Diagnosis and management of acute encephalitis

A practical approach

Arun Venkatesan, MD, PhD
Romergryko G. Geocadin, MD

Summary

Encephalitis results in considerable morbidity and mortality in the United States and worldwide. Neurologists are often consulted or directly care for patients with encephalitis admitted to the hospital and must be able to discriminate between encephalitis and the many conditions that mimic it. Moreover, neurologists must be familiar with the myriad causes of encephalitis in order to develop a practical approach to diagnostic testing and treatment. An understanding of recent advances in management, particularly with respect to autoimmune etiologies and critical care approaches, is equally important. Here, we summarize a general approach to the care of adult patients with encephalitis.

Encephalitis results from inflammation of the brain parenchyma, and may be caused by infections or autoimmune conditions. Diagnosis is typically made by a combination of clinical, laboratory, neuroimaging, and electrophysiologic findings. A number of case definitions have been developed,[1–7] which generally require encephalopathy, as characterized by alteration in consciousness or personality change lasting for a sustained period of time (typically greater than 24 hours). To distinguish encephalitis from other causes of encephalopathy, key features include presence of fever, CSF pleocytosis, or MRI or EEG changes compatible with encephalitis (table 1). Although such definitions likely capture most patients with clinically significant encephalitis, some will be missed. For example, localized forms of brain inflammation (i.e., a unilateral brainstem process) may cause focal neurologic deficits without affecting consciousness or behavior.[8]

Neurologists must be aware of the numerous conditions that may mimic encephalitis. Some examples include vascular disease, systemic infection (with no direct CNS infection)

Johns Hopkins Encephalitis Center, Department of Neurology (AV, RG), and the Departments of Anaesthesiology–Critical Care Medicine, Neurosurgery, and Medicine (RG), Johns Hopkins University School of Medicine, Baltimore, MD.

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Correspondence to: avenkat2@jhmi.edu

Table 1 Diagnostic criteria for encephalitis[a]

Major criterion (required)
Patients presenting to medical attention with altered mental status (defined as decreased or altered level of consciousness, lethargy, or personality change) lasting ≥24 hours with no alternative cause identified
Minor criteria (2 required for possible encephalitis; ≥3 required for probable or confirmed encephalitis)
Documented fever ≥38°C (100.4°F) within the 72 hours before or after presentation
Generalized or partial seizures not fully attributable to a preexisting seizure disorder
New onset of focal neurologic findings
CSF leukocyte count ≥5/mm^3
Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset
Abnormality on EEG that is consistent with encephalitis and not attributable to another cause.

[a] Adapted from reference 7 (Venkatesan et al. *Clinical Infectious Diseases* 2013;57:1114–1128) by permission of Oxford University Press on behalf of the Infectious Diseases Society of America.

or inflammation, toxic exposures, or metabolic derangements (table e-1 at Neurology.org/cp). Such conditions need to be aggressively investigated in all patients with suspected encephalitis. Given the range of conditions that cause and mimic encephalitis, obtaining a thorough history is crucial. Important historical points include the presence of recent illness, ill contacts, unusual exposures (including occupational, vector, and animal), outdoor activities, and ingestions. It is critical to elicit travel history, both recent and remote, since agents such as rabies or malaria can become symptomatic long after initial exposure.

A practical approach to diagnosis in adults is presented in table 2. In addition to routine studies to investigate for causes of encephalopathy, all patients with suspected encephalitis should undergo blood cultures and HIV testing. Extra serum should be drawn during the acute phase of illness and held for later serologic studies, and if the diagnosis is still uncertain, a convalescent serum should be collected 10–21 days later. Lumbar puncture (LP) is recommended in all individuals unless contraindicated (i.e., significant mass effect/edema or effacement of basal cisterns on neuroimaging, or suspected skin or soft tissue abscess in the path of the puncture needle).[9]

Since herpes simplex virus (HSV), varicella-zoster virus (VZV), and enterovirus are 3 of the most commonly identified etiologic agents in acute encephalitis,[1,4,6] these should be routinely screened for in the CSF. With respect to neuroimaging, MRI is preferred to CT given the increased sensitivity and specificity for evaluation of encephalitis.[10–12] Chest imaging should also be performed as focal infiltrates may be suggestive of certain pathogens (e.g., fungal or mycobacterial infections).

