

The Management of Encephalitis: Clinical Practice Guidelines by the Infectious Diseases Society of America

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Guidelines for the diagnosis and treatment of patients with encephalitis were prepared by an Expert Panel of the Infectious Diseases Society of America. The guidelines are intended for use by health care providers who care for patients with encephalitis. The guideline includes data on the epidemiology, clinical features, diagnosis, and treatment of many viral, bacterial, fungal, protozoal, and helminthic etiologies of encephalitis and provides information on when specific etiologic agents should be considered in individual patients with encephalitis.

EXECUTIVE SUMMARY

Encephalitis is defined by the presence of an inflammatory process of the brain in association with clinical evidence of neurologic dysfunction. Of the pathogens reported to cause encephalitis, the majority are viruses. However, despite extensive testing, the etiology of encephalitis remains unknown in most patients. Another major challenge for patients with encephalitis is to determine the relevance of an infectious agent identified outside of the CNS; these agents may play a role in the neurologic manifestations of illness but not necessarily by directly invading the CNS. In addition, it is important to distinguish between infectious encephalitis and postinfectious or postimmunization encephalitis or en-

cephalomyelitis (e.g., acute disseminated encephalomyelitis [ADEM]), which may be mediated by an immunologic response to an antecedent antigenic stimulus from an infecting microorganism or immunization. Noninfectious CNS diseases (e.g., vasculitis, collagen vascular disorders, and paraneoplastic syndromes) can have clinical presentations similar to those of infectious causes of encephalitis and should also be considered in the differential diagnosis.

In the approach to the patient with encephalitis, an attempt should be made to establish an etiologic diagnosis. Although there are no definitive effective treatments in many cases of encephalitis, identification of a specific agent may be important for prognosis, potential prophylaxis, counseling of patients and family members, and public health interventions. Epidemiologic clues that may help in directing the investigation for an etiologic diagnosis include season of the year, geographic locale, prevalence of disease in the local community, travel history, recreational activities, occupational exposure, insect contact, animal contact, vaccination history, and immune status of the patient. Various clinical clues may also be helpful to physicians in considering specific etiologies.

The diagnostic evaluation of a patient who presents with encephalitis needs to be individualized and should be guided by epidemiologic and clinical clues and lab-

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It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The Infectious Diseases Society of America considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

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oratory data; these generally include cultures and analysis (i.e., antigen detection and nucleic acid amplification tests, such as PCR) of body fluid specimens, biopsy of specific tissues (with culture, antigen detection, PCR, and histopathologic evaluation) outside the CNS, and serologic testing (for specific IgM and acute- and convalescent-phase IgG antibody titers). MRI of the brain should be performed in all patients, with CT used only if MRI is unavailable, unreliable, or cannot be performed; neuroimaging findings may also suggest disease caused by specific etiologic agents. CSF analysis is critical, unless contraindicated, and may be quite helpful in establishing an etiology. Detection of specific viral IgM antibodies in CSF specimens obtained from patients with encephalitis caused by numerous viruses is considered to be diagnostic of neuroinvasive disease. CSF cultures are generally of limited value in the determination of the viral causes of encephalitis but are very important in the diagnosis of bacterial and fungal infections. The utility of nucleic acid amplification testing (e.g., PCR) of CSF specimens has greatly increased the ability to diagnose infections of the CNS, especially viral infections caused by the herpesviruses. At present, brain biopsy is rarely performed to establish the etiology of encephalitis, but it may play a role in some patients with encephalitis of unknown etiology whose conditions deteriorate despite treatment with acyclovir.

Despite the wide range of viruses that have been reported to cause encephalitis, specific antiviral therapy is generally limited to infections caused by the herpesviruses—specifically, herpes simplex virus—and HIV. Acyclovir treatment should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. During the appropriate season, patients who present with clinical clues suggestive of rickettsial or ehrlichial infection should be treated empirically with doxycycline. Empirical therapy for acute bacterial meningitis should also be initiated if clinically indicated. In patients with acute disseminated encephalomyelitis, corticosteroids are recommended; plasma exchange should be considered in patients who do not respond to this treatment.

Recommendation categories are shown in table 1.

Etiology

1. Epidemiologic clues and assessment of risk factors to identify potential etiologic agents should be sought in all patients with encephalitis (table 2) (A-III).

2. Clinical clues (general and specific neurologic findings) may be helpful in suggesting certain causative agents in patients with encephalitis (table 3) (B-III).

3. In patients with encephalitis and a history of recent infectious illness or vaccination, the diagnosis of ADEM should be considered (B-III).

Diagnosis

4. Specific diagnostic studies should be performed for the majority of patients who present with encephalitis (table 4) (A-III).

5. Additional diagnostic studies should be performed for patients with encephalitis on the basis of specific epidemiologic and clinical clues (tables 2, 3, and 5) (A-III).

Diagnostic Studies outside the CNS

6. Cultures of body fluid specimens (e.g., from blood, stool, nasopharynx, or sputum), if clinical and epidemiologic clues are suggestive, should be performed in an attempt to identify various viral, bacterial, and fungal etiologies of encephalitis (table 5) (B-III); positive results do not necessarily indicate that the isolated microorganism is the etiology of encephalitis and must be interpreted in the context of the appropriate epidemiologic findings, clinical findings, and other diagnostic study results.

7. Biopsy of specific tissues for culture, antigen detection, nucleic acid amplification tests (such as PCR), and histopathologic examination should be performed in an attempt to establish an etiologic diagnosis of encephalitis (table 5) (A-III).

8. Certain causes of encephalitis may be diagnosed by detection of IgM antibodies in serum (table 5) (A-III).

9. Although acute- and convalescent-phase serum samples are generally not useful in establishing the etiology during the acute presentation in a patient with encephalitis, they may be useful for the retrospective diagnosis of an infectious agent (table 5) (B-III).

10. Nucleic acid amplification tests (such as PCR) of body fluids outside of the CNS may be helpful in establishing the etiology in some patients with encephalitis (table 5) (B-III).

Neurodiagnostic Studies

11. MRI is the most sensitive neuroimaging test to evaluate patients with encephalitis (A-I).

12. CT, with and without contrast enhancement, should be used to evaluate patients with encephalitis if MRI is unavailable, impractical, or cannot be performed (B-III).

13. Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) scanning is not routinely recommended for patients with encephalitis.

14. Electroencephalography (EEG) is rarely helpful in establishing an etiology in patients with encephalitis, but it has a role in identifying patients with nonconvulsive seizure activity who are confused, obtunded, or comatose and should be performed in all patients with encephalitis (A-III).

15. CSF analysis is essential (unless contraindicated) in all patients with encephalitis (A-III).

Table 1. Infectious Diseases Society of America—US Public Health Service Grading System for ranking recommendations in clinical guidelines.

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
Quality of evidence	
I	Evidence from ≥ 1 properly randomized, controlled trial
II	Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytical studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

NOTE. Adapted from Canadian Task Force on the Periodic Health Examination [2].

Diagnostic Studies in the CNS

16. For certain viral agents, the presence of virus-specific IgM in CSF specimens may be indicative of CNS disease caused by that pathogen (table 5) (A-III).

17. Nucleic acid amplification tests (such as PCR) should be performed on CSF specimens to identify certain etiologic agents in patients with encephalitis (table 5) (A-III). Although a positive test result is helpful in diagnosing infection caused by a specific pathogen, a negative result cannot be used as definitive evidence against the diagnosis.

18. Herpes simplex PCR should be performed on all CSF specimens in patients with encephalitis (A-III). In patients with encephalitis who have a negative herpes simplex PCR result, consideration should be given to repeating the test 3–7 days later in those with a compatible clinical syndrome or temporal lobe localization on neuroimaging (B-III).

19. Viral cultures of CSF specimens are of limited value in patients with encephalitis and are not routinely recommended.

20. Brain biopsy should not be routinely used in patients with encephalitis but should be considered in patients with encephalitis of unknown etiology whose condition deteriorates despite treatment with acyclovir (B-III).

Treatment

Empirical Therapy

21. Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies (A-III).

22. Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors (tables 2 and 3), including appropriate therapy for presumed bacterial meningitis, if clinically indicated (A-III).

23. In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens (A-III).

Specific Therapy

Viruses

24. Herpes simplex virus: acyclovir is recommended (A-I).

25. Varicella-zoster virus: acyclovir is recommended (B-III); ganciclovir can be considered an alternative (C-III); adjunctive corticosteroids can be considered (C-III).

26. Cytomegalovirus: the combination of ganciclovir plus foscarnet is recommended (B-III); cidofovir is not recommended, because its ability to penetrate the blood-brain barrier has been poorly studied.

27. Epstein-Barr virus: acyclovir is not recommended; the use of corticosteroids may be beneficial (C-III), but the potential risks must be weighed against the benefits.

28. Human herpesvirus 6: ganciclovir or foscarnet should be used in immunocompromised patients (B-III); use of these agents in immunocompetent patients can be considered (C-III), but there are not good data on their effectiveness.

29. B virus: valacyclovir is recommended (B-III); alternative agents are ganciclovir (B-III) and acyclovir (C-III).

30. Influenza virus: oseltamivir can be considered (C-III).

31. Measles virus: ribavirin can be considered (C-III); intrathecal ribavirin can be considered in patients with subacute sclerosing panencephalitis (C-III).

32. Nipah virus: ribavirin can be considered (C-III).

33. West Nile virus: ribavirin is not recommended.

34. Japanese encephalitis virus: IFN- α is not recommended.

35. St. Louis encephalitis virus: IFN-2 α can be considered (C-III).

Table 2. Possible etiologic agents of encephalitis based on epidemiology and risk factors.

Epidemiology or risk factor	Possible infectious agent(s)
Agammaglobulinemia	Enteroviruses, <i>Mycoplasma pneumoniae</i>
Age	
Neonates	Herpes simplex virus type 2, cytomegalovirus, rubella virus, <i>Listeria monocytogenes</i> , <i>Treponema pallidum</i> , <i>Toxoplasma gondii</i>
Infants and children	Eastern equine encephalitis virus, Japanese encephalitis virus, Murray Valley encephalitis virus (rapid in infants), influenza virus, La Crosse virus
Elderly persons	Eastern equine encephalitis virus, St. Louis encephalitis virus, West Nile virus, sporadic CJD, <i>L. monocytogenes</i>
Animal contact	
Bats	Rabies virus, Nipah virus
Birds ^a	West Nile virus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, St. Louis encephalitis virus, Murray Valley encephalitis virus, Japanese encephalitis virus, <i>Cryptococcus neoformans</i> (bird droppings)
Cats	Rabies virus, <i>Coxiella burnetii</i> , <i>Bartonella henselae</i> , <i>T. gondii</i>
Dogs	Rabies virus
Horses ^a	Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Hendra virus ^b
Old World primates	B virus
Raccoons	Rabies virus, <i>Baylisascaris procyonis</i>
Rodents ^a	Eastern equine encephalitis virus (South America), Venezuelan equine encephalitis virus, tickborne encephalitis virus, Powassan virus (woodchucks), La Crosse virus (chipmunks and squirrels), <i>Bartonella quintana</i> ^b
Sheep and goats	<i>C. burnetii</i>
Skunks	Rabies virus
Swine ^a	Japanese encephalitis virus, Nipah virus ^b
White-tailed deer ^a	<i>Borrelia burgdorferi</i>
Immunocompromised persons	Varicella zoster virus, cytomegalovirus, human herpesvirus 6, West Nile virus, HIV, JC virus, <i>L. monocytogenes</i> , <i>Mycobacterium tuberculosis</i> , <i>C. neoformans</i> , <i>Coccidioides</i> species, <i>Histoplasma capsulatum</i> , <i>T. gondii</i>
Ingestion items	
Raw or partially cooked meat	<i>T. gondii</i>
Raw meat, fish, or reptiles	<i>Gnathostoma</i> species
Unpasteurized milk	Tickborne encephalitis virus, <i>L. monocytogenes</i> , <i>C. burnetii</i>
Insect contact	
Mosquitoes	Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, St. Louis encephalitis virus, Murray Valley encephalitis virus, Japanese encephalitis virus, West Nile virus, La Crosse virus, <i>Plasmodium falciparum</i>
Sandflies	<i>Bartonella bacilliformis</i>
Ticks	Tickborne encephalitis virus, Powassan virus, <i>Rickettsia rickettsii</i> , <i>Ehrlichia chaffeensis</i> , <i>Anaplasma phagocytophilum</i> , <i>C. burnetii</i> (rare), <i>B. burgdorferi</i>
Tsetse flies	<i>Trypanosoma brucei gambiense</i> , <i>Trypanosoma brucei rhodesiense</i>
Occupation	
Exposure to animals	Rabies virus, <i>C. burnetii</i> , <i>Bartonella</i> species
Exposure to horses	Hendra virus
Exposure to Old World primates	B virus

(continued)

Table 2. (Continued.)

