cross-reactivity. One study of 123 patients with anti-*Borrelia* antibody in CSF in France found that another cause was responsible for symptoms in 60% of patients,[339] although determination of the antibody index had a sensitivity of 75% and specificity of 97% for diagnosis. In addition, The C6-peptide ELISA in CSF has also been evaluated in the diagnosis of Lyme neuroborreliosis with a sensitivity of 95% and a specificity of 83%.[340] More recent studies measuring antibodies to C6 have suggested that this is at least as accurate as whole-cell sonicate ELISAs, and may provide a substitute for either the ELISA or Western blot in the two-tier approach.[341,342]

The technique of PCR on CSF samples has also been successfully used to identify *B. burgdorferi* DNA in patients with Lyme neuroborreliosis[170] (see Chapter 241), although PCR must still be considered experimental in the diagnosis of CNS Lyme disease. CSF PCR assay has a low sensitivity but may be useful in very early Lyme neuroborreliosis in those with a negative antibody index or in patients with immunodeficiency.[338] A negative CSF PCR assay does not exclude the diagnosis.[340] Studies have recently suggested that the B-cell attracting chemokine CXCL13 is reliably increased in the CSF of patients with early Lyme neuroborreliosis. One study showed a sensitivity of 94.1% and specificity of 96.1%, which were higher than the sensitivity and equal to the specificity of the antibody index (85.7% and 96.1%, respectively),[343] although there is not enough evidence to recommend CSF measurement of CXCL13 as a routine diagnostic tool.[338]

Radiologic studies may also be useful in patients with CNS manifestations of Lyme disease. CT has shown both enhancing and nonenhancing low-density lesions, mass effect, and cerebral demyelination. MRI may reveal punctate hyperresonant areas without mass effect within the cerebral white matter (Fig. 87.3).

Protozoal and Helminthic Meningitis

Amebas

The CSF formula in patients with the acute form of PAM resembles bacterial meningitis with high opening pressures, a high degree of pleocytosis (median CSF WBCs, 2400 cells/mm^3) with neutrophilia, severe hypoglycorrhachia (median CSF glucose, 23 mg/dL), and high CSF protein concentrations (median, 365 mg/dL).[169–171,344] Patients also may present with a hemorrhagic CSF (median CSF red blood cell count, 265 cells/mm^3), most likely due to necrotizing encephalitis.[169] Gram stain is always negative, but CSF smears should be stained with Giemsa or Wright stains to possibly identify the trophozoite. Examination of fresh, warm specimens of CSF can reveal the ameboid movements of motile trophozoites, or the organism can be identified with PCR at the CDC.[257] In the largest study done to date, a premortem diagnosis was documented in only 27% of 142 patients with PAM.[255] Establishing the diagnosis is very important because miltefosine has been used successfully in some patients.[256] Trophozoites can be demonstrated with light or electron microscopy of brain tissue in autopsy specimens.

Patients with the subacute or chronic form of the illness caused by *Acanthamoeba* species have a less florid CSF inflammatory response with a predominant mononuclear leukocytosis. The CSF protein concentration is elevated, and the glucose content is often normal or reduced.[257] Amebas may be seen in the CSF and the diagnosis confirmed with a CSF *Acanthamoeba* PCR assay performed at the CDC. Patients may present with a chronic meningitis with hydrocephalus resembling tuberculous meningitis.[257] The value of serologic tests is variable.[169] Serum immunofluorescence, amebic immobilization titers, and complement-fixing antibodies support the diagnosis, although demonstration of rising titers is necessary to establish the diagnosis because some healthy persons have circulating antibodies.

Angiostrongylus cantonensis

The combination of a history of ingestion of food suspected to be affected, moderate-to-high peripheral eosinophilia, and CSF eosinophilia leads to the suspicion of angiostrongyloidiasis.[71,175,179] The CSF leukocytosis is moderate, with 16% to 72% eosinophils and an increased protein concentration, but the glucose concentration is normal. However, eosinophilia is not always present in the peripheral blood or in CSF on initial evaluation.[176] In the Jamaican outbreak, eosinophilia was not present in nearly half of the patients at the time of hospital admission, and was initially present in 56% and 44% of CSF and peripheral blood specimens, respectively.[180] Larvae are occasionally found on microscopy of CSF and are seen more often in pediatric patients than in adults. Serologic studies for *A. cantonensis* are not widely available and are not available in a timely manner for making clinical decisions.[176] In one study, serum antibodies were detected in 30 of 31 patients tested, with CSF antibodies positive in 17 of 30 patients.[303] The detection of circulating antigen in serum or CSF may also provide rapid confirmation of infection.[345] PCR for *A. cantonensis* has been used in patients with eosinophilic meningitis in Laos, with promising results.[346]

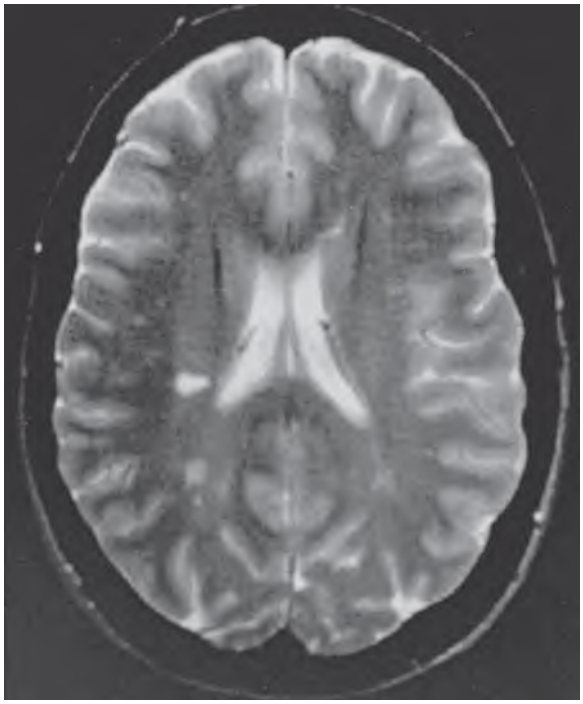
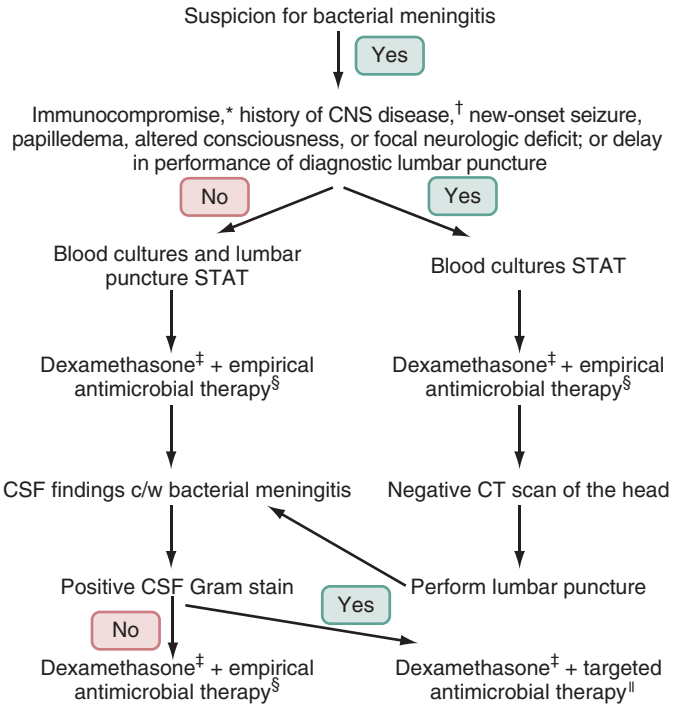


FIG. 87.3 **T2-weighted magnetic resonance image in a patient with Lyme disease reveals areas of increased signal intensity in the cerebral white matter.**

INITIAL MANAGEMENT OF PATIENTS WITH ACUTE MENINGITIS

Who Should Have a Lumbar Puncture?

The initial management of a patient with presumed bacterial meningitis includes performance of a lumbar puncture to determine whether the CSF formula is consistent with that diagnosis (Fig. 87.4).[189,293] If purulent meningitis is present, institution of antimicrobial therapy should be based on the results of Gram staining (Table 87.11). However, if no etiologic agent can be identified by this means or if performance of the lumbar puncture is delayed, institution of empirical antimicrobial therapy, after obtaining blood cultures, should be based on the patient's age and underlying disease status (Table 87.12). Although no prospective data are available on the timing of administration of antimicrobial therapy in patients with bacterial meningitis, a retrospective cohort study in patients with community-acquired bacterial meningitis demonstrated that a delay in initiation of antimicrobial therapy after patient arrival in the emergency department was associated with an adverse clinical outcome when the patient's condition advanced to a high stage of prognostic severity,[347] thus supporting the assumption that treatment of bacterial meningitis before it advances to a high level of clinical severity improves clinical outcome. This concept has also been supported by several retrospective studies, all showing an increase in adverse outcomes with delays of antibiotic therapy; the majority of these studies show an increase in mortality with >6 hours delay.[348–352]



*HIV infection or AIDS, receiving immunosuppressive therapy, or after transplantation.
†Mass lesion, stroke, or focal infection.
‡See text for specific recommendations for use of adjunctive dexamethasone in adults with bacterial meningitis. Dexamethasone and antimicrobial therapy should be administered immediately after CSF sample is obtained.
§See Table 87-12.
‖See Table 87-11. Many authorities would continue empirical antimicrobial therapy (see Table 87-12) pending organism identification.

FIG. 87.4 Management algorithm for adults with suspected bacterial meningitis. *AIDS,* Acquired immunodeficiency syndrome; *CNS,* central nervous system; *CSF,* cerebrospinal fluid; *CT,* computed tomography; *HIV,* human immunodeficiency virus; *STAT,* statim (immediately). *(From Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis.* Clin Infect Dis. *2004;39:1267–1284.)*

TABLE 87.11 Recommended Antimicrobial Therapy for Acute Bacterial Meningitis

MICROORGANISM[a]	ANTIMICROBIAL THERAPY
Haemophilus influenzae type b	Third-generation cephalosporin[b]
Neisseria meningitidis	Third-generation cephalosporin[b]
Streptococcus pneumoniae	Vancomycin plus a third-generation cephalosporin[b,c]
Listeria monocytogenes	Ampicillin or penicillin G[d]

[a]Pathogen presumptively identified by positive Gram stain.
[b]Cefotaxime or ceftriaxone.
[c]Some experts would add rifampin if dexamethasone is also given.
[d]Addition of an aminoglycoside should be considered.
Modified from Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. *2004;39:1267–1284.*

Who Should Undergo Cranial Computed Tomography Before Lumbar Puncture

Obtaining a screening head CT scan before a lumbar puncture to rule out an intracranial mass has become routine practice in the emergency department.[352a] This is done owing to the fear of potentially placing the patient at risk for brain herniation. However, clear evidence that lumbar puncture causes brain herniation is lacking, because the natural course of the disease may itself result in herniation. In patients who present with focal neurologic findings, or who have papilledema and suspected bacterial meningitis, CT of the head is recommended before lumbar puncture in order to rule out the presence of brain shift (as a result of an intracranial mass lesion or generalized brain edema) for the potential risk for herniation,[189,293] despite the fact that up to 43% of patients with bacterial meningitis who had brain herniation had a normal CT scan.[353] Furthermore, the time involved in waiting to perform CT significantly delays the initiation of antimicrobial therapy, with the potential for increased morbidity and mortality in patients with bacterial meningitis. Therefore emergency empirical antimicrobial therapy and adjunctive dexamethasone therapy, after specimens for culture have been obtained, should be initiated before sending the patient for CT.[293] Although CSF cultures may be sterile after the initiation of antimicrobial therapy, pretreatment blood cultures and the CSF formula or Gram stain will provide evidence for or against a diagnosis of bacterial meningitis. In one retrospective review of 177 patients (39 of whom had received prior antimicrobial therapy) with CSF culture-proven bacterial meningitis,[354] the combination of blood culture and CSF Gram stain, with or without latex agglutination, identified the causative bacterium in 92% of patients. In 2004, the IDSA guidelines recommended that the following adult patients should undergo CT prior to lumbar puncture: those with immunocompromised state, history of CNS disease, new-onset seizure, papilledema, abnormal level of consciousness, or focal neurologic deficit.[293] The Swedish guidelines removed altered mental status as an indication for cranial imaging, reporting that this change in practice was associated with earlier treatment and improved outcomes.[355,356] In 2016, both the United Kingdom and the European guidelines further restricted the recommendations to include only focal neurologic findings (except cranial nerve palsy in the European guidelines, new-onset seizures in the European guidelines, and uncontrolled seizure in the UK guidelines) and a lower Glasgow Coma Scale score (≤12 in UK and <10 in European guidelines).[53,287] In addition, the European guidelines and the IDSA guidelines recommend that immunosuppressed patients undergo cranial imaging.[53,293] The Swedish guidelines are the most selective; in these guidelines, a CT is recommended only if there is a suspicion of cerebral mass or abscess (>4 days of cerebral symptoms or neurologic deficit except cranial nerve palsy) or if there are signs of herniation.[355] A study of 815 adults with bacterial meningitis showed a decrease in mortality if there was adherence to the Swedish guidelines in contrast to the IDSA or European guidelines.[356] Compliance in clinical practice with all these guidelines remains low, at about 50% in several recent studies.[328,356–358]

TABLE 87.12 Empirical Therapy for Purulent Meningitis

PREDISPOSING FACTOR	ANTIMICROBIAL THERAPY
Age	
<1 mo	Ampicillin plus cefotaxime; or ampicillin plus an aminoglycoside
1–23 mo	Vancomycin plus a third-generation cephalosporin[a,b]
2–50 yr	Vancomycin plus a third-generation cephalosporin[a,b,c]
>50 yr	Vancomycin plus ampicillin plus a third-generation cephalosporin[a]
Immunocompromised state	Vancomycin plus ampicillin plus either cefepime or meropenem
Basilar skull fracture	Vancomycin plus a third-generation cephalosporin[a]
Head trauma; after neurosurgery	Vancomycin plus either ceftazidime, cefepime, or meropenem

[a]Cefotaxime or ceftriaxone.
[b]Some experts would add rifampin if dexamethasone is also given.
[c]Add ampicillin if meningitis caused by *Listeria monocytogenes* is suspected.
Modified from Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. *2004;39:1267–1284.*

Empirical Therapy of Community-Acquired Acute Bacterial Meningitis in Adults

Without an organism on Gram stain, a positive culture from blood or CSF, or a positive PCR assay result, the recommended treatment for

community-acquired bacterial meningitis in adults is cefotaxime 8 to 12 g/day divided into every 4- or 6-hour doses or ceftriaxone 4 g/day divided into doses every 12 hours. Vancomycin 35 to 45 mg/kg/day divided into doses every 8 or 12 hours is used for the possibility of *S. pneumoniae* with reduced susceptibility to ceftriaxone (MIC ≥2 μg/mL). If *L. monocytogenes* is a concern in patients who are immunosuppressed or older than 50 years, ampicillin can be given as 12 g/day divided into 4- hour intervals. Dexamethasone remains controversial but is recommended to be given at least 20 to 30 minutes before the first dose of antibiotic, beginning with 0.15 mg/kg every 6 hours. Once the first dose of antibiotic has been given, starting dexamethasone is no longer advocated by the 2004 IDSA guidelines, but it is recommended based on expert opinion up to 4 hours after starting antibiotics in the 2016 European guidelines and up to 12 hours in the 2016 UK guidelines. A duration of antimicrobial therapy of at least 14 days is recommended when the pathogen remains unknown.

Selecting the Right Antimicrobial

Once the infecting meningeal pathogen has been isolated and susceptibility testing results are known, antimicrobial therapy can be modified for optimal treatment (Table 87.13).[189,267,304] Recommended dosages of antimicrobial agents for adults with infections of the CNS are shown in Table 87.14, and those for neonates, infants, and children are presented in Table 87.15.

Adjunctive Corticosteroids

Experimental Data

Certain patients should receive adjunctive dexamethasone therapy when presenting with suspected or proven bacterial meningitis.[286,287,293] As stated earlier (see "Pathogenesis and Pathophysiology"), generation of pneumococcal cell wall components in an experimental animal model of pneumococcal meningitis after treatment with bacteriolytic antibiotics may contribute to the inflammatory response in the subarachnoid space.

TABLE 87.13 Specific Antimicrobial Therapy for Acute Meningitis

MICROORGANISM	STANDARD THERAPY	ALTERNATIVE THERAPIES[a]
Bacteria		
Haemophilus influenzae		
β-Lactamase negative	Ampicillin	Ceftriaxone or cefotaxime or cefepime or chloramphenicol or aztreonam or a fluoroquinolone[b]
β-Lactamase positive	Ceftriaxone or cefotaxime	Cefepime or chloramphenicol or aztreonam or a fluoroquinolone[b]
Neisseria meningitidis		
Penicillin MIC <0.1 μg/mL	Penicillin G or ampicillin	Ceftriaxone or cefotaxime or chloramphenicol
Penicillin MIC 0.1–1.0 μg/mL	Ceftriaxone or cefotaxime	Chloramphenicol or a fluoroquinolone[b] or meropenem
Streptococcus pneumoniae		
Penicillin MIC ≤0.06 μg/mL	Penicillin G or ampicillin	Ceftriaxone or cefotaxime or chloramphenicol
Penicillin MIC ≥0.12 μg/mL		
Ceftriaxone or cefotaxime MIC <1.0 μg/mL	Ceftriaxone or cefotaxime	Meropenem or cefepime
Ceftriaxone or cefotaxime MIC ≥1.0 μg/mL	Vancomycin[c] plus ceftriaxone or cefotaxime	Vancomycin plus moxifloxacin[d]
Enterobacteriaceae[e]	Ceftriaxone or cefotaxime	Aztreonam or a fluoroquinolone[b] or trimethoprim-sulfamethoxazole or meropenem or ampicillin
Pseudomonas aeruginosa	Ceftazidime or cefepime	Aztreonam or a fluoroquinolone[b] or meropenem
Acinetobacter baumannii[e]	Meropenem	Colistin (usually formulated as colistimethate sodium)[g] or polymyxin B[g]
Listeria monocytogenes	Ampicillin or penicillin G[f]	Trimethoprim-sulfamethoxazole
Streptococcus agalactiae	Ampicillin or penicillin G[f]	Ceftriaxone or cefotaxime or vancomycin
Staphylococcus aureus		
Methicillin-sensitive	Nafcillin or oxacillin	Vancomycin or linezolid or daptomycin
Methicillin-resistant	Vancomycin[c]	Trimethoprim-sulfamethoxazole or linezolid or daptomycin or ceftaroline
Staphylococcus epidermidis	Vancomycin[c]	Linezolid
Spirochetes		
Treponema pallidum	Penicillin G	Ceftriaxone[h]
Borrelia burgdorferi	Ceftriaxone or cefotaxime	Penicillin G or doxycycline
Protozoa		
Naegleria fowleri	Amphotericin B[i] plus rifampin plus azithromycin plus fluconazole plus miltefosine[j]	—

[a]There may not be clinical data to support all recommendations for alternative antimicrobial agents in patients with bacterial meningitis, but specific agents are suggested based on cerebrospinal fluid (CSF) penetration in experimental animal models and in vitro activity against the offending pathogen, and from isolated case reports documenting successful outcome.
[b]Clinical data are limited on the use of fluoroquinolones for therapy for gram-negative meningitis but may be considered in patients not responding to standard therapy or when disease is caused by resistant organisms.
[c]Addition of rifampin may be considered; see text for indications.
[d]Would recommend moxifloxacin, given its excellent CSF penetration and in vitro activity against *S. pneumoniae,* although there are no clinical data to support its usefulness in patients with pneumococcal meningitis; if used, many authorities would combine moxifloxacin with vancomycin or a third-generation cephalosporin such as cefotaxime or ceftriaxone.
[e]Choice of a specific antimicrobial agent must be guided by in vitro susceptibility testing.
[f]Addition of an aminoglycoside should be considered.
[g]Might also need to be administered by the intraventricular or intrathecal routes.
[h]Alternative agent for use in patients allergic to penicillin. Not well studied. See Chapter 239.
[i]Intravenous and intrathecal administration.
[j]Available by contacting the Centers for Disease Control and Prevention (770-488-7100).
MIC, Minimal inhibitory concentration.
Modified from van de Beek D, Brouwer MC, Thwaites GE, et al. Advances in the treatment of bacterial meningitis. Lancet. *2012;380:1693–1702.*

TABLE 87.14 Recommended Dosages of Antimicrobial Agents for Bacterial Meningitis in Adults With Normal Renal and Hepatic Function

