blood cultures are recommended.
- Serology can be particularly helpful in the diagnosis of tick-borne (eg, *Rickettsia*, *Ehrlichia*, and *Anaplasma* spp) and arboviral (ie, WNV) encephalitis.

IMAGING

- CT and MRI are most frequently used to evaluate patients with encephalitis, with MRI being more sensitive and specific. The MRI must include Fluid-Attenuated Inversion Recovery (FLAIR), diffusion, T2, and T1 sequences with and without gadolinium as well as venous and arterial vascular sequences. These imaging studies can assess anatomic burden of disease, rule out intracranial mass, and investigate concomitant vasculopathy.

ELECTROENCEPHALOGRAM

- EEG should be performed in patients who present with seizures or severely depressed mentation to exclude nonconvulsive status epilepticus.
- In approximately 80% of patients with HSVE, there is a temporal focus demonstrating periodic lateralizing epileptiform discharges.
- The severity of abnormal EEG findings does not usually correlate with the extent of disease in the acute phase of illness, but rapidly improving EEG findings often indicate a good prognosis.

NEXT-GENERATION SEQUENCING

Metagenomic next-generation sequencing (mNGS) is a novel molecular technique that can identify nucleic acids within a specimen. While commercially available multiplex PCR panels report the most common organisms, mNGS technology can identify unexpected and novel pathogens by sequencing all DNA content in a sample and comparing sequences to a genomic library. Some barriers to incorporating mNGS testing into routine encephalitis diagnoses are lack of access to specialized laboratories, high cost, and long turnaround time.[73] However, studies of patients with CNS infections of unknown etiology tested via conventional methods (eg, multiplex NAAT) have been able to identify etiologies of encephalitis in select patient groups via mNGS of CSF.[74] Direct mNGS analysis of brain tissue samples has also shown success in diagnosing infectious causes of encephalitis.[75] In contrast, other studies caution that the sensitivity of NGS may be inferior to standard amplification-based assays.[76] Though data are mixed, some international encephalitis guidelines recommend regular use of mNGS in cases of negative results by conventional methods when clinical suspicion is high.[77] Further studies are needed to determine the comparative utility of mNGS and the optimal patient population for its use as an adjunct to conventional diagnostic microbiology.

BRAIN BIOPSY

Brain biopsy should be considered when no diagnosis is made on initial testing. The highest yield anatomic site should be sampled and at least 1 cm^3 of tissue be removed. A portion of the sample should be sent for pathogen isolation, PCR,

immunofluorescence, mNGS, and electron microscopy; a second portion should be placed in formalin and sent for routine histopathologic examination, with appropriate staining for infectious agents.[1] Though brain biopsy is an invasive procedure, recent large series of brain biopsies reported low frequencies of permanent neurologic morbidity and mortality, between 0% and 4% and between 0% and 3%, respectively.[78] In addition, the diagnosis rate of encephalitis by brain biopsy approaches 31%, a rate expected to increase when mNGS is more regularly applied.[79]

Management

Management of infectious encephalitis is a persistent clinical challenge. Approximately 50% of patients with encephalitis require ICU admission, with a mortality rate of 17%.[80] Predictors of mortality in infectious encephalitis include cerebral edema, status epilepticus, and thrombocytopenia.[81] The initial management of encephalitis should focus on optimization of respiratory status and hemodynamic stabilization. Once the patient is stabilized, the cornerstone of management of infectious encephalitis comprises of empiric, and if applicable, targeted antimicrobial therapy.

ANTIBACTERIAL THERAPY

It is difficult to clinically distinguish bacterial meningitis from meningoencephalitis. The risk of neurologic impairment and death is significantly increased with delay in initiating antibacterials for bacterial meningitis.[82] Therefore, empiric therapy to cover relevant bacterial pathogens should be initiated promptly and can be discontinued once CSF cultures are negative at 48 to 72 hours and/or bacterial PCR testing is negative (**Fig. 2**). Recommended empiric antibiotics for adult community-acquired meningitis are intravenous vancomycin and ceftriaxone (cefepime or meropenem if immunosuppressed), and ampicillin if age is greater than 50 years.