Epidemiology or risk factor	Possible infectious agent(s)
Laboratory workers	West Nile virus, HIV, <i>C. burnetii</i> , <i>Coccidioides</i> species
Physicians and health care workers	Varicella zoster virus, HIV, influenza virus, measles virus, <i>M. tuberculosis</i>
Veterinarians	Rabies virus, <i>Bartonella</i> species, <i>C. burnetii</i>
Person-to-person transmission	Herpes simplex virus (neonatal), varicella zoster virus, Venezuelan equine encephalitis virus (rare), poliovirus, nonpolio enteroviruses, measles virus, Nipah virus, mumps virus, rubella virus, Epstein-Barr virus, human herpesvirus 6, B virus, West Nile virus (transfusion, transplantation, breast feeding), HIV, rabies virus (transplantation), influenza virus, <i>M. pneumoniae</i> , <i>M. tuberculosis</i> , <i>T. pallidum</i>
Recent vaccination	Acute disseminated encephalomyelitis
Recreational activities	
Camping/hunting	All agents transmitted by mosquitoes and ticks (see above)
Sexual contact	HIV, <i>T. pallidum</i>
Spelunking	Rabies virus, <i>H. capsulatum</i>
Swimming	Enteroviruses, <i>Naegleria fowleri</i>
Season	
Late summer/early fall	All agents transmitted by mosquitoes and ticks (see above), enteroviruses
Winter	Influenza virus
Transfusion and transplantation	Cytomegalovirus, Epstein-Barr virus, West Nile virus, HIV, tickborne encephalitis virus, rabies virus, iatrogenic CJD, <i>T. pallidum</i> , <i>A. phagocytophilum</i> , <i>R. rickettsii</i> , <i>C. neoformans</i> , <i>Coccidioides</i> species, <i>H. capsulatum</i> , <i>T. gondii</i>
Travel	
Africa	Rabies virus, West Nile virus, <i>P. falciparum</i> , <i>T. brucei gambiense</i> , <i>T. brucei rhodesiense</i>
Australia	Murray Valley encephalitis virus, Japanese encephalitis virus, Hendra virus
Central America	Rabies virus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, St. Louis encephalitis virus, <i>R. rickettsii</i> , <i>P. falciparum</i> , <i>Taenia solium</i>
Europe	West Nile virus, tickborne encephalitis virus, <i>A. phagocytophilum</i> , <i>B. burgdorferi</i>
India, Nepal	Rabies virus, Japanese encephalitis virus, <i>P. falciparum</i>
Middle East	West Nile virus, <i>P. falciparum</i>
Russia	Tickborne encephalitis virus
South America	Rabies virus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, St. Louis encephalitis virus, <i>R. rickettsii</i> , <i>B. bacilliformis</i> (Andes mountains), <i>P. falciparum</i> , <i>T. solium</i>
Southeast Asia, China, Pacific Rim	Japanese encephalitis virus, tickborne encephalitis virus, Nipah virus, <i>P. falciparum</i> , <i>Gnathostoma</i> species, <i>T. solium</i>
Unvaccinated status	Varicella zoster virus, Japanese encephalitis virus, poliovirus, measles virus, mumps virus, rubella virus

NOTE. CJD, Creutzfeldt-Jacob disease.

^a Unless indicated, these animals are a reservoir or incidental hosts that do not directly transmit the infectious agent to humans, but transmission is via a vector (e.g., mosquito or tick).

^b Agent may be directly transmitted by animal contact.

Table 3. Possible etiologic agents of encephalitis based on clinical findings.

Clinical presentation	Possible infectious agent
General findings	
Hepatitis	<i>Coxiella burnetii</i>
Lymphadenopathy	HIV, Epstein-Barr virus, cytomegalovirus, measles virus, rubella virus, West Nile virus, <i>Treponema pallidum</i> , <i>Bartonella henselae</i> and other <i>Bartonella</i> species, <i>Mycobacterium tuberculosis</i> , <i>Toxoplasma gondii</i> , <i>Trypanosoma brucei gambiense</i>
Parotitis	Mumps virus
Rash	Varicella zoster virus, B virus, human herpesvirus 6, West Nile virus, rubella virus, some enteroviruses, HIV, <i>Rickettsia rickettsii</i> , <i>Mycoplasma pneumoniae</i> , <i>Borrelia burgdorferi</i> , <i>T. pallidum</i> , <i>Ehrlichia chaffeensis</i> , <i>Anaplasma phagocytophilum</i>
Respiratory tract findings	Venezuelan equine encephalitis virus, Nipah virus, Hendra virus, influenza virus, adenovirus, <i>M. pneumoniae</i> , <i>C. burnetii</i> , <i>M. tuberculosis</i> , <i>Histoplasma capsulatum</i>
Retinitis	Cytomegalovirus, West Nile virus, <i>B. henselae</i> , <i>T. pallidum</i>
Urinary symptoms	St. Louis encephalitis virus (early)
Neurologic findings	
Cerebellar ataxia	Varicella zoster virus (children), Epstein-Barr virus, mumps virus, St. Louis encephalitis virus, <i>Tropheryma whipplei</i> , <i>T. brucei gambiense</i>
Cranial nerve abnormalities	Herpes simplex virus, Epstein-Barr virus, <i>Listeria monocytogenes</i> , <i>M. tuberculosis</i> , <i>T. pallidum</i> , <i>B. burgdorferi</i> , <i>T. whipplei</i> , <i>Cryptococcus neoformans</i> , <i>Coccidioides</i> species, <i>H. capsulatum</i>
Dementia	HIV, human transmissible spongiform encephalopathies (sCJD and vCJD), measles virus (SSPE), <i>T. pallidum</i> , <i>T. whipplei</i>
Myorhythmia	<i>T. whipplei</i> (oculomasticatory)
Parkinsonism (bradykinesia, masked facies, cogwheel rigidity, postural instability)	Japanese encephalitis virus, St. Louis encephalitis virus, West Nile virus, Nipah virus, <i>T. gondii</i> , <i>T. brucei gambiense</i>
Poliomyelitis-like flaccid paralysis	Japanese encephalitis virus, West Nile virus, tickborne encephalitis virus; enteroviruses (enterovirus-71, coxsackieviruses), poliovirus
Rhombencephalitis	Herpes simplex virus, West Nile virus, enterovirus 71, <i>L. monocytogenes</i>

NOTE. These findings may or may not be present at the time that the patient presents with encephalitis. sCJD, sporadic Creutzfeldt-Jacob disease; SSPE, subacute sclerosing panencephalitis; vCJD, variant Creutzfeldt-Jacob disease.

36. HIV: HAART is recommended (A-II).
37. JC virus: reversal of immunosuppression (A-III)—or HAART in HIV-infected patients (A-II)—is recommended.

Bacteria

38. *Bartonella bacilliformis*: chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or trimethoprim-sulfamethoxazole is recommended (B-III).
39. *Bartonella henselae*: doxycycline or azithromycin, with or without rifampin, can be considered (C-III).
40. *Listeria monocytogenes*: ampicillin plus gentamicin is recommended (A-III); trimethoprim-sulfamethoxazole is an alternative in the penicillin-allergic patient (A-III).
41. *Mycoplasma pneumoniae*: antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered (C-III).
42. *Tropheryma whipplei*: ceftriaxone, followed by either trimethoprim-sulfamethoxazole or cefixime, is recommended (B-III).

Mycobacteria

43. *Mycobacterium tuberculosis*: 4-drug antituberculous therapy should be initiated (A-III); adjunctive dexamethasone should be added in patients with meningitis (B-I).

Rickettsioses and ehrlichioses

44. *Anaplasma phagocytophilum*: doxycycline is recommended (A-III).
45. *Ehrlichia chaffeensis*: doxycycline is recommended (A-II).
46. *Rickettsia rickettsii*: doxycycline is recommended (A-II); chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy (C-III).
47. *Coxiella burnetii*: doxycycline plus a fluoroquinolone plus rifampin is recommended (B-III).

Spirochetes

48. *Borrelia burgdorferi*: ceftriaxone, cefotaxime, or penicillin G is recommended (B-II).

Table 4. Diagnostic evaluation to consider in determining the microbial etiology in patients with encephalitis (A-III).

Class of microorganism	General diagnostic evaluation	Additional diagnostic studies for immunocompromised patients
Viruses	Culture of respiratory secretions and nasopharynx, throat, and stool specimens	CSF PCR for cytomegalovirus, JC virus, human herpesvirus 6, and West Nile virus
	DFA of sputum for respiratory viruses ^a	...
	PCR of respiratory specimens ^a	...
	Culture and/or DFA of skin lesions (if present) for herpes simplex virus and varicella zoster virus ^a	...
	Serologic testing for HIV ^b	...
	Serologic testing for Epstein-Barr virus	...
	Serologic testing (acute and convalescent phase) for St. Louis encephalitis virus, ^c Eastern equine encephalitis virus, ^c Venezuelan equine encephalitis virus, ^c La Crosse virus, ^c West Nile virus ^c	...
	CSF IgM for West Nile virus, ^c St. Louis encephalitis virus, ^c varicella zoster virus	...
	CSF PCR for herpes simplex virus 1, herpes simplex virus 2, varicella zoster virus, Epstein-Barr virus, ^d enteroviruses	...
	Bacteria	Blood cultures
CSF cultures		...
Serologic testing (acute and convalescent phase) for <i>Mycoplasma pneumoniae</i>		...
PCR of respiratory secretions for <i>M. pneumoniae</i>		...
Rickettsiae and ehrlichiae ^c	Serologic testing (acute and convalescent phase) for <i>Rickettsia rickettsi</i> , <i>Ehrlichia chaffeensis</i> , and <i>Anaplasma phagocytophilum</i>	...
	DFA and PCR of skin biopsy specimen (if rash present) for <i>R. rickettsiae</i>	...
	Blood smears for morulae	...
	PCR of whole blood and CSF specimens for <i>Ehrlichia</i> and <i>Anaplasma</i> species ^e	...
Spirochetes	Serum RPR and FTA-ABS	...
	Serologic testing for <i>Borrelia burgdorferi</i> (ELISA and Western blot),	...
	CSF VDRL	...
	CSF <i>B. burgdorferi</i> serologic testing (ELISA and Western blot); calculate IgG antibody index	...
Mycobacteria	CSF FTA-ABS ^f	...
	Chest radiograph	...
	PCR and culture of respiratory secretions	...
	CSF AFB smear and culture	...
Fungi	CSF PCR (Gen-Probe Amplified <i>Mycobacterium tuberculosis</i> Direct Test)	...
	Blood cultures	...
	CSF cultures	...
	Serum and CSF cryptococcal antigen	...
	Urine and CSF <i>Histoplasma</i> antigen ^g	...
Protozoa	Serum and CSF complement fixing or immunodiffusion antibodies for <i>Coccidioides</i> species ^g	...
	...	Serum IgG for <i>Toxoplasma gondii</i> ^h

NOTE. These tests may not be required in all patients with encephalitis; certain tests should not be performed unless a consistent epidemiology is present. Additional tests should be considered on the basis of epidemiology, risk factors, clinical features, general diagnostic studies, neuroimaging features, and CSF analysis (tables 2, 3, and 5). Recommended tests should not supplant clinical judgment; not all tests are recommended in all age groups. AFB, acid-fast bacilli; DFA, direct fluorescent antibody; FTA-ABS, fluorescent treponemal antibody, absorbed; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory.

