Clinical Infectious Diseases

STATE-OF-THE-ART REVIEW

State of the Art: Acute Encephalitis

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Encephalitis is a devastating neurologic disease often complicated by prolonged neurologic deficits. Best practices for the management of adult patients include universal testing for a core group of etiologies, including herpes simplex virus (HSV)-1, varicella zoster virus (VZV), enteroviruses, West Nile virus, and anti–N-methyl-D-aspartate receptor (anti-NMDAR) antibody encephalitis. Empiric acyclovir therapy should be started at presentation and in selected cases continued until a second HSV-1 polymerase chain reaction test is negative. Acyclovir dose can be increased for VZV encephalitis. Supportive care is necessary for other viral etiologies. Patients in whom no cause for encephalitis is identified represent a particular challenge. Management includes repeat brain magnetic resonance imaging, imaging for occult malignancy, and empiric immunomodulatory treatment for autoimmune conditions. Next-generation sequencing (NGS) or brain biopsy should be considered. The rapid pace of discovery regarding autoimmune encephalitis and the development of advanced molecular tests such as NGS have improved diagnosis and outcomes. Research priorities include development of novel therapeutics.

Keywords. encephalitis review; anti-NMDAR antibody encephalitis; HSV-1 encephalitis; next-generation sequencing; West Nile virus encephalitis.

Encephalitis is a devastating neurologic condition associated with both infectious and autoimmune causes. The healthcare burden of encephalitis is significant: The average duration of hospitalization is 11 days, with a case-fatality rate of 5%–6% [1, 2]. Mortality varies widely across studies and by pathogen. For example, most children with La Crosse virus encephalitis recover fully; in contrast, the mortality with rabies virus approaches 100%. Recovery following encephalitis often takes months to years, and many survivors struggle with significant neurologic sequelae. Total charges for encephalitis-associated hospitalizations in the United States in 2010 were estimated at $2.0 billion [1].

The age-adjusted incidence of encephalitis has remained stable at 5 cases per 100 000 US population between 1990 and 2017 [3]. However, the emergence of new infectious agents, the recognition of an increasing number of autoimmune conditions causing encephalitis, and the rapid development and implementation of molecular diagnostics have led to major changes in the management of this condition since the publication of Infectious Diseases Society of America (IDSA) guidelines on encephalitis in 2008 [4].

This update aims to highlight recent developments in acute encephalitis and provide an evidence-based and practical approach to the management of this complex patient population. Given the unique features of encephalitis in neonates, discussion is limited to adults and children older than 6 months. In the many areas where data are lacking, expert opinion is provided.

CASE DEFINITION

Encephalitis is defined as inflammation of brain parenchyma associated with neurologic dysfunction [4]. Hybrid presentations such as meningoencephalitis or, less commonly, encephalomyelitis occur. As pathologic confirmation of brain inflammation is rarely performed, clinical correlates are necessary to support the diagnosis.

Criteria developed by the International Encephalitis Consortium in 2013 for syndromic surveillance have subsequently been widely adopted for use in clinical practice (Table 1) [5]. These criteria were intentionally crafted to be independent of an underlying diagnosis and are contingent on excluding alternative causes.

INFECTIOUS CAUSES OF ENCEPHALITIS

Pathogens causing encephalitis include common infections that rarely involve the central nervous system (eg, herpes simplex virus [HSV]-1) or uncommon pathogens with recognized neurotropism (eg, rabies virus). For some organisms, causality remains uncertain. For example, coronavirus disease 2019

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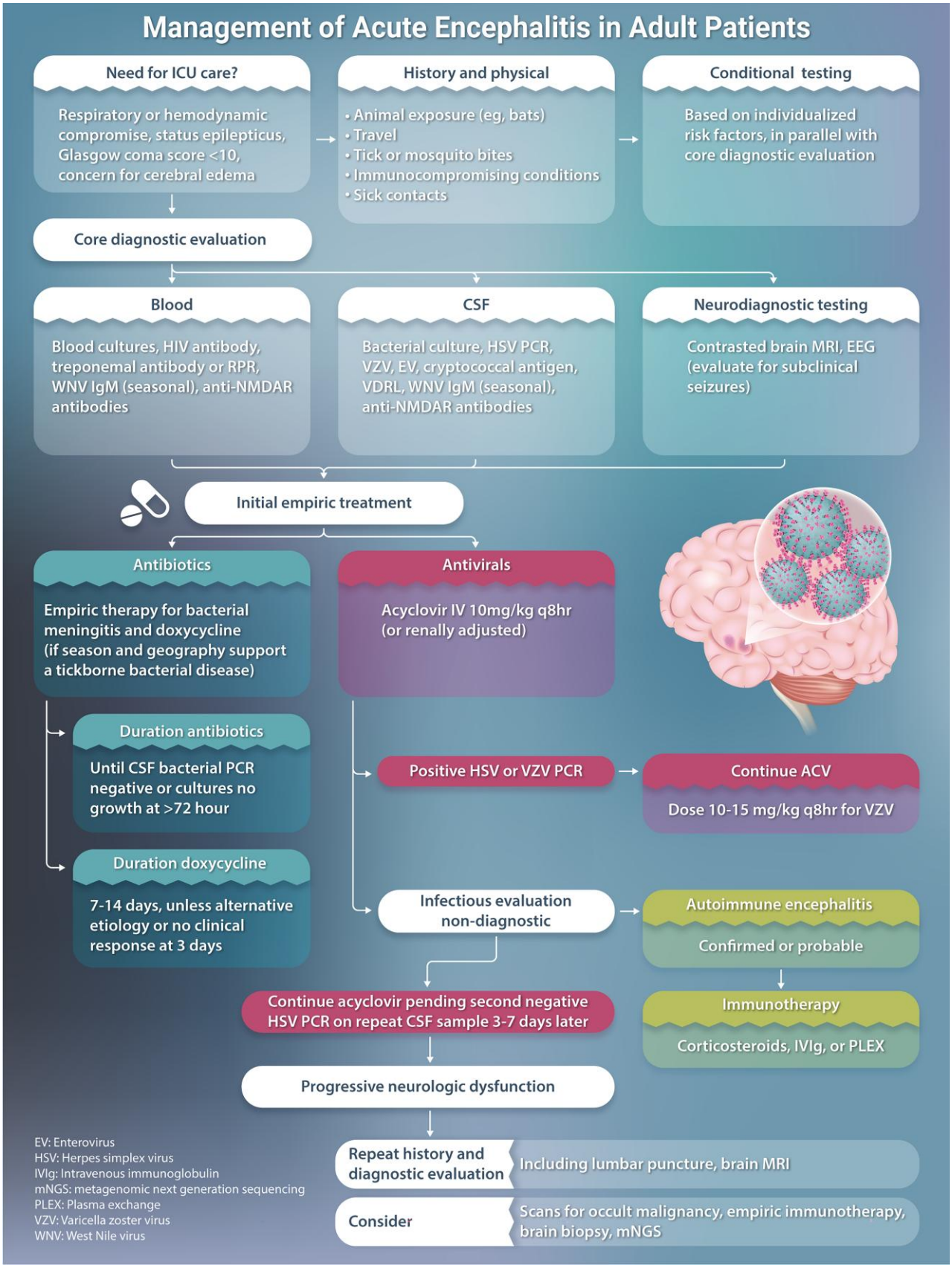

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Table 1. Clinical Criteria for the Diagnosis of Encephalitis

Clinical Criteria
Major criteria (both required)
• Decreased level of consciousness, personality change, or psychiatric manifestations lasting >24 h (in toddlers and infants, may present as increased irritability or lethargy)
• No alternative diagnosis to explain presentation
Minor criteria (presence of ≥2 in addition to both major criteria above)
• Fever (≥38.0°C)
• Seizure (new onset)
• Focal neurologic findings (new onset)
• CSF WBC ≥5/mm^3
• Acute abnormality on brain MRI
• Abnormal EEG consistent with acute neurologic dysfunction

Adapted from reference [5].

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalography; MRI, magnetic resonance imaging; WBC, white blood cell count.

(COVID-19) has been associated with significant neurologic debility [6], but severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is rarely detected in cerebrospinal fluid (CSF) or identified in postmortem brain tissue [7], suggesting that the pathophysiology is not due to direct brain infection.

Infectious etiologies of encephalitis vary significantly by age [8, 9] and geography [10] (Figure 1). One commonality is the high frequency of encephalitis of unknown etiology. A review of encephalitis publications between 2000 and 2015 found that 21%–72% of cases remain undiagnosed [10]. Even with the use of molecular diagnostics, no etiology is identified in more than 50% of cases [1, 2, 11, 12]. Recent publications have reported a lower proportion of unidentified cases [13, 14], likely reflecting increased recognition of autoimmune conditions such as anti–N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis [15]. Inability to identify an etiology is a source of frustration for clinicians, patients, and families; setting realistic expectations about the likelihood of making a diagnosis should be done at the onset of care.