Empiric doxycycline should be initiated when the season and geography are compatible with a tick-borne infection (eg, *Anaplasma phagocytophilum*, *Borrelia burgdorferi*, *Ehrlichia chaffeensis*, and *R rickettsii*). Severely ill patients may require greater than 48 hours of treatment before clinical improvement is noted.[83] Of note, globalization and climate change have contributed to an increased incidence of vector-borne pathogens in the United States, and delaying treatment can lead to severe disease, long-term sequelae, or death.[84]

ANTIVIRAL THERAPY

Regardless of the initial clinical presentation of encephalitis, early initiation of intravenous acyclovir to target HSV and VZV is universally recommended. No definitive exclusion criteria have been established that preclude the need for acyclovir in all patients presenting with presumed encephalitis.[85] Additionally, delay in initiation of acyclovir is a well-documented poor prognostic factor in HSVE.[25] If untreated, HSVE has a mortality rate of approximately 70%, though this diminishes to about 15% with treatment, thereby emphasizing its importance.[12,23]

When there is high clinical suspicion for HSVE, acyclovir should be continued even if the initial CSF HSV PCR is negative, with repeat testing performed in 3 to 7 days. CSF HSV PCR has a high sensitivity but is not infallible; case reports have confirmed diagnosis of HSVE only on autopsy despite negative CSF HSV PCR results.[86]

The recommended dose of intravenous acyclovir is 10 mg/kg every 8 hours, renally adjusted. Renal adjustment is essential in efforts to prevent acyclovir-induced crystalline nephropathy.[87] Immunocompetent patients with HSVE who show signs of improvement should complete a 14 day course; immunocompromised patients or

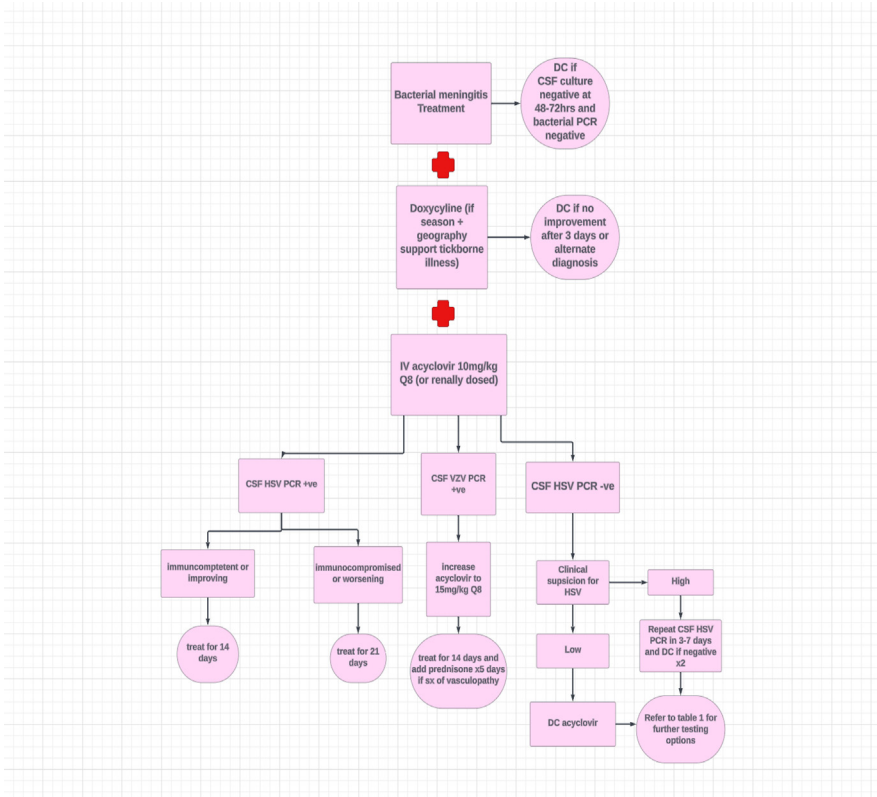

Fig. 2. Empiric antimicrobial therapy in infectious encephalitis.

those without significant improvement can extend acyclovir treatment to 21 days. Repeating CSF HSV PCR to guide treatment duration or prognosis is not recommended.[77] Finally, acyclovir resistance, while rare, can be seen in immunocompromised patients. No consensus exists on treatment, although foscarnet has shown some promise.[88]