In addition to travel, exposure, and medical history, specific signs and symptoms as well as laboratory and neuroimaging features can help to guide further testing (table 2). For example, prominent psychosis or movement disorders should prompt testing for anti-NMDA receptor (NMDAR) encephalitis, those with limbic symptoms should undergo testing for anti–voltage-gated potassium channel [VGKC] and other paraneoplastic encephalitides, and brainstem lesions should prompt further testing for a range of additional pathogens. Notably, the field of autoimmune encephalitis is rapidly advancing, and testing algorithms are likely to continue to evolve.

Diagnostic testing: practical considerations and caveats

During LP, CSF opening pressure should be obtained in all individuals, since abnormalities in intracranial pressure (ICP) may contribute to the neurologic dysfunction in encephalitis or, alternatively, suggest a different diagnosis. Although the typical CSF profile of viral encephalitis demonstrates a mononuclear pleocytosis with cell counts up to 200 cells/mm^3, with more

Table 2 Initial evaluation of encephalitis in adults[a]

Routine studies
CSF (unless contraindicated[b])
Opening pressure, leukocyte count with differential, erythrocyte count, protein, glucose
Gram stain and bacterial culture
HSV-1/2 PCR (if test available, consider HSV CSF IgG and IgM in addition)
VZV PCR (sensitivity may be low; if test available, consider VZV CSF IgG and IgM in addition)
Enterovirus PCR
Cryptococcal antigen or India ink staining
Oligoclonal bands and IgG index
Venereal Disease Research Laboratory
Serum
Routine blood cultures
HIV serology (consider RNA)
Treponemal testing (rapid plasma reagin, specific treponemal test)
Imaging
Neuroimaging (MRI preferred to CT, if available)
Chest imaging (chest x-ray or CT)
Neurophysiology
EEG
Other tissues/fluids
When clinical features of extra-CNS involvement are present, we recommend additional testing (e.g., biopsy of skin lesions; bronchoalveolar lavage or endobronchial biopsy in those with pneumonia/pulmonary lesions; throat swab PCR/culture in those with upper respiratory illness; stool culture in those with diarrhea); also see below
Conditional studies
Host factors
Immunocompromised—CMV PCR, HHV6/7 PCR, *Toxoplasma gondii*; MTB, fungal infections, WNV
Geographic factors
Africa—malaria, trypanosomiasis, dengue
Asia—Japanese encephalitis virus, dengue, malaria, Nipah virus
Australia—Murray Valley encephalitis, Kunjin virus, Australian bat lyssavirus
Europe—tick-borne encephalitis virus; if Southern Europe, consider WNV testing, Toscana virus testing
Central and South America—dengue, malaria, WNV, Venezuelan equine encephalitis
North America—geographically appropriate arboviruses (e.g., WNV, Powassan, LaCrosse, Eastern equine encephalitis virus, St. Louis encephalitis, dengue, Lyme)
Season and exposure
Summer/fall: WNV and other arboviruses, tick-borne disease
Cat (particularly if with seizures, paucicellular CSF)—*Bartonella*
Tick exposure—tick-borne disease
Animal bite/bat exposure—rabies
Swimming or diving in warm freshwater or nasal/sinus irrigation—*Naegleria fowleri*

Continued

Table 2 Continued

Specific signs and symptoms
Psychotic features or movement disorder—anti-NMDAR encephalitis, rabies, Creutzfeldt-Jakob disease
Prominent limbic symptoms—autoimmune limbic encephalitis, HHV6/7
Rapid decompensation (particularly with animal bite history or prior travel to rabies-endemic areas)—rabies
Respiratory symptoms—*Mycoplasma pneumoniae*, respiratory viruses
Acute flaccid paralysis—WNV and other arboviruses, rabies
Parkinsonism—Arbovirus, Toxoplasma
Nonhealing skin lesions—*Balamuthia mandrillaris, Acanthamoeba*
Laboratory features
Elevated transaminases—rickettsia, tick-borne diseases
CSF protein >100 mg/dL, or CSF glucose <2/3 peripheral glucose, or lymphocytic pleocytosis with subacute symptom onset—MTB and fungal testing
CSF protein >100 mg/dL or CSF glucose <2/3 peripheral glucose and neutrophilic predominance with acute symptom onset and recent antibiotic use—*S pneumoniae* and *Neisseria meningiditis*
CSF eosinophilia—MTB and fungal testing, *Baylisascaris procyonis*, *Angiostrongylus cantonensis, Gnathostoma* sp.
Erythrocytes in CSF—*N fowleri*
Hyponatremia—anti-VGKC; MTB
Neuroimaging features
Frontal lobe—*N fowleri*
Temporal lobe—anti-VGKC basal ganglia or thalamus, Arbovirus, MTB
Brainstem—Arbovirus, listeria, Brucella, MTB
Cerebellum—Epstein-Barr virus
Diffuse cerebral edema—respiratory virus testing
Space-occupying or ring-enhancing lesions—MTB and fungal infections, *B mandrillaris* and *Acanthamoeba*, toxoplasma serology
Hydrocephalus or basilar meningeal enhancement—MTB and fungal infections
Infarction or hemorrhage—MTB and fungal infections; respiratory virus testing
Incomplete ring-enhancing lesions—ADEM