ANTIMICROBIAL AGENT	TOTAL DAILY DOSE	DOSING INTERVAL (h)
Amikacin[a]	15 mg/kg	8
Ampicillin	12 g	4
Aztreonam	6–8 g	6–8
Cefepime	6 g	8
Cefotaxime	8–12 g	4–6
Ceftaroline	1800 mg	8
Ceftazidime	6 g	8
Ceftriaxone	4 g	12–24
Chloramphenicol[b]	4–6 g	6
Ciprofloxacin	800–1200 mg	8–12
Daptomycin	6–10 mg/kg	24
Gentamicin[a]	5 mg/kg	8
Linezolid	1200 mg	12
Meropenem	6 g	8
Moxifloxacin[c]	400 mg	24
Nafcillin	12 g	4
Oxacillin	12 g	4
Penicillin G	24 million units	4
Rifampin	600 mg	12–24
Tobramycin[a]	5 mg/kg	8
Trimethoprim-sulfamethoxazole[d]	10–20 mg/kg	6–12
Vancomycin[e]	30–45 mg/kg	8–12

[a]Need to monitor peak and trough serum concentrations.
[b]Higher dose recommended for pneumococcal meningitis.
[c]No data on optimal dosage for patients with bacterial meningitis.
[d]Dosage based on trimethoprim component; many experts would use a dose of 5 mg/kg every 8 hours.
[e]Maintain serum trough concentrations of 15–20 μg/mL; one study recommended continuous infusion of 60 mg/kg/day (see text for details).
Modified from Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. *2004;39:1267–1284.*

The inflammatory response induced by either live pneumococci or pneumococcal cell wall was reduced by agents (e.g., methylprednisolone, oxindanac) that inhibit the cyclooxygenase pathway of arachidonic acid metabolism, and a correlation was noted between CSF concentrations of the arachidonic acid metabolite PGE_2 and CSF leukocytes. In another study, administration of the antiinflammatory agent indomethacin decreased both brain water content and CSF concentrations of PGE_2 during experimental pneumococcal meningitis, although intracranial pressure was not reduced. In addition, the administration of either dexamethasone or oxindanac lessened the massive influx of serum albumin and other proteins of high and low molecular weight into the CSF during the early stages of experimental pneumococcal meningitis. Several corticosteroid agents have also been examined in experimental animal models of meningitis. Early studies revealed that methylprednisolone administration led to a significant reduction in the mass of leukocytes within the meninges of rabbits with pneumococcal meningitis. Another study demonstrated that CSF outflow resistance was reduced by methylprednisolone therapy and to a greater extent than in untreated or penicillin-treated rabbits with pneumococcal meningitis. In further studies that examined the effects of corticosteroids (methylprednisolone or dexamethasone) on brain water content, CSF pressure, and CSF lactate in rabbits with pneumococcal meningitis, it was found that both agents completely reversed the development of brain edema but that only dexamethasone led to a reduction in CSF pressure and lactate; however, neither agent was superior to therapy with ampicillin alone in reducing cerebral edema or intracranial pressure, and no comparison was made between ampicillin alone and the combination of ampicillin plus corticosteroids, a comparison that would have been relevant to the potential clinical usefulness of adjunctive corticosteroid therapy in bacterial meningitis. A subsequent study did examine treatment with ceftriaxone versus ceftriaxone plus dexamethasone in an experimental rabbit model of *H. influenzae* meningitis. Although combination therapy consistently reduced the brain water content, CSF pressure, and CSF lactate to a greater degree than ceftriaxone alone, the differences were not statistically significant. The authors suggested, however, that adjunctive dexamethasone might be more beneficial if administered early or even before antibiotic-induced bacterial lysis and release of microbial products. In a subsequent analysis using the experimental rabbit model of *H. influenzae* type b meningitis, ceftriaxone administration led to a significant increase in CSF endotoxin concentrations 2 hours after administration, which was followed by a rise in CSF TNF concentrations. Simultaneous administration of dexamethasone and ceftriaxone did not affect the release of endotoxin into CSF, but it markedly attenuated CSF concentrations of TNF measured 8 hours later. Adjunctive dexamethasone therapy also resulted in a significant decrease in CSF leukocytosis and a trend toward earlier improvement in CSF concentrations of glucose, lactate, and protein. These parameters improved without any apparent decrease in the rate of bacterial killing within the CSF in vivo.

Clinical Studies of Corticosteroids in Infants and Children

On the basis of these observations, numerous clinical trials were undertaken to determine the effects of adjunctive dexamethasone on outcome in patients with bacterial meningitis.[359–389] One meta-analysis of these clinical studies confirmed the benefit of adjunctive dexamethasone (0.15 mg/kg every 6 hours for 2–4 days) for *H. influenzae* type b meningitis and, if begun with or before parenteral antimicrobial therapy, suggests benefit for pneumococcal meningitis in childhood.[380] Evidence of clinical benefit was strongest for improved hearing outcomes. In contrast, a retrospective, nonrandomized study of children with pneumococcal meningitis, published after the meta-analysis, demonstrated that the use of adjunctive dexamethasone was not associated with a beneficial effect,[371] although the dexamethasone was administered before or within 1 hour of the first dose of antibiotic and the children in the dexamethasone group had a higher severity of illness. In addition, in a published double-blind, placebo-controlled trial of adjunctive dexamethasone in Malawi,[375] the overall number of deaths in the two treatment groups was similar (31% in each group), as was the frequency of neurologic sequelae. The factors that may have accounted for these results include the fact that Malawian children had severe disease associated with undernutrition and HIV infection and the fact that they were presented for medical attention after a delay, which resulted in very high case-fatality rates and significant long-term morbidity.[381] Corticosteroids do not reverse CNS damage that has already resulted from the pathophysiologic consequences of bacterial meningitis (e.g., cerebral edema and increased intracranial pressure). However, even in children with bacterial meningitis in the developing world, use of adjunctive dexamethasone should be considered, because no adverse effects were attributable to its administration in this trial, and its use may benefit some of the children with this devastating disorder. In a retrospective cohort study of 2780 children from 27 tertiary care children's hospitals discharged with bacterial meningitis as their primary diagnosis, adjuvant corticosteroid therapy was not associated with time to death or time to hospital discharge.[377] However, the study was limited by the low mortality rate of bacterial meningitis in children, the number of patients included in each subgroup was small, the dose or timing of corticosteroid administration could not be ascertained, and potential benefits in terms of morbidity were not assessed.

Clinical Studies of Corticosteroids in Adults

In adult patients with bacterial meningitis, use of adjunctive dexamethasone is generally recommended.[286,287] In a prospective, randomized, double-blind trial in 301 adults with bacterial meningitis,[376] adjunctive dexamethasone was associated with a reduction in the proportion of

TABLE 87.15 Recommended Dosages of Antimicrobial Agents for Bacterial Meningitis in Neonates, and Infants and Children With Normal Renal and Hepatic Function

	TOTAL DAILY DOSE (DOSING INTERVAL IN HOURS)		
ANTIMICROBIAL AGENT	**NEONATES (BIRTH–7 DAYS OLD)[A]**	**NEONATES (8–28 DAYS OLD)[A]**	**INFANTS AND CHILDREN**
Amikacin[b]	15–20 mg/kg (12)	30 mg/kg (8)	20–30 mg/kg (8)
Ampicillin	150 mg/kg (8)	200 mg/kg (6–8)	300 mg/kg (6)
Cefepime	—	—	150 mg/kg (8)
Cefotaxime	100–150 mg/kg (8–12)	150–200 mg/kg (6–8)	225–300 mg/kg (6–8)
Ceftazidime	100–150 mg/kg (8–12)	150 mg/kg (8)	150 mg/kg (8)
Ceftriaxone	—	—	80–100 mg/kg (12–24)
Chloramphenicol	25 mg/kg (24)	50 mg/kg (12–24)	75–100 mg/kg (6)
Gentamicin[b]	5 mg/kg (12)	7.5 mg/kg (8)	7.5 mg/kg (8)
Meropenem	—	—	120 mg/kg (8)
Nafcillin	75 mg/kg (8–12)	100–150 mg/kg (6–8)	200 mg/kg (6)
Oxacillin	75 mg/kg (8–12)	150–200 mg/kg (6–8)	200 mg/kg (6)
Penicillin G	0.15 mU/kg (8–12)	0.2 mU/kg (6–8)	0.3 mU/kg (4–6)
Rifampin[c]	—	10–20 mg/kg (12)	10–20 mg/kg (12–24)
Tobramycin[b]	5 mg/kg (12)	7.5 mg/kg (8)	7.5 mg/kg (8)
Trimethoprim-sulfamethoxazole[d]	—	—	10–20 mg/kg (6–12)
Vancomycin[e]	20-30 mg/kg (8–12)	30–45 mg/kg (6–8)	60 mg/kg (6)

[a]Smaller dosages and longer intervals of administration may be advisable for very-low-birth-weight neonates (<2000 g).
[b]Need to monitor peak and trough serum concentrations.
[c]Maximum daily dose of 600 mg.
[d]Dosage based on trimethoprim component; many experts would use a dose of 5 mg/kg every 8 hours.
[e]Maintain serum trough concentrations of 15–20 µg/mL.
Modified from Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. *2004;39:1267–1284.*

patients who had unfavorable outcomes (15% vs. 25%, $P = .03$) and in the proportion of patients who died (7% vs. 15%, $P = .04$). Neurologic sequelae were not reduced, although neurologic sequelae were seen predominantly in the most severely ill patients and the proportion of severely ill patients who survived to be tested was larger in the dexamethasone group. The benefits were most striking in the subgroup of patients with pneumococcal meningitis (unfavorable outcome in 26% of those receiving dexamethasone vs. 52% in those receiving placebo, $P = .006$; and death in 14% of those receiving dexamethasone vs. 34% in those receiving placebo, $P = .02$) and in those with moderate-to-severe disease as assessed by the admission Glasgow Coma Scale score. On the basis of these data and the apparent absence of serious adverse outcomes in the patients who received dexamethasone, the routine use of adjunctive dexamethasone (given concomitantly with or just prior to the first dose of an antimicrobial agent for maximal attenuation of the subarachnoid space inflammatory response) is warranted in most adults with pneumococcal meningitis.[382] Adjunctive dexamethasone should not be used in patients who have already received antimicrobial therapy; if the meningitis is subsequently found not to be caused by *S. pneumoniae,* dexamethasone should be discontinued, although some experts recommend use of adjunctive dexamethasone regardless of microbial etiology. In patients with meningococcal meningitis who received adjunctive dexamethasone, there was no improvement in rates of unfavorable outcome, although its use was not associated with harm.[383] Despite these positive benefits in terms of morbidity and mortality, there were some concerns regarding cognitive long-term outcome in patients treated with dexamethasone. However, a follow-up study of 87 eligible patients in which 46 were treated with adjunctive dexamethasone and 41 with placebo, neuropsychologic evaluation showed no significant differences between patients treated with dexamethasone or placebo.[384] In an evaluation of 357 episodes of pneumococcal meningitis from 2006 to 2009 in the Netherlands since implementation of adjunctive dexamethasone on a large-scale basis, the prognosis improved, with mortality rates decreasing from 30% to 20%.[385] A significant reduction in the mortality in pneumococcal meningitis has also been observed in the United States that is temporarily related to the introduction of adjunctive dexamethasone.[390] Approximately 1% to 4% of adults with community-acquired bacterial meningitis develop a delayed cerebral thrombosis after they have had an excellent initial recovery from their episode of meningitis.[386,387] A recent study showed a potential association with the use of adjunctive steroids, but further studies are needed.[391]

Despite the positive benefits of adjunctive dexamethasone in adults with bacterial meningitis described previously, the routine use of adjunctive dexamethasone in patients with bacterial meningitis in the developing world has been controversial. In one randomized, double-blind, placebo-controlled study in adolescents and adults in Vietnam with confirmed bacterial meningitis,[65] patients who received adjunctive dexamethasone experienced a significant reduction in the risk for death at 1 month (RR, 0.43) and the risk for death or disability at 6 months (RR, 0.56); the highest proportion of cases in this study were caused by *S. suis,* followed by *S. pneumoniae.* In contrast, in a randomized, double-blind, placebo-controlled study from Malawi, there were no significant differences in mortality at 40 days in the intention-to-treat analysis (56% in the dexamethasone group vs. 53% in the placebo group) or when the analysis was restricted to patients with proven pneumococcal meningitis (53% in the dexamethasone group vs. 50% in the placebo group).[379] However, in this trial, almost 90% of the patients were infected with HIV and most likely had advanced disease; delayed presentation was also associated with a poorer outcome, although adjusting for this factor in the analysis had no effect. These data suggest that adjunctive dexamethasone is not beneficial in resource-poor countries where a substantial number of patients are infected with HIV.[388] In a Cochrane Database systematic meta-analysis of 24 studies involving 4041 participants, adjunctive dexamethasone did not reduce overall mortality, but there was a trend toward lower mortality in adults; corticosteroids were associated with lower rates of severe hearing loss, any hearing loss, and neurologic sequelae, although these benefits were seen only in studies from high-income countries.[389] In a subgroup analysis based on causative microorganism, corticosteroids reduced severe hearing loss in patients

with *H. influenzae* meningitis and mortality in patients with *S. pneumoniae* meningitis.

The use of adjunctive dexamethasone is of particular concern in patients with pneumococcal meningitis caused by highly penicillin- and cephalosporin-resistant strains, in which case patients may require antimicrobial therapy with vancomycin.[286,293] A diminished CSF inflammatory response after dexamethasone administration might significantly reduce vancomycin penetration into CSF and delay CSF sterilization, as shown in an experimental rabbit model of penicillin- and cephalosporin-resistant pneumococcal meningitis. This result was confirmed in another rabbit model of pneumococcal meningitis in which significantly lower CSF vancomycin concentrations and differences in bacterial killing were found in the dexamethasone-treated rabbits. However, CSF vancomycin penetration was not reduced by dexamethasone in a study in children[392]; and in another study in which a continuous infusion of vancomycin was used (60 mg/kg/day), adequate CSF concentrations (7.9 μg/mL) were achieved despite the concomitant administration of adjunctive dexamethasone.[393] CSF concentrations of ceftriaxone are not significantly altered in animals or patients treated with adjunctive dexamethasone.[394,395]

Dexamethasone is the only adjunctive therapy that has been advocated by the IDSA, UK guidelines, and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines in patients with bacterial meningitis.[53,287,293] Available evidence suggests that, in high-income countries, dexamethasone treatment should be started with or even before the first dose of antibiotics and continued for 4 days in both children and adults (although with different dose regimens). Guidelines recommend suspending dexamethasone treatment if the bacterial meningitis diagnosis is not confirmed or if the causative pathogen is other than *H. influenzae* or *S. pneumoniae* (although some experts advise dexamethasone to be continued irrespective of the meningeal pathogen).[53,287]

ANTIMICROBIAL THERAPY

Viral Meningitis

Specific antiviral chemotherapy for the EVs is not currently available; treatment is supportive. Pleconaril, an agent that has been evaluated in enteroviral infections,[396,397] is a novel compound that integrates into the hydrophobic pocket of picornaviruses (including EVs) and prevents viral replication by inhibiting viral uncoating and blocking viral attachment to host cell receptors. It is orally bioavailable in all age groups, and CNS concentrations are four times higher than those in serum, making it a possible agent for the treatment of enteroviral neurologic infection (see Chapter 48).[396] In a preliminary report on the outcome of potentially life-threatening EV infections in patients treated with pleconaril by compassionate-use protocol,[397] the drug had beneficial effects on the clinical, virologic, laboratory, and radiologic parameters in patients with EV infections. Of the 16 patients with CEMA, 12 improved on pleconaril and 4 were unchanged and stable. In placebo-controlled clinical studies of pleconaril treatment of adults and children with non–life-threatening enteroviral meningitis, clinical benefits (i.e., faster resolution of headache and return to work or school) and virologic benefits, and a favorable safety profile, were documented.[219] In a double-blind, placebo-controlled trial in infants (<12 months) with enteroviral meningitis, efficacy of pleconaril was not demonstrated, which may have been a result of the low yield of serial viral cultures, relatively short and benign clinical courses, and the small number of subjects enrolled.[398] In another randomized, multicenter, double-blind placebo-controlled trial of 607 patients with enteroviral meningitis, pleconaril shortened the course of illness compared with placebo-treated patients, especially early in the disease course.[399] Benefits were only modestly achieved in the subgroup of patients with more severe disease. Pleconaril is not active against EV 71.[396] Despite potential for its use in neonates with enteroviral sepsis,[396] its use in enteroviral meningitis is debated, given that most patients with enteroviral meningitis recover quickly and with minimal sequelae. Furthermore, pleconaril has not achieved approval from the FDA because it induces CYP3A enzyme activity and has the potential for drug interactions, such that the sponsor did not pursue approval.

Recovery of patients with HSV-2 meningitis is usually complete without neurologic sequelae. It is not clear whether antiviral treatment alters the course of mild meningitis.[359,363] In one retrospective observational study, neurologic outcomes were significantly improved in immunocompromised patients with HSV meningitis who were treated with antiviral therapy, but not in immunocompetent patients, suggesting that immunocompromised patients with HSV meningitis may benefit from antiviral therapy[400]; however, more data are needed. A recent retrospective study showed that all patients with herpes simplex meningitis had good clinical outcomes irrespective of antiviral therapy.[19] It is also unclear whether treatment with prophylactic antiviral therapy is necessary in patients with recurrent HSV-2 meningitis. In one double-blind randomized controlled trial, patients with acute primary or recurrent HSV-2 meningitis were assigned to placebo or valacyclovir suppressive therapy after acute treatment with valacyclovir for 1 week; suppressive therapy was not shown to prohibit recurrent meningitis and was associated with a higher frequency of meningitis after cessation of active drug.[21] Therefore suppressive therapy cannot be currently recommended in patients with recurrent episodes of HSV-2 meningitis pending further study.

Bacterial Meningitis

Principles of Therapy

Many factors influence the choice of an antimicrobial agent in the treatment of bacterial meningitis. Use of animal models of infection has permitted quantification of the relative penetration of drug into CSF, the effects of meningitis on this entry parameter, and the relative bactericidal efficacy (defined as the rate of bacterial eradication) within purulent CSF.[290,401,402]

The first factor relates to penetration of the antimicrobial agent into CSF, which depends, to a great extent, on the status of the BBB.[290,401] For example, β-lactam antibiotics such as penicillin penetrate into CSF poorly (about 0.5%–2.0% of peak serum concentrations) when the BBB is normal. In the presence of meningeal inflammation, CSF penetration of the antibiotic is enhanced because of increased permeability across the BBB, perhaps as a result of separation of intercellular tight junctions and increased numbers of pinocytotic vesicles in cerebral microvascular endothelial cells. Antimicrobial entry decreases as inflammation subsides, indicating that maximal parenteral doses of antimicrobial agents should be continued throughout the course of therapy to maintain adequate CSF concentrations. Antibiotic entry into CSF is also enhanced by drugs with a high lipid solubility, low molecular weight, low degree of protein binding in serum, and low degree of ionization at physiologic pH.

The second factor is the bactericidal activity of the antimicrobial agent within purulent CSF.[290,401,402] Because of the accumulation of lactate in CSF during bacterial meningitis, the pH of CSF is decreased, thereby inhibiting the bactericidal activity of the aminoglycosides; this is likely to have contributed to the poor response observed with the aminoglycosides in the therapy of meningitis in experimental animal models and in patients. Elevated CSF protein concentrations may decrease the efficacy of antimicrobial agents that are highly protein bound because free drug is needed for the antibacterial effect. Drug that penetrates the CSF may be removed by an active transport system that exists in the choroid plexus (as for the penicillins and cephalosporins), or it may be converted to an inactive metabolite. In addition, other drugs may influence antibiotic activity within purulent CSF. In experimental animal models of meningitis, antagonism has been shown when a bactericidal agent is coadministered with a bacteriostatic antibiotic (e.g., chloramphenicol plus gentamicin). However, in other instances the combination of antibiotics may be synergistic, as in the combination of penicillin or ampicillin with gentamicin in *L. monocytogenes* meningitis and that of ampicillin plus gentamicin against *S. agalactiae*.

A third factor concerns the importance of bactericidal activity in CSF for optimal therapy inasmuch as bacterial meningitis represents an infection in an area of impaired host defense. Multiple studies in experimental animal models have shown that rapid bacterial killing is observed in vivo only when CSF concentrations of β-lactams or aminoglycosides exceed the minimal bactericidal concentration (MBC) by about 10- to 20-fold.[290,401] The importance of rapid bacterial killing has also been examined in patients with bacterial meningitis. One study that compared outcomes in infants and children with bacterial meningitis

who had negative or positive CSF cultures 18 to 36 hours after the initiation of antimicrobial therapy revealed an increased rate of neurologic complications (i.e., ataxia, hemiparesis, developmental delay, moderate-to-severe hearing impairment) in the group in which the causative organism could still be recovered after this interval.