VZV encephalitis treatment recommendations are based on case series alone.[30] The role of time-to-acyclovir start, dose, and duration of acyclovir remain poorly characterized for VZV encephalitis as compared to HSVE. As with HSVE, intravenous acyclovir for 14 days is recommended in VZV, which can be increased to 15 mg/kg every 8 hours if the suspicion for VZV CNS disease is high, as demonstrated either by a positive CSF VZV PCR/IgG or by the presence of a vesicular rash.[77]

CORTICOSTEROIDS AND IMMUNOMODULATORY THERAPY

Thus far, retrospective studies have not demonstrated a benefit to corticosteroid use in infectious encephalitis.[89]

It is theorized that the use of corticosteroids in HSVE may downregulate the inflammatory response and help prevent autoantibody formation and autoimmune sequelae.[63] While small case series suggest a potential benefit for adjunctive corticosteroids in the treatment of HSVE, clinical trial validation is lacking.[90] A multinational randomized controlled trial is currently underway in efforts to answer this important clinical question.[91]

As opposed to HSVE, in VZV vasculopathy, a short course of oral prednisone (1 mg/kg daily for 5 days) has shown some benefit. In a case series of 30 patients, improvement or stabilization of neurologic deficits was seen in 75% of those treated with both acyclovir and steroids compared to 66% of those treated with acyclovir alone.[32]

The use of other immunomodulatory therapies (eg, IVIG in enterovirus and West Nile virus) in infectious encephalitis has been investigated but is not well defined.[44,48]

FUTURE DIRECTIONS

With regards to diagnostics, it is hoped that the increasing use of mNGS may help reduce the high percentage of encephalitis cases that currently remain undiagnosed. However, controlled trials are needed to determine optimal patient population, specimen, and timing for mNGS use. With regards to therapeutics, time-to-starting acyclovir is the only modifiable factor affecting morality in infectious encephalitis to date; thus, general provider education on recognizing encephalitis and initiating early empiric treatment is vital. The infectious burden of HSVE and VZV encephalitis remains high, and additional studies investigating novel antivirals and the role for corticosteroids are needed and currently underway.[91] In addition, climate change and globalization have made neurotropic arboviruses including WNV increasingly more common. Preliminary data on a potential West Nile vaccine (ChimeriVax-WN02 - Sanofi Pasteur, Lyon, France) has shown it to be safe and effective in multiple age groups, but trials have yet to progress beyond phase II.[92] In the absence of promising therapeutics for vector-borne etiologies of encephalitis, prevention (eg, mosquito repellant and checking for ticks) is key.

Infectious encephalitis remains a prevalent clinical challenge with significant burden of disease. Current best practices for this syndrome involve understanding the subtleties of its varied presentation, prioritizing CSF sampling with broad diagnostic testing, and initiating timely empiric therapy.

CLINICS CARE POINTS

- Encephalitis is defined by altered mental status in the setting of at least 2 of fevers, seizures, new neurologic deficits, CSF WBC greater than 5, and abnormal MRI or abnormal EEG findings.
- The most important diagnostic step for encephalitis is LP with CSF analysis.
- CT head is recommended before LP only if a cerebral mass is suspected, for example, immunocompromised state, seizures, and focal neurologic deficits.
- Up to 50% of encephalitis cases remain undiagnosed.
- Most diagnosed infectious causes of encephalitis are viral, for example, HSV, VZV, enteroviruses, and West Nile virus.
- Key diagnostics for encephalitis include CSF cell count, protein, glucose, and bacterial culture, CSF HSV PCR, VZV PCR, VZV IgG, enterovirus PCR, and WNV IgM.
- mNGS testing of CSF or brain biopsy should be considered when initial testing is negative for cause of encephalitis symptoms, or for travelers to areas of known outbreaks of vector-borne infections.
- MRI with contrast is the imaging modality of choice for patients with encephalitis.
- All encephalitis patients should receive empiric bacterial meningitis therapy + high-dose IV acyclovir.

- If season and geography support a tick-borne cause of encephalitis, empiric doxycycline should also be started.
- Steroids and immunomodulatory agents have no clear role in infectious encephalitis.

DISCLOSURE

The authors have nothing to disclose.

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