Abbreviations: ADEM = acute disseminated encephalomyelitis; CMV = cytomegalovirus; HHV = human herpesvirus; HSV = herpes simplex virus; IgG = immunoglobulin G; IgM = immunoglobulin M; NMDAR = NMDA receptor; VZV = varicella-zoster virus; WNV = West Nile virus.
[a] Adapted from reference 7 (Venkatesan et al. *Clinical Infectious Diseases* 2013;57:1114-1128) by permission of Oxford University Press on behalf of the Infectious Diseases Society of America. This table is not intended to encompass all causes of encephalitis, nor all epidemiologic or laboratory-based risk factors. We recommend utilizing this table as a guideline for initial management of acute encephalitis in adults.
[b] Lumbar puncture is recommended in all individuals with suspected encephalitis unless contraindicated (i.e., significant mass effect/edema, effacement of basal cisterns on imaging; skin or soft tissue infection in needle path; see reference 9).

substantial pleocytosis typically suggesting a bacterial infection, some viruses can be associated with CSF leukocyte counts greater than 1,000 cells/mm^3 (i.e., mumps, lymphocytic choriomeningitis virus). Moreover, neutrophils, which are generally accepted to be present in the first 24 hours after viral infection, may persist beyond 24 hours.[13]

It is critical to elicit travel history, both recent and remote, since agents such as rabies or malaria can become symptomatic long after initial exposure.

Selected viral etiologies The 2 most common human herpesviruses identified in the setting of encephalitis are HSV-1 and VZV. The HSV PCR test can result in false-negatives, particularly among children and early in the course of disease.[14–16] If herpes simplex encephalitis is still suspected despite negative testing from the first LP, a second CSF examination should be repeated within 3 to 7 days.[17] Since VZV reactivation may occur without demonstrable skin lesions (zoster sine herpete), testing for VZV in all individuals with suspected encephalitis is recommended regardless of whether vesicular lesions are present.[18] Notably, testing of the CSF for VZV PCR, though recommended, appears to have suboptimal sensitivity. Indeed, detection of CSF antibodies to VZV may be a more sensitive approach to diagnosing VZV encephalitis.[19]

Diagnosis of arboviral encephalitis presents a unique set of challenges. In general, serologic testing of serum and CSF is preferable to PCR, since the peak viral load typically occurs before the onset of symptoms. This has been well described in West Nile virus (WNV) neuroinvasive disease, for example, where the sensitivity of CSF PCR is low compared with CSF WNV immunoglobulin M (IgM).[20] Since the percentage of seropositive patients increases over the first week of illness, repeat testing can be useful if the suspicion for disease is high despite initial negative results.[21,22] Following acute infection, IgM antibodies may persist for months, and thus their presence does not necessarily indicate current or active infection.[23,24] Seroconversion of the IgM antibody or a 4-fold or greater rise in titer, or both, can substantiate the diagnosis.

Selected autoimmune etiologies Cardinal clinical features of anti-NMDAR encephalitis include changes in behavior or cognition, seizures, orofacial dyskinesias, and autonomic instability.[25,e1] In a large series of patients in whom both CSF and serum were tested for NMDAR antibodies, approximately 15% of individuals had positive CSF antibodies in the absence of serum antibodies.[e2] Thus, CSF testing is recommended in those with a compatible clinical picture and negative serum antibodies. Recent evidence has linked the development of antibodies to NMDAR to preceding or concurrent herpes simplex encephalitis. In a study of patients with PCR-proven herpes simplex encephalitis (HSE), NMDAR antibodies were detected in one-third of patients (13 of 44),[e3] while more recently, some pediatric cases with neurologic relapse (movement disorders or new cognitive dysfunction, or both) following herpes encephalitis have been found to have NMDAR antibodies and responded to immunotherapy.[e4,e5] These reports suggest that patients who experience a neurologic decline following treatment for HSE should be tested for NMDAR antibodies.