A final factor that may contribute to response to antimicrobial therapy in bacterial meningitis is pharmacodynamics,[290,401–404] which is concerned with the time course of antimicrobial therapy at the site of infection and is important in determining a dosing regimen for optimal effectiveness. In time-dependent antimicrobial activity, as observed with β-lactam agents, the bactericidal activity of an antimicrobial agent depends on the time for which its concentration exceeds the MIC as a proportion of the dosing interval. As stated earlier, CSF concentrations of β-lactams need to exceed the MBC by at least 10- to 20-fold for the maximal bactericidal effect to be obtained, although peak CSF antimicrobial concentrations and the time for which the antimicrobial concentrations exceed the MBC are interrelated and time greater than MBC increased in parallel with peak CSF concentrations. This explains why the bactericidal effect did not improve with larger antimicrobial doses. The second pattern of antimicrobial activity is concentration dependent, and it is characterized by killing over a wide range of antimicrobial concentrations and a prolonged recovery period (i.e., postantibiotic effect) after drug concentrations fall below the MIC; this is seen with the aminoglycosides and fluoroquinolones. Although single-dose gentamicin therapy was as effective as divided-dosage regimens in an experimental animal model despite different times for which CSF gentamicin concentrations exceeded the MBC, the applicability of these findings to humans needs to be established. The pharmacodynamic characteristics of the fluoroquinolones are very similar to those of the aminoglycosides, although features of both time dependency and concentration dependency have been demonstrated with the fluoroquinolones in animal models of meningitis. There have also been investigations to determine whether continuous infusion of antimicrobial agents improves outcome in patients with bacterial meningitis. In a study of 723 African children with bacterial meningitis randomly assigned to receive boluses or continuous infusion of cefotaxime for the first 24 hours of therapy, 272 children died, but the mode of administration did not significantly change the proportion of children who died or were severely disabled at the time of hospital discharge[405]; however, in a planned subgroup analysis, children with pneumococcal meningitis given continuous cefotaxime infusion were significantly less likely to die or have sequelae.

Specific Antimicrobial Therapy

Haemophilus influenzae

Therapy for meningitis caused by *H. influenzae* type b has been markedly altered by the emergence of β-lactamase–producing strains.[290] Resistance of *H. influenzae* to chloramphenicol has also been described, although more commonly in areas such as Spain (>50% of isolates) than the United States (<1% of isolates). In Brazil, the prevalence of β-lactamase–producing strains of *H. influenzae* was 18.4% (range, 6.6%–57.7%), with almost 17% of strains also resistant to chloramphenicol.[406] Chloramphenicol resistance is of particular concern in developing countries of the world, where it is often used as first-line treatment for suspected bacterial meningitis.[290] In an observational study with a retrospective control group conducted in Papua New Guinea, where chloramphenicol was used as empirical treatment followed by ceftriaxone when in vitro resistance to chloramphenicol was found in *H. influenzae,* there was invariably a very poor outcome (i.e., death or severe neurologic sequelae) in patients with chloramphenicol-resistant disease (71% vs. 9% when chloramphenicol was used as first-line therapy).[407] Even in patients with chloramphenicol-sensitive isolates, a prospective study found chloramphenicol to be bacteriologically and clinically inferior to ampicillin, ceftriaxone, or cefotaxime in the treatment of childhood bacterial meningitis caused predominantly by *H. influenzae* type b.[408] Furthermore, the use of chloramphenicol can be problematic because of its unpredictable metabolism in young infants and its pharmacologic interactions with other concomitantly administered drugs, such as phenobarbital, rifampin, phenytoin, and acetaminophen, which increase the likelihood of toxicity.[189]

Several studies have documented the efficacy of third-generation cephalosporins (particularly cefotaxime or ceftriaxone) to be similar to that of the combination of ampicillin plus chloramphenicol for bacterial meningitis.[290] Based on these findings, the third-generation cephalosporins are recommended as empirical antimicrobial therapy for children with bacterial meningitis. The second-generation cephalosporins should not be used for therapy for bacterial meningitis. A prospective randomized study comparing ceftriaxone with cefuroxime for the treatment of childhood bacterial meningitis documented more rapid CSF sterilization (2% vs. 12% of CSF cultures positive at 18–36 hours, $P = .11$) and a lower incidence of hearing impairment (4% vs. 17%, $P = .05$) in the patients receiving ceftriaxone.[409] Cefepime has been studied in the treatment of bacterial meningitis.[410] Cefepime has in vitro activity and cure rates similar to those of cefotaxime and ceftriaxone in patients with meningitis caused by *H. influenzae, N. meningitidis,* and *S. pneumoniae*; it also has greater in vitro activity against *Enterobacter* species and *P. aeruginosa.* In a prospective randomized comparison of cefepime and cefotaxime for the treatment of bacterial meningitis in infants and children,[411] cefepime was found to be safe and therapeutically equivalent to cefotaxime and can be considered a suitable therapeutic alternative for the treatment of patients with this disease.

Neisseria meningitidis

Penicillin G and ampicillin are the antimicrobial agents of choice for meningitis caused by *N. meningitidis.*[290] However, these recommendations may need to be modified in the future because of trends in the antimicrobial susceptibility of meningococci. Meningococcal strains that are of intermediate susceptibility to penicillin G and have an MIC range of 0.1 to 1.0 μg/mL have been reported from several areas (particularly Spain). For example, of 3264 strains of *N. meningitidis* isolated from blood and CSF in Spain during 1978 to 1985,[412] only one resistant isolate was observed, whereas 9 (5%) of 168 invasive isolates of intermediate susceptibility to penicillin G were found in the first 6 months of 1986; this figure reached 20% in 1989. This decreased susceptibility was reported to be mediated by a reduced affinity of the antibiotic for penicillin-binding proteins 2 and 3. Decreased meningococcal susceptibility to penicillin has also been reported in Greece, Switzerland, Romania, France, Belgium, the United Kingdom, Malawi, South Africa, Canada, Croatia, and Turkey.[290,412–416] High-level penicillin resistance resulting from β-lactamase production has also been reported, and the MICs for these strains may be as high as 256 μg/mL.[416] Furthermore, high-level chloramphenicol resistance (MIC ≥64 μg/mL) has been described as resulting from the presence of the *catP* gene on a truncated transposon that has lost mobility because of internal deletions[417]; transmission of genetic material between strains of *N. meningitidis* probably played an important role in dissemination of the gene.

In the United States, meningococcal strains with reduced susceptibility to penicillin have also been described.[418–421] In a population-based surveillance study of invasive meningococcal disease in selected areas of the United States, 3 of 100 isolates had penicillin MICs of 0.125 μg/mL.[418] In another active, population-based surveillance in seven geographically dispersed areas of the United States during 1997,[421] 3 of 90 isolates were of intermediate susceptibility to penicillin, with MICs of 0.12 μg/mL, whereas 49 of the remaining 87 isolates had MICs of 0.06 μg/mL. In Ontario, Canada, the prevalence of invasive meningococcal disease caused by strains with decreased in vitro susceptibility to penicillin was much higher (21.7%) in 2006,[422] although it did not change in frequency between 2000 and 2006. These data indicate the importance of continued surveillance for these strains.

The clinical significance of these isolates is unclear at present because many patients with meningitis caused by these meningococci have recovered with standard penicillin therapy. However, isolated reports of treatment failure have been described.[423,424] Furthermore, in a study from Spain, reduced susceptibility of *N. meningitidis* to penicillin was seen in 34% of 213 children with meningococcal meningitis[425]; in this report, reduced penicillin susceptibility was more frequent in strains responsible for death or sequelae (60% vs. 32%, $P = .04$). On the basis of these data, some authorities would treat patients who have meningococcal meningitis with a third-generation cephalosporin (either cefotaxime or ceftriaxone), and these agents are likely to emerge as

first-line treatment in the future. Susceptibility testing of the isolate should be performed for patients who fail to respond appropriately.

Streptococcus pneumoniae

Therapy for meningitis caused by pneumococci has recently been modified according to current pneumococcal susceptibility patterns.[282,290,293] In the past, pneumococci were uniformly susceptible to penicillin, with MICs of 0.06 μg/mL or less. Numerous reports from throughout the world then documented strains of pneumococci that are of intermediate susceptibility to penicillin (MIC range, 0.1–1.0 μg/mL), and strains that were highly resistant to penicillin (MIC, 2.0 μg/mL or higher). The Clinical and Laboratory Standards Institute has redefined the in vitro susceptibility breakpoints for pneumococcal isolates from patients with meningitis as either susceptible or resistant, with intravenous penicillin breakpoints of 0.06 μg/mL or lower and 0.12 μg/mL or greater, respectively.[426] The mechanism of this resistance is an alteration in the structure and molecular size of penicillin-binding proteins. Resistance has been reported in several different pneumococcal serotypes, although the overwhelming majority of resistant strains are serotypes 6, 14, 19, and 23; most of the multidrug-resistant strains isolated in the United States disseminated from a multiresistant serotype 23F clone of *S. pneumoniae* that was isolated in Spain as early as 1978. In Brazil, penicillin resistance was mainly detected in isolates of serotypes 14 (61%), 23F (16%), 6B (10%), and 19F (3%).[427] Results of recent surveillance studies in the United States show that the prevalence of penicillin-nonsusceptible *S. pneumoniae* ranges from 25% to more than 50%[428]; rates are as high as 60% in some parts of Latin America and as high as 80% in some countries in Asia. Factors reported to predispose to resistance include the patient's age (<10 or >50 years), immunosuppression, prolonged hospital stay, children in daycare settings, infection by serotypes 14 and 23, and frequent, prolonged, or prophylactic use of antimicrobial therapy. However, penicillin-nonsusceptible strains have been isolated even when no risk factors or comorbidities are identified.[429]

Several alternative agents for the treatment of meningitis caused by penicillin-resistant pneumococci have been evaluated by in vitro susceptibility testing, in animal models, and in patients.[282,290,293] Here, we will restrict our discussion to agents that have been examined in clinical trials, unless animal model data have influenced treatment recommendations. Chloramphenicol is one agent that has been studied for the treatment of pneumococcal meningitis. However, clinical failures with chloramphenicol have been reported in patients with penicillin-resistant isolates, probably because of the poor bactericidal activity of chloramphenicol against these strains; 20 of 25 children had an unsatisfactory outcome (i.e., death, serious neurologic deficit, poor clinical response) in one study.[430] Despite susceptibility on disk testing, chloramphenicol MBCs of the penicillin-resistant pneumococcal isolates were significantly higher than those for the penicillin-sensitive isolates, with subsequent subtherapeutic bactericidal activity and treatment failure. Chloramphenicol resistance was also found in 27% of pneumococcal isolates in Malawi during 2004 to 2006[431] and in 43% of isolates in Papua New Guinea.[432]

Third-generation cephalosporins have been considered the treatment of choice in pneumococcal meningitis caused by strains that are of intermediate susceptibility to penicillin.[290,293] Cefotaxime and ceftriaxone are the third-generation agents of choice; ceftizoxime is not recommended because its MIC to resistant pneumococci tends to be higher than that of either cefotaxime or ceftriaxone. However, some reports of meningitis treatment failure with the third-generation cephalosporins have appeared, and pneumococcal strains have emerged that are resistant to these agents (MIC ≥2 μg/mL).). In 2011–2012, 8.9% of 1190 *S. pneumoniae* isolates from the United States were ceftriaxone resistant.[433] When the MIC to the third-generation cephalosporin is 1 μg/mL or less, some patients have been treated successfully with either high-dose cefotaxime or ceftriaxone alone, although one study found that high-dose cefotaxime did not have reliably sufficient CSF bactericidal activity against cephalosporin-resistant pneumococci.

Vancomycin has been evaluated in 11 adult patients with meningitis caused by pneumococcal strains that are of intermediate susceptibility to penicillin.[434] This therapy was associated with clinical failure in 4 patients; no failures occurred in 14 subsequent patients treated with ceftriaxone. In 2 of the patients in whom therapy failed, CSF vancomycin concentrations were undetectable at 48 hours, and in a third patient, symptoms recurred on the eighth day of antimicrobial therapy. The concomitant administration of dexamethasone and the subsequent decreased inflammation and poor entry of vancomycin into CSF may have contributed to this negative outcome; this explanation has been supported in an experimental rabbit model of pneumococcal meningitis. These data support the concept that vancomycin should not be used alone for the treatment of pneumococcal meningitis.[435] Of additional concern is the description of *S. pneumoniae* strains that are tolerant to vancomycin.[436,437] A vancomycin- and cephalosporin-tolerant strain of *S. pneumoniae* was isolated from the CSF of a patient with meningitis who then developed recrudescence of meningitis despite therapy with vancomycin plus a third-generation cephalosporin[438]; these data may have important implications in the use of vancomycin for pneumococcal meningitis. Appropriate CSF concentrations of vancomycin, however, may be attained even when patients are receiving adjunctive dexamethasone as long as appropriate dosages of vancomycin are used. In a study of 14 patients, intravenous administration of vancomycin (at a continuous infusion of 60 mg/kg/day, after a 15-mg/kg loading dose) led to mean serum and CSF vancomycin concentrations of 25.5 μg/mL and 7.9 μg/mL, respectively.[393] These data indicate that appropriate CSF concentrations can be attained when appropriate doses are used. Trough serum vancomycin concentrations of 15 to 20 μg/mL are recommended.[440]

In view of the aforementioned data, penicillin can never be recommended as empirical therapy in patients with suspected pneumococcal meningitis. As an empirical regimen, the combination of vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone) is recommended,[290,293,406,407] although UK and ESCMID guidelines recommend use of a third-generation cephalosporin alone in countries where the prevalence of cephalosporin-resistant pneumococcus is <1%.[53,287,441] The combination of vancomycin plus a third-generation cephalosporin was synergistic in a rabbit model of penicillin-resistant pneumococcal meningitis and was synergistic, or at least additive, in the CSF of children with meningitis. The addition of rifampin to vancomycin with or without a third-generation cephalosporin has been recommended by some authorities, although clinical data are lacking; rifampin should be added only if the organism is demonstrated to be susceptible, the expected clinical or bacteriologic response is delayed, or the pneumococcal isolate has a cefotaxime or ceftriaxone MIC greater than 4.0 μg/mL. However, in a retrospective study of 109 children with pneumococcal meningitis who received empirical vancomycin in combination with cefotaxime or ceftriaxone, patients with hearing loss had a significantly shorter median vancomycin start time than those with normal hearing (<1 hour vs. 4 hours).[442] In a multiple logistic regression analysis, hearing loss was independently associated with a vancomycin start time of 2 hours or less, suggesting that the first vancomycin dose should be given 2 hours or more after administration of the cephalosporin for suspected or confirmed bacterial pneumococcal meningitis, although more studies are needed. Any patient who is not improving as expected or who has a pneumococcal isolate for which the cefotaxime or ceftriaxone MIC is greater than 2.0 μg/mL should undergo a repeat lumbar puncture to document sterility of CSF after 36 to 48 hours of therapy; this may be especially important for patients who are receiving adjunctive dexamethasone therapy. In patients not responding, intrathecal or intraventricular vancomycin also remains a reasonable option.[293] Once susceptibility studies of the isolated pneumococcus are performed, antimicrobial therapy can be modified for optimal treatment (see Table 87.13).

With continued emergence of penicillin- and cephalosporin-resistant strains of *S. pneumoniae,* other antimicrobial agents have been evaluated for their efficacy in pneumococcal meningitis.[290,293] Meropenem, a carbapenem with a broad spectrum of in vitro activity, including activity against penicillin-resistant pneumococci, has been approved by the FDA for the treatment of bacterial meningitis in children 3 months and older. Meropenem has been studied for the treatment of meningitis in both adults and children in several clinical trials, with microbiologic and clinical outcomes similar to those with either cefotaxime or ceftriaxone. Meropenem was also used successfully in one patient with multidrug-resistant pneumococcal meningitis. In one prospective study of 258

children with bacterial meningitis, patients were randomly assigned to receive either meropenem or cefotaxime; there were no significant differences in outcome, with clinical cure (with or without sequelae) in 97% and 96% of patients treated with meropenem and cefotaxime, respectively.[443] However, in a study of 20 cefotaxime-resistant *S. pneumoniae* isolates,[444] 4 were of intermediate susceptibility and 13 were resistant to meropenem, suggesting that meropenem may not be a useful alternative agent for the treatment of pneumococcal isolates that are highly resistant to penicillin and cephalosporins.[293] Further studies are needed to determine the efficacy of meropenem in pneumococcal meningitis caused by penicillin- and cephalosporin-resistant strains, although isolated case reports have shown efficacy.

The fluoroquinolones have previously lacked sufficient in vitro activity against *S. pneumoniae* to warrant their investigation in the treatment of CNS infections. However, newer agents (moxifloxacin, gemifloxacin, gatifloxacin, garenoxacin) have shown excellent in vitro activity and have been evaluated in experimental animal models of infection.[293,445] Trovafloxacin has been compared with ceftriaxone with or without vancomycin in a multicenter, randomized, comparative trial enrolling 311 children from 11 countries; *S. pneumoniae* was isolated in 27% of cases.[445] The overall efficacy of both treatment groups was comparable in terms of CSF sterilization (94% in the trovafloxacin group and 96% in the comparator) and clinical success at the end of treatment (75% in the trovafloxacin group and 82% for the comparator). Although trovafloxacin is no longer used because of concerns about liver toxicity, these data suggest the potential usefulness of the newer fluoroquinolones in the treatment of bacterial meningitis. However, further clinical trials are needed before these agents can be recommended. Of concern are the reports of decreased pneumococcal susceptibility to the fluoroquinolones, the development of fluoroquinolone-resistant *S. pneumoniae* associated with levofloxacin therapy,[446] and the report of a case of fatal meningitis caused by a levofloxacin-resistant strain of *S. pneumoniae*[447]; these data highlight the need to monitor the in vitro susceptibility of pneumococci to these agents. Nevertheless, a combination regimen of a third-generation cephalosporin plus a newer-generation fluoroquinolone may emerge as the treatment option of choice for pneumococcal meningitis in the future.

Listeria monocytogenes

Despite their broad range of in vitro activity, third-generation cephalosporins are inactive in meningitis caused by *L. monocytogenes.* For patients with *Listeria* meningitis, therapy should consist of ampicillin or penicillin G[117–119,290,293]; the addition of an aminoglycoside should be considered in proven infection because of in vitro synergy and enhanced killing in vivo, as documented in a variety of animal models of *Listeria* infection. Nevertheless, it is important to emphasize that a controlled clinical trial comparing ampicillin alone with ampicillin plus gentamicin has never been performed in humans with listeriosis, although many authorities recommend the addition of an aminoglycoside to ampicillin for at least the first week of therapy for CNS infection.[119] In contrast, in a cohort of 118 patients with listeriosis, the aminoglycoside-treated group had increased rates of kidney injury and mortality.[448] In addition, in a retrospective review of patients with listeriosis (58% with primary bacteremia and 42% with meningitis), differences in mortality were not seen in those treated with ampicillin or with the combination of ampicillin and gentamicin.[449] In contrast, in a national prospective observational cohort study, those receiving amoxicillin-gentamicin combination therapy had an improved survival.[252] However, more data are needed.[450] An alternative agent in a penicillin-allergic patient is trimethoprim-sulfamethoxazole, which is bactericidal against *Listeria* in vitro. In one retrospective series, therapy with trimethoprim-sulfamethoxazole plus ampicillin was associated with a lower failure rate and fewer neurologic sequelae than the combination of ampicillin plus an aminoglycoside,[450] although more data are needed before this combination can be recommended. Oral therapy with trimethoprim-sulfamethoxazole has been used in some patients with *Listeria* meningitis and may be considered in those who demonstrate a rapid clinical response to intravenous therapy and in whom good adherence is expected.[451] Although chloramphenicol has varying activity against *Listeria* in vitro, its use has been associated with an unacceptably high failure rate in patients with *Listeria* meningitis. Vancomycin is also unsatisfactory for *Listeria* meningitis despite favorable in vitro susceptibility results. However, intraventricular administration of vancomycin was successful in one case of recurrent *L. monocytogenes* meningitis. Rifampin is bacteriostatic against *L. monocytogenes* in vitro and was no better than penicillin alone when evaluated in the experimental rabbit model of meningitis. Meropenem is active in vitro and in experimental animal models of *L. monocytogenes* meningitis and may be a useful alternative if found to be clinically efficacious. The fluoroquinolones and linezolid have also demonstrated good in vitro activity against *L. monocytogenes,* although there is limited clinical experience to recommend these agents in patients with *Listeria* meningitis.[449]

Streptococcus agalactiae

Standard therapy for neonatal meningitis caused by group B streptococci is the combination of ampicillin plus an aminoglycoside,[133] which is also recommended for adult patients with meningitis caused by this organism.[134] This combination is recommended because of documented in vitro synergy and reports detailing the presence of penicillin-tolerant strains. Alternative agents are the third-generation cephalosporins; vancomycin is reserved for patients who are allergic to penicillin.