PATHOGENS OF UNIVERSAL IMPORTANCE

The pathogens below are leading causes of encephalitis globally. These core pathogens should be included in the diagnostic evaluation of all patients with suspected encephalitis (Table 2). Diagnosis and management are discussed in more detail in subsequent sections.

Herpes Simplex Virus-1

Herpes simplex virus-1 is the leading identified cause of encephalitis globally and accounts for more than one-third of diagnosed cases in the United States [1, 2, 10]. Herpes simplex encephalitis (HSE) disproportionately affects older adults, with a median age of 57 years [16]. In contrast to arboviral infections, and to a lesser degree enteroviruses (EVs), there is no seasonality to HSE. Herpes simplex virus-2 infrequently causes encephalitis outside of the neonatal period but can cause disease in immunosuppressed patients [17]. Herpes simplex encephalitis results from reactivation of latent virus with spread to the olfactory bulb or, less frequently, can occur at the time of acute infection; orolabial lesions are present in a minority of cases.

Classically, HSE presents as a necrotizing temporal lobe encephalitis, although cases not fitting this profile are increasingly recognized. Atypical presentations including ischemic stroke or intracranial hemorrhage [16, 18–20] are most commonly reported in children [21, 22] and immunocompromised individuals [23, 24]. Herpes simplex encephalitis in patients receiving whole-brain irradiation [25] or following a neurosurgical procedure [26] may be difficult to recognize, leading to a delay in initiation of acyclovir.

Despite acyclovir therapy, mortality remains at 5%–10% and neurologic or cognitive deficits persist in more than 70% of survivors [27]. Poor prognostic features include age greater than 30 years, Glasgow Coma Score of 10 or less, extensive brain involvement on magnetic resonance imaging (MRI), and delay in initiation of acyclovir [28, 29]. This latter variable represents a modifiable risk factor, underscoring the importance of starting empiric therapy at the time of presentation and continuing until the diagnosis has been definitively excluded [30].

Varicella Zoster Virus

The epidemiology of varicella zoster virus (VZV) encephalitis has shifted with the introduction of the pediatric varicella vaccination in 1995. Varicella zoster virus is the second leading identified cause of encephalitis in adults after HSV-1 [10], while rates in children have declined significantly [31, 32]. Immunocompromised patients are disproportionately affected, with more severe illness seen in this population.

Central nervous system (CNS) infection in unvaccinated children occurs at the time of primary varicella infection (chickenpox) with wild-type virus. Varicella zoster virus can rarely cause encephalitis following immunization due to the vaccine strain. These cases, which may occur years after vaccination, are typically attenuated compared with infection with wild-type virus [32, 33].

Following primary infection, VZV establishes latency within the dorsal root ganglion along the neuroaxis. Varicella zoster virus encephalitis in adults is due to viral reactivation, and CNS manifestations can occur before, during, or after dermatomal zoster lesions erupt. Varicella zoster virus encephalitis in the absence of typical skin findings ("zoster sine herpete") has been reported in up to one-third of cases [34]. A related syndrome, VZV vasculopathy, is caused by reactivated virus infecting intracranial arteries and may present with ischemic or hemorrhagic strokes, cerebral aneurysms, arterial dissection, cerebral venous thrombosis, or spinal artery thrombosis [35].

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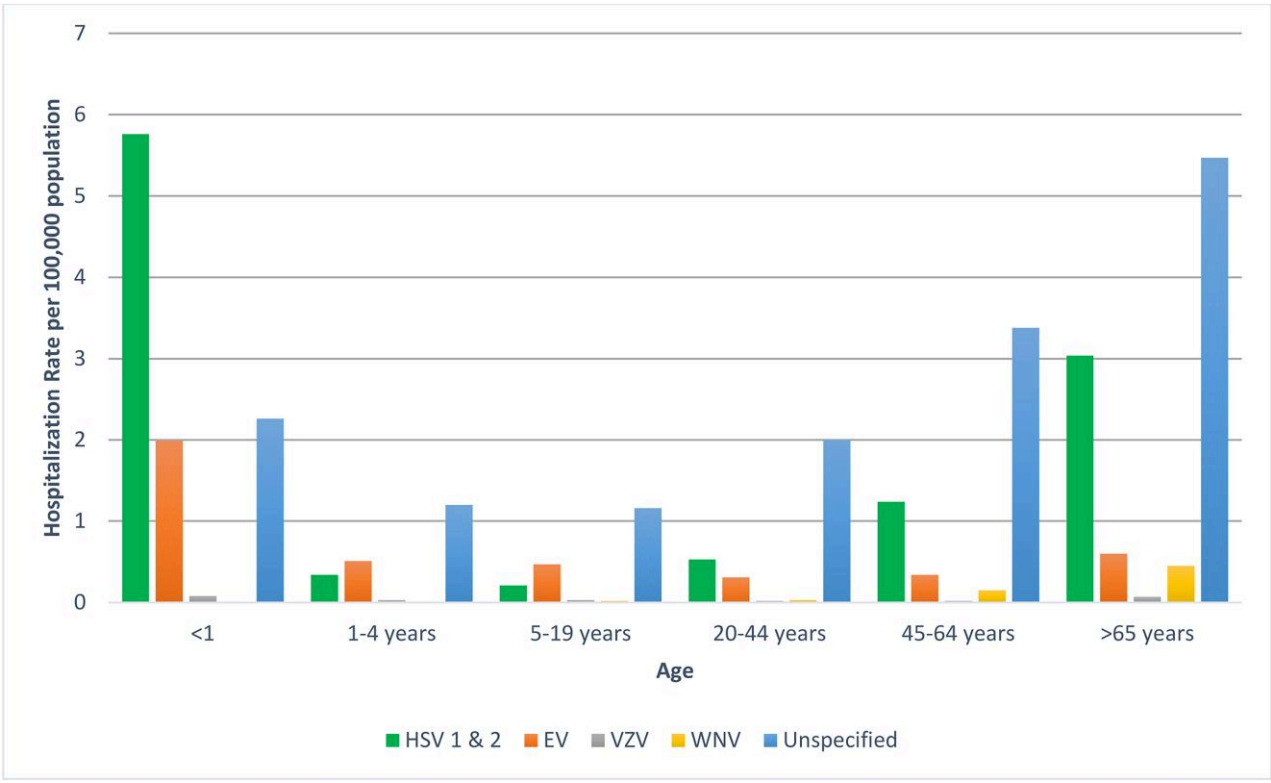

Figure 1. Encephalitis hospitalizations by age and cause, United States, 2000–2010. Abbreviations: EV, enterovirus; HSV, herpes simplex virus; VZV, varicella zoster virus; WNV, West Nile virus. Adapted from reference [2].

In contrast to encephalitis, CSF polymerase chain reaction (PCR) is less sensitive than intrathecal antibody measurement for the diagnosis of VZV vasculopathy [36].

West Nile Virus

West Nile virus (WNV), first detected in the United States in 1999 following a cluster of encephalitis cases in New York City, has subsequently emerged as a leading cause of epidemic encephalitis. The number of West Nile neuroinvasive disease (WNND) cases in the United States varies, with a median of 1328 cases reported annually between 2009 and 2018 [37]. The majority of cases present between July and September when mosquitos are active in temperate climates [37].

Most WNV infections are asymptomatic, with neurologic involvement in less than 1% of cases. Encephalitis accounts for 53% of these cases, followed by meningitis (37%) and acute flaccid myelitis (7%), although this may reflect diagnostic bias with more rigorous testing of the sickest patients [37]. Cerebrospinal fluid pleocytosis may be absent in up to 5% of cases [38]. Older age, immunocompromise (especially solid-organ transplantation), hypertension, cardiovascular diseases, diabetes, and male sex are recognized risk factors for WNND [39, 40]. Genetic polymorphisms affecting interferon response have also been associated with increased risk for neurologic involvement [40]. The case-fatality rate for WNV encephalitis remains 10%–14%, reflecting the absence of effective antiviral therapy [37, 41].

Enteroviruses

Encephalitis is a rare complication of EV infection, but given the pervasiveness of this infection, it is a leading cause of pediatric encephalitis [10]. Enterovirus encephalitis (EVE) accounts for 10%–15% of cases in children but is not exclusive to pediatrics. In a large prospective series of EVE, 27% of cases occurred in adults [42]. Enterovirus encephalitis may present as chronic meningoencephalitis in patients with hypogammaglobulinemia [43].

Clinical findings supporting EVE include skin or oral lesions, such as in hand-foot-and-mouth disease or herpangina. Enterovirus encephalitis is generally milder than other viral etiologies. An important exception is encephalitis due to EV-A71, which localizes to the brainstem. Outbreaks of EV-A71 encephalitis have occurred throughout the Asia-Pacific region since the late 1990s. Occasional outbreaks and sporadic cases have also been reported in the United States [44].