^a See table 3 for likely infecting microorganisms.

^b In patients who are HIV seronegative but in whom there is a high index of suspicion for HIV infection, plasma HIV RNA testing should be performed.

^c Depending on time of year and/or geographic locale.

^d Results should be interpreted in conjunction with Epstein-Barr virus serologic testing; quantitative PCR should be done, because a low CSF copy number may be an incidental finding.

^e Low yield of CSF PCR.

^f CSF FTA-ABS is sensitive but not specific for the diagnosis of neurosyphilis; a nonreactive CSF test result may exclude the diagnosis, but a reactive test result does not establish the diagnosis.

^g Depends on a history of residence in or travel to an area of endemicity.

^h Positive results may suggest the possibility of reactivation disease in an immunocompromised host.

49. *Treponema pallidum*: penicillin G is recommended (A-II); ceftriaxone is an alternative (B-III).

Fungi

50. *Coccidioides* species: fluconazole is recommended (A-II); alternatives are itraconazole (B-II), voriconazole (B-III),

and amphotericin B (intravenous and intrathecal) (C-III).

51. *Cryptococcus neoformans*: initial treatment with amphotericin B deoxycholate plus flucytosine (A-I) or a lipid formulation of amphotericin B plus flucytosine (A-II) is recommended.

52. *Histoplasma capsulatum*: liposomal amphotericin B followed by itraconazole is recommended (B-III).

Table 5. Epidemiology, clinical features, diagnosis, and treatment of selected causes of encephalitis.

Etiology	Epidemiology	Clinical features	Diagnosis	Treatment ^a
Viruses				
Adenoviridae				
Adenovirus	Children and immunocompromised patients Sporadic	Associated pneumonia	Viral culture or PCR of respiratory site specimen Culture or PCR of CSF or brain specimen	Supportive
Bunyaviridae				
La Crosse virus	Mosquito vector; chipmunk and squirrel reservoir Midwestern and eastern United States School-aged children	Most cases presumed to be subclinical Fulminant onset, with seizures, paralysis, focal weakness Fatality rare	Serologic testing ^b CSF IgM	Supportive
Flaviviridae				
Japanese encephalitis virus	Mosquito vector; swine and bird reservoirs Most common cause worldwide of epidemic encephalitis Japan, China, Korea, Taiwan, Southeast Asia, India, Nepal, northern Australia Mainly children; epidemic, endemic	Seizures and parkinsonian features common Poliomyelitis-like flaccid paralysis Case-fatality rate, 20%–30%	Serum IgM; IgG capture ELISA ^b CSF IgM; CSF antigen MRI shows mixed intensity or hypodense lesions in thalami, basal ganglia, and midbrain on T1 which are hyperintense on T2 and FLAIR images	Supportive IFN- α not recommended
Murray Valley encephalitis virus	Mosquito vector; bird reservoir Australia, New Guinea Mostly affects aboriginal children	Rapid disease progression in infants Case-fatality rate, 15%–30%	Serologic testing ^b MRI may show high signal intensities in basal ganglia	Supportive
Powassan virus	Tick vector; rodent reservoir New England states, Canada, Asia	Case-fatality rate, 10%–15% Focal findings in >50% of patients	Serum IgM; serologic testing ^b CSF IgM	Supportive
St. Louis encephalitis virus	Mosquito vector; bird reservoir North America (endemic in western United States, with large periodic outbreaks in eastern United States), Central and South America Adults aged >50 years	Most severe in elderly persons May have tremors, seizures, headache, nausea, vomiting, stupor, paresis Urinary symptoms (dysuria, urgency, and incontinence) may be early features SIADH (one-third) Case-fatality rate, 3%–30%	Serum IgM; serologic testing ^b (may cross-react with other flaviviruses) CSF capture IgM ELISA (nearly 100% of samples yield positive results by day 7 of illness) MRI may show hyperintense lesions in substantia nigra, basal ganglia, and thalami	Supportive IFN- α 2b (C-III)
Tickborne encephalitis virus	Tick vector; rodent reservoir Unpasteurized milk Eastern Russia, central Europe, Far East Epidemic; sporadic	Acute encephalitis Poliomyelitis-like paralysis	Serum IgM; serologic testing ^b Virus may be cultured from blood in early viremic phase CSF IgM	Supportive
West Nile virus	Mosquito vector; bird reservoir North and Central America, Africa, parts of Asia, Middle East, and southern Europe Increased incidence in older persons (age, >50 years) and immunocompromised persons Transmission reported via transfusion, transplantation, breast-feeding	Abrupt onset of fever, headache, neck stiffness, and vomiting More severe in elderly persons; 1 in 150 develop neuroinvasive disease (meningitis, encephalitis, acute flaccid paralysis) Clinical features include tremors, myoclonus, parkinsonism, and poliomyelitis-like flaccid paralysis (may be irreversible)	Serum IgM; serologic testing ^b CSF IgM (preferred); CSF PCR (<60% of results are positive) T2-weighted and FLAIR MRI findings (~30% of cases) may reveal hyperintense lesions in the substantia nigra, basal ganglia, and thalami; similar lesions may also be seen in the spinal cord	Supportive Ribavirin not recommended
Herpesviridae				
B virus	Old World primates (macaques); transmitted by bite or scratch Human-to-human transmission reported	Vesicular eruption at site of bite or scratch, followed by neurologic symptoms in 3–7 days Transverse myelitis is a prominent finding	Culture and PCR of vesicles at site of bite, conjunctivae and pharynx (only available at specific laboratories); serologic testing difficult because of cross-reactivity with HSV CSF PCR; low yield of CSF culture	Wound decontamination Prophylactic antiviral therapy after bite or scratch (valacyclovir; B-III) Acyclovir (C-III), valacyclovir (B-III), or ganciclovir (B-III) for established disease

CMV	Immunocompromised persons (especially those with AIDS); rarely reported in immunocompetent patients Congenital infection in 1% of neonates	Evidence of widespread CMV disease (e.g., retinitis, pneumonitis, adrenalitis, myelitis, polyradiculopathy)	CSF PCR for CMV (for immunocompromised persons, sensitivity, 82%–100%; specificity, 86%–100%); quantitative PCR available MRI may reveal subependymal gadolinium enhancement with nonspecific white matter abnormalities on T2-weighted images Viral culture of brain biopsy specimens, if needed	Ganciclovir plus foscarnet (B-III)
EBV	Exposure to saliva from those with asymptomatic shedding	Seizures, coma, personality changes, cerebellar ataxia, cranial nerve palsies Transverse myelitis	Serologic testing CSF PCR for EBV (results may be false positive) T2-weighted MRI may reveal hyperintensities in cortical white and gray matter and in spinal cord	Supportive Corticosteroids (C-III); (see text) Acyclovir not recommended
HSV-1 and -2	5%–10% Of all cases; one of the most common causes of identified sporadic encephalitis worldwide All age groups; all seasons HSV-1 infection more common in adults; HSV-2 infection more common in neonates	Fever, hemicranial headache, language and behavioral abnormalities, memory impairment, seizures Less commonly, a brainstem syndrome SIADH	CSF PCR for HSV-1 and HSV-2 (sensitivity and specificity, >95% and >99%, respectively); quantitative PCR available; CSF antibodies (may be of benefit if obtained >1 week into therapy) MRI in patients with HSV-1 infection reveals temporal and/or inferior frontal lobe edema with high signal intensity on FLAIR and T2-weighted images; bilateral temporal lobe involvement is nearly pathognomonic Viral culture and antigen detection in brain biopsy specimen, if needed	Acyclovir (A-I)
Human herpesvirus 6	Immunocompromised (reactivation), particularly in transplant recipients; role in immunocompetent hosts unclear No seasonal predilection	Recent exantham Seizures	Serologic testing; culture CSF PCR (sensitivity, >95%); high rate of detection in healthy adults (positive predictive value, 30%) MRI may reveal hyperintense T2-weighted signal in white matter of frontal and parietal lobes to edema of temporal lobes and limbic system; limbic encephalitis described	Ganciclovir or foscarnet (B-III in immunocompromised persons; C-III in immunocompetent persons)
VZV	All age groups, but incidence highest in adults; all seasons Recrudescence disease (herpes zoster) seen in immunocompetent persons but more often in immunocompromised persons (e.g., those with AIDS) Can occur in patients without rash, especially if immunocompromised	Primary cerebellar involvement in children, usually self-limited or severe encephalitis; delirium is common; seizures are unusual; vasculitis reported Reactivation leads to encephalitis with focal neurologic deficits and seizures Large vessel granulomatous arteritis presents with delayed contralateral hemiplegia weeks to months after reactivation in the ophthalmic division of the trigeminal nerve (herpes zoster ophthalmicus)	DFA of skin lesions; serum IgM for primary varicella CSF PCR for VZV (sensitivity, 80%–95%, and specificity, >95% in immunocompromised person); CSF VZV IgM antibody Brain biopsy, if needed MRI and MRA may reveal large vessel arteritis and ischemic, hemorrhagic infarctions, or small infarcts mixed with demyelinating lesions; homogeneous enhancement around the ventricles or increased periventricular signal on T2-weighted images also observed	Acyclovir (B-III) Ganciclovir (C-III) Corticosteroids (C-III)
Orthomyxoviridae Influenza virus	Worldwide; sporadic; rare cause of encephalitis; often affects children Reye's syndrome (now uncommon)	Prior or concomitant respiratory tract symptoms May be associated with bilateral thalamic necrosis (ANE)	Viral culture, antigen detection, and PCR of respiratory tract specimen	Oseltamivir (C-III)
Papovaviridae JC virus (PML)	Cell-mediated immunodeficiencies (e.g., AIDS, hematologic malignancies) Immunomodulating therapy (natalizumab, rituximab)	Cognitive dysfunction Limb weakness, gait disturbance, coordination difficulties Visual loss Focal neurologic findings, especially visual field cuts	CSF PCR (for diagnosis of PML, sensitivity 50%–75%; specificity, 98%–100%); quantitative PCR available MRI shows ≥ 1 nonenhancing, confluent subcortical white matter hyperintensity (on T2 or FLAIR) Brain biopsy, if needed	Reversal or control of immunosuppression (A-III) HAART in patients with AIDS (A-II)

Table 5. (Continued.)