Aerobic Gram-Negative Bacilli

Treatment of bacterial meningitis caused by aerobic gram-negative bacilli has been revolutionized by the availability of third-generation cephalosporins.[290,293] Previous mortality rates with standard regimens (usually an aminoglycoside with or without chloramphenicol) ranged from 40% to 90% versus cure rates of 78% to 94% with the third-generation cephalosporins. Cefotaxime is preferred over ceftriaxone as the third-generation cephalosporin for use in neonates because it has been used more extensively and is not excreted in bile, which may have an inhibitory effect on the bacterial flora of the intestinal tract.[290] Ceftriaxone also has increased protein binding. One particular third-generation cephalosporin, ceftazidime, has enhanced in vitro activity against *P. aeruginosa* and resulted in the cure of 19 of 24 patients in one study of *P. aeruginosa* meningitis when administered alone or in combination with an aminoglycoside.[452] In another study of 10 pediatric patients with *Pseudomonas* meningitis, 7 patients were cured clinically and 9 were cured bacteriologically when treated with ceftazidime-containing regimens.[453]

Concomitant intrathecal or intraventricular aminoglycoside therapy should be considered in patients with gram-negative meningitis who are not responding to conventional parenteral therapy. However, this mode of administration is rarely needed at present and was associated with a higher mortality rate than systemic therapy alone in infants with gram-negative meningitis and ventriculitis.[454]

Given the emergence of strains of gram-negative bacilli that are resistant to the third-generation cephalosporins,[420] the use of other intravenous agents, with or without intraventricular or intrathecal antimicrobials, may need to be considered, and several have been used in patients with meningitis caused by aerobic gram-negative bacilli.[290,293] Aztreonam attains excellent CSF concentrations and has been shown to be efficacious in the treatment of gram-negative meningitis. Imipenem was found to be efficacious in one case of *Acinetobacter* meningitis and in eradication of bacteria from CSF in a study of 21 children with bacterial meningitis (most cases caused by *H. influenzae* type b and *N. meningitidis*), although a high rate of seizure activity (33%) limits its usefulness in the treatment of bacterial meningitis. High-dose meropenem (2 g every 8 hours) given for 18 weeks was successful in a lymphoma patient with *P. aeruginosa* meningitis in whom therapy with ceftazidime plus gentamicin had failed, and in a patient with posttraumatic meningitis caused by *P. aeruginosa.* Cefepime was successful in a patient with postoperative meningitis caused by *Enterobacter aerogenes.*[455] Ceftazidime-avibactam plus intraventricular gentamicin was successfully used in a patient with carbapenem-resistant *Klebsiella pneumoniae* meningitis,[456] and the intravenous and intracerebroventricular administration of tigecycline was safe and effective in another case of multidrug-resistant *K. pneumoniae* meningitis.[457] For empirical treatment of *Acinetobacter* meningitis, intravenous use of meropenem, with or without an aminoglycoside administered through an intraventricular or intrathecal route, has been recommended[458]; if the organism is later found to be resistant to carbapenems, colistin (usually formulated as colistimethate sodium) or polymyxin B should

be substituted for meropenem and may also need to be administered through an intraventricular or intrathecal route.[459] Colistin (5 mg/kg/day as colistin base or 13.3 mg/kg/day as colistimethate) was successfully administered intravenously to treat a patient with meningitis caused by multidrug-resistant *Acinetobacter baumannii*[460]; it was also efficacious when given intrathecally in other cases of meningitis caused by this same multidrug-resistant organism,[461,462] and intrathecally administered polymyxin E has also been used in a patient with *Acinetobacter* meningitis.[463] In a summary of treatment of multidrug-resistant *A. baumannii,* a total of 14 patients were treated for CNS infection (ventriculitis or meningitis) with colistin given intravenously and/or either intrathecally or intraventricularly[464]; sterilization was achieved in all cases and cure was reported in 13 of 14 cases. In the presence of meningitis, CSF concentrations of colistin were shown to be 0.5 μg/mL (34%–67% of serum concentrations).[465] Two cases of *A. baumannii* meningitis were also successfully treated with tigecycline.[466] The fluoroquinolones (e.g., ciprofloxacin, pefloxacin) have been used successfully in some patients with gram-negative meningitis.[467] In one case series of 12 neonates and infants with nosocomial meningitis (in which 6 cases were attributed to gram-negative bacilli), 10 patients were cured and in 7 children no neurologic sequelae appeared after a 2- to 4-year follow-up.[468] Another patient who developed *P. aeruginosa* meningitis after a laminectomy was cured with the addition of high-dose ciprofloxacin (400 mg IV every 8 hours) to the previous regimen of ceftazidime and gentamicin,[469] and a preterm infant with *Stenotrophomonas maltophilia* meningitis was successfully treated with ciprofloxacin.[469] The limited published literature on use of the fluoroquinolones suggests that the primary area of usefulness of these agents is for the treatment of multidrug-resistant gram-negative organisms (e.g., *P. aeruginosa*) or when the response to conventional β-lactam therapy is slow (e.g., meningitis caused by *Salmonella* species).[290,293] Data are currently insufficient to recommend any fluoroquinolone for empirical therapy in any patient with community-acquired bacterial meningitis.

Staphylococci

S. aureus should be treated with nafcillin or oxacillin,[470,471] and vancomycin should be reserved for patients allergic to penicillin or when methicillin-resistant organisms are suspected or isolated. However, given the likelihood of MRSA in patients with *S. aureus* meningitis, vancomycin should be used as empirical therapy pending results of in vitro susceptibility testing.[471] The addition of rifampin or trimethoprim-sulfamethoxazole should be considered in patients not responding to therapy and if the organism is susceptible. Linezolid has been used successfully in some patients with MRSA CNS infections.[472,473] Daptomycin has been shown to have similar antibacterial activity to vancomycin in an experimental model of MRSA meningitis,[474] and daptomycin plus rifampin has been successfully used in patients with MRSA meningitis.[475–477] Ceftaroline has also been successfully used in two patients with MRSA meningitis,[478] one with a ventriculoperitoneal shunt infection[479] and the other with MRSA bacteremia and meningitis who was also treated with rifampicin during the initial 2 weeks of therapy.[480] Meningitis caused by coagulase-negative staphylococci, the most commonly encountered organisms in CSF shunt infections, should be treated with vancomycin; rifampin should be added if the patient fails to improve. Removal of the shunt is often necessary to optimize therapy (see Chapter 92). In one review of 14 cases, removal of the neurosurgical devices and intravenous vancomycin therapy led to survival in 12 of 14 patients.[481]

Other Bacteria

Salmonella meningitis should be treated with a third-generation cephalosporin, with or without a fluoroquinolone, because conventional antimicrobial agents (e.g., chloramphenicol, ampicillin, co-trimoxazole) have an unacceptable cure rate and relapse rate and high associated mortality[63]; the fluoroquinolones have a cure rate of approximately 89%, and the third-generation cephalosporins have a cure rate of about 85%. Ampicillin plus gentamicin should be used for enterococcal meningitis caused by susceptible strains; given its success in enterococcal endocarditis (see Chapter 80), the combination of ampicillin plus ceftriaxone may be a reasonable approach to therapy in patients with enterococcal meningitis. Vancomycin, or ampicillin-sulbactam, is substituted for ampicillin for β-lactamase–producing strains. In patients with meningitis caused by VRE, several case reports have shown successful treatment with intravenous linezolid[482,483]; given the failures associated with other alternative agents, use of linezolid is reasonable in meningitis caused by this multidrug-resistant organism. One patient with VRE meningitis was successfully treated with intravenously and intraventricularly administered chloramphenicol.[484] Other isolated case reports have demonstrated success with use of intraventricular administration of daptomycin combined with intravenous linezolid[485] and with intravenous combination daptomycin and gentamicin or linezolid.[486]

Duration of Therapy

The duration of therapy for bacterial meningitis has been based more on tradition than on scientific evidence.[290,293,407] The duration of antimicrobial therapy in patients with bacterial meningitis has been 10 to 14 days for cases of nonmeningococcal meningitis. Several studies comparing 7 with 10 days of treatment in infants and children with *H. influenzae* type b meningitis, however, have documented that 7 days of therapy is safe and effective, although therapy must be individualized and some patients may require longer courses. Meningococcal meningitis can be treated for 7 days with intravenous penicillin, and some authors have also suggested that 4 days of therapy is adequate; this study requires confirmation because only 50 patients were studied and no control group was included. A single dose, or even two to three doses, of long-acting penicillin or chloramphenicol has been used successfully in developing countries to treat meningococcal meningitis, although this therapy is not considered standard. In one randomized trial of 4 versus 7 days of ceftriaxone therapy in children with bacterial meningitis who had an initial rapid recovery, no significant differences in outcome were observed in the two groups at completion of therapy or at a follow-up of 1 to 3 months after discharge. In another trial, the clinical outcome of patients treated for 7 days with ceftriaxone was similar to 10-day therapy for acute bacterial meningitis in children in developing countries and was associated with a lower incidence of nosocomial infection and earlier hospital discharge. In a double-blind randomized trial of 5 or 10 days of therapy with ceftriaxone for bacterial meningitis in children beyond the neonatal period, it was determined that ceftriaxone could be discontinued in those patients who were stable after 5 days of treatment,[487] although the uncertainties around organism-specific data (especially for *S. pneumoniae*) and the need for clinical judgment at day 5 should lead to caution in reducing treatment duration.[488] In adults with meningitis caused by enteric gram-negative bacilli, treatment regimens should be continued for 3 weeks because of the high rate of relapse in patients treated with shorter courses of therapy. Ten to 14 days is recommended for the treatment of meningitis caused by *S. pneumoniae* and 14 to 21 days for group B streptococci. Patients with *L. monocytogenes* meningitis should be treated for at least 21 days.[53,290,293]

Outpatient antimicrobial therapy may also be appropriate for certain patients with bacterial meningitis. The following criteria have been suggested to guide outpatient antimicrobial therapy[290,293]: inpatient therapy for at least 6 days; no fever for at least 24 to 48 hours before initiation of outpatient therapy; no significant neurologic dysfunction, focal findings, or seizure activity; clinically stable or improving condition; intake of all fluids by mouth; first dose of outpatient antimicrobial therapy given under medical supervision and without reaction; access to home health nursing for antimicrobial administration; reliable intravenous line and infusion device, if needed; daily examination by a physician and an established plan for physician visits, nurse visits, laboratory monitoring, and emergencies; patient and/or family compliance with the program; and a safe environment with access to a telephone, utilities, food, and a refrigerator. In addition, completion of antimicrobial therapy in a skilled nursing facility may be appropriate for selected patients who need continued care but do not require acute hospitalization.

Spirochetal Meningitis

Treponema pallidum

In patients with syphilis with CSF abnormalities but without clinically apparent disease, the goals of therapy are to prevent progression to symptomatic disease and ameliorate the laboratory abnormalities believed to indicate disease activity.[489] For patients with clinical neurosyphilis

syndromes, the goal may be to reverse clinical symptoms and signs or to arrest disease progression. In patients with syphilitic meningitis whose clinical picture is that of meningeal inflammation as a result of the acute inflammatory response, clinical findings other than cranial nerve abnormalities usually resolve without therapy. In patients with meningovascular syphilis, the prognosis after therapy is quite good, except perhaps in patients with larger, clinically apparent neurologic deficits before therapy; therapy in this situation may halt progression and prevent further ischemic events caused by neurosyphilis.

The drug of choice for the treatment of neurosyphilis is penicillin G (see Table 87.13), although considerable controversy remains regarding the most appropriate total dose and the formulation and duration of therapy.[329] Therapy with benzathine penicillin (2.4 million units intramuscularly) does not reliably produce CSF penicillin concentrations above 0.018 μg/mL and should not be used for the treatment of neurosyphilis. Furthermore, in a small but poorly defined proportion of patients with syphilis treated with benzathine penicillin, therapy fails, defined as persistent CSF abnormalities with clinically apparent neurosyphilis. However, in many patients treated with benzathine penicillin, their CSF abnormalities resolve and their condition does not progress, which suggests that factors other than CSF concentrations of penicillin play a role in response to therapy.

The preferred antimicrobial regimen for the treatment of CNS syphilis is intravenous aqueous crystalline penicillin G at a dose of 18 to 24 million units daily in divided doses every 4 hours or by continuous infusion for 10 to 14 days.[329] Alternatively, procaine penicillin, 2.4 million units intramuscularly daily, plus probenecid, 500 mg orally four times daily, both for 10 to 14 days, can be used. Some experts also recommend follow-up therapy with one injection of benzathine penicillin G (2.4 million units intramuscularly once per week for 3 weeks), although no data support this recommendation. No large studies have been performed to evaluate alternative antimicrobial agents for neurosyphilis. On the basis of case reports, clinical experience, and extrapolations from experimental animal studies, the tetracyclines, chloramphenicol, and ceftriaxone have all been described to be of potential clinical usefulness in penicillin-allergic patients. One experimental study, however, suggested that ceftriaxone may not be adequate therapy for neurosyphilis.[490] Furthermore, a study of 43 HIV-infected patients with latent syphilis or neurosyphilis treated with ceftriaxone (1 or 2 g daily for 10–14 days) had a 23% failure rate,[459] similar to that seen in 13 HIV-infected patients with latent syphilis or neurosyphilis treated with benzathine penicillin (30%). Despite these concerns, ceftriaxone (2 g either intramuscularly or intravenously for 10–14 days) can be used as an alternative agent for treatment of neurosyphilis in patients allergic to penicillin.[491] In HIV-infected patients with neurosyphilis, careful monitoring for response to therapy is needed.[492] Follow-up lumbar puncture should be performed every 6 months in all patients until the CSF changes have normalized. However, a report demonstrated that in most patients with neurosyphilis, normalization of the serum RPR in patients treated for neurosyphilis correctly predicted the success of therapy and normalization of CSF parameters after treatment,[493] suggesting that repeat CSF analysis can be avoided. The accuracy is lower among HIV-infected patients not receiving ART than in those receiving ART. Several reports of failures in HIV-infected patients receiving standard therapy for neurosyphilis have appeared; these failures probably occurred because the patient's immunologic response has an important role in controlling the infection even in the presence of "adequate" antimicrobial therapy.

Borrelia burgdorferi

Parenteral antimicrobial therapy is usually needed to treat the neurologic manifestations of Lyme disease, including meningitis (see Table 87.13).[494,495] Initial studies used high-dose (15–20 million units daily) intravenous penicillin G for 10 to 14 days, although one author found the benefits limited to patients treated within 5 weeks of the onset of neurologic symptoms. The meningeal and systemic reactions tend to improve within days, whereas radicular pain and motor deficits improve over many weeks. CNS abnormalities are arrested by treatment and may slowly improve, but some residual deficit is common. Some patients have also responded to treatment with oral or intravenous administration of doxycycline, which has been found to be as efficacious as penicillin in several studies.[495] Patients who have not responded to intravenous penicillin have responded to intravenous therapy with cefotaxime, ceftriaxone, or chloramphenicol. In one prospective randomized trial, ceftriaxone was superior to penicillin in therapy for late Lyme borreliosis. The current recommendation is to treat most patients with Lyme meningitis with intravenously administered ceftriaxone at a dosage of 2 g daily for 14 days (range, 10–28 days)[494]; the literature contains no agreement on the duration of therapy or on the minimal adequate dose of the antimicrobial agent. No evidence supports treatment durations longer than 4 weeks. However, no regimen has proved to be universally effective. Although one report has indicated that high-dose oral doxycycline may produce inhibitory concentrations against *B. burgdorferi* in CSF, parenteral regimens are generally necessary for CNS infection. In contrast, in a randomized, double-blind trial including 118 patients with neuroborreliosis, use of a 2-week regimen of oral doxycycline was not inferior to parenteral ceftriaxone[495]; the patients in this trial generally had mild neurologic symptoms, suggesting that oral treatment with doxycycline might be sufficient in patients with mild symptoms.

Protozoal and Helminthic Meningitis

Amebas

Many antimicrobial agents, including amphotericin B, the tetracyclines, the imidazoles, artemisinin compounds, and rifampin, have in vitro activity against free-living amebas; phenothiazines are amebicidal only at high concentrations. Amphotericin B is rapidly amebicidal against *N. fowleri* in vitro, but it is much less active against *Acanthamoeba*. Rare patients have survived after therapy for PAM,[496–498] and all received amphotericin B along with various other antimicrobial agents. One documented survivor received amphotericin B and miconazole intravenously and intrathecally and rifampin, sulfisoxazole, and dexamethasone. Another received amphotericin B, rifampicin, and ornidazole. However, no clearly effective regimen has been established. An effective regimen used in recent cases has consisted of amphotericin B (intravenous and intrathecal administration), azithromycin, fluconazole, rifampin, and miltefosine, which is available from the CDC; the addition of dexamethasone, hyperosmolar therapy (with mannitol and 3% saline), moderate hyperventilation, and induced hypothermia was also used to aggressively treat cerebral edema and resulting increased intracranial pressure.[169] The addition of miltefosine has led to survival in some patients,[257,498–502] although failures have been reported.[502] Therapy is usually continued for 2 to 4 weeks if the clinical response is good and no complications occur.

Angiostrongylus cantonensis

Treatment of symptoms such as headache, nausea, and vomiting with analgesics and rehydration is indicated for eosinophilic meningitis caused by *A. cantonensis*.[175–179] Most patients recover within 1 to 2 weeks. Treatment with specific anthelmintic agents is controversial; exacerbation of neurologic symptoms after larval death is a theoretical complication of anthelmintic therapy. The benzimidazoles have been tried in humans without definite benefit. Thiabendazole cleared *A. cantonensis* from rats in one study, and it has been used in the early stages of migration of the larvae of *A. cantonensis,* but the drug fails as soon as the worm reaches the CNS. Clinicians in Taiwan routinely treat eosinophilic meningitis with anthelmintics[176]; agents used include mebendazole, levamisole, and albendazole. However, no randomized study of use of anthelmintic agents for eosinophilic meningitis has been reported, and there are insufficient data to recommend their use.[178]

ADJUNCTIVE THERAPY

Viral Meningitis

Adjunctive measures have been used in seriously ill patients with enteroviral meningitis. Because enteroviral clearance from the host is antibody mediated, exogenously administered antibody has been examined.[219,220] Administration of immune globulin through multiple routes (including directly into the CNS) has led to stabilization or improvement of agammaglobulinemic patients with chronic enteroviral meningitis or meningoencephalitis, but results have varied. Neonates with overwhelming enteroviral sepsis and meningitis have received intravenous immune globulin (IVIG), maternal plasma, and exchange

transfusions with occasional success. In a single randomized trial of IVIG plus standard therapy versus standard therapy alone in neonates suspected of having enteroviral infection during the first 2 weeks of life, IVIG failed to reduce viremia or lead to significant outcome differences, although the study enrolled too few patients for a definitive conclusion[220]; 75% of these patients had clinical or laboratory evidence of meningitis. IVIG has been routinely used for the treatment of disease caused by EV 71, although uncertainty remains as to whether this therapy is effective.[9]

Bacterial Meningitis

Despite the availability of effective bactericidal antimicrobial agents in the treatment of bacterial meningitis, morbidity and mortality from this disorder remain unacceptably high. The complexity of the management of bacterial meningitis, which includes a number of important complications, such as meningoencephalitis, systemic compromise, stroke, and raised intracranial pressure, has led to examination of various adjunctive strategies to improve outcome.[503] These have included antiinflammatory agents and methods to reduce increased intracranial pressure. Management in an intensive care unit (ICU) is recommended in patients with bacterial meningitis in order to recognize changes in the patient's consciousness, monitor for development of new neurologic signs, monitor for seizures, treat severe agitation, and manage complications (e.g., septic shock, hyponatremia, and increased intracranial pressure).[503] In one study of patients with pneumococcal meningitis, mortality was reduced to 5.5% (from 24% in a previous analysis), likely a result of routine use of adjunctive corticosteroids and other interventions performed in the ICU,[504] although the direct impact of a single intervention remains unclear.