Detection of EV by CSF PCR is insensitive [42]. EV-A71 and EV-D68 are notorious for low rates of detection in CSF, likely related to the limited duration of viremia [45, 46]. Prolonged viral shedding may occur in the respiratory and gastrointestinal tracts [44], and in children molecular testing of these sites

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Table 2. Core Pathogens and Recommended Universal Testing for Adult and Pediatric Patients With Encephalitis

Specimen	Etiology	Testing	Age		Comments
			Adult (≥18 y)	Child (<18 y)	
Cerebrospinal fluid (CSF)					Freeze residual CSF for additional testing
	Bacteria				
		Routine studies, Gram stain, culture	+	+	OP, WBC and differential, RBC, glucose, protein
		VDRL	+	–	Testing for syphilis not routinely indicated in children
	Autoimmune conditions				
		Oligoclonal bands	+	+	
		IgG index	+	+	Testing should be performed for older children and teenagers; consider in younger children if sufficient CSF
		Anti-NMDAR antibodies	+	+	
	Viruses				
		Herpes simplex virus (HSV)-1 and HSV-2 PCR[a]	+	+	If the initial HSV-1 PCR is negative and there is a clinical suspicion for HSE, repeat testing on a new CSF specimen in 3–7 d is recommended (HSV-1 PCR usually remains positive despite acyclovir treatment during this period).
		Varicella zoster virus (VZV) PCR[a]	+	+	Consider CSF VZV IgG testing if PCR negative and clinical features suggest VZV vasculopathy (see text).
		Enteroviruses (EV) PCR[a]	+	+	
		West Nile virus (WNV) IgM antibody (seasonal)	+	+	Detectable after ≥8 d of symptom onset. In severely immunosuppressed patients (particularly after therapy with an anti-CD20 antibody such as rituximab) consider WNV CSF PCR (see text).
	Fungi				
		Cryptococcal antigen[b]	+	–	
Serum/blood					Freeze residual serum for additional testing
	Bacteria				
		Blood cultures	+	+	
		Treponemal antibody or RPR	+	–	
		Mycoplasma pneumoniae IgG/IgM antibody	–	+	Paired acute and convalescent antibody testing preferred (see text)
	Autoimmune conditions				
		Anti-NMDAR antibodies	+	+	Serum testing complements CSF testing
	Viruses				
		4th generation HIV antibody	+	+	
		WNV IgM antibody (seasonal)	+	+	Detectable after ≥8 d of symptoms; seroconversion may be delayed in immunosuppressed patients. IgM may remain positive for >1 y after acute infection.

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Table 2. Continued

Specimen	Etiology	Testing	Age		Comments
		Epstein-Barr virus (EBV) VCA IgG/IgM, EBNA IgG	–	+	Preferred over heterophile antibody.
Other lab test					
		Multiplex respiratory molecular testing on oropharyngeal or throat swab for respiratory pathogens	–	+	If multiplex panel not available, single-analyte PCR testing for EV and *Mycoplasma* recommended.
		EV PCR on stool or rectal swab	–	+	In addition to testing respiratory and CSF specimens for EV.
Imaging and neurodiagnostic testing					
		Chest x-ray	+	–	Consider in children if signs or symptoms of respiratory involvement.
		Brain MRI with contrast	+	+	Strongly preferred to CT scan
		EEG	+	+	EEG can identify subclinical seizures and allows localization of inflammation.

Adapted from reference 5.

Abbreviations: anti-NMDAR, anti-N-methyl-D-aspartate receptor; EBNA, Epstein-Barr nuclear antigen; EEG, electroencephalography; HIV, human immunodeficiency virus; HSE, herpes simplex encephalitis; IgG, immunoglobulin G; IgM, immunoglobulin M; ME, meningoencephalitis; OP, opening pressure; PCR, polymerase chain reaction; RBC, red blood cell; RPR, rapid positive reagin; VCA, viral capsid antigen; VDRL, veneral disease research lab test; WBC, white blood cell.

+: universal testing recommended; –: testing individualized based on clinical or epidemiologic features.

[a]If multiplex meningitis/encephalitis PCR panel available this can be used in place of single analyte PCR test.

[b]Preferred over PCR due to higher sensitivity.

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Table 3. Selected Epidemiologic Risk Factors for Encephalitis

Variable and Exposure	Pathogen (Disease)	Comments
Region (USA)		
Northeastern, mid-Atlantic, East North Central regions	Powassan virus[a]	*Ixodes* tick vector, transmission can occur with <1 h attachment
	Borrelia burgdorferi (Lyme disease, Neuroborreliosis)	*Ixodes* tick vector, neurologic symptoms occur months after initial infection (encephalitis uncommon)
Coastal Northeastern, mid-Atlantic, Gulf Coast and Great Lakes areas	Eastern equine encephalitis (EEE) virus[a]	Mosquito vector; most cases in areas of freshwater hardwood swamps
Northeastern, mid-Atlantic, Southeastern, East South Central, East North Central regions	La Crosse virus[a]	Mosquito vector; most cases in children <16 y
Eastern and Central states; sporadic cases and outbreaks in Southwest and California	St Louis encephalitis virus[a]	Mosquito vector
Mid-Atlantic, Southeastern, East South-central regions	*Ehrlichia chaffeensis*[a] (Ehrlichiosis)	Tick vector; lab abnormalities (leukopenia, thrombocytopenia, and elevated transaminases) common
Animal exposure		
Mammals (many species)	Rabies virus	Highest risk associated with bat (bite may not be recognized) and raccoon (East Coast) exposure. Dog-associated infection uncommon in USA due to vaccination, but common internationally
Cat	*Bartonella* species (cat scratch encephalopathy)	Seen more frequently in children than adults, associated with seizures, usually with rapid recovery
Bat	Nipah virus	Indonesia, India, and South-East Asia
Raccoon	*Baylisascaris procynosis*	Exposure to feces, causes cerebrospinal fluid eosinophilic pleocytosis
Rodents	Lymphocytic choriomeningitis virus	More common in cool weather, exposure to droppings, meningitis more common than encephalitis
Swine	Nipah virus	Indonesia, India, and South-East Asia
Macaque primates	Herpes B virus	Saliva exposure (bite)
Animal urine	*Leptospira* spp. (neuroleptospirosis)	Biphasic illness, often associated with cholestasis, conjunctival injection
Outdoor exposure		
Work or recreation with soil	*Balamuthia mandrillaris, Accanthamoebae* spp.	Granulomatous amoebic encephalitis
Fresh water	*Naegleria fowleri*[a]	Primary amoebic meningoencephalitis, most common with freshwater recreation but can see with nasal rinsing or ablution
	Leptospira spp. (neuroleptospirosis)	Tropical or temperate climates
Hiking, camping, gardening	Tick- and mosquito-borne infections[a]	See regional distribution section for specific pathogens

This table highlights established epidemiologic features associated with specific infections but is not inclusive. Testing for core pathogens should be performed in addition to selected testing based on factors above.

[a]Most central nervous system infections are seasonal and, in general, testing can be limited to warmer months (spring through fall).

should be pursued, with the caveat that detection outside of the CNS does not prove causation [47].

Conditional Pathogens

Evaluation for other less common causes of encephalitis is guided by individualized factors that allow cost-effective and targeted testing (Tables 3–6). An illustrative case is the report of a child with a delayed diagnosis of rabies following repeated failure to elicit the history of a bat bite 2 months previously, resulting in the exposure of multiple healthcare workers to infectious secretions in this ultimately fatal case [48].

Emerging and Re-emerging Pathogens

Encephalitis due to pathogens that are newly discovered, occurring in new geographic locations, or with markedly increased incidence has all been described in the past decade. In many cases, these infections are driven by changing pathogen/reservoir/vector ecology related to extreme weather and loss of natural habitat [49, 50]. Vector-borne infections have emerged as significant public health concerns over the last decade (Table 7). Cases of Powassan virus, a tick-borne infection with a mortality rate greater than 10%, have increased from an average of 1 case/year prior to 2006 to 21–43 cases/year between 2016 and 2019 [51]. This increase is directly related to a new strain, termed Powassan virus lineage II/Deer Tick virus, spread by the aggressive *Ixodes scapularis* tick [52]. Transmission from tick vector to human host can occur after just 15 minutes of attachment.