Etiology	Epidemiology	Clinical features	Diagnosis	Treatment ^a
Paramyxoviridae				
Hendra virus	Australia Natural host reservoirs thought to be fruit bats Horses likely infected from secretions of bats; humans from body fluids or excretions from horses	Fever, drowsiness, seizures, and coma accompanying severe flu-like illness	Contact Special Pathogens Branch at CDC	Supportive
Measles virus	Unvaccinated children and adults Worldwide; sporadic Measles inclusion body encephalitis within 1–6 months SSPE has variable incubation, with most cases seen 4–8 years after primary infection (most important risk factor is acquisition of measles before 2 years of age)	Decline of consciousness; focal neurologic signs and seizures are common SSPE has insidious onset, with subtle personality changes and declining intellectual performance progressing to mental deterioration, seizures, myoclonic jerks, motor signs, coma, and death	Serologic testing for recent measles ^b Culture of nasopharynx and urine specimens RT-PCR of nasopharynx and urine specimens for viral RNA CSF antibodies; CSF PCR (sensitivity and specificity unknown) Detection of viral RNA in brain tissue In SSPE, EEG reveals well-defined periodic complexes with a 1:1 relationship with the myoclonic jerks	Ribavirin (investigational for life-threatening disease; C-III) Intrathecal ribavirin for SSPE (C-III)
Mumps virus	Unvaccinated persons	Previous parotitis (~50%) Headaches and vomiting, seizures, altered consciousness; sensorineural hearing loss	Serologic testing ^b Culture of saliva specimens CSF culture (positive results in 17%–58%); CSF PCR	Supportive
Nipah virus	Close exposure to infected pigs (probably respiratory); pteropid bat reservoir; exposure to infected bats or bat roosting sites; close contact exposure to infected humans South Asia	Fever, headache, altered mental status, dizziness and vomiting Myoclonus, dystonia, areflexia, and hypotonia; pneumonitis	Serologic testing ^b CSF culture MRI may demonstrate discrete focal lesions throughout the brain, but mainly in subcortical and deep white matter of cerebral hemispheres Contact Special Pathogens Branch at CDC	Supportive Ribavirin (C-III)
Picornaviridae				
Nonpolio enteroviruses	Echoviruses, coxsackieviruses, and enterovirus 71 and various other numbered enteroviruses Peak incidence in late summer and early fall Worldwide in distribution	Aseptic meningitis more common than encephalitis Severe illness in neonates; syndrome of chronic enteroviral meningoencephalitis in agammaglobulinemia (rare) Enterovirus 71 outbreak in children with rhombencephalitis (myoclonus, tremors, ataxia, cranial nerve defects)	Stool and throat cultures (only suggestive of CNS etiology) CSF RT-PCR; CSF culture (less sensitive than PCR) MRI in enterovirus 71 outbreak revealed increased signal abnormalities in midbrain, pons, and medulla	Supportive Intraventricular γ -globulin for chronic and/or severe disease (C-III)
Poliovirus	Principally in infants Africa and Asia; unvaccinated in developed countries Fecal-oral spread Related to administration of oral vaccine	Disturbances in consciousness, seizures; flaccid paralysis	Serologic testing ^b Throat and stool cultures CSF cultures; CSF PCR	Supportive
Poxviridae				
Vaccinia	Most cases postinfectious, but neuroinvasive disease also documented Rare adverse event of smallpox vaccination	Abrupt onset of encephalopathy Focal neurologic deficits 2–30 days after vaccination	Antibody testing in serum not helpful CSF PCR; CSF IgM	Supportive Corticosteroids (if suggestive of postimmunization vaccination; C-III)
Retroviridae				
HIV	Risk factors for HIV infection Worldwide	Acute encephalopathy with seroconversion Most commonly presents as HIV dementia (forgetfulness, loss of concentration, cognitive dysfunction, psychomotor retardation)	HIV serologic testing; quantitative HIV RNA (viral load) CSF PCR MRI may reveal high signal intensity on T2 and FLAIR images in periventricular regions and centrum semiovale; may also be seen in advanced HIV without neurologic complications	HAART (A-II)

Rhabdoviridae				
Rabies virus	Transmitted by the bite of an infected animal; may be transmitted after unrecognized bites from bats Organ donation (few recognized cases) Rare and sporadic in the United States, but worldwide in distribution (50,000–100,000 deaths annually)	Furious form (most common) consisting of agitation, hydrophobia, bizarre behavior, and delirium progressing to disorientation, stupor, and coma Paralytic form consisting of ascending paralysis and later cerebral involvement	Serum antibodies in unvaccinated patients ^b Culture of saliva specimens; RT-PCR of saliva specimens Immunofluorescent detection of viral antigens in nuchal biopsy specimen CSF antibodies in unvaccinated patients; RT-PCR of CSF specimens Antigen detection and histopathologic examination (Negri bodies) of brain biopsy specimen	Supportive Postexposure prophylaxis with rabies immunoglobulin and vaccine (ineffective after onset of disease)
Togaviridae				
Eastern equine encephalitis virus	Mosquito vector; bird reservoir in North America, and rodents and marsupials in South America North America (especially Atlantic and Gulf states), Central and South America (uncommon) Mainly affects children and elderly persons; sporadic	Most infections presumed to be subclinical Abrupt onset with fulminant course; seizures common; headache, altered consciousness Case-fatality rate, 50–70%, with high frequency of sequelae among survivors	Serologic testing ^b CSF WBC count may be higher than expected for viral illness (>300 cells/mm ³) Viral culture or antigen detection in brain MRI may show nonenhancing focal lesions in basal ganglia, thalami, and brainstem	Supportive
Rubella virus	More common in adults Unvaccinated	Rash followed within 1–6 days by headache, dizziness, behavioral abnormalities Seizures	Serologic testing ^b CSF IgM	Supportive
Venezuelan equine encephalitis virus	Mosquito vector; horse, rodent, and bird reservoir Florida and southwestern United States, Central and South America Sporadic; epidemic	Most infections presumed to be subclinical Prominent myalgias; headache; pharyngitis Respiratory tract infections may occur	Serologic testing ^b Culture of blood and pharynx specimens (results are positive up to the eighth day of illness) CSF IgM; CSF PCR	Supportive
Western equine encephalitis virus	Mosquito vector; bird reservoir North America (west of the Mississippi and in prairie provinces in Canada); Central and South America Mainly affects children and adults (age, >50 years) Epidemic, but no human cases in the United States since 1994	Most infections presumed to be subclinical Headache, altered consciousness, seizures Case-fatality rate, <5%	Serologic testing ^b with detection of IgM in serum CSF IgM; viral antigen detection in brain CT results reported as normal; data extremely limited	Supportive
Transmissible spongiform encephalopathies				
Human transmissible spongiform encephalopathy	Sporadic CJD in patients aged ≥40 years Variant CJD in setting of exposure to BSE	Sporadic CJD characterized by dementia and ataxia followed by myoclonic jerks or other movement disorders, rapidly progressive dementia, and ultimately death Variant CJD produces early psychiatric and sensory abnormalities, followed by cerebellar ataxia and rapidly progressive dementia; survival somewhat longer than that for sporadic CJD	Normal or slightly elevated CSF protein concentration, absence of pleocytosis; 14-3-3 protein generally present (limited specificity) EEG in sporadic CJD reveals generalized slowing early, followed by bisynchronous periodic sharp wave discharges that have a 1:1 relationship with the myoclonic jerks In sporadic CJD, MRI may be normal or show increased signal on T2 and FLAIR in basal ganglia, as well as cortical ribboning on FLAIR and diffusion-weighted studies In variant CJD, high signal intensity in the pulvinar on T2-weighted MRI images is considered to be pathognomonic	Supportive
Bacteria				
<i>Bartonella bacilliformis</i> (Oroya fever)	Sandfly vector Middle altitudes of Andes mountains	Acute onset of severe headache Seizures, hallucinations, delirium, and/or reduced consciousness Profound hemolytic anemia	Serologic testing ^b Culture of blood and/or CSF specimens (low yield) CSF PCR	Chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or trimethoprim-sulfamethoxazole (B-III)
<i>Bartonella henselae</i> and other <i>Bartonella</i> species (Cat scratch disease)	Cat bite or scratch (especially kittens and feral cats); can be transmitted by other animals (e.g., rodents, dogs) or fleas Encephalopathy almost exclusively in children and young adults	Regional lymphadenopathy at site of bite or scratch Seizures in >50% Neuroretinitis	Serologic testing ^b Culture of blood, CSF, and/or lymph node specimens (low yield) PCR of lymph node tissue specimens CSF PCR (low yield)	Doxycycline or azithromycin, with or without rifampin (C-III)

Table 5. (Continued.)

Etiology	Epidemiology	Clinical features	Diagnosis	Treatment ^a
<i>Listeria monocytogenes</i>	Neonates <1 month of age; adults >50 years of age Pregnancy, alcohol abuse Immunocompromise (especially defects in cell-mediated immunity)	Rhombencephalitis (ataxia, cranial nerve deficits, nystagmus)	Culture of blood specimens Culture of CSF specimens	Ampicillin plus gentamicin (A-II) Trimethoprim-sulfamethoxazole (if penicillin allergic), (A-III)
<i>Mycoplasma pneumoniae</i>	More common in children; year-round Causality in encephalitis remains controversial	Previous upper or lower respiratory tract disease Diffuse or focal encephalitis	Serum IgM; IgG serologic testing ^b PCR of respiratory sample	Antimicrobial therapy (azithromycin, doxycycline, or fluoroquinolone) (C-III)
<i>Tropheryma whipplei</i> (Whipple's disease)	Uncommon etiology of meningoencephalitis	Most commonly presents with progressive subacute encephalopathy May have dementia, ophthalmoplegia, myoclonus, cerebellar ataxia, psychiatric signs Oculomasticatory myorhythmia thought to be pathognomonic	Small bowel biopsy with histopathologic examination and PCR PAS-positive cells in CSF; CSF PCR	Ceftriaxone for 2–4 weeks, followed by trimethoprim-sulfamethoxazole or cefixime for 1–2 years (B-III)
Mycobacteria				
<i>Mycobacterium tuberculosis</i>	More common in developing areas of the world Risk factors include very young and advanced age, immunosuppressive drug therapy, transplantation, lymphoma, gastrectomy, pregnancy, diabetes mellitus, alcoholism, and HIV infection	Patients more commonly present with basilar meningitis followed by lacunar infarctions and hydrocephalus	Microorganism detection at sites outside CNS CSF AFB smear and culture; CSF PCR has been reported to have a low sensitivity, although higher sensitivity with the Gen-Probe Amplified <i>Mycobacterium tuberculosis</i> Direct Test (~94%)	Isoniazid, rifampin, pyrazinamide, ethambutol (A-III) Dexamethasone in patients with meningitis (B-I)
Rickettsioses and ehrlichioses				
<i>Anaplasma phagocytophilum</i> (human granulocytotropic ehrlichiosis)	Tick vector Europe and mid-Atlantic and northern United States	Abrupt onset of fever, headache, and myalgias followed by altered mental status	Morulae within PMNs in blood smears (sensitivity ~20%); PCR of whole-blood specimens Serologic testing ^b PCR of CSF specimens (low yield)	Doxycycline (A-III)
<i>Coxiella burnetii</i> (Q fever)	Contact with cats, sheep, goats (especially placental tissues); rarely through tick bite Inhalation of small particle aerosols Interhuman spread reported Ingestion of unpasteurized milk products	Meningoencephalitis rare (1%) Seizures and coma	Serologic testing ^b	Doxycycline plus a fluoroquinolone plus rifampin (B-III)
<i>Ehrlichia chaffeensis</i> (human monocytotropic ehrlichiosis)	Tick vector South central, southeastern, mid-Atlantic, and coastal states of the United States	Confusion, photophobia, stupor, hallucinations Eventually seizures and coma	Morulae in mononuclear cells of blood smears (<20%); PCR of whole blood specimens Serologic testing ^b PCR of CSF specimens (low yield)	Doxycycline (A-II)
<i>Rickettsia rickettsii</i> (Rocky Mountain spotted fever)	Tick vector North, Central, and South America; in the United States, area of highest endemicity extends from North Carolina to Oklahoma	Maculopapular (often petechial) rash on wrists and ankles beginning 3–5 days after onset of illness with rapid spread, including variable spread to palms and soles Altered mental status; intractable seizures	Serologic testing ^b PCR and direct immunofluorescence of skin biopsy specimens at site of rash	Doxycycline (A-II) Chloramphenicol in selected clinical scenarios, such as pregnancy (C-III)
Spirochetes				
<i>Borrelia burgdorferi</i> (Lyme disease)	Tick vector North America, Europe, and Asia	Can occur early (often shortly after erythema migrans) or late (often with arthritis) Facial nerve palsy, particularly bilateral, meningitis, and radiculitis are most common neurologic manifestations	Blood serologic testing (ELISA plus Western blot) Serologic testing of CSF (ELISA plus Western blot); CSF antibody index; CSF PCR (low sensitivity) MRI may demonstrate areas of inflammation with increased signal on T2 and FLAIR	Ceftriaxone (B-II) Cefotaxime (B-II) Penicillin G (B-II)
<i>Treponema pallidum</i> (syphilis)	Sexual contact	General paresis; rapidly progressive, dementing illness Psychiatric features Rarely can mimic HSV encephalitis with temporal lobe focality	Serum RPR and FTA-ABS CSF VDRL specific but not sensitive CSF FTA-ABS sensitive but not specific	Penicillin G (A-II) Ceftriaxone (B-III)