Autoimmune limbic encephalitis results in a combination of acute or subacute onset of short-term memory deficits, behavioral changes, and seizures. It occurs in association with several types of antibodies, including those associated with cancer (onconeuronal antibodies to antigens such as Hu, CV2, and Ma2) and those directed against synaptic or neuronal cell surface antigens (i.e., VGKC, glutamic acid decarboxylase, and AMPA receptor, among others). In general, serum testing may be sufficient.[e6]

Management

The management of acute encephalitis can be guided by a practical approach involving 3 "Es": emergent issues, epilepsy, and etiology. An overview of acute management of patients is provided in the figure, and typical doses of therapeutic agents are listed in table 3.

Supplemental Data
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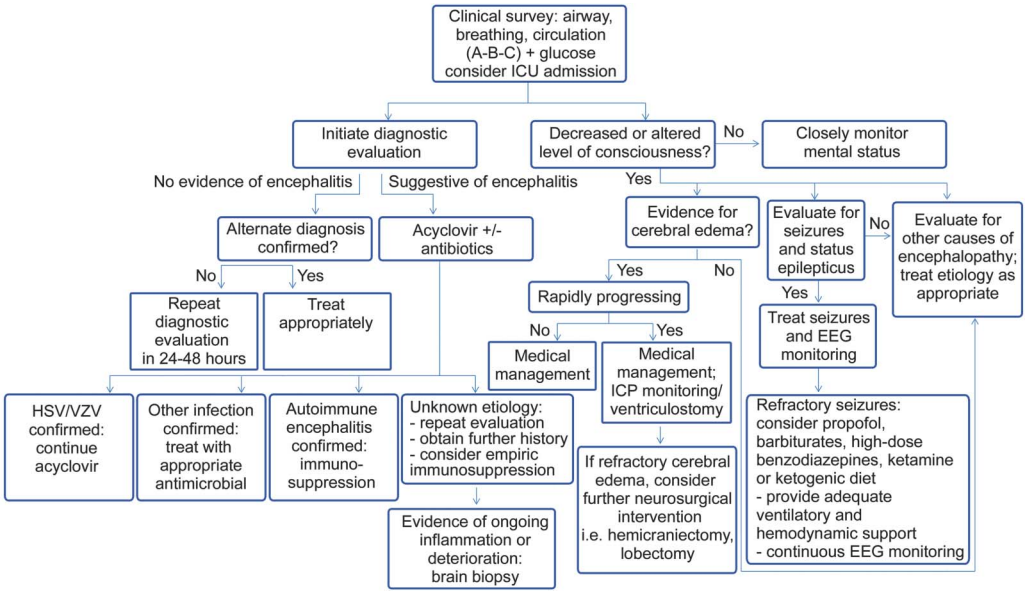
Figure Approach to management of patients with suspected encephalitis



HSV = herpes simplex virus; ICU = intensive care unit; VZV = varicella-zoster virus.

Emergent issues

Upon presentation, a careful evaluation is important to quickly identify and address all evolving and impending emergent neurologic and systemic issues. The immediate goal is to ensure patient safety while efficient and effective diagnosis and management are undertaken. Assessing the ABCs is an essential first step. Is the patient's airway protected? Reduced level of consciousness, which can result from metabolic encephalopathy, seizures, or cerebral edema, can lead to impaired airway reflexes that may necessitate endotracheal intubation. Is breathing adequate? Similar neurologic conditions that impair airway reflexes can also impair respiratory drive, while systemic conditions such as pneumonia may impair oxygenation. Hypoxemia or hypercarbia may necessitate mechanical ventilatory support after endotracheal intubation.

Is circulation sufficient? A number of etiologies of encephalitis, including anti-NMDAR encephalitis and HSE, have been associated with autonomic dysfunction, and hemodynamic stability must be ensured.