Animal–human spillover infections are increasingly recognized as risk factors for emerging encephalitides. Variegated squirrel bornavirus 1 (VSBV-1) was identified following a cluster of

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Table 4. Select Findings on Physical Exam Suggestive of Causes of Encephalitis

Sign or Symptom	Pathogen or Disease	Comments
Neurologic		
Abnormal behavior (new psychosis, mania, delirium, aggression, agitation, catatonia)	Rabies	Agitated delirium more frequent than catatonia
	Autoimmune conditions	Anti-NMDAR antibody encephalitis and others
Myoclonus	Measles virus/SSPE	Unvaccinated or history of measles at young age before receiving vaccine; latency of 2–10 y after infection
	Prion disease	Creutzfeld-Jakob and variant disease
	Autoimmune conditions	Anti-NMDAR antibody encephalitis and others
Bulbar or ocular dysfunction	HHV-6 virus	Primarily in stem cell transplant patients, rarely immunocompetent young children
	Listeria monocytogenes	Both immunocompetent and immunocompromised hosts
	Autoimmune conditions	Paraneoplastic syndromes
Rapid neurologic decompensation	Rabies	
Parkinsonism or tremor	Arboviruses	WNV, JEV, SLE virus
	Toxoplasma gondii	
Acute flaccid paralysis	West Nile virus	Older adults at highest risk
	EV-D68 or EV-A71	Children
	Rabies	
Nonneurologic findings		
Vesicular skin eruption	VZV	Neurologic symptoms may precede onset of zoster
Rash on palms and soles and/or oral ulcers	EV	Hand, foot, and mouth disease, herpangina
Petechial rash	*Rickettsia rickettsii* (Rocky Mountain spotted fever)	Seasonal onset, associated with lab abnormalities (see Table 5)
Chronic skin ulcer	*Acanthamoeba*, *Balamuthia*	Subacute or chronic meningoencephalitis; skin findings more frequent in South America than in USA
Lymphadenopathy	*Bartonella*	Often with seizures, occurs in children more frequently than in adults; usually cat exposure

This table highlights established physical exam features associated with specific infections but is not inclusive. Testing for core pathogens should be performed in addition to selected testing based on factors above.

Abbreviations: anti-NMDAR, anti–N-methyl-D-aspartate receptor; EV, enteroviruses; HHV-6, human herpes virus-6; JEV, Japanese encephalitis virus; SLE, systemic lupus erythematosus; SSPE, subacute sclerosing panencephalitis; VZV, varicella zoster virus; WNV, West Nile virus.

encephalitis deaths in exotic animal breeders in Germany [53] and was subsequently diagnosed in fatal encephalitis among zoo employees [54]. Exotic animals have also been linked to rabies, as in the recent case in an anteater from a Tennessee zoo [55]. Nipah virus was initially described as a cause of encephalitis in Malaysian pig farmers in 1998, with fruit bats identified as the primary reservoir [56]. Subsequent outbreaks in Bangladesh and India have been traced to ingestion of date palm sap virally contaminated by bat saliva, or to person-to-person transmission [57]. A 2014 outbreak of Nipah virus encephalitis in the Philippines was associated with exposure to infected horses [58].

Primary amoebic meningoencephalitis (PAM), caused by *Naegleria fowleri*, is an almost universally fatal form of encephalitis historically seen in southern states in the US. In 2022, cases were reported in Iowa and Nebraska [59], hypothesized to be due to warming of natural bodies of water promoting the growth of this thermophilic organism. As temperatures rise and extreme weather events become more common, cases of PAM are expected to increase globally [60].

Baylisascaris procyonis causes a severe and often fatal eosinophilic encephalitis following ingestion of soil containing raccoon feces. Encephalitis with this parasite is most common in young children or adults with neuropsychiatric conditions predisposing to pica. A recent report identified encephalitis in a previously healthy adult infected through occupational exposure in combination with poor hand hygiene [61].

Rates of routine childhood vaccination have fallen, leading to an increasingly susceptible population. Measles can cause encephalitis at the time of acute infection or can cause subacute sclerosing panencephalitis (SSPE) years later. Measles was declared eradicated in the United States in 2000 but has re-emerged due to infections in unvaccinated international travelers, with spread through undervaccinated communities [62]. The United Kingdom recently reported an increase in cases of SSPE resulting from exposure to measles during infancy [63].

PEDIATRIC ENCEPHALITIS

Causes of childhood encephalitis have evolved following vaccine programs targeting measles, mumps, varicella, and poliovirus. As in adults, HSV-1, EV, and autoimmune conditions are leading causes of encephalitis in pediatric patients. Additional infections of particular significance in children are provided in Table 8.

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Table 5. Select Laboratory Findings Suggestive of Specific Causes of Encephalitis and Meningoencephalitis

Body Fluid and Abnormality	Pathogen or Condition	Comments
CSF		
Eosinophilic pleocytosis	*Angiostrongylus cantonensis*	Transmitted by eating infected slugs or snails, found in tropical areas (including Hawaii)
	Baylisascaris procyonis	Transmitted by ingestion of raccoon feces; primarily children or adults with pica
	Coccidioides immitis	Fungus endemic to Western and Southwestern USA
	Gnathostoma sp.	Nematode most common to South-East Asia, causes migratory skin swelling
Lymphocytic pleocytosis with elevated protein and hypoglycorrhachia	Tuberculosis	Subacute onset, variable pulmonary findings
	Endemic fungi (*Histoplasma*, *Blastomyces*, *Coccidioides*)	Subacute onset, often concomitant pulmonary findings, testing guided by geography
	Balamuthia mandrillaris	Granulomatous amoebic encephalitis, subacute onset
	Acanthamoebae species	Granulomatous amoebic encephalitis, subacute onset
Whole blood		
Leukopenia or thrombocytopenia	*Ehrlichia chaffensis*	Tick-borne seasonal pathogen, most common in Southeast, South Central and mid-Atlantic regions of the US
	Rickettsia rickettsii	Tick-borne seasonal pathogen
	EBV	Acute infection (mononucleosis)
Serum		
Elevated transaminases	*Ehrlichia chaffensis*	Tick-borne seasonal pathogen, most common in Southeast, South Central, and mid-Atlantic regions
	Rickettsia rickettsii	Tick-borne seasonal pathogen
	EBV	Acute infection (mononucleosis)
Elevated bilirubin	Leptospirosis	Associated with animal urine or freshwater exposure

Abbreviations: CSF, cerebrospinal fluid; EBV, Epstein-Barr virus.

Table 6. Select Neuroimaging Findings Suggestive of Specific Causes of Encephalitis

Radiographic Finding	Pathogen or Condition	Comments
Frontal lobe involvement	*Naegleria fowleri* (primary amoebic meningoencephalitis)	Seasonal, associated with freshwater exposure and fulminant infection
Temporal lobe involvement	HSV-1	Often asymmetric, HSV-1 is part of core testing regardless of MRI findings
	Autoimmune limbic encephalitis	Often symmetric, involving the mesial temporal lobes
	HHV-6	Rare condition presenting shortly after stem cell transplantation; false positives may occur due to chromosomal integration or latency
Deep gray matter (basal ganglia or thalamus) involvement	West Nile virus	Part of core testing during appropriate season regardless of MRI findings
	Japanese encephalitis virus	Associated with travel to Asia, emerging infection in Australia
Brainstem involvement	*Listeria monocytogenes*	Lower brainstem ("rhombencephalitis"), can occur in immunocompetent individuals
	Enteroviruses	EV-A71, and less commonly other EV; seen primarily in children
Cerebellar involvement	EBV	Associated with acute infection, more common in children
	VZV	CSF PCR part of core testing, typically seen in acute infection (chickenpox)
White matter involvement	Acute disseminated encephalomyelolitis (ADEM)	Demyelination often following minor respiratory or gastrointestinal infection or vaccination; can also affect gray matter
	Parechoviruses	Consider in young children
Acute ischemic lesions	VZV	VZV-associated vasculopathy can occur in immunocompetent and immunocompromised individuals
	Syphilis	Acute or chronic presentation
	Fungal infections	Aspergillus and mucormycosis are particularly angioinvasive
	Rickettsia rickettsii	RMSF "starry sky" pattern, especially in children
	Tuberculosis	Deep portions of the brain
Multifocal cerebral cortical lesions	MOG-associated disease	Autoimmune encephalitis

Abbreviations: CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; EV, enterovirus; HHV-6, human herpes virus-6; HSV-1, herpes simplex virus-1; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; RMSF, Rocky Mountain spotted fever; VZV, varicella zoster virus.

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Table 7. Selected Emerging Arboviral Causes of Encephalitis

Virus	Vector	Distribution	Notes
Cache Valley	Mosquito	United States, Canada, Caribbean	Approximately 10 cases reported, transmission through blood transfusion may occur
Eastern equine encephalitis	Mosquito	Americas	5–15 cases/y, outbreak in Northeast USA in 2019 with 36 cases
Jamestown Canyon	Mosquito	North America	25–50 cases annually in recent years
Japanese encephalitis	Mosquito	South-East Asia, Australia	2022 outbreak in Australia (see text)
Powassan	Tick, *Ixodes* spp.	Northeastern United States and Great Lakes, Canada, Eastern Russia	20–40 cases reported in USA annually in recent years (see text)
St Louis encephalitis	Mosquito	United States	New focus of cases in Arizona and California in 2016–2019
Tick-borne encephalitis virus	Tick, *Ixodes* spp.	Europe, Russia	More than 10 000 infections annually; multiple viral subtypes
Umbre	Mosquito	India, France	Two human cases, both fatal, in patients with hypogammaglobulinemia
Usutu	Mosquito	Africa, Europe, and Middle East	Presentation similar to West Nile virus, although neuroinvasion may be less common

Adapted from reference [49]. This table highlights emerging arboviral infections but is not inclusive.