Fungi				
<i>Coccidioides</i> species	Semiarid regions of the southwestern United States, Mexico, and South America Dissemination associated with infancy and old age, male sex, nonwhite race, pregnancy, and immunosuppression	Usually a subacute or chronic meningitis Approximately 50% of patients develop disorientation, lethargy, confusion, or memory loss	Serum complement fixing or immunodiffusion antibodies CSF complement fixing or immunodiffusion antibodies; CSF culture	Fluconazole (A-II) Itraconazole (B-II) Voriconazole (B-III) Amphotericin B (intravenous and intrathecal) (C-III)
<i>Cryptococcus neoformans</i>	Sporadic Most common among immunocompromised persons (especially those with AIDS) but may occur in immunocompetent patients Bird droppings	More commonly a chronic meningitis May present acutely as meningoencephalitis	Blood fungal culture; serum cryptococcal antigen CSF fungal culture; CSF cryptococcal antigen	Amphotericin B deoxycholate plus flucytosine for 2 weeks, followed by fluconazole for 8 weeks (A-I) Lipid formulation of amphotericin B plus flucytosine for 2 weeks, followed by fluconazole for 8 weeks (A-II) Amphotericin B plus flucytosine for 6–10 weeks (A-I; B-I in HIV-infected patients) Reduction of increased intracranial pressure by lumbar puncture (A-II); may need to consider placement of lumbar drain or VP shunt
<i>Histoplasma capsulatum</i>	Endemic in Ohio and Mississippi River valleys in the United States, and other microfoci throughout Americas, Africa, eastern Asia, and Australia More common in immunocompromised persons	More commonly a chronic meningitis; may present as acute encephalitis Isolated meningoencephalitis or associated with systemic findings (hepatosplenomegaly, pneumonia, bone marrow suppression)	Urine for <i>Histoplasma</i> antigen; visualization of yeast in sputum or blood by special stains Yeast in CSF visualized by special stains; CSF <i>Histoplasma</i> antigen; CSF <i>Histoplasma</i> antibody	Liposomal amphotericin B for 4–6 weeks, followed by itraconazole for at least 1 year and until resolution of CSF abnormalities (B-II)
Protozoa				
<i>Acanthamoeba</i> species	Immunocompromise (especially deficiencies in cell-mediated immunity, such as AIDS) Chronic alcoholism	Subacute presentation with altered mental status and/or focal deficits Seizures, hemiparesis, and fever	Serologic testing (available in specialized laboratories) Brain biopsy (including culture)	Trimethoprim-sulfamethoxazole plus rifampin plus ketoconazole (C-III) Fluconazole plus sulfadiazine plus pyrimethamine (C-III)
<i>Balamuthia mandrillaris</i>	Immunocompromised persons (especially those with deficiencies in cell-mediated immunity) and immunocompetent hosts	Fever, headache, vomiting, ataxia, hemiparesis, cranial nerve palsies Encephalopathy	Most cases diagnosed postmortem Serologic testing (IFA through CDC and California Encephalitis Project) MRI with space occupying lesions that enhance and/or hydrocephalus Histopathologic examination and indirect immunofluorescence of brain biopsy specimen	Macrolide (azithromycin or clarithromycin) plus pentamidine plus flucytosine plus fluconazole plus sulfadiazine plus a phenothiazine (thioridazine or trifluoperazine) (C-III)
<i>Naegleria fowleri</i>	Swimming in lakes and brackish water	Change in taste or smell 2–5 days after swimming; meningismus, papilledema, and nystagmus are common; occasional cranial nerve abnormalities and ataxia Acute progression to coma and death	CSF neutrophilic pleocytosis, low glucose concentration Motile trophozoites may be seen in wet mount of warm CSF	Amphotericin B (intravenous and intrathecal) plus rifampin plus other agents (e.g., azithromycin, sulfisoxazole, miconazole) (C-III)
<i>Plasmodium falciparum</i> (malaria)	Travel to tropical and subtropical areas of endemicity Severe disease more common in children and in adults from areas of nonendemicity who do not receive prophylaxis	Impaired consciousness, seizures, focal neurologic deficits, and/or psychosis in a patient exposed to malaria	Thin and thick blood smears revealing <i>P. falciparum</i>	Quinine, quinidine, artesunate, or artemether (A-III) Atovaquone/proguanil (B-III) Corticosteroids not recommended Exchange transfusion with >10% parasitemia or cerebral malaria (B-III)

Table 5. (Continued.)

Etiology	Epidemiology	Clinical features	Diagnosis	Treatment ^a
<i>Toxoplasma gondii</i>	Reactivation of disease in immunocompromised patients (especially those with AIDS) Intrauterine infection may lead to severe necrotizing encephalitis	Extrapyramidal symptoms and signs; usually nonfocal in transplant recipients, mixture of nonfocal and focal in those with malignancies, and focal in those with AIDS Seizures, hemiparesis, and cranial nerve abnormalities common Convulsions and chorioretinitis in congenital toxoplasmosis	Serum IgG may define those at risk for reactivation disease CSF PCR has lack of sensitivity and standardization MRI shows multiple ring-enhancing lesions in patients with AIDS; in congenital toxoplasmosis, may reveal hydrocephalus and calcifications	Pyrimethamine plus either sulfadiazine or clindamycin (A-I) Trimethoprim-sulfamethoxazole (B-I) Pyrimethamine plus either atovaquone, clarithromycin, azithromycin, or dapsone (B-III)
<i>Trypanosoma brucei gambiense</i> (West African trypanosomiasis)	Tsetse fly vector Humans primary reservoir	Chronic, with late CNS disease developing in months to years Irritability, personality changes, inability to concentrate, sleep disturbances, severe headache, ataxia, extrapyramidal signs Progressive neurologic impairment with coma and death	Giemsa staining of chancre (if present) and lymph nodes; serologic testing; serial Giemsa stained thin and thick smears of peripheral blood or bone marrow specimens Card agglutination test for trypanosomiasis used in the field (sensitivity, 96%) CSF smears; CSF IgM	Eflornithine (A-II) Melarsoprol (A-II)
<i>Trypanosoma brucei rhodesiense</i> (East African trypanosomiasis)	Tsetse fly vector Antelope and cattle are primary reservoir	Acute, with early CNS disease Sleep disturbances; refractory headaches; leads to death within weeks to months	Giemsa staining of chancre (if present); serologic testing; serial Giemsa stained thin and thick smears of peripheral blood or bone marrow specimens CSF smears; CSF IgM Inoculation of patient specimens into mice or rats	Melarsoprol (A-II)
Helminths				
<i>Baylisascaris procyonis</i>	Raccoon exposure; playing in or eating dirt contaminated with raccoon feces Children	Severity of disease based on number of eggs ingested Symptoms range from CNS dysfunction to severe deficits, coma, and death	CSF and peripheral eosinophilia CSF and serum antibodies (Purdue Department of Veterinary Pathobiology) Identification of larvae in tissue MRI reveals deep white matter lesions	Albendazole plus diethylcarbamazine (C-III) Corticosteroids (B-III)
<i>Gnathostoma</i> species	Southeast Asia (particularly Thailand and Japan) and Latin America Ingestion of undercooked fish, frogs, snakes, and fowl	Myeloencephalitis Headache and radicular pain with later paralysis and bladder incontinence	CSF and peripheral eosinophilia Identification of worms in tissues	Albendazole (B-III) Ivermectin (B-III)
<i>Taenia solium</i> (cysticercosis)	Mexico, Central America, South America, Southeast Asia Increasingly recognized among immigrants from areas of endemicity worldwide Acquired by egg ingestion; larval stage causes CNS disease	Seizures most common presentation; hydrocephalus; chronic meningitis Encephalitis can rarely occur when burden of cysts in parenchyma is very high or after therapy	Serologic testing; immunoblot testing against purified glycoprotein fraction of cyst fluid CSF antibodies (negative test does not rule out the diagnosis) CT or MRI reveals cystic lesions, some with calcifications; ring enhancement and edema suggest cyst degeneration	Need for treatment should be individualized Albendazole (B-II) Praziquantel (C-II) Corticosteroids (B-II) Occasional surgical resection, when necessary
Postinfectious/postimmunization encephalomyelitis				
Acute disseminated encephalomyelitis	More common in children Generally a history of recent infection or vaccination	Abrupt onset of neurologic symptoms several days after viral illness or vaccination Generally absence of fever Multifocal neurologic signs including optic neuritis, and brain and spinal cord demyelinating lesions Disturbances of consciousness range from stupor and confusion to coma Monophasic illness	MRI reveals multifocal, usually bilateral but asymmetric and large hyperintense lesions on T2 and FLAIR involving mainly subcortical, brainstem, cerebellum, and periventricular white matter, but sometimes subcortical gray matter; MRI may be normal	Corticosteroids (B-III) Plasma exchange in patients not responding to corticosteroids (B-III) IVIg in patients not responding to plasma exchange (C-III)

NOTE. AFB, acid-fast bacilli; ANE, acute necrotizing encephalopathy; BSE, bovine spongiform encephalopathy; CDC, Centers for Disease Control and Prevention; CJD, Creutzfeldt-Jacob disease; CMV, cytomegalovirus; DFA, direct fluorescent antibody; EBV, Epstein-Barr virus; EEG, electroencephalography; FLAIR, fluid-attenuated inversion recovery; FTA-ABS, fluorescent treponemal antibody, absorbed; HSV, herpes simplex virus; IFA, immunofluorescent antibody; IVIG, intravenous immunoglobulin; MRA, magnetic resonance angiography; PAS, periodic acid-Schiff; PML, progressive multifocal leukoencephalopathy; PMN, polymorphonuclear; RPR, rapid plasma reagin; SIADH, syndrome of inappropriate release of antidiuretic hormone; SSPE, subacute sclerosing panencephalitis; VCA, viral capsid antibody; VDRL, Venereal Disease Research Laboratory; VP, ventriculo-peritoneal; VZV, varicella zoster virus.

^a Although grade C indicates that there is poor information to support a recommendation, the treatment should be considered if no other option is available.

^b A 4-fold increase in convalescent-phase IgG antibody titers may be necessary to establish the diagnosis.

Protozoa

53. *Acanthamoeba*: trimethoprim-sulfamethoxazole plus rifampin plus ketoconazole (C-III) or fluconazole plus sulfadiazine plus pyrimethamine (C-III) can be considered.

54. *Balamuthia mandrillaris*: pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered (C-III).

55. *Naegleria fowleri*: amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered (C-III).

56. *Plasmodium falciparum*: quinine, quinidine, or artemether is recommended (A-III); atovaquone-proguanil is an alternative (B-III); exchange transfusion is recommended for patients with >10% parasitemia or cerebral malaria (B-III); corticosteroids are not recommended.

57. *Toxoplasma gondii*: pyrimethamine plus either sulfadiazine or clindamycin is recommended (A-I); trimethoprim-sulfamethoxazole alone (B-I) and pyrimethamine plus either atovaquone, clarithromycin, azithromycin, or dapsone (B-III) are alternatives.

58. *Trypanosoma brucei gambiense*: eflornithine is recommended (A-II); melarsoprol is an alternative (A-II).

59. *Trypanosoma brucei rhodesiense*: melarsoprol is recommended (A-II).

Helminths

60. *Baylisascaris procyonis*: albendazole plus diethylcarbamazine can be considered (C-III); adjunctive corticosteroids should also be considered (B-III).

61. *Gnathostoma* species: albendazole (B-III) or ivermectin (B-III) is recommended.

62. *Taenia solium*: need for treatment should be individualized; albendazole and corticosteroids are recommended (B-III); praziquantel can be considered as an alternative (C-II).

Postinfectious/postvaccination status

63. Acute disseminated encephalomyelitis: high-dose corticosteroids are recommended (B-III); alternatives include plasma exchange (B-III) and intravenous immunoglobulin (C-III).

INTRODUCTION

Encephalitis is defined by the presence of an inflammatory process of the brain in association with clinical evidence of neurologic dysfunction [1]. The syndrome of acute encephalitis shares many clinical features with acute meningitis, such that patients with either syndrome may present with fever, headache, and altered level of consciousness. Although mental status changes early in the disease course are generally more common in patients with encephalitis, this finding does not reliably dif-

ferentiate patients with encephalitis from those with bacterial meningitis, and it is important to consider both diagnoses at presentation. Other findings in patients with encephalitis include acute cognitive dysfunction, behavioral changes, focal neurologic signs, and seizures. In most cases, there is some concomitant meningeal inflammation, in addition to the encephalitic component—a condition commonly referred to as “meningoencephalitis.”