Antiinflammatory Agents

Because the subarachnoid space inflammatory response is a major factor contributing to morbidity and mortality, investigators have examined whether attenuation of this response would improve outcome in bacterial meningitis. Adjunctive dexamethasone has been the agent most extensively studied in experimental animal models and in patients, and it should now be used in the initial approach to most patients with acute bacterial meningitis (see earlier section, "Initial Management of Patients With Acute Meningitis," for a description of experimental studies and clinical trials of adjunctive dexamethasone in bacterial meningitis).

Other agents that reduce subarachnoid space inflammation have also been examined as possible adjuncts in the treatment of bacterial meningitis. Pentoxifylline (a phosphodiesterase inhibitor that decreases endotoxin-induced TNF-α production, attenuates the inflammatory action of IL-1 and TNF on leukocyte function, and blocks the lipooligosaccharide–induced release of TNF and IL-1 from microglial cell cultures) has been examined in an experimental rabbit model of *H. influenzae* type b meningitis.[505] Administration of pentoxifylline 20 minutes before intracisternal challenge with *H. influenzae* type b lipooligosaccharide significantly reduced CSF concentrations of leukocytes, protein, and lactate. However, dexamethasone was superior to pentoxifylline in modulation of these CSF inflammatory changes, and no appreciable synergism was observed when both agents were administered. Thalidomide, which also inhibits TNF-α production, was studied in an experimental rabbit model of meningitis. Thalidomide reduced TNF-α production after intracisternal challenge with either *H. influenzae* type b or *S. pneumoniae,* although it had a relatively greater effect on the inflammatory response to *S. pneumoniae.*[506] Adjunctive treatment with a C5-specific monoclonal antibody (C5-Ab) was studied in an experimental pneumococcal mouse model. Neutralization experiments showed that adjunctive treatment with C5-Ab improved outcome in mice with pneumococcal meningitis. The observed effect of C5-Ab was superior to that of adjunctive dexamethasone.[503]

Other studies have examined the effects of a monoclonal antibody (IB4) directed against the CD18 family of receptors on leukocytes to reduce CSF inflammation. Intravenous inoculation of IB4 blocked the accumulation of leukocytes in CSF despite intracisternal challenge with *H. influenzae* type b, *N. meningitidis,* pneumococcal cell wall, or lipooligosaccharide.[507] Furthermore, the monoclonal antibody was effective in preventing the development of cerebral edema and death in animals challenged with lethal doses of *S. pneumoniae.* In a study using an experimental rabbit model of *H. influenzae* type b meningitis,[508] the concomitant administration of dexamethasone and IB4 led to a marked attenuation of all indices of meningeal inflammation and a reduction in brain water content when compared with the results obtained in untreated animals or when each agent was used alone.

Bactericidal/permeability-increasing protein, which is present in the azurophilic granules of neutrophils and binds to and neutralizes the biologic activity of the lipid A portion of lipooligosaccharide, has also been studied for its effects on CSF inflammation in bacterial meningitis. In an experimental rabbit model, the intracisternal inoculation of recombinant bactericidal/permeability-increasing protein significantly reduced CSF inflammation in response to meningococcal endotoxin.[509] This effect was not seen after systemic administration, probably because of failure of this protein to cross the BBB.

Although experimental results with these agents have shown a benefit in reduction of CSF inflammation in animals with bacterial meningitis, none has been studied in clinical trials. The main goal for new therapies will be based on studies that assess attenuation of the inflammatory response and studies of other agents that regulate damage mediated by reactive oxygen species and reactive nitrogen species, caspase inhibition, complement system activation, vascular integrity, or release of danger-associated molecular patterns that sustain the immune reaction and drive forward brain damage even after CSF sterilization[510–512] Pending randomized clinical trials of these therapies, likely in combination with antimicrobial therapy and dexamethasone, their use in patients cannot be recommended at present.

Another promising strategy has been to use nonbacteriolytic antibiotics to attenuate the inflammatory response generated after antimicrobial-induced lysis. In a pilot study in children (3 months to 12 years of age) with bacterial meningitis, patients were randomly assigned to receive one dose of rifampin 30 minutes before administration of ceftriaxone compared with use of ceftriaxone alone.[511] Children in the rifampin pretreatment group had significantly lower CSF concentrations of TNF-α, S100B, and neuron specific enolase; rifampin-pretreated patients also had reduced morbidity and neurologic sequelae, although the differences were not statistically significant. However, given the small and heterogeneous nature of these groups, more data are needed.

Reduction of Intracranial Pressure

For patients with bacterial meningitis who have signs of increased intracranial pressure (e.g., altered level of consciousness; dilated, poorly reactive, or nonreactive pupils; ocular movement disorders) and who are stuporous or comatose, it has been suggested that intracranial pressure–guided treatment could be beneficial.[513] However, it is unclear which patients may benefit from such an approach, and interventions to decrease the intracranial pressure may be harmful as well. A study in 1412 episodes of bacterial meningitis showed that half of the patients had a very CSF high openings pressure at the lumbar puncture (>40 cm H_2O/>29 mm Hg), of whom the majority had a favorable outcome.[60] Studies advocating reduction in intracranial pressure have advised to reduce the pressure below 20 mm Hg. In one study of 15 patients with bacterial meningitis in whom intracranial pressure was measured,[514] intracranial pressure was successfully lowered in most patients by a broad range of measures and using unconventional volume-targeted ("Lund concept") intracranial pressure management, which consisted of sedation, corticosteroids, normal fluid and electrolyte homeostasis, blood transfusion, albumin infusion, decrease of mean arterial pressure, treatment with a prostacyclin analogue, and eventually thiopental, ventriculostomy, and dihydroergotamine. In nonsurvivors, mean intracranial pressure was significantly higher and cerebral perfusion pressure was markedly lower than in survivors despite treatment; however, this was not a comparative study and the results should be interpreted with caution.

Several methods are available to reduce intracranial pressure,[290,513] including elevation of the head of the bed to 30 degrees to maximize venous drainage with minimal compromise of cerebral perfusion; hyperventilation to maintain the $Paco_2$ between 27 and 30 mm Hg, which causes cerebral vasoconstriction and a reduction in cerebral blood volume; use of hyperosmolar agents (e.g., mannitol) to make the intravascular space hyperosmolar to the brain and permit movement

of water from brain tissue into the intravascular compartment; and corticosteroids. However, some experts have questioned the routine use of hyperventilation to reduce intracranial pressure in patients with bacterial meningitis. In infants and children with bacterial meningitis who have initially normal CT scans of the head, hyperventilation can safely reduce elevated intracranial pressure because it is unlikely that cerebral blood flow would be reduced to ischemic thresholds. However, in children with cerebral edema evident on head CT, cerebral blood flow is more likely to be normal or reduced. Although hyperventilation might decrease intracranial pressure, it would do so at the cost of a significant reduction in cerebral blood flow, possibly approaching ischemic thresholds. These patients may benefit more from the early use of diuretics, osmotically dehydrating agents (provided that intravascular volume is protected), and corticosteroids; however, controlled trials exploring these issues have yet to be performed.

Glycerol, an osmotic dehydrating agent that can be given orally, has been evaluated in a trial of 122 infants and children with bacterial meningitis.[515] Patients in this study were randomized to receive adjunctive intravenous dexamethasone, oral glycerol, dexamethasone plus glycerol, or neither. Seven percent of the glycerol-treated patients and 19% of those not given glycerol had audiologic or neurologic sequelae (P = .052). A more recent clinical trial suggested that oral glycerol (6 g/kg/day in four divided doses) prevented severe neurologic sequelae in children with bacterial meningitis,[516] although methodologic questions have been raised about this study.[517] In a study of 383 children with bacterial meningitis randomly assigned to receive dexamethasone, dexamethasone plus glycerol, glycerol, or placebo, neither dexamethasone nor glycerol prevented hearing loss[518]; presenting status and young age were the factors that predicted hearing impairment. In addition, a randomized controlled trial of 265 Malawian adults with bacterial meningitis showed that adjuvant glycerol was harmful and increased mortality[519]; therefore adjunctive glycerol cannot be recommended in adults with bacterial meningitis in resource-poor settings with a high HIV prevalence.[520] Further placebo-controlled, blinded studies are required before glycerol can be routinely recommended in patients with bacterial meningitis.

Induced hypothermia, used for treatment of cerebral hypoxemia after cardiac arrest and in animal models, has also been shown to reduce intracranial hypertension in meningitis.[488] Despite some observational studies showing benefit, a randomized controlled trial was stopped early because of an increased risk of death in patients in the intervention group.[521]

Patients who continue to have elevated intracranial pressures despite the aforementioned measures may be treated with high-dose barbiturate therapy,[290,522] which decreases cerebral metabolic demands and cerebral blood flow. Barbiturates can also cause vasoconstriction in normal tissue, thereby shunting blood to ischemic tissue and protecting the brain from ischemic insult. During the administration of pentobarbital, the patient is monitored to measure decreases in intracranial pressure or the dose can be titrated to the development of a burst suppression pattern on the EEG. Cardiac parameters also need to be monitored (by placement of a Swan-Ganz catheter) because of the risk for cardiac toxicity (e.g., decreased cardiac output, decreased contractile force, arrhythmias) with high-dose barbiturate therapy. This mode of treatment of meningitis and elevated intracranial pressure is of unproven benefit, however, and must be considered experimental.

In patients who develop hydrocephalus, repeated lumbar punctures or placement of a lumbar drain can reduce intracranial pressure,[523] although invasive procedures should be withheld in patients with mild enlargement of the ventricular system and without clinical deterioration.

Surgery

Surgical intervention may be required in some patients with bacterial meningitis. Patients who have sustained a basilar skull fracture with CSF leak may have persistent dural defects that can lead to recurrent episodes of bacterial meningitis.[20] Many leaks will cease spontaneously, but surgery is indicated for leaks that persist for several weeks or in patients who present with delayed or recurrent infection. Surgery is not indicated in the acute phase (before 7 days) of leakage[70]; no difference in outcome is seen when patients with acutely repaired leaks are compared with those whose leaks stop spontaneously within 7 days. Surgical intervention may also be required in patients in whom recurrent meningitis develops from congenital or acquired cranial defects and dermal sinuses.

Helminthic Meningitis

In seriously ill patients with *A. cantonensis* meningitis, the major treatment objective is control of intracranial pressure; repeated lumbar punctures can produce dramatic, although transient, clinical improvement.[523–527] Anecdotal case series have shown benefits of corticosteroids, although one large observational study in Thailand concluded that prednisone was not effective. However, in another placebo-controlled study from Thailand, a 2-week course of prednisolone (60 mg/day) was effective and safe in patients with eosinophilic meningitis (most cases presumptively caused by *A. cantonensis*).[524] Those patients who received corticosteroids demonstrated improved rates of headache resolution, a more rapid improvement in symptoms, and less need for repeat lumbar punctures. A Cochrane Database systematic review concluded that corticosteroids did significantly help relieve headache in patients with eosinophilic meningitis.[525] Although the role of anthelmintic therapy is controversial, some studies have evaluated combined therapy with corticosteroids and anthelmintics (albendazole and mebendazole) and have suggested a potential benefit.[526,527] More studies are needed.

PREVENTION

Bacterial Meningitis

Haemophilus influenzae

Chemoprophylaxis

It has become clear that the spread of several types of bacterial meningitis can be prevented with prophylaxis of contacts of cases with antimicrobial agents. Several studies have documented the transmission of *H. influenzae* type b from patients with meningitis to household contacts.[290] The risk is markedly age dependent, highest for children younger than 2 years. Most secondary cases (75%) occur within 6 days of onset of the index case, although untreated household contacts remain at increased risk for *H. influenzae* type b disease for at least 1 month after onset in the index patient. Daycare outside the home is considered another risk factor for transmission.[528] Secondary disease is more likely to develop in children younger than 2 years. Controversy regarding the magnitude of the risk to children in daycare settings, however, has led to disagreement concerning the recommendation for chemoprophylaxis of children in these facilities.

The rationale for the use of chemoprophylaxis for prevention of secondary disease is eradication of nasopharyngeal colonization of *H. influenzae* type b, thereby preventing transmission to young, susceptible contacts and the development of invasive disease in those already colonized. The recommended chemoprophylactic agent of choice is rifampin (20 mg/kg, maximum 600 mg, daily for 4 days) for all individuals, including adults, in households with at least one unvaccinated or incompletely vaccinated child younger than 48 months (see Chapter 225).[290] One study suggested that 2 days of rifampin therapy was as efficacious as 4 days of treatment, although further study is required before a recommendation to shorten the duration of prophylaxis can be made. The index patient may also need to receive rifampin prophylaxis. Ampicillin and chloramphenicol, unlike ceftriaxone and cefotaxime, do not effectively eliminate nasopharyngeal colonization. Rifampin is not recommended for pregnant women who are contacts of infected infants, because the risk of rifampin to the fetus has not been established. Chemoprophylaxis is not currently recommended for daycare contacts 2 years old or older unless two or more cases occur in the daycare center within a 60-day period. For children younger than 2 years, the CDC recommends prophylaxis for daycare contacts whereas the American Academy of Pediatrics does not in most cases. The question of whether to administer prophylaxis in this setting needs to be individualized and should be considered more strongly in daycare centers that resemble households, where children have prolonged contact.

Neisseria meningitidis

Chemoprophylaxis

Chemoprophylaxis is also necessary for close contacts of patients with invasive meningococcal disease[290]; up to 10% of patients with

meningococcal meningitis have had contact with an individual with another known case. The definition of "close contact" has not been clearly elucidated but generally refers to persons who have had prolonged (≥8 hours) contact while in close proximity (≤3 feet) to the patient or who have been directly exposed to the patient's oral secretions (e.g., through kissing, mouth-to-mouth resuscitation, endotracheal intubation, or endotracheal tube management) within 1 week before the onset of the patient's symptoms until 24 hours after initiation of appropriate antimicrobial therapy.[528,529] The estimated prevalence of meningococcal carriage in the United States is 5% to 10% under nonepidemic conditions. In closed populations such as military recruits, carriage rates can reach levels of 40% to 90%. Carriage may last for a long time (at least months) in about 25% of carriers, is intermittent in one-third, and is transient or infrequent in the remaining 40%.[528,529] Household contacts exposed to an individual with meningococcal disease have a 500- to 800-fold increased risk for invasive disease.[290] College students, especially those living in dormitories, are at moderately increased risk for meningococcal disease compared with other persons of their age.[530] Secondary systemic meningococcal disease often develops within 5 days of recognition of the index case, with 70% to 80% of secondary cases occurring within 14 days of the primary case; in one report, 9 of 17 (53%) secondary cases occurred 5 to 39 weeks after the primary case. Transmission of *N. meningitidis* has also been documented in a campus bar, a dance club, and a sports club.

Chemoprophylaxis is recommended for close contacts of the index patient, defined as household contacts, daycare center members, and anyone directly exposed to the patient's oral secretions; chemoprophylaxis should also be administered to close contacts who have received vaccination with the meningococcal conjugate vaccine (see later discussion), because the vaccine does not confer protection against all meningococcal serogroups.[86] Meta-analysis of data from high-resource settings has shown that prophylaxis of household contacts was associated with an 84% reduction in the risk of meningitis.[530] For travelers, chemoprophylaxis should be considered for any passenger who had direct contact with respiratory secretions from an index patient or anyone seated directly next to an index patient in a prolonged flight (lasting 8 hours or longer). Chemoprophylaxis is not recommended for school, work, or transportation contacts. Chemoprophylaxis may also need to be administered to the index patient before hospital discharge because certain antimicrobial agents (e.g., high-dose penicillin or chloramphenicol) do not reliably eradicate meningococci from the nasopharynx of colonized patients. Chemoprophylaxis should be administered as soon as possible (ideally within 24 hours) after the case is identified; administration 14 or more days after the onset of illness in the index patient is probably of limited value.

The optimal chemoprophylactic agent to prevent invasive meningococcal disease is controversial.[290] The CDC currently recommends the administration of rifampin, ciprofloxacin, or ceftriaxone, which are all 90% to 95% effective at eradicating nasopharyngeal carriage.[86] Rifampin is given at 12-hour intervals for 2 days in the following doses: adults, 600 mg; children 1 month or older, 10 mg/kg; and infants younger than 1 month, 5 mg/kg. However, rifampin has several shortcomings, including adverse events, necessity for multiple doses over a 2-day period, and emergence of resistant organisms (up to 10%–27% of isolates), which may then cause invasive disease. In the search for alternative agents, ceftriaxone (250 mg IV in adults and 125 mg IV in children) eliminated the serogroup A carrier state in 97% of patients in one study for up to 2 weeks, although parenteral administration is required. Additional studies have demonstrated a single oral dose of ciprofloxacin (500 mg in adults) to be very effective in elimination of the nasopharyngeal carriage of *N. meningitidis*. Ciprofloxacin concentrations in nasal secretions have been shown to exceed the MIC_{90} for meningococci. Ciprofloxacin may well supplant rifampin for chemoprophylaxis in adults. Ciprofloxacin is not recommended for use in children because of concern regarding cartilage damage. However, three cases of ciprofloxacin-resistant *N. meningitidis* have been reported in North Dakota and Minnesota, leading the CDC to no longer recommend ciprofloxacin for meningococcal chemoprophylaxis in selected counties of these states.[531] Decreased in vitro susceptibility to fluoroquinolones has also been reported in South Africa,[532] indicating the necessity for continued surveillance. In pregnant patients, ceftriaxone is probably the safest alternative agent for chemoprophylaxis. Azithromycin (500 mg orally once) was also shown to be as effective as a four-dose regimen of rifampin in the eradication of meningococci from the nasopharynx.[533] Azithromycin is safe, easy to administer, and also available in a suspension form, but further evaluation is needed. Widespread chemoprophylaxis to low-risk contacts should be discouraged because of the concern over emergence of resistant organisms and possible future limitations on this approach.

Streptococcus pneumoniae

Chemoprophylaxis

The risk for secondary pneumococcal disease in contacts of infected patients has not been defined, although outbreaks have been described in closed populations such as gold miners, military recruits, and jail inmates.[290] In one outbreak in a daycare center,[534] treatment of 97% of the daycare center children and staff with rifampin (10 mg/kg twice daily for 2 days) resulted in a 70% reduction (i.e., only partial eradication) of positive nasopharyngeal cultures for *S. pneumoniae* but did not prevent new acquisition of this organism by three children and one family member. Further studies are needed before chemoprophylaxis is recommended for contacts of patients with pneumococcal meningitis. Some authors do recommend prophylaxis with oral penicillin in patients with sickle cell disease; therapy in such patients has been shown to reduce the incidence of pneumococcal bacteremia by 84%.[290]

Streptococcus agalactiae

Chemoprophylaxis

Administration of ampicillin during labor to mothers with prenatal vaginal or rectal group B streptococcal colonization and obstetric risk factors (e.g., premature labor, prolonged rupture of membranes, or intrapartum fever) has been associated with reduced rates of colonization and early-onset streptococcal sepsis in the neonate.[535] The CDC has established guidelines for the prevention of group B streptococcal infection by chemoprophylaxis.[536] Indications are a previous infant with invasive group B streptococcal disease, group B streptococcus bacteriuria during any trimester of the current pregnancy (unless a cesarean delivery is performed before onset of labor in a woman with intact amniotic membranes), or positive group B streptococcus vaginal-rectal screening culture in late gestation (optimally at 35–37 weeks' gestation). If the group B streptococcus status at the onset of labor is unknown, intrapartum antimicrobial prophylaxis should be administered for delivery at less than 37 weeks' gestation, amniotic membrane rupture greater than or equal to 18 hours, intrapartum temperature greater than or equal to 38.0°C (100.4°F), or an intrapartum nucleic acid amplification test positive for group B streptococcus. Chemoprophylaxis should consist of intrapartum intravenous penicillin G (5 million units initially, and then 2.5–3 million units every 4 hours) or alternatively intravenous ampicillin (2 g initially, and then 1–2 g every 4 hours) until delivery. Intravenous cefazolin can be used in patients with penicillin allergy, although intravenous clindamycin should be used in those with severe penicillin allergy (i.e., anaphylaxis, angioedema, respiratory distress, or urticaria) when the isolate is susceptible to clindamycin and erythromycin; if the isolate is not susceptible to clindamycin and erythromycin, vancomycin is recommended.