Table 8. Causes of Infectious Encephalitis of Particular Significance in Children

Pathogen	Clinical Features	Diagnostic Testing	Notes
Bartonella henselae	Encephalopathy characterized by seizures (often status epilepticus) with acellular CSF and rapid recovery	*Bartonella* serology (IgG typically ≥1:256); if lymphadenopathy present, *Bartonella* PCR or Warthin-Starry stain on tissue	Etiologic agent of cat scratch disease; associated with cat, kitten or flea exposure; lymphadenopathy variably present
EBV	Typically follows acute mononucleosis by 1–3 wk, metamorphopsia variably present, isolated cerebellar involvement can occur	EBV serologic panel; CSF EBV PCR often negative	Positive EBV CSF PCR may represent nonspecific reactivation, or in adults, primary CNS lymphoma and should be interpreted in the clinical context
Enteroviruses (EV)	EV A-71 causes brainstem encephalitis; other types present with nonspecific findings	EV PCR on CSF, respiratory specimens, and stool; CSF PCR insensitive for some types	Rash or herpangina (oral lesions) may be present
HHV-6	Most frequently occurs at time of primary infection (roseola infantum) in children <2 y	HHV-6 CSF PCR	False positive HHV-6 PCR can be due to chromosomal integration or detection of latent virus (see text)
Human parechoviruses (HPeV)	HPeV3 leading cause of aseptic meningoencephalitis, usually in infants <90 d	Parechovirus PCR testing of respiratory sites may increase yield	Cases peak in summer and fall, CSF often pauci-cellular
La Crosse virus	Nonspecific presentation, good prognosis	La Crosse virus serology (positive IgM or 4-fold increase IgG on paired specimens)	Spread by mosquitos with summer or late fall onset, most cases east of the Mississippi River
Mycoplasma pneumoniae	Typically follows respiratory infection (often mild), wide spectrum of presentations	*Mycoplasma* PCR of nasopharyngeal or throat swab; positive *Mycoplasma* IgM (see text); CSF PCR rarely positive	One of the most frequently identified causes of pediatric encephalitis; multiple mechanisms postulated
Respiratory viruses, especially influenza virus	Diffuse cerebral edema or focal thalamic necrosis due to acute necrotizing encephalopathy (ANE)	Respiratory PCR; virus almost never found in CSF or brain tissue	ANE most reported in South-east Asia

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; HHV-6, human herpes virus-6; IgG, immunoglobulin G; IgM, immunoglobulin M; PCR, polymerase chain reaction.

Epstein-Barr virus (EBV) encephalitis occurs following acute mononucleosis. While the presentation is usually nonspecific, a notable feature of EBV-associated encephalitis is the "Alice-in-Wonderland" presentation with metamorphopsia, the perception of distorted shapes and sizes. Infection localizing to the cerebellum can also be seen with EBV encephalitis. Human herpes virus-6 (HHV-6) causes roseola infantum in children younger than 2 years of age and may rarely cause encephalitis. Due to chromosomal integration and HHV-6 latency, a positive PCR test should be interpreted with caution. In a large pediatric study, HHV-6 was amplified in 2.5% of CSF samples, but only 20% of these positive results represented actual meningoencephalitis [64].

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Mycoplasma pneumoniae is one of the most frequently implicated causes of encephalitis in children [14, 65, 66]; however, causality remains controversial [67]. PCR of spinal fluid and brain tissue is often negative [68], with serology or detection of *Mycoplasma* in respiratory specimens providing tangential support for CNS infection [66, 69].

Influenza virus and *Bartonella* are frequently cited as causes of encephalitis in children but are more aptly classified as causing encephalopathy, as CNS invasion is almost never detected [8, 70]. Acute necrotizing encephalopathy, associated with influenza, causes brain edema. Patients present with fever, rapid decline in mental status, and seizures, progressing to obtundation and sometimes death [71]. Imaging demonstrates bilateral thalamic necrosis with hemorrhage, cavitation, and later atrophy.

ENCEPHALITIS IN IMMUNOSUPPRESSED PATIENTS

Immunocompromised hosts are at risk for the pathogens previously discussed but also are susceptible to opportunistic infections (Table 9). These patients represent a heterogenous population, and identifying the specific immunologic defect narrows the differential diagnosis and allows strategic testing.

Encephalitis in solid-organ transplant recipients may be due to transplantation from donors with unrecognized neurologic infection. Donor-derived encephalitis due to Eastern equine encephalitis virus [72], WNV [73], *Balamuthia* [74], *Encephalitozoon* [75], and rabies virus [76] has been described. For this reason, the American Society of Transplantation recommends against solid-organ harvest from deceased donors with encephalitis [77].

ENCEPHALITIS IN RETURNING INTERNATIONAL TRAVELERS

Travelers returning from outside the United States may present with unusual pathogens acquired abroad. A detailed history focusing on dates and duration of travel, pre-travel immunizations, prodromal gastrointestinal or respiratory illness, ill contacts, urban versus rural domiciles, and exposure to water, soil, arthropods, or animals allows formulation of a comprehensive differential diagnosis.

A few pathogens bear specific consideration in returning travelers [78]. Japanese encephalitis virus (JEV) is the leading cause of encephalitis in Asia. Symptoms develop within 5–15 days following infection, with year-round transmission in tropical climates. Vaccination for JEV is recommended for all travelers to endemic regions staying for more than 1 month or whose activities place them at risk for exposure to mosquitos.

Rabies is a zoonotic infection with nearly worldwide distribution, with most human infections acquired in Asia and Africa. In contrast to the United States, where bats serve as the primary vector, dogs constitute the main source of human transmission internationally. Rabies should be considered in a returning traveler with severe encephalitis who reports exposure to a sick or aggressive animal. The incubation period is typically 1–3 months but can be prolonged; 1 documented case presented more than 8 years after international exposure to an infected dog [79].

AUTOIMMUNE ENCEPHALITIS

Autoimmune encephalitis is a heterogenous syndrome encompassing multiple distinct conditions (Table 10). Research on neuronal cell surface autoantibodies has proliferated over the past decade [80]. The pace of discovery and the potential for rapid and substantive neurologic recovery have spurred tremendous interest in the field.

Although there is substantial overlap between infectious and autoimmune encephalitides, differences do exist [81, 82] (Table 11). Autoimmune encephalitis often presents in a subacute fashion, may include psychiatric or memory complaints, and CSF white blood cell (WBC) count is typically less than 50/μL; fever is uncommon. These differences have been incorporated into proposed criteria for the clinical diagnosis of autoimmune encephalitis [83].

ANTI-NMDAR ENCEPHALITIS

First described over 15 years ago [84], anti-NMDAR encephalitis is the most frequently recognized autoantibody-mediated encephalitis. This syndrome is characterized by prominent behavioral changes, including psychosis and catatonia, movement disorders such as orofacial dyskinesias or myoclonus, and seizures. Affected individuals can decline rapidly with status epilepticus and dysautonomia [85]. Anti-NMDAR encephalitis is most common in children and young adults and exhibits a 4:1 female to male predominance. About half of cases occur as a paraneoplastic syndrome, often associated with ovarian teratoma [86]. Brain MRI is typically unremarkable, electroencephalogram (EEG) may demonstrate an "extreme delta brush" pattern, and the CSF WBC count is usually under 50 WBCs/μL.

POSTINFECTIOUS AUTOIMMUNE ENCEPHALITIS

Autoimmune encephalitis following infection may represent molecular mimicry due to cross-reactivity between pathogen epitopes and self-antigens. Increasingly recognized is the association between HSE and postinfectious anti-NMDAR encephalitis. The development of antineuronal antibodies has been reported in up to 25% of patients with HSE, typically within 16 weeks of the infection, although, in some cases, a more prolonged interval has been described [87]. Younger patients more often develop movement disorders such as choreoathetosis [87]. Other CNS infections, including JEV and VZV, have also been associated with generation of antineural antibodies.

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Table 9. Selected Causes of Encephalitis in Immunocompromised Hosts

Condition and Pathogen	Comments
HIV/AIDS[a]	
Toxoplasma gondii	CNS mass lesions; trimethoprim-sulfamethoxazole prophylaxis decreases risk
Cryptococcus spp.	Subacute or chronic symptoms; meningitis significantly more common than encephalitis
Endemic fungi[b]	Subacute or chronic meningoencephalitis, often associated with pulmonary imaging abnormalities
Mycobacterium tuberculosis	Subacute or chronic meningoencephalitis
Cytomegalovirus	White matter changes, classically in a periventricular distribution
JCV	Progressive multifocal leukoencephalopathy (PML), radiographically may appear as diffusion restriction in white matter lesions
Solid-organ or stem cell transplant	
Toxoplasma gondii	Primarily following cardiac transplant
Cryptococcus spp.	May occur either early or late following transplant
Endemic fungi[b]	May occur either early or late following transplant
Herpes group viruses	VZV or CMV; EBV associated with post-transplant lymphoproliferative disorder
West Nile virus	Cases may be more severe or prolonged in this population
HHV-6	Almost exclusively following stem cell transplant
Leptospira spp.	Chronic meningoencephalitis in immunocompromised patients
Acanthamoeba spp.	Mimics TB CNS disease
Balamuthia madrillaris	Can occur in immunocompetent host as well

This table highlights selected infections associated with immunocompromise but is not inclusive.