It is important to try to distinguish between infectious encephalitis and postinfectious or postimmunization encephalitis or encephalomyelitis; these latter syndromes are presumed to be mediated by an immunologic response to an antecedent antigenic stimulus provided by the infecting microorganism or immunization or to other antigens revealed as part of the initial infection or vaccination. One example of this condition is termed “ADEM” and is more commonly seen in children and adolescents. Distinction between acute infectious encephalitis and ADEM is important, because the management approach is different. Encephalitis should also be distinguished from encephalopathy (e.g., secondary to metabolic disturbances, hypoxia, ischemia, drugs, intoxications, organ dysfunction, or systemic infections), which is defined by a disruption of brain function in the absence of a direct inflammatory process in the brain parenchyma.

The objective of this guideline is to provide clinicians with evidence-based recommendations in the approach to patients with encephalitis. Recommendation categories are shown in table 1 [2]. The initial treatment approach to the patient with suspected encephalitis includes early recognition of the clinical syndrome, appropriate diagnostic evaluation (including neuroimaging, serologic testing, and CSF analysis, which often includes serologic and molecular studies), and emergent administration of certain antimicrobial agents (see below). Unfortunately, despite extensive testing to identify an etiologic agent, most cases of presumed infectious encephalitis remain unexplained. Another major challenge in patients with encephalitis is to determine the significance of an infectious agent found outside the CNS, usually identified by serologic testing or culture of a non-CNS site in the clinical context of encephalitis; these agents (e.g., hepatitis C virus, rotavirus, *M. pneumoniae*, *Chlamydia* species, and respiratory syncytial virus) may play a role in the CNS manifestations of illness, but not necessarily by directly invading the CNS, or they may be present and unrelated to the encephalitis.

The Guidelines Panel addressed the following clinical questions in patients with suspected or proven encephalitis:

1. What are the epidemiologic and clinical clues that suggest a specific etiology of encephalitis?
2. What general diagnostic studies outside the CNS should be performed in patients with suspected encephalitis?

3. What neurodiagnostic tests should be performed in patients with encephalitis?
4. What tests of CSF and brain tissue specimens can help in establishing the etiology of encephalitis?
5. What specific empirical antimicrobial agents(s) should be used in patients with suspected encephalitis?
6. Once the etiology of encephalitis is determined, what specific treatment regimen should be administered?

METHODOLOGY

Panel composition. A panel of experts comprising infectious diseases specialists (pediatric and adult) and neurologists from North America who are experts in encephalitis was convened. The panelists had both laboratory and clinical experience with patients with encephalitis and other CNS infections.

Literature review and analysis. For the guideline, the panel reviewed the literature on the diagnosis and management of encephalitis through articles obtained via searches of the Medline database that were published since 1996, as well as articles in published reviews and authoritative book chapters. Computerized searches included only review of articles published in the English language and were limited to human-only studies. In evaluating the evidence in regard to diagnosis and management of encephalitis, the panel followed the process used in the development of other guidelines published by the Infectious Diseases Society of America (table 1). Given the lack of randomized, controlled data on the diagnosis and management of encephalitis, many recommendations were developed from case reports and small series, combined with the opinion of expert panel members.

Consensus development based on evidence. The development of the guideline was done initially via drafts prepared by the panel Chair, followed by intensive review by panel members and comment via e-mail on specific aspects of the guideline. The panel met via teleconference on 2 occasions and in person at the 2006 Annual Meeting of the Infectious Diseases Society of America. Additional work on the guideline was performed via e-mail and telephone between the Chair and specific panel members. All members of the panel participated in the preparation and review of the guideline. Feedback from external peer reviewers was obtained. The guideline was reviewed and approved by the Standards and Practice Guidelines Committee and Board of Directors prior to dissemination.

Guidelines and conflicts of interest. All members of the panel complied with the Infectious Diseases Society of America policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the panel were provided with the Infectious Diseases Society of America conflict of interest disclosure statement and were

asked to identify ties to companies developing products that might be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership in company advisory committees. The panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of conflict. No limiting conflicts were identified.

ETIOLOGY

A wide variety of pathogens have been reported to cause encephalitis (table 5), most of which are viruses [1, 3–10]. The epidemiology of various causes of encephalitis has changed in recent years in the United States, primarily as a result of the decrease in vaccine-preventable conditions, such as measles, mumps, rubella, and varicella. In general, the most commonly identified etiologies in the United States are herpes simplex virus, West Nile virus, and the enteroviruses, followed by other herpesviruses. Although *M. pneumoniae* is the most common agent identified in some studies in patients with encephalitis, the significance is unclear; *M. pneumoniae* is generally diagnosed by serologic methods (which are inherently problematic), is not neurotropic, and is rarely detected within the CNS. In many cases of encephalitis (32%–75%), however, the etiology remains unknown, despite extensive diagnostic evaluation. In the California Encephalitis Project, an underlying cause of encephalitis was not identified in 208 (62%) of 334 patients during 1998–2000, despite extensive testing and evaluation [11]; of note, ~10% of patients initially thought to have an infectious cause of their encephalitis ultimately received a diagnosis of a noninfectious condition. In a follow-up report of 1570 cases over a 7-year period [12], a confirmed or probable etiologic agent was identified for only 16% of cases of encephalitis, and an additional 13% of cases had a possible etiology identified. Of the confirmed or probable cases, 69% were viral, 20% were bacterial, 7% were prion related, 3% were parasitic, and 1% were fungal. However, it is important to note that the failure to identify an etiologic agent in many of these cases may be related to referral bias towards diagnostically challenging cases, as well as lack of access to appropriate specimens and suboptimal specimen handling. In another study from Finland, the etiology of encephalitis remained undefined in as many as 64% of patients, despite extensive laboratory evaluation [13].

Although many cases of encephalitis go without an identified etiology, attempts at identification of a specific etiologic agent are important for prognosis, potential prophylaxis, counseling of patients and families, and public health interventions. For the majority of patients who present with encephalitis, we recommend that specific diagnostic studies be performed (table 4).

Additional diagnostic studies should be performed on the basis of specific epidemiologic and clinical clues (tables 2 and 3).

It is beyond the scope of this guideline to review, in detail, every specific infectious etiology of encephalitis. Instead, the text of the guideline will concentrate on those etiologies that are most common and those with particular public health significance that should be considered in patients who present with a clinical syndrome consistent with encephalitis. The tables also contain the specifics of other etiologic agents that clinicians should consider in individual patients who present with encephalitis.

What Are the Epidemiologic and Clinical Clues that Suggest a Specific Etiology of Encephalitis?

Evidence summary. Epidemiologic clues that may help in establishing the etiologic diagnosis of encephalitis include season of the year, geographic locale, prevalence of disease in the local community, travel history, recreational activities, occupational exposures, insect or animal contacts, vaccination history, and the immune status of the patient (table 2) [1, 3–10, 14–36]. Although the clinical features of many of these infectious agents overlap, certain pathogens may be associated with distinct neurologic features based on tropism for specific areas in the CNS. In addition, other systemic physical examination findings (e.g., rash or upper respiratory or pulmonary findings) may also suggest certain etiologic agents (table 3). Epidemiologic and clinical clues that may suggest a particular etiologic diagnosis often cannot be elicited from the patient, who may be confused, disoriented, obtunded, or comatose; therefore, relevant information may need to be provided by relatives or friends.

In patients with encephalitis and a history of recent infectious illness or vaccination, the diagnosis of ADEM should be considered [1, 37–39]. ADEM is a monophasic illness thought to be an autoimmune response to a preceding antigenic challenge; a febrile illness or immunization often precedes the neurologic syndrome and varies according to the precipitant (e.g., it typically occurs 1–14 days after vaccination or \leq 1 week after the appearance of a rash in an exanthematous illness). A number of different viral infections have been associated with ADEM, including measles, mumps, rubella, varicella zoster, Epstein-Barr virus infection, cytomegalovirus infection, herpes simplex, hepatitis A, influenza, and enterovirus infections. Immunizations temporally associated with this syndrome include vaccines against anthrax and against Japanese encephalitis, yellow fever, measles, influenza, smallpox, and rabies viruses; however, a causal association in the context of these immunizations is difficult to establish. Fever is usually absent at the onset of neurologic illness, and patients present with multifocal neurologic signs affecting the optic nerves, brain, and spinal cord

[37, 38]. The disturbance of consciousness ranges from stupor and confusion to coma.

DIAGNOSIS

Certain diagnostic studies should be performed or considered in patients who present with encephalitis (table 4), in hopes of identifying treatable infectious etiologies; additional studies are based on specific epidemiologic and clinical findings (tables 2 and 3). The diagnostic evaluation in patients with encephalitis should include a complete blood cell count, tests of renal and hepatic function, coagulation studies, and chest radiography, although results of these studies are generally nonspecific. Neuroimaging studies and CSF analyses are critical to document CNS pathology (table 5). Although there may be no definitive treatment for many causes of encephalitis, establishing the diagnosis may still affect management (e.g., discontinuation of therapy that is not necessary). More details, with discussion of available evidence based on specific etiologic agents, are shown in table 5 and discussed in the text below [1, 3–10, 14–36, 40–45].

What General Diagnostic Studies Outside the CNS Should Be Performed in Patients with Suspected Encephalitis?

Evidence Summary

Cultures. Cultures of specimens of body fluids other than CSF may be useful in establishing the etiologic diagnosis in selected patients with encephalitis. All patients with encephalitis should undergo blood culturing to identify potential bacterial and fungal etiologies, although positive culture results may be indicative of encephalopathy secondary to systemic infection rather than encephalitis. Specific clinical findings should also direct other sites for culture (e.g., stool, nasopharynx, and sputum). In patients with varicella or herpes zoster, the etiology may be determined by scrapings from the base of active vesicles and testing by direct fluorescent antibody to identify viral antigen. However, a positive result for a vesicular fluid sample does not necessarily indicate that this is the etiology of encephalitis, because varicella zoster virus may be reactivated in the context of CNS disease caused by other agents; furthermore, a negative result cannot be used to exclude the diagnosis. For most arboviral infections in humans, viremia is of such low magnitude and brief duration that virus is generally undetectable by the time the patient seeks medical attention.

Biopsy. Biopsy of specific tissues with culture, antigen detection, nucleic acid amplification testing (e.g., PCR), and histopathologic examination of specimens may aid in the etiologic diagnosis. Biopsy of skin lesions should be performed; for example, biopsy with direct fluorescent antibody of maculopapular or petechial lesions may identify *R. rickettsii*, the etiologic agent of Rocky Mountain spotted fever. In patients with rabies,

full-thickness skin biopsy from the nape of the neck with staining of sensory neurons using immunofluorescent antibodies has a sensitivity of 50%–94% and a specificity that approaches 100%; the diagnosis of rabies can also be established by identification of rabies virus in the brain (via immunofluorescence or histopathologic examination) of the infecting animal if the animal is available for testing.

Serologic testing. Some causes of encephalitis may be diagnosed by detection of IgM antibodies in serum (e.g., primary varicella virus and many arboviruses). In recent years, IgM and IgG capture ELISAs have become the most useful and widely used tests for the diagnosis of arboviral encephalitis, although there may be cross-reactivity, particularly among the flaviviruses (e.g., Japanese encephalitis, St. Louis encephalitis, and West Nile viruses). Plaque-reduction neutralization testing is recommended in areas where multiple flaviviridae cocirculate or in patients who have received previous vaccination against a related arbovirus (e.g., prior Japanese encephalitis or yellow fever immunization in the setting of suspected flavivirus encephalitis). Antibodies (ELISA and confirmatory Western blot) to *B. burgdorferi* and serologic testing for *Rickettsia*, *Ehrlichia*, and *Anaplasma* species should be performed in all patients with encephalitis who reside in or have traveled to an area of endemicity, given that positive results would identify a treatable etiology; however, empirical therapy directed towards these latter microorganisms should never be withheld, because acute-phase serologic test results may be negative.

Because of the amount of time involved, assessment of acute- and convalescent-phase serum samples to show seroconversion to a specific pathogen is generally not useful in the decision to institute specific therapy, but this does remain a helpful tool for the retrospective diagnosis of infection with a specific agent. At the time of initial presentation, we recommend that serum specimens be stored and tested at a later time with convalescent-phase serum samples. In other diseases in which encephalitis may be a result of reactivation of previously acquired infection (e.g., toxoplasmic encephalitis in patients with AIDS), detection of serum IgG antibodies may identify persons at risk for encephalitis with a specific agent.