Basilar Skull Fracture

A number of studies have used prophylactic antibiotics in patients with basilar skull fractures and CSF leak on the premise that in patients with a dural defect the CSF is exposed to pathogenic organisms from the nasopharynx, nasal or mastoid sinuses, or external auditory canal.[537,538] Interpretation and comparison of the various studies examining this question are confounded by multiple variables, including patient selection, choice of antimicrobial agents, and definition of infection. No prospective controlled trials have examined the efficacy of prophylactic antimicrobial agents in these patients, although a meta-analysis suggested that antibiotic prophylaxis did not prevent meningitis in patients with basilar skull fracture.[537] These data have also been analyzed in a Cochrane Database systematic review[538] in which prophylactic antibiotic use in patients with basilar skull fracture, whether or not there was evidence of CSF leak, was not supported. However, published studies have biases and

randomized controlled trials are needed. Antibiotic use does not appear to change the incidence of posttraumatic bacterial meningitis and may result in the selection and growth of resistant organisms.

Haemophilus influenzae

Immunoprophylaxis

Vaccination to prevent infection with specific meningeal pathogens is a very useful measure for decreasing the incidence of bacterial meningitis. For *H. influenzae* type b, the availability of conjugate vaccines has decreased the number of cases of *H. influenzae* type b meningitis more than 90% in recent years.[41,62,63] Three *H. influenzae* type b conjugate vaccines are now licensed for infant immunization. The Advisory Committee on Immunization Practices (ACIP) has recommended vaccine doses at 2, 4, and 6 months of age[539]; if PRP-OMP (PedvaxHIB; Merck & Co., Whitehouse Station, NJ) is administered at 2 and 4 months, a dose at 6 months is not required. A booster dose of vaccine is also administered at 12 to 15 months of age, no matter which vaccine was administered for the primary series. In addition to preventing invasive disease caused by *H. influenzae* type b, conjugate vaccines are effective in reducing nasopharyngeal colonization and therefore may confer protection to populations not targeted for immunization through herd immunity. However, this reduction may open ecologic niches for non–type b strains of *H. influenzae.* In a surveillance study conducted in Brazil before and after the introduction of *H. influenzae* type b conjugate vaccine immunization, the incidence of *H. influenzae* type b meningitis decreased by 69%, but the incidence of *H. influenzae* type a meningitis increased eightfold,[540] highlighting the importance of maintaining surveillance to monitor potential increases in disease due to serotype replacement. Of additional concern is the report of cases of invasive *H. influenzae* type b disease in children previously vaccinated against this disease in Nottingham, United Kingdom.[541] There are several possible reasons for this increase, most notably that the vaccination schedule used in the United Kingdom is to vaccinate at 2, 3, and 4 months of age; the absence of a booster dose may have led to this increase in invasive disease.[542] In the developing world, declining rates of *H. influenzae* type b meningitis have also been reported since introduction of the *H. influenzae* type b conjugate vaccines,[543] with effectiveness of 88% to 94%.[544–546]

Neisseria meningitidis

Immunoprophylaxis

On the basis of the success of conjugate *H. influenzae* type b conjugate vaccines (see earlier discussion), conjugate vaccines for use against disease caused by serogroups A and C meningococci have been developed. The United Kingdom became the world's first country to implement vaccination with a monovalent serogroup C conjugate meningococcal vaccine, in which children are vaccinated at 2, 3, and 4 months of age.[547] The efficacy of the meningococcal serogroup C conjugate vaccine in adolescents and toddlers was evaluated after the first 9 months after vaccine introduction in a catch-up program in which toddlers and adolescents received a single dose of CRM_{197}-meningococcal C vaccine.[548] The short-term vaccine efficacies in toddlers and adolescents were 92% and 97%, respectively. In an update of the epidemiologic effect of the first 18 months of the UK meningococcal C conjugate vaccine program, the overall reduction of cases of serogroup C disease from 1998–1999 to 2000–2001 was 81%,[549] with some variability based on age group. In another case-control study in teenagers in the United Kingdom to assess vaccine efficacy, the protective effectiveness of the vaccine was 93%.[550] Furthermore, carriage of meningococci was reduced by 66% in students aged 15 to 17 years,[551] demonstrating that meningococcal C conjugate vaccines protect against carriage of meningococci that express serogroup C polysaccharide capsules. Although concerns have been raised that use of the serogroup C meningococcal conjugate vaccine would result in an increase in meningococcal disease caused by non–serogroup C isolates, this has not been realized.[552] The reduction in serogroup C carriage lasted for at least 2 years in one multicenter survey of carriage since vaccine introduction, also with no evidence of serogroup replacement.[553]

The first meningococcal conjugate vaccine (meningococcal polysaccharide–diphtheria toxoid conjugate vaccine containing serogroups A, C, W, and Y polysaccharides) was licensed for use in the United States in January 2005 for routine administration, starting at age 11 to 12 years with catch-up vaccination for 15-year-old adolescents and those entering high school.[554] These recommendations were later revised to include routine vaccination of all persons aged 11 to 18 years with one dose.[555] In updated guidelines, a booster dose is now recommended at age 16 years, and a two-dose primary series is administered 2 months apart for persons aged 2 through 54 years with persistent complement component deficiency or functional or anatomic asplenia and for adolescents with HIV infection[556]; other persons at risk for meningococcal disease (e.g., microbiologists or travelers to an epidemic or highly endemic country) should receive a single dose. A two-dose primary series is also recommended for any child 9 to 23 months of age at increased risk for invasive meningococcal disease.[557] In adolescents, protective antibodies will likely persist as long as and probably longer than after administration of the meningococcal polysaccharide vaccine.[558,559] The vaccine may also provide herd immunity by decreasing nasopharyngeal colonization.[560] Immunization of infants with a novel tetravalent CRM_{197}-conjugated meningococcal vaccine was well tolerated and immunogenic,[558] suggesting its usefulness in this patient population.

After decades of research toward this end, two vaccines for the prevention of meningococcal serogroup B disease were recently approved for use in the United States.[529,561–564] The first of these, Trumenba (Pfizer, New York, NY), was approved for use in 2014 for individuals aged 10 through 25 years, administered in three intramuscular injections on a 0-, 2-, and 6-month schedule. The second, Bexsero (Novartis, New York, NY), approved in 2015 also for persons aged 10 through 25 years, is administered in two intramuscular injections at least 1 month apart. Both are associated with high rates of local and systemic adverse reactions (i.e., injection site pain, myalgias, fatigue, and headaches). The multicomponent meningococcal B vaccine has been shown to achieve satisfactory immune response in children and adolescents within 30 days of vaccination.[566] The ACIP recommendation is that adolescents and young adults, ages 16 to 23 years, *may* be vaccinated for short-term protection against most strains of *N. meningitidis* serogroup B (Category B) but that the risk of that infection in the United States is currently low (see Chapter 211 for more information).[566]

Streptococcus pneumoniae

Immunoprophylaxis

Use of the current 23-valent pneumococcal vaccine in the prevention of pneumococcal meningitis has never been proved, although it may be assumed that the overall efficacy of the vaccine is about 50% against pneumococcal meningitis (with a wide 95% confidence interval [CI]); in addition, no data have proved efficacy in infants and very young children.[189] One study examined the efficacy of a heptavalent conjugate pneumococcal vaccine in 37,868 infants and children and demonstrated an efficacy of 97.4% in the prevention of invasive pneumococcal disease in fully vaccinated children,[567] leading to the recommendation to vaccinate all infants younger than 2 years of age with the currently licensed heptavalent pneumococcal conjugate vaccine (Prevnar; Wyeth Pharmaceuticals, Philadelphia, PA)[568]; the vaccine is administered in four doses at 2, 4, 6, and 12 to 15 months of age.[569] In a study conducted in Israel, administration of a 9-valent pneumococcal conjugate vaccine to toddlers attending daycare centers led to a reduction in nasopharyngeal carriage of *S. pneumoniae,*[569] suggesting that widespread vaccination may result in marked herd immunity. In a study of population-based data from the Active Bacterial Core surveillance system of the CDC on trends in the rate of invasive pneumococcal disease after licensure of the heptavalent pneumococcal vaccine, there was a decline in the rate of invasive pneumococcal disease, with the largest decline (69%) in children younger than 2 years.[571] Disease also fell in adults (32% lower for those 20–39 years of age, 8% lower for those 40–64 years of age, and 18% lower for those 65 years and older) and in persons with invasive disease caused by pneumococcal strains that were not susceptible to penicillin (35% reduction). These findings were verified in other studies that reported a decrease in the incidence of invasive pneumococcal disease[572–574]; the rate of antimicrobial resistant pneumococcus decreased with use of the conjugate vaccine. Significant decreases in the case-fatality and mortality rates for invasive pneumococcal disease have also been

reported.[575] However, questions have arisen regarding an increase in disease caused by serotypes not in the vaccine and the fact that vaccine efficacy has not yet been studied in the developing world.[576] Since the introduction of the pneumococcal conjugate vaccine in the United States, pneumococcal meningitis rates have decreased by 33% from 0.8 to 0.55 cases per 100,000 population, with the decrease greatest in children younger than 5 years[577]; hospitalization for pneumococcal meningitis has also decreased in both children and adults. Declines in the incidence of pneumococcal meningitis have been reported in Spain without evidence of an increase in disease caused by serotype replacement.[578] However, since introduction of the heptavalent pneumococcal conjugate vaccine, there has been an emergence in cases of invasive pneumococcal disease caused by serotypes that are not in the vaccine.[104,578–580] In a CDC review, the overall incidence of invasive pneumococcal disease among children younger than 5 years declined from 98.7 cases per 100,000 population in 1998–1999 to 23.4 cases per 100,000 population in 2005,[580] although there was an increase in cases caused by serotype 19A (from 2.6 to 9.3 cases per 100,000 population). This increase in nonvaccine serotypes has been small compared with the decline in disease caused by serotypes in the vaccine. Although rates of pneumococcal meningitis have been reported to decrease among children and adults since introduction of the heptavalent pneumococcal conjugate vaccine (1.13 cases to 0.79 cases per 100,000 persons between 1998–1999 and 2004–2005), the increase in meningitis caused by serotypes not in the vaccine (specifically serotypes 19A, 22F, and 35B) is of concern and has included some strains that are not susceptible to many antibiotics.[104] There was also a 59% reduction in pneumococcal meningitis in children younger than 14 years of age in Uruguay after introduction of heptavalent vaccine into the routine vaccination schedule.[582] However, it should be noted that serotype replacement has occurred after introduction of the heptavalent pneumococcal conjugate vaccine,[583,584] with invasive pneumococcal disease seen in most populations. The ACIP now recommends use of the 13-valent pneumococcal conjugate vaccine to prevent pneumococcal disease in infants and young children aged younger than 6 years[585]; this vaccine has activity against the serotypes that were present in the heptavalent vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F) along with six additional serotypes (1, 3, 5, 6A, 7F, and 19A). Adults 19 years of age and older and with immunocompromising conditions should receive the 13-valent pneumococcal conjugate vaccine followed by the 23-valent pneumococcal polysaccharide vaccine at least 8 weeks later.[585,586] Most recently, the ACIP has recommended that all adults aged 65 years and older should also receive both the 13-valent pneumococcal conjugate vaccine and the 23-valent pneumococcal polysaccharide vaccine.[587]

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The complete reference list is available online at Expert Consult.

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88 Chronic Meningitis

John E. Bennett and Susan E. Hoover

SHORT VIEW SUMMARY

Definition
- Chronic meningitis, defined here as at least 4 weeks of symptoms with signs of inflammation in the cerebrospinal fluid (CSF), must be distinguished from recurrent aseptic meningitis, chronic myeloradiculitis, and chronic encephalitis.

Etiology
- Major causes are fungal infections, tuberculosis, syphilis, and malignancy (see Table 88.2)

Diagnosis
- Major diagnostic tools are gadolinium-enhanced magnetic resonance imaging (MRI) and CSF studies (see Table 88.1). Surgical biopsy has a low yield.
- Polymerase chain reaction assay has taken on an increasing role, including its use in the diagnosis of Whipple disease, chronic enteroviral meningitis, lymphoma, and tuberculosis.

Therapy
- Empirical therapy for suspected tuberculous meningitis is often used because of disease severity, but addition of prednisone may cause deterioration of unsuspected fungal meningitis. Worsening of infection may not be detected initially because corticosteroids can temporarily improve hypoglycorrhachia, fever, and cerebral edema on T2-weighted MRI. The same issue arises with corticosteroid treatment of suspected sarcoidosis or autoimmune meningitis. Only when subsequent, potentially irreversible deterioration occurs despite corticosteroids is an infectious cause found. The benefit of corticosteroids in empirical regimens is usually outweighed by the harm.

This chapter focuses on the differential diagnosis of chronic meningitis. The reader is referred to the chapters on individual infections for discussions of their management.

DISTINCTION FROM OTHER CHRONIC CENTRAL NERVOUS SYSTEM INFECTIONS

Indolent infections in the spinal cord and brain manifest quite differently from infections in the meninges and are discussed briefly before addressing the topic of chronic meningitis.

MYELITIS, MYELORADICULITIS, AND POLYRADICULITIS

Although "myelo" refers to spinal cord and "radiculo" refers to the nerve roots, infection of the spinal cord generally results in a pathologic process of the nerve roots and vice versa. The clinical presentation may be acute or chronic. Examples of acute presentations are transverse myelitis, Guillain-Barré syndrome, poliomyelitis, and infections due to West Nile virus and coxsackievirus. Chronic myeloradiculitis can result from syphilis (tabes dorsalis),[1] human T-cell lymphotropic virus type 1 (tropical spastic paraparesis),[2] cytomegaloviral polyradiculopathy in patients with acquired immunodeficiency syndrome (AIDS),[3] herpes simplex virus infection, human immunodeficiency virus type 1 (HIV-1) infection, and schistosomiasis (usually caused by *Schistosoma haematobium*).[4] Meningeal carcinomatosis, spinal cord tumors, and spinal epidermoid cysts may manifest as chronic myeloradiculitis. Patients with cat-scratch encephalomyelitis may present subacutely with spinal cord signs.[5] Myeloradiculitis may be a prominent feature of tuberculous meningitis, but the severe systemic features of disseminated tuberculosis easily distinguish this entity from other causes of chronic myeloradiculitis. Initial symptoms of chronic myeloradiculitis commonly include decreased muscular strength in the extremities, loss of bladder control, and, less commonly, back pain or shooting pains in the torso or extremities. Examination may reveal decreased deep tendon reflexes, loss of proprioception in the extremities, decreased rectal sphincter tone, or decreased perception of pain or light touch in the extremities. Symptoms and signs are most marked in the lower extremities. Mild-to-moderate cerebrospinal fluid (CSF) pleocytosis and increased CSF protein level are usual findings, but hypoglycorrhachia is not found. Gadolinium-enhanced magnetic resonance imaging (MRI) may show meningeal enhancement along the cord or cauda equina. Nerves in the cauda equina may appear clumped on axial views of MRI. Epidural or intradural abscess and malignant lesions causing spinal cord symptoms can be distinguished from myeloradiculitis on MRI.

Cauda equina syndrome is a constellation of neurologic symptoms and signs due to myeloradiculitis in the conus medullaris, including urinary incontinence, residual bladder urine, unilateral or bilateral leg or sciatic pain, leg weakness, saddle anesthesia, sexual dysfunction, and loss of ankle tendon reflexes. Some patients receiving *Exserohilum*-contaminated methylprednisolone injections developed cauda equina syndrome as infection crossed the dura mater to form abscesses in the cauda equina.[6]

ENCEPHALITIS

Patients with encephalitis (see Chapter 89) most often present with an acute disease, although infection may be diphasic, and sequelae may persist long after the acute infection has resolved. Acute disseminated encephalomyelitis manifests typically 1 to 3 weeks after a viral infection with a monophasic, rapidly progressing illness—usually with fever, headache, somnolence, and seizures. Cranial nerve palsies and other focal neurologic signs may appear. Indolent onset is usual in some causes of chronic encephalitis such as syphilis (general paresis), subacute sclerosing panencephalitis (measles virus), Lyme disease *(Borrelia burgdorferi)*, African trypanosomiasis, Whipple disease *(Tropheryma whipplei)*, bartonellosis (cat-scratch disease), autoimmune encephalopathy with anti–*N*-methyl-D-aspartate receptor antibody, HIV-1 infection, and progressive multifocal leukoencephalopathy (polyomavirus). Rabies is delayed in onset but rapidly becomes more severe once symptoms develop. Although chronic encephalitis symptoms overlap symptoms of chronic meningitis, dementia and personality change are early and prominent signs in chronic encephalitis. In contrast to acute presentations

of viral encephalitis with fever and headache, patients with chronic encephalitis may have little fever or headache. Depending on the etiology, seizures and focal signs may occur. CSF pleocytosis and increased protein are usual, but hypoglycorrhachia is rare.

BRAIN ABSCESS

Brain abscess (see Chapter 90) may cause intense headache, but focal signs and seizures soon predominate. Similar to chronic meningitis, fever is not a predominant symptom in brain abscess. Gadolinium-enhanced MRI is the most sensitive imaging technique for focal intracerebral lesions but does not reliably distinguish abscesses from tumors or intracerebral granulomas such as those due to toxoplasmosis, tuberculosis, cryptococcosis, or histoplasmosis. Cystic lesions and intracerebral calcifications of neurocysticercosis are well visualized on computed tomography. Fluorodeoxyglucose-labeled positron emission tomography can be used alone or with computed tomography to assess metabolic activity of the lesion, but distinction between infectious and malignant lesions is not simple.

Recurrent aseptic meningitis should be distinguished from chronic meningitis and should suggest herpes simplex virus (Mollaret meningitis), repeated episodes of drug-induced meningitis (e.g., from nonsteroidal antiinflammatory drugs or intravenous immune globulin), or epidermoid cysts and craniopharyngiomas intermittently discharging keratinaceous debris into the CSF.

CHRONIC MENINGITIS

Clinical Manifestations

For the purposes of this chapter, patients with chronic meningitis have the indolent onset of symptoms compatible with chronic central nervous system (CNS) infection for at least 4 weeks and have signs of chronic inflammation in the CSF.[7–9] Chronic meningitis must be distinguished from recurrent aseptic meningitis or persistent sequelae of encephalitis. A careful history from the patient or family member may be needed to date the onset of symptoms and to distinguish chronic from recurrent meningitis. What may have seemed like a sudden onset may, on further questioning, have been the culmination of a much longer process. Symptoms of chronic meningitis can wax and wane over weeks and months. An abnormal result of CSF testing may not have been repeated to see if improved symptoms were accompanied by an improvement in CSF abnormalities. Early symptoms of chronic meningitis include headache, nausea, and decreased memory and comprehension. When hydrocephalus complicates indolent meningitis, dementia can be a prominent finding, which is better related by family members than by the patient. Later symptoms of chronic meningitis include decreased vision, double vision, cranial nerve palsies, unsteady gait, emesis, and confusion.

Diagnosis

Physical Examination

Patients with chronic meningitis may have a normal physical examination, including absence of fever. Neurologic examination is the most frequent abnormality, with decreased recent and remote memory, confusion, apathy, papilledema, and cranial nerve palsies, particularly sixth nerve palsy and deafness. As cerebral edema causes brainstem compression, upper motor neuron signs, increased deep tendon reflexes, ankle clonus, a positive Babinski sign, and Cheyne-Stokes respiration may be noted. Other than cranial nerve palsies, neurologic signs are decidedly symmetrical. Resting tremor, rigidity, and decreased mental acuity occasionally suggest Parkinson disease.

Skin lesions may be an important source of biopsy material in sarcoidosis, cryptococcosis, coccidioidomycosis, blastomycosis, or sporotrichosis. Vitiligo and poliosis may suggest Vogt-Koyanagi-Harada syndrome. This syndrome may manifest as aseptic meningitis, although the most common manifestation is bilateral posterior uveitis. Lymphadenopathy may point toward sarcoidosis, lymphoma, or hematogenously disseminated tuberculosis or histoplasmosis. A dilated funduscopic examination may reveal retinal lesions of Behçet syndrome, Vogt-Koyanagi-Harada syndrome, sarcoidosis, tuberculosis, coccidioidomycosis, or cryptococcosis. The Argyll Robertson pupil sign is highly suggestive of neurosyphilis.

History

Exposure history can be helpful in that coccidioidomycosis is rare in patients who have never been in the southwestern United States or northern Mexico (see later discussion). The endemic area for histoplasmosis is broad, although in the United States it is uncommon in the Pacific Northwest and Rocky Mountain states. Immigrants from countries where tuberculosis is prevalent are at increased risk for reactivation, as are patients who have lived in a household where someone had tuberculosis. Neurocysticercosis occurs in residents of endemic countries but rarely in travelers to these regions. Lyme borreliosis is endemic in the northeastern United States. A history of a typical lesion of erythema migrans may suggest the diagnosis of Lyme disease. Travelers outside the United States may have been exposed to *Angiostrongylus* or *Brucella.*

A patient's occupation is rarely helpful diagnostically. Age is important, in that cryptococcosis is uncommon in the first decade of life. A history of risk factors for sexually transmitted disease should suggest the possibility of neurosyphilis or HIV-associated infections. Underlying disease is important in that AIDS and corticosteroid therapy are major predisposing factors to cryptococcal and *Acanthamoeba* meningitis.