Abbreviations: CMV, cytomegalovirus; CNS, central nervous system; EBV, Epstein-Barr virus; HHV-6, human herpes virus-6; HIV, human immunodeficiency virus; JCV, John Cunningham virus; TB, tuberculosis; VZV, varicella zoster virus.

[a]Opportunistic infections causing meningoencephalitis typically seen with CD4 <200 cells/μL.

[b]Endemic fungi vary by region, and include *Histoplasma capsulatum* (Southeast, Southcentral, and mid-Atlantic USA), *Blastomyces* species (central USA), and *Coccioides immitis* (Southwest and West Coast).

Table 10. Categories of Autoimmune Encephalitis

Category	Examples
Autoantibody-mediated encephalitis (antigens present on neuronal cell surface)	Anti-NMDAR, anti-LGI1, anti-CASPR2, anti-AMPAR, anti-GABA-A-R, anti-GABA-B-R, anti-GlyR, anti-mGluR5
Autoantibody-associated encephalitis (intracellular antigens)	Anti-Hu, anti-Ma/Ta, anti-GAD65, anti-GFAP
CNS demyelinating disorders	ADEM, MOGAD
Systemic autoimmune disorders	SLE, Behcet's disease, sarcoidosis
Iatrogenic	Checkpoint inhibitor or CAR-T cell therapy
Neurodegenerative	CAA-related inflammation
Other postinfectious	Following CNS or systemic infections (including HSE)

Abbreviations: ADEM, acute disseminated encephalomyelitis; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPAR, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CAA, cerebral amyoid antiopathy; CAR-T, chimeric antigen receptor T cells; CASPR2, Contactin-associated protein 2; CNS, central nervous system; GABA, gamma-aminobutyric acid; GAD, glutamic acid decarboxylase; GFAP, glial fibrillary acidic protein; GlyR, glycine receptor; HSE, herpes simplex encephalitis; LGI1, leucine-rich glioma-inactivated; mGluR5, metabotropic glutamate receptor 5; MOGAD, myelin oligodendrocyte glycoprotein-associated disease; NMDAR, N-methyl-D-aspartate receptor; SLE, systemic lupus erythematosus.

AUTOIMMUNE LIMBIC ENCEPHALITIS

Autoimmune limbic encephalitis is characterized by the triad of short-term memory loss, behavioral changes, and seizures. In up to 70% of individuals, brain MRI demonstrates abnormalities in the mesial temporal region and hippocampus. Numerous autoantibodies have been associated with autoimmune limbic encephalitis, with the most common being leucine-rich glioma-inactivated (LGI1) and Contactin-associated protein 2 (CASPR2) encephalitis. The former is characterized by distinct, rapid twitching movements of the face and arm termed "faciobrachial dystonic seizures" [88]; the latter is often accompanied by peripheral neuropathy and neuropathic pain [89]. Autoimmune limbic encephalitis seen with small cell lung cancer is associated with antibodies to intracellular antigens such as Hu and Ma/Ta, with antibodies to the GABA-B receptor increasingly recognized [90]

DEMYELINATING CONDITIONS

Acute disseminated encephalomyelitis (ADEM) is a frequent cause of encephalitis in children, often preceded by a viral respiratory illness [91] or vaccination [92]. The hallmark of ADEM is white matter demyelination, variably in concert with gray matter abnormalities. Serum antibodies to myelin oligodendrocyte glycoprotein (MOG) are detectable in approximately half of cases [93]. MOG antibodies can also be present with spinal cord and optic nerve inflammation, as well as in a distinct form of autoimmune encephalitis, cerebral cortical encephalitis, characterized by multiple lesions in the cortical gray matter [94].

DIAGNOSTIC APPROACH FOR PATIENTS WITH SUSPECTED ENCEPHALITIS

Guidelines for the diagnostic evaluation of acute encephalitis have been published by professional societies in the United States [4] and internationally [5, 95–97]; yet, real-world adherence is suboptimal [98]. A pragmatic approach combines universal testing for a limited number of common or treatable pathogens, with ancillary testing based on patient-specific features. The suggested core testing in Table 2 was developed for patients in the United States, with modification needed if applied to other locations based on organisms of regional importance. Conditional testing is guided by individualized findings (Tables 3–6) and unique risk factors (Tables 8 and 9). Core and ancillary testing can be performed in parallel. When initial results are nondiagnostic, probing for exposures or risk factors that may have initially been overlooked is recommended.

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Table 11. Clinical Presentations of Infectious and Autoimmune Encephalitis

	Infectious	Autoimmune
Acuity	Acute (hours to several days)	Subacute (days to weeks)
Clinical symptoms	Encephalopathy, focal deficits	Short-term memory loss, psychosis, movement disorders
Neuroimaging	Often demonstrates focal abnormalities	Often normal, although distinctive abnormalities seen in autoimmune limbic encephalitis, ADEM, and anti–GABA-A receptor encephalitis[a]
Routine CSF findings	WBC pleocytosis; elevated protein	Cell counts, protein, and glucose may be normal[b]

Abbreviations: ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; GABA, gamma-aminobutyric acid; WBC, white blood cell.

[a]Autoimmune limbic encephalitis: bilateral T2 hyperintensities, and/or post-gadolinium enhancement in mesial temporal lobes; ADEM: diffuse, multifocal, incompletely rim-enhancing lesions, most typically in the subcortical white matter; anti–GABA-A receptor encephalitis: multifocal cortical and subcortical T2-weighted/FLAIR (fluid attenuated inversion recovery) hyperintensities.

[b]Examination of immunoglobulin G (IgG) index and oligoclonal banding pattern can provide support for autoimmune encephalitis.

Routine Diagnostic Studies

Lumbar puncture is essential in the evaluation unless there is a clear contraindication. Ascertainment of the opening pressure allows documentation of intracranial pressure; when elevated, patients are best managed in an intensive care setting. Freezing an aliquot of CSF (at least 2 cc) is recommended to allow additional testing if no pathogen is identified on the initial diagnostic battery.

Neuroimaging, ideally brain MRI with contrast, can guide diagnostic testing (Table 6). EEG should be performed in patients who present with seizures or with severely depressed mentation to exclude nonconvulsive status epilepticus as a cause of obtundation. Repeat lumbar puncture or neurodiagnostic testing should be pursued when no cause is identified or for patients who experience progressive clinical decline.

Nonmolecular Infectious Evaluation

Bacterial culture of CSF is necessary to exclude bacterial meningitis; however, molecular testing has made CSF viral culture obsolete [99]. Serology is the preferred diagnostic test for tick-borne and arboviral encephalitis. Testing acute and convalescent serum allows detection of seroconversion or a 4-fold or greater increase in titers. When serologic testing is performed sequentially rather than in parallel, performance at the same laboratory using the identical assay allows direct comparison of results.

Interpreting results of serologic testing requires understanding of the dynamics of the immune response. For example, antibodies are often not detectable on the initial serum sample for patients with Rocky Mountain spotted fever meningoencephalitis [100]. In contrast, although most patients with WNV encephalitis have detectable serum and CSF immunoglobulin M (IgM) antibody at presentation, IgM antibody can persist for more than 1 year, complicating the interpretation of a positive result [101, 102].

The role of CSF antibody testing varies by organism. With WNV and many other arboviral infections, viremia peaks before symptom onset, limiting the utility of PCR testing. West Nile virus IgM in CSF is detectable early after the onset of symptoms and is indicative of intrathecal synthesis. Patients with impaired humoral response, such as those receiving rituximab, may be an exception; in this population, antibody production may be delayed or absent, and WNV PCR is indicated [103, 104].

Intrathecal antibody testing for other organisms is not routinely performed as assays are poorly standardized and the results are difficult to interpret. One exception is VZV vasculopathy, a condition where intrathecal antibody detection may be more sensitive than CSF PCR [105]. The role of intrathecal antibody testing for VZV encephalitis requires further investigation.

Molecular Diagnostics

Single Analyte and Multiplex Nucleic Acid Amplification Techniques

Nucleic acid amplification techniques (NAAT), including PCR testing, play an important role in identifying pathogens causing encephalitis. Molecular testing of CSF allows rapid and sensitive diagnosis for HSV-1, VZV, and, to a lesser extent, EV, and is increasingly available onsite at hospital laboratories. When performed at presentation, molecular diagnostics are associated with decreased length of stay, shortened time to appropriate antimicrobial use, and diminished overall costs [106, 107].