Where should the patient be admitted? In one series of patients with encephalitis, approximately 25% of cases were admitted to the intensive care unit (ICU).[e7] Factors involved in making the decision to admit to the ICU include level of consciousness, impairment in the ABCs, comorbid conditions, and specific etiologic concerns. The clinical needs of patients with encephalitis in the ICU are complex and a multidisciplinary team is essential. While no dedicated data exist, the complexities of the neurologic issues, along with critical care concerns, are reasons to favor admission in a dedicated neurologic critical care unit. In the absence of one, it is key that neurologic consultants work closely and in real time with the ICU team to ensure the best outcome of patients.

Acute reduction or alteration of consciousness The acute reduction or alteration of consciousness is an emergent neurologic issue. In the setting of encephalitis, the top concerns include ICP and mass effect, direct and global effect of inflammation or infection to the brain, and systemic issues that affect brain function (i.e., hypoglycemia, fever, electrolyte abnormality, O_2 and CO_2, and systemic infections). Here, we focus on management of increased ICP and mass effect. Seizures will be addressed separately.

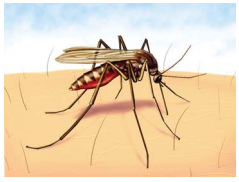
Concerns for ICP abnormalities and mass effect should prompt rapid bedside assessment and immediate neurologic imaging (a head CT typically suffices). A reduction in level of

Table 3 Therapeutics agents commonly used in encephalitis

Indication	Typical dosing/administration[a]
Cerebral edema[e8]	Mannitol 0.25 to 1 g/kg bolus every 4–6 hours
	Hypertonic saline
	Active brain herniation, 23% saline (30 mL bolus via central venous access)
	Maintenance, 2%–3% saline (250–500 mL boluses or continuous venous infusion; 3% saline via central venous access)
Seizures and status epilepticus[e12]	
First line, initial dosing	Lorazepam 0.1 mg/kg IV up to 4 mg per dose
	Midazolam 0.25 mg/kg IM up to 10 mg maximum
	Diazepam 0.15 mg/kg IV up to 10 mg per dose
Second line, initial dosing	Fosphenytoin 20 mg PE/kg IV
	Levetiracetam 1,000–3,000 mg IV
	Valproate sodium, 20–40 mg/kg IV
Third line, loading dose	Propofol 1–2 mg/kg
	Phenobarbital 20 mg/kg IV
	Pentobarbital 5–15 mg/kg IV
Herpes simplex encephalitis[17]	Acyclovir, 10 mg/kg IV q 8 hrs × 14–21 days
Autoimmune encephalitis, acute[e16,e17]	
First line	Methylprednisolone 1,000 mg IV q day × 5 days
	IV immunoglobulin, 0.4 g/kg IV q day × 5 days
	Plasma exchange, 5–7 exchanges administered every other day
Second line	Cyclophosphamide, body surface area × 800 mg IV
	Rituximab, 1,000 mg IV × 1, followed by second dose in 2 weeks

[a] Drugs and dosing recommendations are provided only as guide; clinical conditions and drug effects must be carefully considered prior to drug administration.

consciousness (LOC) associated with unilateral or bilateral pupillary dilation and nonreactivity to light may indicate transtentorial brain herniation. A recent review addressed the reversal of brain herniation.[e8] Normal oxygenation (O_2 sats >90%) and hyperventilation to pCO_2 30 ± 2 mm Hg and mean arterial pressure to at least 60 mm Hg are reasonable initial targets. If mass effect from significant cerebral edema is noted, hyperosmolar therapy with the use of mannitol or hypertonic saline may be necessary. IV mannitol at 0.25 to 1 g/kg bolus every 4–6 hours can be given via a peripheral line, though it is important to correct the diuresis associated with mannitol with normal saline solution in order to avoid dehydration. Our preference has been the use of hypertonic saline rather than mannitol; we typically use concentrations of 2% Na via a peripheral line, and 3% or 23.4% Na via a central line. We administer 2% or 3% Na as boluses of 250–500 cc to attain a serum Na of 150–155; maintenance infusion may be necessary over several days. The administration of a 30-cc bolus of 23.4% Na is reserved for active brain herniation. One important caveat in the use of saline solutions is in the setting of hyponatremia, as can occur in CNS infection. Long-term hyponatremia needs to be corrected slowly over several days to avoid myelin injury, and therefore mannitol may be preferred in such settings. However, for those with normal Na, hypertonic saline is typically safe and may be used aggressively as needed. Mass effect