Imaging

Contrast-enhanced MRI is the preferred test for imaging the brain and may show intracranial mass lesions, hydrocephalus (Fig. 88.1), pachymeningitis, or parameningeal foci such as mold sinusitis or actinomycosis of the paranasal sinuses or middle ear. Increased intracranial pressure may be deduced from flattening of the sulci over the cerebral convexities, particularly in younger patients without preexisting atrophy. Increased width of the optic sheath is sometimes evident in patients with cerebral edema or papilledema. Granuloma may be seen within the brain of patients with tuberculosis (Fig. 88.2)[10] or cryptococcal or *Histoplasma* meningitis. Patients with blastomycosis or nocardiosis usually have one or more brain abscesses in addition to chronic meningitis. Spillage of the contents of an intracranial epidermoid cyst or craniopharyngioma may occur spontaneously or result from surgery. Rarely, repeated rupture can lead to chronic granulomatous meningitis.[11] Epidermoid cysts are readily seen on MRI but must be distinguished from cystic tumors and cysticercosis.[12]

Laboratory Findings

Cerebrospinal Fluid

The opening pressure is usually elevated beyond 120 mm of fluid when measured with the patient in the lateral decubitus position. CSF glucose, protein, cell count, and differential should be measured in all

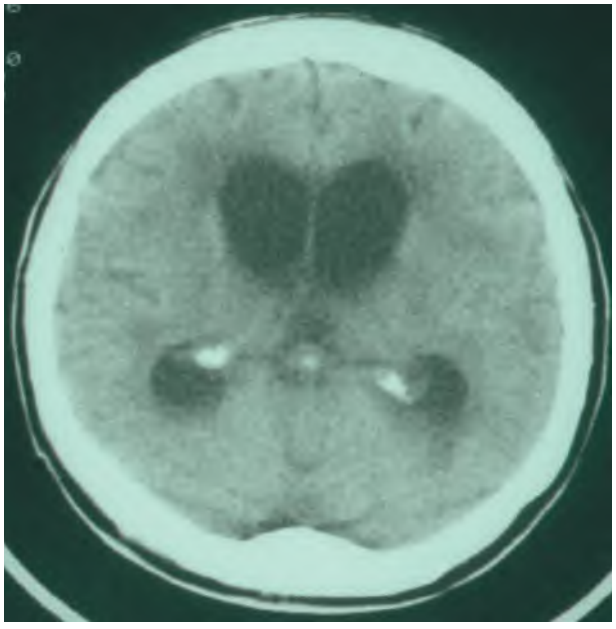

FIG. 88.1 Computed tomography scan showing enlarged lateral cerebral ventricles from cryptococcal meningitis.

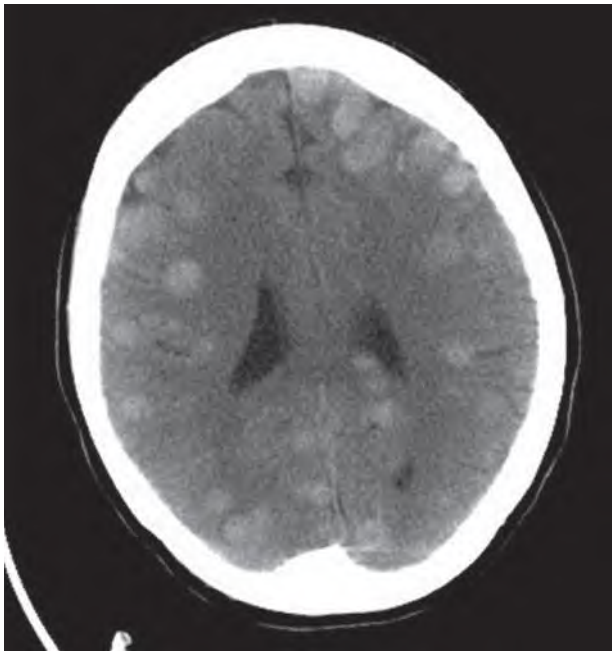

FIG. 88.2 Computed tomography scan of a patient with tuberculous meningitis and numerous intracerebral granulomas.

cases of suspected chronic meningitis. Care should be taken in ordering additional tests to prioritize them by the clinical likelihood of a particular diagnosis, as the amount of CSF may be limiting. Glucose concentrations below 40 mg/dL are a valuable indication of fungal or mycobacterial chronic meningitis and are uncommon in syphilis, Lyme disease, parameningeal infections, or most noninfectious causes. Patients with the lowest CSF glucose level generally have the greatest increase in cell count and protein levels, but there is an exception to this rule. Profound hypoglycorrhachia with nearly normal cell count and protein levels should suggest carcinomatous meningitis. In infectious causes of chronic meningitis, a lymphocytic pleocytosis is usual, but the cell count and cell type are variable, with a neutrophilic predominance not being rare. Culture of an adequate volume of CSF is imperative for optimal recovery of fungi and *Mycobacterium tuberculosis*. Culture of at least 3 to 5 mL for fungi and an equivalent amount for mycobacteria is recommended. Microbiology laboratory technicians will need to be asked to culture the entire volume or may culture their usual volume, usually 1 mL or less, and save the remaining volume in the refrigerator.

Sampling the ventricular CSF is less helpful in chronic meningitis than sampling lumbar fluid. Ventricular fluid is often surprisingly normal, even in the absence of obstructive hydrocephalus and in the presence of very abnormal lumbar fluid. Postneurosurgical infections with a ventriculoperitoneal shunt or a foreign body in the surgery site typically produce negative cultures of lumbar fluid, although cultures taken from an infected ventriculoperitoneal shunt or at neurosurgery in the area of the infection may be positive.

Other potentially helpful tests are listed in Table 88.1. Lymphomatous meningitis may be diagnosed by polymerase chain reaction (PCR) assay of CSF in patients with nondiagnostic cytology results by showing a clonal population of lymphocytes having the same immunoglobulin or T-cell receptor genes.[13] Flow cytometry of CSF can also be used to detect a malignant monoclonal lymphocyte population and lymphoblasts.[14]

Peripheral Blood

Serum serology can be helpful in the diagnosis of coccidioidomycosis, brucellosis (agglutinin only), Lyme disease, and syphilis. In patients with a clinical syndrome compatible with neurosyphilis but a negative Venereal Disease Research Laboratory (VDRL) or rapid plasmin reagin test result, a treponemal test should be requested. Positive treponemal tests preferably should be confirmed by a different treponemal test because false-positive reactions occur. Serum cryptococcal and *Histoplasma* antigen tests can be done, although urine can also be tested for *Histoplasma* antigen.

TABLE 88.1 Diagnostic Tests for Chronic Meningitis

Cerebrospinal Fluid Tests
Glucose, protein, and cell count and differential (including eosinophils)
India ink on centrifuged sediment
Fungal culture of 3–5 mL of cerebrospinal fluid
Cytopathology for malignant cells, including polymerase chain reaction assay or flow cytometry for monoclonal B cells
Periodic acid–Schiff stain of cytopathologic specimen for Whipple disease
VDRL test for syphilis
Cryptococcal antigen
Histoplasma antigen
Aspergillus galactomannan antigen
Coccidioides antibody (complement fixation or immunodiffusion)
Nucleic acid tests for *Mycobacterium tuberculosis,* Whipple disease, enterovirus infection, lymphoma
Culture for enterovirus, *Acanthamoeba*
Serum Tests
Rapid plasma reagin test or antitreponemal antibody test
Antibody to *Coccidioides, Histoplasma, Toxoplasma, Brucella*
Histoplasma antigen

RPR, Rapid plasma reagin; *VDRL,* Venereal Disease Research Laboratory.

Brain Biopsy

Biopsy of meninges and cerebral cortex has had a low yield in chronic meningitis. The highest yield has been biopsy of lesions that were enhancing on MRI and located in the posterior fossa or pterional area, rather than over the cerebral convexities.[15,16] Malignancies constitute the majority of diagnoses. An exception is immunoglobulin G4 (IgG4)–related hypertrophic pachymeningitis, in which biopsy of the thickened dura mater is the most reliable diagnostic method.

Differential Diagnosis

Cryptococcus Meningitis

Cryptococcus neoformans and *Cryptococcus gattii* (see Chapter 262) are the most common causes of fungal meningitis (Table 88.2). Most patients are immunosuppressed, but a previously healthy patient with cryptococcosis has fewer organisms in the CSF and may present more of a diagnostic dilemma. In the latter group, symptoms can be indolent, with headaches present for weeks or months. Dementia may attract attention only after a vehicular accident or if inattention to business or personal matters creates a crisis. Skin lesions precede meningeal symptoms in about 10% of patients and are useful for diagnosis. MRI is most often normal unless hydrocephalus has supervened (see Fig. 88.1). CSF cultures of patients with AIDS with cryptococcal meningitis become positive in a few days, but CSF cultures from indolently ill patients may require a 2-week incubation and culture of more than 1 mL of CSF. CSF antigen is more often positive than serum antigen, with the CSF antigen being negative only in the most indolent patients (i.e., patients with profound hypoglycorrhachia, high protein level, and high cell count).

Coccidioides Meningitis

Principal areas of exposure for coccidioidal meningitis (see Chapter 265)[17–19] are central and southern Arizona and the Central Valley of California, although the endemic area is much broader. Spotty endemic areas exist in contiguous parts of the Southwest. Extremely brief exposures of visitors from outside the endemic area are sufficient to cause infection. The initial infection may be asymptomatic or a community-acquired pneumonia. Previously healthy people with meningitis may present with the indolent onset of headache, which has been present for weeks or months at the time of diagnosis. The pulmonary portal, prominent earlier, may be visible only as hilar adenopathy or a small pulmonary infiltrate at the time symptoms of meningitis appear. The patient may recall the pneumonia as a period of fever and cough occurring 2 to 4 weeks after exposure. Immunosuppressed patients, including patients with AIDS, are more likely to present with a systemic illness, including

TABLE 88.2 Differential Diagnosis of Chronic Meningitis

Mycoses
Cryptococcus (cryptococcosis)
Coccidioides (coccidioidomycosis)
Histoplasma (histoplasmosis)
Candida (candidiasis)
Sporothrix (sporotrichosis [rare])
Blastomyces (blastomycosis [rare])
Other molds (rare): *Scedosporium, Aspergillus, Cladophialophora,* and other dark-walled molds
Bacteria
Mycobacterium tuberculosis (tuberculosis)
Treponema pallidum (syphilis)
Borrelia burgdorferi (Lyme disease)
Tropheryma whipplei (Whipple disease)
Actinomyces (actinomycosis [parameningeal, rare])
Nocardia (nocardiosis [with brain abscess])
Brucella (brucellosis [rare])
Parasites
Acanthamoeba (acanthamebiasis)
Balamuthia (balamuthiasis)
Taenia solium (cysticercosis)
Angiostrongylus cantonensis (angiostrongyliasis)
Viruses
Echovirus (meningoencephalitis)
Postneurosurgical Causes
Infected cerebrospinal fluid shunt
Infected prosthetic material
Tumors
Diffuse gliomatosis
Metastatic meningeal malignancy, including lymphomatous meningitis
Other Causes
Sarcoidosis
Vogt-Koyanagi-Harada syndrome
Behçet syndrome
IgG4-related hypertrophic pachymeningitis

fever, headache, profound malaise, and lesions in the bone or skin. The chest radiograph of immunosuppressed patients may show single or diffuse infiltrates. Low-grade eosinophilia in the blood and more commonly in the CSF is a valuable sign, although Wright-Giemsa staining of the CSF may be needed to detect eosinophilia. The single best test is not culture or smear of CSF, either of which is uncommonly positive, but rather a positive antibody test done in a reliable reference laboratory. The complement fixation test on CSF is specific and sensitive. CSF antibody detected by an immunodiffusion test with a band of identity is a useful screen because it is sensitive, but it is less specific than the complement fixation test. None of the commercially available enzyme-linked immunosorbent assays has sufficient specificity or sensitivity in CSF to be useful. Serum complement fixation and enzyme immunoassay tests are usually positive but may remain positive after remote infection, a so-called serologic scar.

Histoplasma Meningitis

An extremely indolent, chronic meningitis can be the presenting sign of *Histoplasma* meningitis (see Chapter 263) in previously healthy patients. A more subacute meningitis may be part of more systemic illness, particularly in immunosuppressed patients. Patients at risk for dissemination to the brain and other organs include patients with AIDS, solid-organ transplant recipients, and patients taking adrenal corticosteroids or tumor necrosis factor-α inhibitors.[20] Signs of dissemination outside the neuraxis, if present, are extremely variable including Addison disease, chronic granulomatous hepatitis, endocarditis, or pancytopenia. Patients do not give a history suggesting acute pulmonary histoplasmosis before the diagnosis of meningitis. Accompanying pulmonary symptoms are minimal or absent. MRI may show an intracerebral granuloma in some patients. *Histoplasma* antigen or antibody may be detectable in the CSF. CSF cultures are usually negative, although a high-volume culture (at least 5 mL) held for 6 weeks is occasionally successful. A serum or urine antigen test is usually negative unless dissemination is suggested by nonneural findings. Empirical use of corticosteroids can worsen infection and inadvertently make diagnosis more detectable.[21]

Candida Meningitis

Candida (see Chapter 256) is commonly found in multiple small brain abscesses in patients dying of disseminated candidiasis, but presentation as chronic meningitis is rare. Most such patients are very-low-birth-weight neonates or postneurosurgical or immunosuppressed patients.[22,23] Patients with a homozygous *CARD9* mutation are predisposed to *Candida* meningitis.[24] Neonates with *Candida* meningitis have typically had long stays in a neonatal intensive care unit and required prolonged use of intravascular catheters. Others are infants with severe congenital abnormalities of the intestine or urinary tract that required complicated surgical repair. *Candida* enters the bloodstream through an intravascular catheter, from complications of intestinal surgery, or from an obstructed urinary tract. Difficulty assessing the neurologic status of these neonates and the absence of fever cause delays in diagnosis. Hydrocephalus may already be present when the diagnosis of *Candida* meningitis is made. CSF is markedly abnormal, but culture has such few organisms that contamination of the CSF culture may be suspected. Cases of CSF shunts infected with *Candida* may manifest as partial or complete blockage of the shunt, usually in children with multiple shunt revisions or skin ulcers over the shunt valve or tubing. Patients with hematologic malignancies may develop meningitis as a part of disseminated candidiasis. Meningitis may be recognized only after antifungal therapy and return of marrow function has allowed control of the other manifestations of disseminated candidiasis.

Sporothrix Meningitis

The published cases of sporotrichosis meningitis (see Chapter 259) have presented formidable diagnostic difficulties because the organism has proven very difficult to recover in CSF culture.[25] A few patients have had disseminated skin lesions that provided a site for biopsy. Infection has occurred in previously healthy patients and in immunosuppressed patients.

Blastomyces Meningitis

Patients with blastomycosis (see Chapter 264) present with one or more abscesses in the brain or spinal cord. When a brain abscess ruptures into the ventricular system, a rapidly progressive purulent meningitis results with a strong tendency to obstruct the aqueduct of Sylvius, accelerating the progression to coma. Skin, bone, or lung lesions of blastomycosis are present in most patients and permit diagnosis.

Phaeohyphomycotic Meningitis

Dark-walled molds have a predisposition for spread from the lung to the brain, causing a brain abscess, phaeohyphomycotic meningitis, or both (see Chapter 268). CSF cultures are often sterile, but direct detection of fungal DNA may have a higher yield.[26] Brain biopsy is sometimes required for diagnosis.[27,28] Most patients are previously healthy and have no visible pulmonary portal or other disease outside the CNS. Both of the outbreaks of epidural abscess and meningitis due to contaminated epidural methylprednisolone injections were due to phaeohyphomycetes: *Exophiala* and *Exserohilum.*[6,27,29] In the latter cases, extension to the brain led to vascular invasion and stroke.[30]

Other Molds Causing Meningitis

Scedosporium prolificans and *Scedosporium apiospermum* infections have a predisposition for hematogenous spread to the CNS, usually manifesting as brain abscess but occasionally as chronic meningitis. Immunosuppression is present in most patients, although intravenous drug abusers may also develop the infection. *Aspergillus* may enter the CSF as an extension of sphenoid or ethmoid sinusitis, as mastoiditis, or rarely as a complication of neurosurgery and manifest as chronic meningitis.[31–33] Immunosuppressed patients with aspergillosis and mucormycosis in

the CNS most commonly present with angioinvasion with hemorrhagic infarction, not chronic meningitis.

Mycobacterium tuberculosis Meningitis

Tuberculous meningitis (see Chapter 249) is probably the most common cause of chronic meningitis, and because diagnosis can be difficult, empirical treatment for *Mycobacterium tuberculosis* may be started when all other diagnostic measures fail (see later discussion). Children with hematogenously disseminated tuberculosis are prone to a more rapid course than is typical for adults, with symptoms present for only 2 to 4 weeks before diagnosis. Fever, miliary lesions in the lung and retina, marrow suppression, and hepatosplenomegaly may herald the systemic disease, whereas headache followed by confusion and coma portend a poor prognosis from the CNS disease. Disease in previously healthy adults tends to be more indolent with fewer signs of disseminated tuberculosis other than fever, weight loss, night sweats, and malaise. Chest radiography is abnormal in only about half of patients. Diagnosis is suspected from country of origin or household exposure to tuberculosis, both typically occurring years before symptoms are evident. Tuberculin skin test and interferon-γ release tests may be negative and neither support nor exclude the diagnosis. MRI may be normal or show small lesions in the cortical sulci (see Fig. 88.2) or may show hydrocephalus. Hypoglycorrhachia is usual, as are pleocytosis of up to a few hundred cells and an elevated protein level. The adenosine deaminase level may be elevated in the CSF, but this finding is not more helpful than a low CSF glucose level. Smear rarely demonstrates acid-fast bacilli. Culture in automated broth culture techniques is positive in about half of the cases but requires about 2 weeks of incubation, which is often too long a period to assist early therapeutic decisions. The old literature referred to taking the clot that forms in the CSF from patients with tuberculosis as it stands, the so-called pellicle, and using those clumped strands of cells and clot from several milliliters of CSF for smear and culture. Although no modern laboratory would consider using such a time-consuming technique, the popularity of that technique speaks to the small inoculum of organisms in the CSF and the need for culturing more than minimal volumes of CSF. Nucleic acid–based tests such as the *Mycobacterium tuberculosis* Direct Test (Hologic Gen-Probe, San Diego, CA) and Xpert MTB/RIF (Cepheid, Sunnyvale, CA) (see Chapter 16) are approved for use on sputum samples but not CSF. Although highly specific, these tests lack sensitivity when performed on CSF.[34,35] The Xpert MTB/RIF Ultra test provided superior results in the diagnosis of tuberculous meningitis in patients with HIV in Uganda.[36] This study also found that culturing more than 6 mL of CSF significantly improved yield. Although many referral laboratories offer PCR diagnosis, the lack of standardization makes interpretation difficult. The issue of empirical therapy for tuberculous meningitis is discussed later in this chapter.