Decisions regarding the use of molecular testing of CSF for organisms other than those listed above are best made in consultation with the laboratory medical director. These interdisciplinary discussions ensure that appropriate testing is performed, incorporating pre-test probability, an understanding of the pathophysiology of the suspected infectious agent, and test performance characteristics. For instance, pediatric patients with EBV encephalitis often have negative CSF PCR testing [108]. Conversely, detection of EBV in CSF may represent re-activation of latent virus in the setting of a concomitant, unrelated infection [109].

Approaches using NAAT are divided into tests targeting a single pathogen (or genetically related pathogens, such as HSV-1 and HSV-2) and multiplexed panels targeting multiple genetically distinct pathogens. Single analyte tests may be more sensitive than multiplex panel testing for the identification of certain organisms [110, 111]. Multiplex panel assays offer the practical advantage of testing for multiple pathogens using a single CSF specimen and can often be performed onsite,

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allowing rapid turnaround time and improved patient outcomes [112].

Despite the many advantages of molecular testing for the diagnosis of encephalitis, limitations exist. For example, HSV-1 PCR may be negative early in the course of infection [21, 113, 114]. Based on this, repeat testing with a separate CSF specimen obtained 3–7 days later should be performed when clinical suspicion for HSE is high [4, 5, 96]. Some authorities recommend a similar approach to an initial negative VZV CSF PCR result [96]; however, data supporting this approach are limited [115]. Further limitations to molecular panels include the inability to type epidemiologically significant strains (such as EV D68) as well as the generation of potentially confounding results (such as detection of HHV-6 or cytomegalovirus [CMV] in the CSF of immunologically competent patients) [116].

Next-Generation Sequencing

Clinical metagenomic testing is a developing field that holds great promise for the diagnosis of infectious encephalitis [117]. This approach utilizes next-generation sequencing (NGS) technologies and bioinformatic techniques to identify nucleic acids within specimens, allowing detection of unexpected or novel pathogens [117–119]. Application of this technology to CSF from patients with meningoencephalitis identified a pathogen in 16% of cases; notably, more than half of these diagnoses were also made by conventional methods, and an additional 13% were identified solely by conventional testing [120]. This may reflect that metagenomic testing is less sensitive than molecular tests targeting specific pathogens [121] and that, for many pathogens (eg, WNV), serology is superior to molecular testing regardless of methodology. Unresolved questions regarding NGS include optimal patient population, specimen source, and timing in the disease course. Currently, the role of metagenomic testing is as an adjunct to, rather than a replacement for, conventional diagnostic microbiology.

Diagnosis of Autoimmune Encephalitides

Diagnosis of autoimmune encephalitis is supported by the detection of antineural antibodies, typically via cell-based assays (CBAs) in the setting of an inflammatory brain syndrome. Universal testing for autoimmune encephalitis should, at a minimum, include CBA for anti-NMDAR antibodies and be performed on both serum and CSF (Table 2).

For most syndromes, testing of CSF is more sensitive and specific than serum. For example, CSF testing identifies an additional 15% of patients with anti-NMDAR antibody encephalitis, with fewer false positives compared with serum testing alone. On the other hand, MOG antibodies are more readily detected in serum than in CSF [122].

Testing for LGI1, which, along with CASPR2 and other proteins comprise the neuronal voltage gated potassium channel (VGKC) receptor, deserves special mention. Cell-based assays have identified distinct autoimmune encephalitis syndromes associated with antibodies to LGI1 or CASPR2. In contrast, general reactivity to the VGKC complex in the absence of a positive CBA is nonspecific and is common in healthy controls [123].

Clinical findings suggestive of autoimmune encephalitis in the absence of detectable antibody (antibody-negative autoimmune encephalitis) represent a particular challenge. In some cases, rodent brain immunohistochemistry may demonstrate binding of patient samples to neural cells or their processes, consistent with an undifferentiated autoimmune encephalitis. The diagnosis of antibody-negative autoimmune encephalitis rests on comprehensive testing with exhaustive evaluation for alternate possibilities. Given the complexity of these cases, neuroimmunology consultation is strongly recommended.

Brain Biopsy/Autopsy

Brain biopsy is often considered when no diagnosis is found on the initial battery of testing. A retrospective review identified a specific diagnosis in just 15% of patients with encephalitis undergoing brain biopsy, although this may have been impacted by the significant delay (median of 66 days after symptom onset) in the timing of surgery [124]. More recent literature reported that brain biopsy identified a cause in 31% of patients with encephalitis, with immunocompromise the sole predictor of a diagnostic result on multivariate analysis [125, 126]. Multidisciplinary discussion between the medical, neurosurgical, and laboratory teams should occur beforehand to ensure the highest-yield anatomic site is sampled, appropriate neurologic tissue samples (both fixed and fresh-frozen) are sent, and optimal testing is performed.

MANAGEMENT

The initial management of encephalitis focuses on core essentials of emergent care: maintenance of adequate airway, optimization of respiratory status, and hemodynamic stabilization [127, 128]. Overall, approximately 20% of patients with encephalitis require admission to an intensive care unit [129] where aggressive measures to manage cerebral edema or status epilepticus can be performed. An important distinction is empiric versus directed therapy, with the approach to the former outlined below.

Empiric Therapy

The clinical presentation of infectious causes of encephalitis is sufficiently nonspecific that universal initiation of antimicrobial therapy active against treatable pathogens is warranted [130], particularly as the outcome may hinge on the rapidity with which treatment is begun [4, 131]. The algorithm in Figure 2 reflects recommendations from encephalitis guidelines as well

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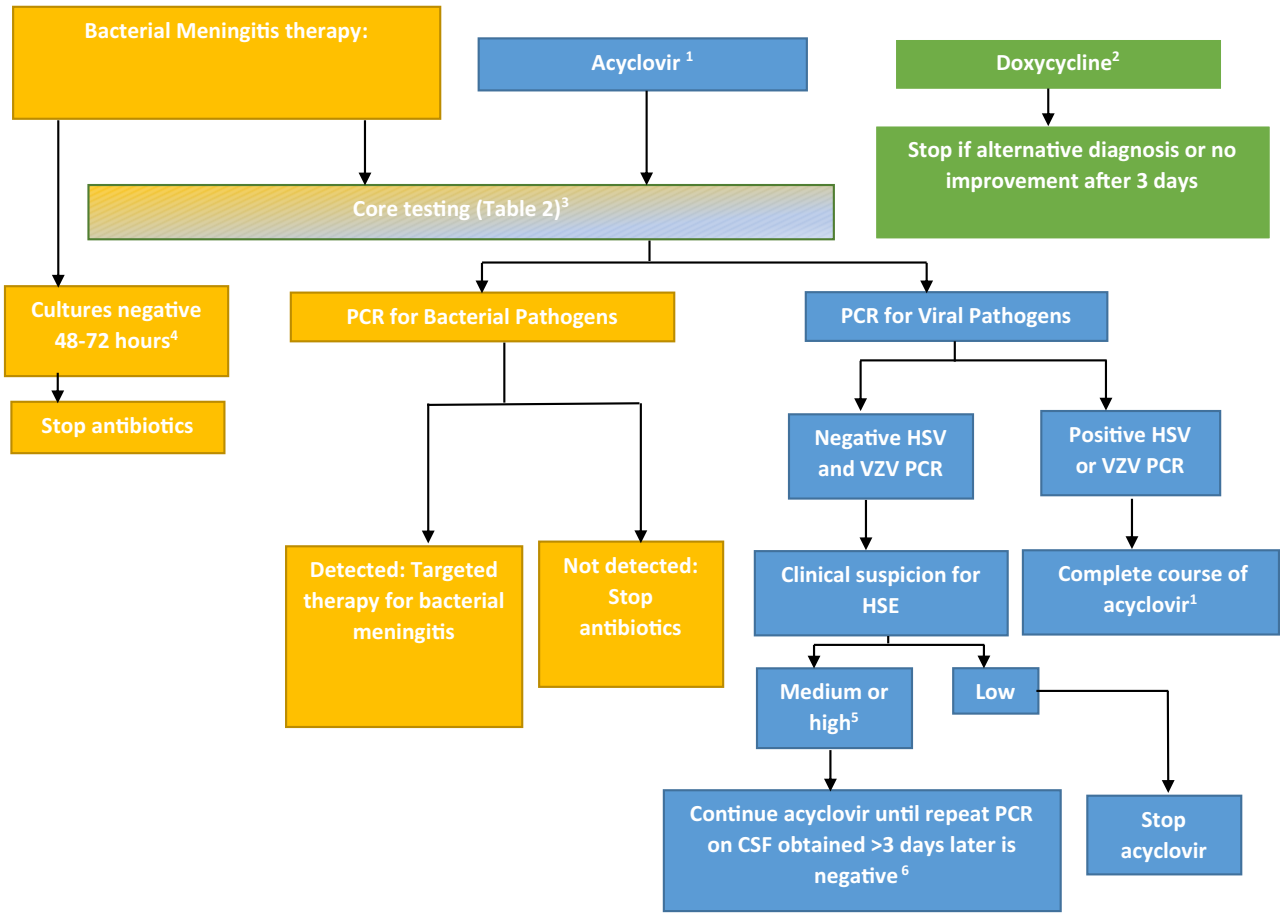
as expert opinion regarding initiation and duration of empiric antimicrobial therapy. Once a diagnosis is made, treatment can shift to directed therapy or, for the many viral agents for which no treatment is available, supportive care.