Nucleic acid amplification tests. PCR of biologic specimens for amplification of microbial nucleic acid from outside the CNS has been used to establish the etiology of some cases of encephalitis and should be performed in the proper clinical setting. For example, molecular testing of saliva samples may establish the diagnosis of rabies [46, 47]. In patients with human monocytotropic ehrlichiosis (caused by *E. chaffeensis*) and in those with human granulocytotropic ehrlichiosis (caused by *A. phagocytophilum*), the diagnostic sensitivity of PCR with whole blood samples ranges from 56% to 100% and from 54% to 86%, respectively [48–50]. PCR of lymph node

tissue specimens is also useful in establishing the diagnosis of *B. henselae* infection [51].

What Neurodiagnostic Tests Should Be Performed in Patients with Suspected Encephalitis?

Evidence Summary

Neuroimaging. CT and MRI are most frequently used to evaluate patients with encephalitis, with MRI being more sensitive and specific [52]. These studies may also be useful in excluding other conditions with a clinical presentation similar to that of encephalitis. CT (with and without intravenous contrast administration) should only be used if MRI is unavailable, impractical, or cannot be performed. Although MRI is useful for detection of early changes in encephalitis, it does not necessarily assist in differentiation of a specific etiology of encephalitis, and the findings may initially be normal or remain normal during the course of illness. Diffusion-weighted imaging is superior to conventional MRI for the detection of early signal abnormalities in viral encephalitis caused by herpes simplex virus, enterovirus 71, and West Nile virus [52].

Some characteristic neuroimaging patterns have been observed in patients with encephalitis caused by specific agents (table 5). In patients with herpes simplex encephalitis, there may be significant edema and hemorrhage in the temporal lobes, as well as hypodense areas on T1-weighted images and nonhomogeneous contrast enhancement; bilateral temporal lobe involvement is nearly pathognomonic for herpes simplex encephalitis, but this is a late development. More than 90% of patients with herpes simplex encephalitis documented by CSF PCR will have abnormalities seen on MRI [53]. In patients with encephalitis caused by flaviviruses and Eastern equine encephalitis virus, MRI may display a characteristic pattern of mixed intensity or hypodense lesions on T1-weighted images in the thalamus, basal ganglia, and midbrain; these lesions are hyperintense on T2 and fluid-attenuated inversion recovery (FLAIR) images. In patients with enterovirus 71 encephalitis, MRI may demonstrate hyperintense T2 and FLAIR lesions localized to the midbrain, pons, and medulla. Follow-up MRI may also be useful for evaluation of evolving necrosis or demyelination.

In cases of suspected ADEM, MRI is the diagnostic neuroimaging procedure of choice, generally revealing multiple focal or confluent areas of signal abnormality in the subcortical white matter and, sometimes, subcortical gray matter on T2 and FLAIR sequences [37–39]. Lesions are generally enhancing and display similar stages of evolution, with most or all lesions either enhancing or nonenhancing, a feature that helps distinguish these lesions from the subcortical white matter lesions of multiple sclerosis. This also differs from MRI findings for patients with progressive multifocal leukoencephalopathy, in which the lesions are similar but rarely enhance and uncom-

monly affect the gray matter. Because MRI findings may be negative early in the clinical course in patients with ADEM, scanning should be repeated if clinically indicated.

FDG-PET scanning has been studied in patients with encephalitis, with findings published in case reports and small case series. FDG-PET scanning usually shows hypermetabolism, although there can also be areas of hypometabolism [54], indicating that there are no clear characteristics that distinguish encephalitis from other conditions. Therefore, FDG-PET is not routinely recommended for patients with encephalitis, although it could be used as an adjunct in patients with other compatible clinical and diagnostic findings.

EEG. EEG is a sensitive indicator of cerebral dysfunction and may demonstrate cerebral involvement during the early stage of encephalitis [55]. The results of EEG are generally nonspecific but can be helpful in suggesting a specific etiologic diagnosis of encephalitis. In >80% of patients with herpes simplex encephalitis, there is a temporal focus demonstrating periodic lateralizing epileptiform discharges [56]. These stereotypical sharp and slow wave complexes occur at intervals of 2–3 s and are typically seen on days 2–14 after symptom onset. The EEG abnormalities in brainstem encephalitis may be disproportionately mild, compared with the clinical state of the patient; diffuse slow wave activity and intermittent rhythmic δ activity have been described in these patients. Although EEG is rarely useful in identifying a pathogen, it has a role in identifying patients with nonconvulsive seizure activity who are confused, obtunded, or comatose. The severity of abnormal EEG findings does not usually correlate with the extent of disease in the acute phase of illness, but rapidly improving EEG findings often indicate a good prognosis.

CSF analysis. Evaluation of CSF samples is essential (unless contraindicated) for all patients with encephalitis. In instances in which CSF specimens are not available, the likely etiology of the encephalitis should be based on epidemiology, clinical features, and results of other diagnostic studies (tables 2, 3 and 5). In patients with viral encephalitis, CSF analysis typically reveals a mild mononuclear pleocytosis, although a polymorphonuclear cell predominance may initially be seen if the sample is obtained early in the course of illness; persistent neutrophilic pleocytosis has been observed in patients with West Nile virus encephalitis. CSF protein concentration is generally mildly or moderately elevated. Patients may have significant numbers of RBCs in the CSF, as a result of the development of hemorrhagic encephalitis. The presence of CSF eosinophils may suggest certain etiologic agents (i.e., highest with the helminths, but this may be seen with *T. pallidum*, *M. pneumoniae*, *R. rickettsii*, *C. immitis*, and *T. gondii*), and accurate laboratory identification of these cells is important. Eosinophils can be mistaken for neutrophils if CSF cell counts are done in an automated cell counter; eosinophils can also be easily distorted

or destroyed during CSF processing, and the cytologic features of eosinophils are not easily discernible without Wright or Giemsa staining. A decreased CSF glucose concentration is unusual in viral encephalitis and suggests disease caused by bacteria (e.g., *L. monocytogenes* and *M. tuberculosis*), fungi, or protozoae (e.g., *Naegleria* species). Up to 10% of patients with viral encephalitis can have completely normal CSF findings. Despite clues provided by conventional CSF analysis, additional CSF studies (see below) (table 5) are needed to establish the specific cause of encephalitis.

The CSF findings in patients with ADEM are generally similar to those seen in patients with viral encephalitis—that is, lymphocytic pleocytosis, elevated protein concentration, and normal glucose concentration. Pleocytosis in ADEM tends to be less marked than in acute infectious encephalitis, and it may be absent. Markers of intrathecal immunoglobulin synthesis, including oligoclonal bands and elevated IgG index and synthesis rate, may be present, although less frequently than in multiple sclerosis.

What Tests of CSF and Brain Tissue Specimens Can Help in Establishing the Etiology of Encephalitis?

Evidence Summary

Antibody. Detection of CSF antibody is a helpful diagnostic tool in some patients with encephalitis. New diagnostic assays have simplified the diagnosis of certain viral CNS infections. The presence of virus-specific IgM in CSF is usually indicative of CNS disease, because IgM antibodies do not readily diffuse across the blood-brain barrier. For example, the detection of IgM antibodies by an ELISA assay in CSF specimens obtained from patients with presumed flavivirus encephalitis is considered to be diagnostic of neuroinvasive disease. CSF varicella zoster virus IgM antibodies may also be present in patients with a negative CSF varicella zoster virus PCR result (see “Nucleic acid amplification tests,” below).

Nucleic acid amplification tests. The development of PCR for amplification of microbial nucleic acids has greatly increased the ability to diagnose infections of the CNS, especially viral infections that are caused by herpesviruses and enteroviruses [57–60]. The utility of PCR assays for the diagnosis of herpes simplex encephalitis (usually caused by herpes simplex virus type 1 in adults) has been reliably demonstrated, with reported sensitivities and specificities of 96%–98% and 95–99%, respectively, in adults [61]; CSF PCR results are positive early in the disease course and remain positive during the first week of therapy, although false-negative results may occur if hemoglobin or other inhibitors are present in CSF. The sensitivity and specificity of CSF PCR for herpes simplex encephalitis in neonates and infants is more variable, with a reported sensitivity of 75%–100% [62]. An initially negative CSF PCR result for herpes simplex virus may become positive if the test is repeated

1–3 days after the initiation of treatment [63, 64], and the presence of <10 WBCs/mm³ in CSF has been associated with a higher likelihood of a negative CSF PCR result [65]. Therefore, in undiagnosed cases in which patients have clinical features of herpes simplex encephalitis or temporal lobe lesions on neuroimages, consideration should be given to repeating the PCR for herpes simplex virus 3–7 days later on a second CSF specimen. In this instance, a negative CSF PCR result may allow discontinuation of acyclovir therapy.

PCR can detect varicella zoster virus DNA, although a negative test result does not exclude the diagnosis of varicella encephalitis. PCR is also of value for detection of cytomegalovirus, with a high sensitivity and specificity for CNS involvement. Epstein-Barr virus can be detected by PCR, although a positive test result does not necessarily denote CNS infection, because latently infected mononuclear cells can cause a false-positive result and should be correlated with clinical findings and a compatible serologic test result. Results of CSF PCR for West Nile virus are positive in $<60\%$ of serologically confirmed cases. Measurement of JC virus DNA concentrations in CSF samples may be a useful virologic marker of disease activity for progressive multifocal leukoencephalopathy in HIV-infected patients receiving HAART [66], because it may indicate response to therapy. CSF PCR may detect evidence of *M. pneumoniae* in children with acute encephalitis [67], but the yield of this test was very low (2%) in one recent review [29], indicating that evidence of suspected infection with this microorganism should be determined by serologic testing or PCR of respiratory specimens. Although a positive CSF PCR result is very helpful for documentation of infection caused by a specific pathogen, a negative PCR result cannot be used as definitive evidence against the diagnosis.

Culture. CSF cultures are of limited value in the isolation of viral causes of encephalitis. In a review of 22,394 viral cultures of CSF samples, viruses were recovered from only 5.7% of specimens, the majority of which were enteroviruses (98.4%) and herpes simplex viruses (1.3%) [68]. Because viruses can be detected more rapidly and with greater sensitivity through nucleic acid amplification, viral culture generally offers no benefit and is, therefore, not routinely recommended. CSF cultures remain important in the diagnosis of nonviral causes of encephalitis, especially encephalitis caused by bacteria (e.g., *L. monocytogenes*) and fungi, although a number of the bacterial causes (e.g., *Mycoplasma*, *Bartonella*, *Ehrlichia*, and *Rickettsia* species and *T. pallidum*) cannot be isolated in culture.

Brain biopsy. Brain biopsy to establish the etiology of encephalitis is rarely used today and is not routinely recommended, given the availability of diagnostic PCR and antibody assays. However, biopsy will continue to play a limited role in the diagnosis of some cases of encephalitis and should be considered in patients with encephalitis of unknown etiology who

deteriorate neurologically despite treatment with acyclovir. For example, in patients with diffuse toxoplasmic encephalitis without focal lesions, definitive diagnosis can only be established by brain biopsy. The importance of this approach was reflected by a study from the National Institutes of Allergy and Infectious Diseases and Collaborative Antiviral Study Group that revealed that 43% of patients with suspected herpes simplex encephalitis had an alternative diagnosis [69], although this study was conducted prior to routine use of MRI; this high percentage of alternative diagnoses identified through brain biopsy is now unlikely. Neuroimaging should be used to guide the neurosurgeon to a specific area of the brain for biopsy; a biopsy specimen is obtained from an area of abnormality, in a noneloquent area of the brain, with a recommendation that at least 1 cm³ of tissue be removed. Once tissue is obtained, a portion of the sample should be sent for pathogen isolation, PCR, immunofluorescence, and electron microscopy; a second portion should be placed in formalin and sent for routine histopathologic examination, with appropriate staining for infectious agents. If considering brain biopsy in a patient with encephalitis, the biopsy should be performed earlier—rather than later—in the clinical course, in hopes of identifying a potentially treatable infectious etiology.