The clinical needs of patients with encephalitis in the ICU are complex and a multidisciplinary team is essential.

associated with vasogenic edema may benefit from high doses of corticosteroids, the use of which is described later (Etiology). Fevers may increase ICP and worsen neurologic injury, and should be treated.[e9] Rapidly evolving hydrocephalus typically requires placement of a ventriculostomy for CSF drainage and ICP monitoring. In some case, cerebral edema and ICP elevation may progress despite the above interventions, and initiation of barbiturate coma or hemicraniectomy to relieve global pressure may be necessary.

While issues of increased ICP are being addressed, other factors that may contribute to encephalopathy need to be continually evaluated. The list can be exhaustive but some entities to consider include septic encephalopathy due to an extraneural infection; endocrine pathology (i.e., thyroid, adrenals); metabolic issues (i.e., hyperammonemia, electrolyte disorder, syndrome of inappropriate antidiuretic hormone secretion); and cerebral hypoperfusion states.

Seizures and status epilepticus

The occurrence of seizures is common and status epilepticus in critically ill patients with encephalitis is noted in 15%.[e7] In encephalitic patients with reduced or altered LOC, seizures represent a potentially treatable entity and should be treated immediately if diagnosed. Emergent EEG is crucial and prolonged continuous EEG is recommended to improve diagnostic ability and to monitor treatment effects of antiepileptic agents in real time. The clinical approach to seizures and status epilepticus highlights the need for close collaboration between the neurologist and the intensivist. The goal of treatment is to control epileptic activity, but in many cases it is necessary to induce a burst-suppression pattern on EEG.

In patients suspected or diagnosed with seizures, concurrent with the ABCs is the need to administer first-line agents such as lorazepam IV[e10] or midazolam IM.[e11] For definite or continued seizure activity, choices for second-line antiepileptic drugs (AEDs) can be tailored to the clinical situation with IV agents such as fosphenytoin, levetiracetam, and valproic acid. It is not uncommon for encephalitic patients to progress to more refractory epileptic states that typically require a third-line AED with anesthetic properties, such as barbiturates (i.e., pentobarbital or high-dose phenobarbital), propofol, and ketamine. As the aggressiveness of epilepsy treatment increases, so does the need for increasing ICU support due to potential adverse effects such as hypotension, loss of protective airway reflex, and respiratory drive. Other potential systemic complications include pneumonia and sepsis. Continuous monitoring for seizures and their resolution is important to optimize AED therapy while minimizing duration of drug exposure and attendant complications. A guideline to the management of status epilepticus has recently been published.[e12]

Etiology

The diagnostic approach provided above may require days to weeks to ascertain a specific etiologic basis for treatment. At the time of presentation, it is important to consider empiric management for common etiologies of encephalitis. Foremost is HSV and the need to start IV acyclovir as early as possible. Delay in acyclovir treatment in those suspected with HSV infection resulted in increased risk of death and severe disability.[e13] Depending on the CSF profile, any suspicion of bacterial infection may necessitate broader coverage with appropriate antibiotics and corticosteroids as necessary.[e14] In addition, results of the diagnostic evaluation may prompt administration of other appropriate antiviral, antibacterial, or antifungal agents.

In patients with autoimmune etiology, appropriate strategies for immune modulation must be initiated. First-line immunotherapies for acute immune-mediated encephalitis generally include corticosteroids (i.e., IV methylprednisolone, 1,000 mg daily for 5 days), IV immunoglobulin

(typically 2 g/kg body weight given over 5 days), and plasmapheresis (typically 5 exchanges, administered every other day), either alone or in combination. Response to these agents is typically monitored over several weeks and, if suboptimal, then second-line treatments, including cyclophosphamide (i.e., 1,000 mg/kg body weight, given once) or rituximab (i.e., 1,000 mg IV given once, then repeated in 2 weeks), are recommended.[e2] In the case of paraneoplastic syndromes, the resection of the offending tumor (i.e., oophorectomy in NMDAR encephalitis) is often critical for achieving control of neuroinflammation.[e15] Notably, empiric immunosuppressive therapy may be considered in those with encephalitis of unknown etiology, although clinical or radiologic deterioration in such patients should prompt a brain biopsy.[8]

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