Antibacterial Therapy

Empiric antibiotic therapy is indicated given the challenge in differentiating acute meningoencephalitis from bacterial meningitis at presentation, and the potential for adverse outcomes for the latter if treatment is delayed. With the use of molecular diagnostic panels, antibiotic therapy can often be discontinued after a single dose if bacterial testing returns negative, although clinical judgment should be exercised if there is a significant neutrophilic pleocytosis or the patient has been pretreated with antibiotics.

Listeria monocytogenes is a leading cause of encephalitis in Europe [10, 132]; in the United States, where this is not the case, ampicillin can be discontinued when culture or a CSF PCR test returns negative, acknowledging that the sensitivity of this latter test is less than 60% [96]. When there is a strong suspicion for neurolisteriosis based on consumption of a contaminated food product or suggestive neuroimaging findings (eg, rhomboencephalitis), continued therapy may be appropriate.

Doxycycline has not traditionally been included as first-line empiric treatment, although several treatable tick-borne infections are known to cause encephalitis [133–135]. Considering the expanding range and incidence of tick-borne pathogens in the United States [136, 137] and the potential for adverse outcomes associated with delay in therapy [138], it is appropriate to include empiric doxycycline when the season and



Abbreviations: CSF, cerebrospinal fluid; HSE, herpes simplex encephalitis; HSV, herpes simplex virus; PCR, polymerase chain reaction; VZV, varicella zoster virus.

Figure 2. Empiric antimicrobial therapy for suspected acute encephalitis. [1]See Table 12 for specific recommendations on acyclovir dosing and duration. [2]Empiric doxycycline should be included if concern for a rickettsial infection; it can be deferred if suspicion is low (eg, during winter or in regions of low endemnicity). [3]If multiplex meningitis/encephalitis panel is available this can be performed for bacterial and viral pathogens. [4]Culture results may be impacted by antibiotic pre-treatment (see text for details). [5]Temporal lobe abnormalities. [6]HSV-1 PCR sensitivity remains high despite short course of acyclovir.

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Table 12. Acyclovir Dosing and Duration for Encephalitis

Population	Dose[a]	Route	Duration	Notes
Empiric therapy	Adult: 10 mg/kg every 8 h; pediatric (>4 mo to 12 y): 30–45 mg/kg every 8 h	IV	Until CSF HSV-1 and VZV PCR negative (see Notes)	If there is a high clinical suspicion for HSE, continue until HSV-1 PCR on a second CSF sample >3 d later is negative
CSF HSV PCR positive	10 mg/kg every 8 h	IV	14–21 d (see text for details)	Acyclovir resistance rare; consider if progression despite treatment (see text for details)
CSF VZV PCR positive	10–15 mg/kg every 8 h	IV	10–14 d in adults	If progressive neurologic symptoms or radiographic progression on treatment, consider extension to 4–6 wk

Adapted from reference [96].

Abbreviations: CSF, cerebrospinal fluid; HSE, herpes simplex encephalitis; HSV, herpes simplex virus; IV, intravenous; PCR, polymerase chain reaction; VZV, varicella zoster virus.

[a]Dosing for normal renal function, dose reduction required for decreased creatinine clearance.

Table 13. Immunotherapy for Autoimmune Encephalitis

Therapy	Typical Adult Dosing	Typical Pediatric Dosing
Corticosteroids	1000 mg IV methylprednisolone daily for 3–5 d, followed by oral prednisone at 1 mg/kg	500–1000 mg IV methylprednisolone daily for 3–5 d, followed by oral prednisone at 1 mg/kg
Intravenous immunoglobulin	2 g/kg body weight, given over 2–5 d	2 g/kg body weight, given over 5 d
Plasmapheresis	3–7 exchanges, typically administered every other day	3–7 exchanges, typically administered every other day
Rituximab	Two doses of 1000 mg IV, separated by 2 wk	375 mg IV, given weekly for 4 wk
Cyclophosphamide	800–1000 mg/m^2 BSA	500–1000 mg/m^2 BSA

Abbreviations: BSA, body surface area; IV, intravenous.

geography are compatible with a tick-borne infection. A single course of doxycycline is not associated with discoloration of permanent teeth in young children [139], and this potentially lifesaving treatment should not be deferred in pediatric patients with encephalitis.

Antiviral Therapy

There is universal agreement in domestic and international encephalitis guidelines that intravenous acyclovir should be initiated at the time of presentation (Table 12) and continued despite an initially negative HSV-1 PCR when there is a high clinical suspicion for HSE pending repeat testing on a subsequent CSF sample obtained 3–7 days later [113]. Reports of patients with multiple negative HSV-1 PCR tests on sequential CSF samples, with the diagnosis of HSE ultimately confirmed on autopsy [140–144], suggest that a full course of empiric acyclovir therapy may be warranted in a subset of patients [145].

Immunocompetent patients with HSE and significant improvement can discontinue acyclovir after 14 days. When neurologic recovery is limited, a persistently positive HSV-1 CSF PCR at day 14 mandates treatment extension to 21 days [96, 146]. Practically, many clinicians forego repeat lumbar puncture and extend therapy for all immunocompromised patients or those with ongoing neurologic symptoms.

Acyclovir-resistant herpes simplex is uncommon, present in less than 1% of immunocompetent and 3.5%–10% of immunocompromised hosts [147], but can occur in acyclovir-naive patients [148]. There is no consensus regarding treatment for acyclovir-resistant HSE; foscarnet has been used in case reports with clinical response [149, 150].

Many authorities suggest the use of a higher dose of intravenous acyclovir when treating VZV encephalitis [96], with doses of 10–15 mg/kg per day recommended in various guidelines.

Empiric Corticosteroids and Immunomodulatory Therapy

The administration of empiric corticosteroids has not been shown to improve outcomes in infectious encephalitis [151]. A separate question is whether adjuvant corticosteroids may improve outcomes specifically for patients with HSE by downregulating the inflammatory response [152] or preventing the subsequent development of autoimmune antibodies [87]. The DexEnceph study is an ongoing multinational, European randomized controlled trial enrolling patients to answer this important clinical question [153].

Management of Autoimmune Encephalitis

The management of autoimmune encephalitis is guided by clinical judgment, comorbidities, and side effects. First-line immunotherapy consists of corticosteroids, often in combination with intravenous immunoglobulin or plasmapheresis [154] (Table 13). For responders, therapy is continued for 3–6 months. For patients with limited response, second-line therapies such as rituximab or, for intracellular autoantibodies, cyclophosphamide should be initiated [154]. A comprehensive assessment for malignancy should be performed. If an underlying tumor is found, excision can be curative. Patients who are refractory to second-line treatments may require less-established immunotherapy regimens [155].

Posthospitalization Management

Residual neurologic deficits are common following hospitalization. Limited information on rehabilitation services for encephalitis and challenges in accessing posthospitalization care are sources of intense frustration for patients and their families.

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Research on the impact of rehabilitation programs in improving patient outcomes has been limited by small sample sizes and heterogenous neurologic deficits [156]. A recent report noted improvement in functional status with intensive inpatient rehabilitation [157], but programs geared specifically to patients recovering from encephalitis are often difficult to identify. Patient-advocacy groups are important resources for support and information following hospital discharge.

CONCLUSIONS

Since the publication of the IDSA Encephalitis Guidelines in 2008, advances in molecular diagnostics and elucidation of novel autoimmune causes of encephalitis have led to significant improvements in the management of this syndrome. However, with these advances, new questions and controversies have emerged. Standardized management of encephalitis using a locally validated testing strategy targeting the most common pathogens coupled with empiric antimicrobials for the limited number of treatable organisms represents current best practices for this challenging syndrome, with the hope that new innovations will lead to improved outcomes in the foreseeable future.

Note

Potential conflicts of interest. K. C. B., A. V., and C. G. had a role as a Medical Advisor of Encephalitis 411 (unpaid). K. C. B. and A. V. report unpaid participation on a Data Safety and Monitoring Board for the French Dex Enceph Study. A. V. received payment for expert testimony as an expert witness for the Vaccine Injury Compensation Program and an expert witness for medicolegal cases; travel support partly paid directly to the author for the UK Encephalitis Society Annual Meeting; and an unpaid role as a scientific advisory panel member, UK Encephalitis Society. D. G. received research reagents from Illumina, Inc, and IDbyDNA, Inc; serves on the Scientific Advisory Board for bioMerieux; reports grants or contracts from the Fisher Center Discovery Program, Johns Hopkins; and payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing, or educational events from the American Association of Clinical Chemistry and Pan American Society of Clinical Virology. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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