TREATMENT

What Specific Empirical Antimicrobial Agent(s) Should Be Used in Patients with Suspected Encephalitis?

Evidence summary. Although a wide range of viruses have been reported to cause encephalitis, specific antiviral therapy for viral encephalitis is generally limited to disease caused by the herpesviruses, especially herpes simplex virus. Because the earlier that treatment is started for herpes simplex encephalitis, the less likely that death or serious sequelae will result, acyclovir (10 mg/kg intravenously every 8 h in children and adults with normal renal function; 20 mg/kg intravenously every 8 h in neonates) should be initiated in all patients with suspected encephalitis as soon as possible, pending results of diagnostic studies. Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors (tables 2 and 3), including appropriate therapy for presumed bacterial meningitis if clinically indicated [70]. In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens [71].

Once the Etiology of Encephalitis Is Determined, What Specific Treatment Regimen Should Be Administered?

Evidence summary. Following the identification of a particular microorganism (by antibody studies, molecular methods, or culture) in a patient with encephalitis, appropriate antimicrobial therapy or management should be initiated (table 5)

(or continued, if herpes simplex virus is identified as the etiology). In the following sections, we review some of the specific data for our recommendations for treatment of encephalitis caused by selected treatable viruses and ADEM. Although other therapies may be appropriate if some of these infectious agents cause disease outside the CNS, only therapy specific for encephalitis is included. The rationale for recommendations for therapy of other microorganisms that are not discussed below can be found in other reviews, book chapters, and published guidelines (table 5) (<http://www.idsociety.org>) [3, 29–39, 70–86].

Herpes simplex virus. Acyclovir is the treatment of choice for patients with herpes simplex encephalitis [3, 4, 61, 87], but morbidity and mortality remain high (mortality at 18 months after treatment, 28%). In patients with herpes simplex encephalitis, predictors of an adverse outcome include age of the patient (>30 years), level of consciousness (Glasgow coma score, <6), and duration of symptoms prior to starting acyclovir therapy (>4 days) [88]; mortality decreased to 8% if therapy was initiated <4 days after onset of clinical symptoms. In a retrospective, multicenter trial of 93 adult patients, multivariate analysis also identified a Simplified Acute Physiology Score ≥ 27 at hospital admission and a delay of >2 days between hospital admission and administration of acyclovir therapy as independent predictors of poor outcome [89]. The dosage of acyclovir in patients with normal renal function is 10 mg/kg intravenously every 8 h for 14–21 days. Recently, the use of higher-dose acyclovir (20 mg/kg intravenously every 8 h for 21 days) in neonates with herpes simplex encephalitis has decreased mortality to 5%, with ~40% of survivors developing normally [90, 91]. Relapse of herpes simplex encephalitis has been reported after completion of acyclovir therapy [92]. In studies of neonates, ~8% had a documented relapse if treated with acyclovir for 10 days at a dosage of 10 mg/kg intravenously every 8 h, although relapse has not been documented when higher doses (20 mg/kg intravenously every 8 h) were administered for 21 days. A negative CSF PCR result at the end of therapy was associated with a better outcome, suggesting that another CSF specimen should be subjected to PCR for herpes simplex virus at the end of therapy in patients who have not had the appropriate clinical response; if the result is positive, antiviral therapy should be continued [93]. It is not clear how often relapse occurs in children or adults, but relapse rates as high as 5% have been reported.

Use of adjunctive corticosteroids was assessed in one non-randomized, retrospective study of 45 patients with herpes simplex encephalitis treated with acyclovir [94]. Although a worse outcome was observed in patients who were not treated with corticosteroids, these results need to be confirmed before this adjunctive treatment can be recommended.

Varicella zoster virus. Although no clinical trial has estab-

lished the efficacy of antiviral therapy for varicella zoster virus-associated encephalitis, on the basis of case reports and small series, acyclovir (10–15 mg/kg intravenously every 8 h for 10–14 days) is the drug of choice [95]. Ganciclovir has shown efficacy in some patients with varicella zoster virus meningo-encephalitis [96] and can be considered as an alternative agent for treatment.

Corticosteroids have been proposed for primary varicella zoster virus encephalitis and in immunocompetent patients with severe varicella zoster virus encephalitis and vasculopathy [41, 95], but there are no reliable data to support their use.

Cytomegalovirus. The optimal approach to the antiviral treatment of cytomegalovirus encephalitis is not clearly defined [97]. Ganciclovir (5 mg/kg intravenously every 12 h for 2–3 weeks) has been used, although therapeutic failures are common. Response to treatment in patients who have cytomegalovirus encephalitis with ganciclovir or foscarnet alone has not improved survival; even prophylaxis with ganciclovir or foscarnet, at doses used for maintenance in cases of cytomegalovirus retinitis, does not guarantee protection against development of cytomegalovirus encephalitis [16]. A combination of ganciclovir (5 mg/kg intravenously every 12 h) and foscarnet (60 mg/kg intravenously every 8 h or 90 mg/kg intravenously every 12 h) for 3 weeks, followed by maintenance therapy, is recommended and has led to success in HIV-infected patients, with improvement or stabilization in 74% of 31 patients with either cytomegalovirus encephalitis or myelitis [98]. However, cytomegalovirus ventriculoencephalitis was reported in a severely immunocompromised bone marrow transplant recipient receiving combination ganciclovir and foscarnet for treatment of cytomegalovirus viremia and retinitis, as a result of development of drug resistance [17]. Effective concentrations of ganciclovir and foscarnet may be difficult to achieve in the CSF. In HIV-infected infants with cytomegalovirus encephalitis, combination ganciclovir and foscarnet, along with HAART, has shown efficacy in some patients [99]. Cidofovir is not an alternative, because its ability to penetrate the blood-brain barrier is poorly studied. Because CMV encephalitis almost always develops in the context of profound suppression of cell-mediated immunity, the treatment approach should include attempts to decrease immunosuppression whenever possible.

Epstein-Barr virus. Acyclovir inhibits replication of Epstein-Barr virus in vitro, but a meta-analysis of 5 clinical trials did not show benefit in the treatment of infectious mononucleosis [100]. Although acyclovir has been used in some cases of CNS disease [101], it probably provides little or no benefit and is not recommended.

Corticosteroids were reported to be helpful in several anecdotal reports of neurologic complications of infection with Epstein-Barr virus (including encephalomyelitis) and have been used in patients with increased intracranial pressure [3]; these

data suggest that they may be beneficial in selected patients, but their potential benefits must be weighed against potential risk of perpetuating viral infection or of delaying the diagnosis of or partially treating AIDS-related CNS lymphoma.

Human herpesvirus 6. Randomized, controlled clinical trials to evaluate the usefulness of antiviral agents in patients with primary or viral reactivation caused by human herpesvirus 6 are lacking. Case reports have described the successful treatment of human herpesvirus 6-associated encephalitis in bone marrow transplant recipients with ganciclovir or foscarnet [102–104], but reactivation and neurologic symptoms have also developed while patients were receiving antiviral prophylaxis with these medications. Despite these contradictions, treatment with one of these agents, alone or in combination, in immunocompromised patients with human herpesvirus 6 encephalitis may be reasonable, because no other therapies are currently available. The data are less clear for benefit of treatment in immunocompetent patients [105], but therapy with one of these agents can be considered.

B Virus. Prophylactic antiviral therapy is recommended for individuals who have a high risk exposure to B virus [106]; use of valacyclovir (1 g orally every 8 h for 14 days) is recommended, because it leads to higher serum concentrations. Acyclovir (12.5–15 mg/kg intravenously every 8 h) has been suggested for acute infection; case reports in patients with B virus encephalitis have demonstrated full recovery, although the efficacy of this approach has not been systematically examined. Valacyclovir (1 g orally every 8 h) is recommended because higher serum concentrations can be achieved. Some experts recommend ganciclovir (5 mg/kg intravenously every 12 h for a minimum of 14 days or until all CNS symptoms have resolved) if the CNS is involved; subsequent administration of valacyclovir for suppression of latent infection may also be considered.

Other viruses. The use of antiviral therapy is less well defined in patients with encephalitis caused by other viruses (table 5). Although no controlled trials are available for the treatment of measles virus encephalitis, ribavirin may decrease the severity and duration of measles in normal adults and immunocompromised children with life-threatening disease [107]. Although ribavirin therapy is not currently recommended for treatment of measles virus encephalitis, if administered, it should be continued for 2–3 weeks. In 5 patients with subacute sclerosing panencephalitis, use of intraventricular ribavirin was associated with clinical improvement in 4 patients [108], suggesting that this mode of therapy should be further studied for its efficacy in this condition. Ribavirin has been used in an open-label trial in patients with Nipah virus encephalitis [109]; the results suggested that the drug was able to reduce the mortality of acute Nipah encephalitis with no associated serious side effects, but more data are needed. One study that examined the efficacy

of oral ribavirin in patients during an outbreak of West Nile virus infection in Israel found no significant benefit, but there was a potentially deleterious effect in 11% of patients who survived and 45.4% of patients who died [110]; although multivariate analysis suggested that use of ribavirin may have been a surrogate marker for use in sicker patients [111], its use is not recommended. Oseltamivir has been used in children with influenza B-associated encephalitis [26], although it is unclear that therapy aided in the recovery of the patients; oseltamivir and its metabolite, oseltamivir carboxylate, were not detected in the CSF in another report of a patient with influenza B-associated encephalitis [112].

Various adjunctive agents have been studied for their use in patients with viral encephalitis. IFN- α has been used in the context of nonrandomized, nonblinded assessments of patients with West Nile virus encephalitis, but the results are inconclusive [113], and a randomized, placebo-controlled trial among children infected with the closely related Japanese encephalitis virus demonstrated no benefit [114]. A recently concluded study sponsored by the National Institutes of Allergy and Infectious Diseases and Collaborative Antiviral Study Group assessed the efficacy of intravenous immunoglobulin containing high anti-West Nile virus antibody titers in patients with West Nile virus neuroinvasive disease in a randomized, placebo-controlled trial; results of this trial are still pending. Early initiation of therapy with IFN- α -2b was shown, in a limited series, to reduce the severity and duration of complications of St. Louis encephalitis virus meningoencephalitis [115]; however, a prospective, randomized trial is needed before this approach is warranted. In children with x-linked agammaglobulinemia and enteroviral encephalitis, intraventricular γ -globulin therapy (0.2 mL/kg) via an Ommaya reservoir could be considered, although benefits are unproven [116].

The recommended treatment for exposure to rabies virus is postexposure prophylaxis with rabies immunoglobulin and vaccination [117–119]. One recent case involving a 15-year-old girl who survived without postexposure vaccination was reported after she was treated with ribavirin and drug-induced coma [120]. Despite the recovery of this patient, the protocol has been unsuccessful in other cases [121, 122], and no proven therapy for clinical rabies has been established.

ADEM. Although not fully assessed in randomized, placebo-controlled trials, high-dose intravenous corticosteroids (methylprednisolone, 1 g intravenously daily for at least 3–5 days) are generally recommended for ADEM [39]. Reports of successful treatment with plasma exchange have also been documented, although no data from randomized trials are available. Plasma exchange should be considered in patients who respond poorly to corticosteroids [123]; responses in ADEM have been reported with plasma exchange, although the coadministration of corticosteroids and cyclophosphamide is fre-

quent and makes interpretation of these results difficult. There are limited data on the use of intravenous immunoglobulin for the treatment of ADEM, but this approach may be considered in patients who have not responded to corticosteroids or plasma exchange [124–126].

PERFORMANCE MEASURES

1. The diagnostic approach to patients with encephalitis must include neuroimaging—either MRI or CT. If neuroimaging is not used, the medical record should include documentation of the specific reasons.

2. Empirical antimicrobial therapy for patients with suspected encephalitis should include rapid administration of intravenous acyclovir at appropriate dosages; if appropriate, treatment for bacterial meningitis and rickettsial or ehrlichial infection should be included.

3. Once an etiologic agent of encephalitis is identified, antimicrobial therapy should be targeted to that infectious agent, or therapy should be discontinued if treatment directed against the etiologic agent is not available.

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