Treponema pallidum Meningitis

CNS manifestations of syphilis (see Chapter 237) are not easily divided into categories. Secondary syphilis causes aseptic meningitis, but illness resolves either spontaneously or with therapy so that chronicity at this stage of infection is uncommon. Meningovascular syphilis is a later complication that occurs 2 to 10 years after infection as an ischemic stroke in a young person. Presenting symptoms of parenchymal disease are gumma formation or general paresis 15 to 20 years after infection or tabes dorsalis even later. General paresis has prominent encephalopathic signs and may have ocular signs as well. Tabes dorsalis has prominent spinal cord signs and symptoms with radicular pain ("lightning pains") that sets it apart from the usual patient with chronic meningitis, in whom spinal cord symptoms are uncommon. Patients with neurosyphilis may present simply with chronic meningitis with a CSF pleocytosis and elevated protein levels but normal glucose level. Some of these patients have a waxing and waning course, perhaps beginning when they had secondary syphilis. In a patient with compatible neurologic signs or symptoms and an abnormal CSF, a positive VDRL on CSF is diagnostic of neurosyphilis, but the test is insensitive. In the appropriate setting, a fluorescent treponemal antibody absorption test on CSF may be indicated. A significant minority of patients with neurosyphilis have negative nontreponemal tests, such as VDRL or rapid plasmin reagin on serum, in which case a treponemal antibody test should be considered.[37]

Borrelia burgdorferi

CNS disease (Lyme borreliosis) can occur weeks to months after infection with *Borrelia burgdorferi* (see Chapter 241). Cranial nerve palsies are common, in contrast to syphilitic meningitis. Cognitive decline and ataxia may occur because of encephalitis. Seizures, ataxia, painful radiculopathy, or, rarely, meningitis may also occur. The CSF shows a modest pleocytosis, slight elevation of protein levels, and normal glucose level. Enzyme immunoassay and Western blot for IgG antibody in CSF are helpful but probably insensitive. PCR detection in CSF also appears to be of low sensitivity.[38,39]

Tropheryma whipplei Meningitis

Whipple disease of the CNS most often manifests as the indolent onset of dementia with memory loss or personality change (see Chapter 210). Other frequent clinical signs include ophthalmoplegia, nystagmus, or myoclonus. Elevated CSF protein and mixed cellularity pleocytosis are found in half of the cases.[40] Periodic acid–Schiff–positive inclusions of macrophages in a cytospin of CSF may be seen. The PCR assay of CSF is the single best test. Duodenal biopsy for periodic acid–Schiff–positive inclusions in submucosal macrophages may be useful even in the absence of diarrhea.[40]

Nocardia and *Actinomyces* Meningitis

Nocardiosis (see Chapter 253) has a strong tendency for hematogenous spread from the lungs to the brain. An acute or subacute meningitis can result from rupture of an abscess into the CSF. Actinomycosis (see Chapter 254) can cross the dura mater from a contiguous infection in the paranasal sinus or middle ear and cause an indolent meningitis. The organisms can rarely be isolated from the CSF. Actinomycotic meningitis predominantly results from a parameningeal focus.

Brucella Meningitis

Although brucellosis (see Chapter 226) is now rare in the United States, it remains a common disease in many countries. Ingestion of unpasteurized dairy products such as soft cheeses from other countries is a common source of infection in the United States. Illness is usually acute but may be relapsing or occasionally chronic. A few patients with chronic meningitis have been reported, but positive CSF cultures have been unusual. Serum *Brucella* agglutinins and an exposure history are helpful to screen patients. Serologic studies for brucellosis other than agglutinin-based tests are not recommended.

Amebic Granulomatous Meningitis

In contrast to *Naegleria,* which causes acute meningitis, cerebral manifestations of *Acanthamoeba* (see Chapter 273) infections evolve over a few weeks, with decreased mental status, seizures, fever, headache, meningitis, visual disturbance, and ataxia, with hemiparesis as a later manifestation. Most reported patients have suppressed immune function, such as patients with AIDS or stem cell transplant recipients. Others have been chronically ill and debilitated.

Balamuthia mandrillaris (see Chapter 273) can infect both immunocompetent and immunocompromised hosts. The course can be indolent with fever, headache, and seizures. Mortality is high due to difficulty in diagnosis, which is often made by immunohistochemistry or PCR at autopsy. There are no well-established treatments.

Angiostrongylus cantonensis Meningitis

Most cases of meningitis caused by *Angiostrongylus cantonensis* (see Chapter 290) in the United States have been in travelers recently returned from the South Pacific, Hawaii, or the Caribbean who acquired infection from eating uncooked produce.[41] Patients present with an acute eosinophilic meningitis, although symptoms can linger for several weeks.

Taenia solium Meningitis

In patients with neurocysticercosis (see Chapter 289), the cystic lesions can occur anywhere in the neuraxis, usually causing seizures, but patients occasionally present with chronic meningitis. A cyst in the third ventricle can obstruct the aqueduct of Sylvius, and patients can present with hydrocephalus.

Enteroviral Meningitis

Enteroviruses (see Chapter 172) cause acute aseptic meningitis or myelitis in children and young adults. Patients with X-linked agammaglobulinemia or with large B-cell lymphoma treated with rituximab may acquire chronic enteroviral meningoencephalitis.[42,43] Diagnosis can be made by culture or real-time PCR assay of CSF.

Postneurosurgical Meningitis

Patients may present with persistent low-grade fever, headache, and low-grade CSF pleocytosis after neurosurgery. These same findings in the immediate postoperative period are difficult to distinguish from the usual postoperative findings. Persistence of these findings, particularly if a plastic implant was used, increases the likelihood of infection with a low-grade pathogen, most often *Staphylococcus epidermidis*. Recovery of the organism from lumbar CSF is rare, but the organism may be found on implanted material when removed at neurosurgery. *S. epidermidis* is difficult to eradicate from implanted intracranial material because of the relatively poor penetration of vancomycin into the CSF and likely because of the organism's ability to form a biofilm on foreign bodies. Linezolid has better penetration into the CSF, but removal of the material may be required for cure despite temporary improvement with systemic antibiotics. Infected ventricular or lumbar CSF shunts share many of these same problems and are discussed in Chapter 92.

Sarcoidosis Meningitis

Chronic meningitis due to sarcoidosis is a diagnosis of exclusion, with many patients reported to have the diagnosis even in the absence of extraneural signs of sarcoidosis. Cranial nerve palsies are the most common presenting sign.[44,45] Biopsy of a skin lesion, lung, or enlarged lymph node may show noncaseating granuloma, supporting the diagnosis. Treatment with corticosteroids may reveal a fungal or other infectious cause of meningitis.

Vogt-Koyanagi-Harada Syndrome Meningitis

Vogt-Koyanagi-Harada syndrome is an autoimmune disease targeting melanocytes. Manifestations include bilateral eye disease, chronic meningitis, and, later in the disease course, skin findings. Ocular findings are diffuse choroiditis or chronic iridocyclitis. CNS findings include headache, nausea, neck stiffness, tinnitus, and CSF pleocytosis. Alopecia, vitiligo, or poliosis occurs late in the disease.[46]

Behçet Syndrome Meningitis

Behçet syndrome technically does not belong on this list because it does not cause chronic meningitis. It causes recurrent episodes of aseptic meningitis and in some cases progressive parenchymal involvement. Diagnosis is made by the presence of recurrent oral ulcerations and at least one of the following: recurrent genital ulcers, eye lesions, skin lesions, or a positive pathergy test.[47,48]

Neoplastic Meningitis

Dissemination of cancer to the leptomeninges is most commonly from breast cancer, non-Hodgkin lymphoma, non–small cell lung carcinoma, acute leukemia, or melanoma. Presenting symptoms may be cranial nerve palsy, spinal cord symptoms, or headache. Diagnosis is usually known from a prior diagnosis of a malignancy elsewhere or by CSF cytology. Hypoglycorrhachia may be profound, but pleocytosis and elevated protein levels are modest at most. Rarely, leptomeningeal gliomatosis can originate from a primary supratentorial lesion too small to be detected by MRI and not detected by CSF cytology.[49] Lymphomatous meningitis may not be readily detectable by cytospin cytology, so demonstration of lymphocyte clonality by PCR assay or flow cytometry may be required. Meningeal biopsy over an area of enhancement on MRI may be necessary for diagnosis. Although the lymphoma may be known from other sites in the body, distinguishing lymphoma in the meninges from cryptococcal meningitis or other infectious causes is vital.

IgG4-Related Hypertrophic Pachymeningitis

IgG4-related disease is a chronic, indolent fibroinflammatory disease that can affect any organ. In the CNS, fibrous thickening of the dura mater can be focal or diffuse, involving the cranial dura mater, spinal cord, or both.[50] Cranial lesions resemble idiopathic hypertrophic pachymeningitis, manifesting as progressive cranial nerve palsies, headache, or vestibular symptoms. CSF may show mild abnormalities of cell count and protein. Focal or diffuse thickening of the dura mater is seen on MRI. Biopsy of the dura in patients with hypertrophic pachymeningitis associated with IgG4-related disease shows storiform fibrosis with an increased number of plasma cells that are IgG4-positive on immunostaining (IgG4+/IgG+ plasma cell/ratio). Relative concentrations of IgG4 in serum and CSF (IgG4 index) are increased.[51] Treatment is usually with corticosteroids or other immunosuppressive agents.

EMPIRICAL THERAPY FOR PRESUMED TUBERCULOUS MENINGITIS

Delay in diagnosis of tuberculous meningitis is strongly associated with neurologic damage and death. Patients with high fever and rapid decline in consciousness may be candidates for empirical therapy for tuberculous meningitis with a four-drug regimen (see Chapters 39, 87, and 249). Immigrants from countries with a high incidence of tuberculosis and patients with a history of tuberculosis in a household member are at especially high risk. Before therapy, several milliliters of CSF should be cultured for mycobacteria, and the centrifuged sediment should be examined by fluorochrome stain for acid-fast bacilli. If there are lung lesions, sputum should be smeared and cultured for acid-fast bacteria as well. Acid-fast stains should be done, and nucleic acid amplification testing of CSF should be requested. Repeat weekly lumbar punctures during therapy should show an improvement in hypoglycorrhachia, if present, in the second or third week, along with clinical improvement. Pleocytosis and elevated CSF protein levels are more variable and slower to respond. Administration of corticosteroids should not be routine during empirical therapy for tuberculous meningitis because corticosteroids can cloud the clinical response by nonspecifically decreasing fever, decreasing cerebral edema on MRI, and improving CSF pleocytosis and hypoglycorrhachia. If meningitis is due to a fungus, infection may increase and be undetected initially because of the antiinflammatory effects of corticosteroids.

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89 Encephalitis

J. David Beckham and Kenneth L. Tyler

SHORT VIEW SUMMARY

Definition
- Encephalitis is an inflammatory process involving the brain parenchyma associated with clinical or laboratory evidence of neurologic dysfunction.

Epidemiology
- It occurs most frequently in infants younger than 1 year and in elderly patients older than 65, with intermediate incidence in individuals between these age extremes.

Etiology
- Up to 60% of encephalitis cases result from an unidentified etiologic agent.
- Viruses, bacteria, and autoimmune inflammation cause the majority of known encephalitis cases.

Diagnosis
- A compatible febrile syndrome with evidence of central nervous system impairment exists (see Table 89.1).
- Standard cerebral spinal fluid (CSF) analysis and neuroimaging with magnetic resonance imaging are preferred.
- Specific CSF and/or serum studies for defined etiologies of encephalitis are warranted (see Table 89.3).

Therapy
- Early empirical use of high-dose acyclovir is warranted to treat possible herpes simplex encephalitis pending diagnostic studies.
- Antiviral therapy is indicated for the treatment of other herpesviruses that cause encephalitis.
- Empirical antiviral therapy is recommended for suspected encephalitis associated with influenza.
- There is currently no therapy of known benefit for patients with encephalitis due to arthropod-borne viruses.

Prevention
- Routine vaccination for common pathogens and vaccination for Japanese encephalitis virus in selected travelers may prevent some cases of encephalitis.
- Procedures to decrease exposure to mosquito bites may decrease the risk for arthropod-borne virus–related cases of encephalitis.

Viral invasion of the central nervous system (CNS) can result in various clinical syndromes, including encephalitis, meningitis, myelitis, and neuritis.[1] *Encephalitis* is defined as an inflammatory process of the brain parenchyma associated with clinical or laboratory evidence of neurologic dysfunction. The infectious causes of encephalitis, predominantly viruses, are the focus of this chapter. Noninfectious forms of encephalitis may result from inflammatory processes associated with autoimmune, paraneoplastic, neoplastic, or collagen vascular diseases and are discussed only as they affect the differential diagnosis. Focal suppurative infections of the CNS including cerebritis, brain abscess, and empyema are discussed in Chapters 90 and 91.

Patients with suspected encephalitis often have prolonged hospitalizations, may require a multitude of expensive diagnostic tests, and frequently have poor outcomes including disability and death.[2] There were an estimated 263,352 encephalitis-associated hospitalizations in the United States from 1998 to 2010, with an overall mortality rate of approximately 6%.[3] Total medically related charges for encephalitis-associated hospitalizations were an estimated $2 billion per year in 2008–2010.[4] A diagnosis of encephalitis was most frequent in infants younger than 1 year (11.1 per 100,000) and elderly patients older than 65 years (13.2 per 100,000), with an intermediate incidence of 4.0 to 8.4 per 100,000 individuals between these age extremes.[4]

In patients with encephalitis, the success in finding a specific defined pathogen varies widely and is influenced by factors such as season of the year, geographic location, vector exposure, patient age, patient immune status, and case definition. In general, approximately half of the patients diagnosed with encephalitis have no defined etiology identified despite an extensive diagnostic workup.[1,2,4] Using the Nationwide Inpatient Sample for 1998 through 2010, one study found that 50% of hospitalizations due to encephalitis had no specified etiology.[3]

In a retrospective series reviewing etiologies of "neuroinfectious diseases" in hospitalized patients from an academic tertiary referral center, a specific pathogen was identified in 62.5% of patients who tested negative for human immunodeficiency virus (HIV) and 89% of HIV-positive patients.[2] The most common identified pathogens and conditions in HIV-negative patients were viruses (38%), bacteria (33%), Lyme disease (7%), fungi (7%), syphilis (5%), mycobacteria (5%), prions (3%), and *Pneumocystis jirovecii* (2%). Among HIV-positive patients, the common pathogens included viruses (46%), fungi (32%), and *Toxoplasma* (11%), with bacteria, tuberculosis, and syphilis accounting for the remaining infections (11%).[2] Among the 22 cases of viral encephalitis, the most commonly identified viruses in HIV-negative patients were varicella-zoster virus (VZV; 36%), herpes simplex virus (HSV; 32%), cytomegalovirus (CMV; 9%), West Nile virus (WNV; 9%), enteroviruses (9%), and hepatitis C virus (5%).[2] In HIV-positive patients, the viral etiologies included HIV encephalopathy (54%), JC virus–induced progressive multifocal leukoencephalopathy (PML; 31%), VZV (7.5%), and CMV (7.5%).

The California Encephalitis Project (CEP) searched for etiologies of encephalitis in immunocompetent hospitalized patients who met defined criteria for encephalitis, including altered consciousness for 24 hours or more and at least one of the following characteristics: fever, seizures, focal neurologic findings, cerebrospinal fluid (CSF) pleocytosis, or consistent electroencephalogram (EEG) or neuroimaging findings.[1,5] A confirmed or probable cause was found in only 16% of cases; these causes included viruses (69%), bacteria (20%), prions (7%), parasites (3%), and fungi (1%). The most commonly identified viruses included enteroviruses (25%), HSV-1 (24%), VZV (14%), WNV (11%), and Epstein-Barr virus (EBV) (10%), with other agents accounting for 16%.[5] In a prospective study in England, 42% of patients had encephalitis due to an infection; HSV(19%) and VZV(5%) were the most commonly identified infectious agents.[6] Acute immune-mediated encephalitis (21%) was a major cause of encephalitis, and unknown causes (37%) of encephalitis were still common.

CLINICAL SYNDROMES

Clinicians frequently encounter patients with fever and signs or symptoms of CNS disease in whom infectious encephalitis is part of a larger differential diagnosis. This clinical presentation is nonspecific with a broad differential diagnosis including diseases as diverse as viral

encephalitis; viral meningitis; bacterial meningitis; focal suppurative infections (brain abscess, subdural or epidural empyema, and cerebral venous sinus thrombophlebitis); acute disseminated encephalomyelitis (ADEM); autoimmune encephalitis; and encephalopathy. The challenge to the clinician is to differentiate among these clinical entities quickly and efficiently, because appropriate diagnosis and therapy can have an important effect on neurologic outcomes and mortality.

When evaluating a patient with possible encephalitis, it is important to distinguish among (1) infectious processes; (2) encephalopathy; and (3) autoimmune processes such as autoimmune encephalitis (Fig. 89.1).[7] *Encephalopathy* refers to diffuse cerebral dysfunction without associated inflammation of brain tissue.[8] Although there are multiple causes of encephalopathy, the most commonly encountered causes include toxins (e.g., alcohol, licit or illicit drugs) and metabolic dysfunction (e.g., hypoxia, hypoglycemia or hyperglycemia, electrolyte disorders, renal or hepatic failure).[8] Table 89.1 lists common factors that can be used to differentiate encephalitis from encephalopathy. Fever, headache, peripheral leukocytosis, and CSF pleocytosis all favor encephalitis. Although some encephalopathies may produce focal neurologic signs, these are more typical in encephalitis, as are focal seizures. Neuroimaging studies are generally normal in patients with encephalopathy, and EEG abnormalities are generally limited to diffuse slowing and the occasional appearance of triphasic waves. Conversely, patients with encephalitis frequently have neuroimaging abnormalities and may show focal EEG

TABLE 89.1 Comparison of Encephalitis and Encephalopathy

	ENCEPHALITIS	ENCEPHALOPATHY
Clinical Features		
Fever	Common	Uncommon
Headache	Common	Uncommon
Depressed mental status	May fluctuate	Steady decline in mental status
Focal neurologic signs	Common	Uncommon
Seizures	Common	Uncommon
Types of seizures	Generalized or focal	Generalized
Laboratory Results		
Complete blood count	Leukocytosis common	Leukocytosis uncommon
Cerebrospinal fluid	Pleocytosis common	Pleocytosis uncommon
Electroencephalogram	Diffuse slowing and occasional focal abnormalities or periodic patterns	Diffuse slowing
Magnetic resonance imaging	May have focal abnormalities	No focal abnormalities

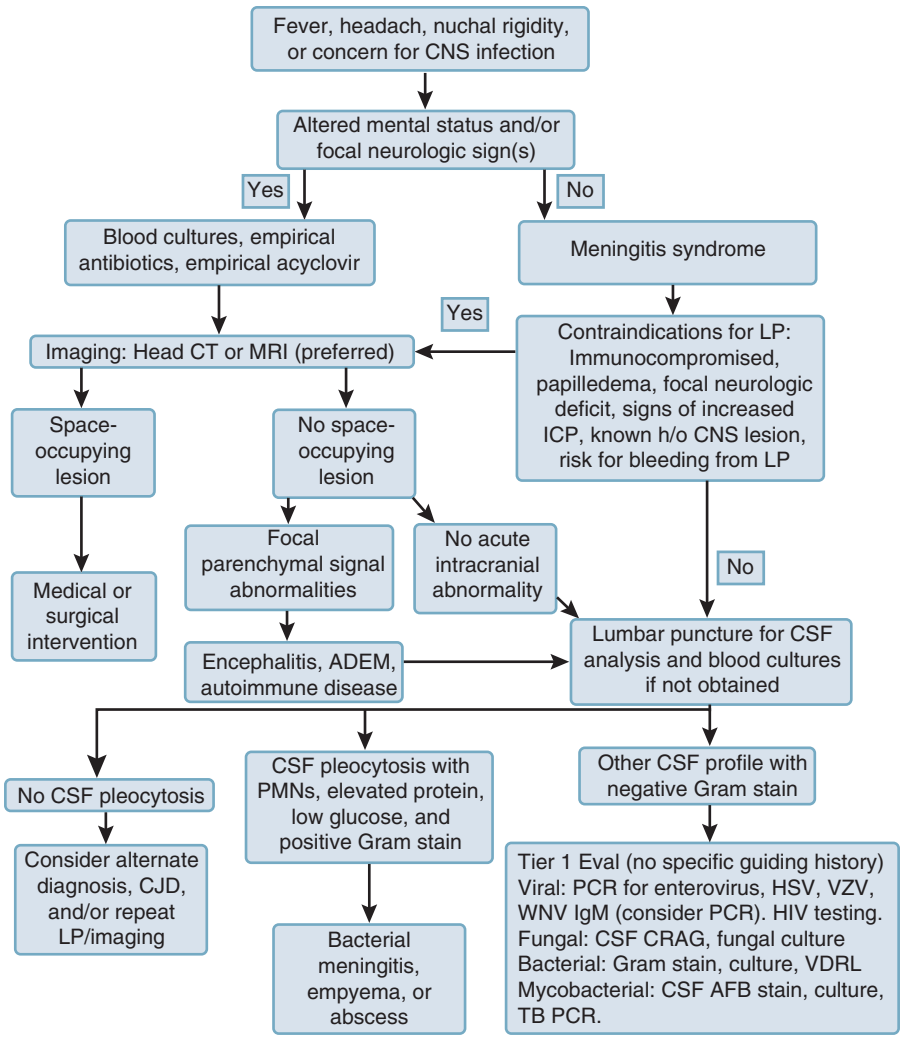

FIG. 89.1 Approach to the patient with possible central nervous system *(CNS)* infection. *ADEM,* Acute disseminated encephalomyelitis; *AFB,* acid-fast bacilli; *CJD,* Creutzfeldt-Jakob disease; *CSF,* cerebrospinal fluid; *CRAG,* cryptococcal antigen; *CT,* computed tomography; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus; *ICP,* intracranial pressure; *IgM,* immunoglobulin M; *LP,* lumbar puncture; *MRI,* magnetic resonance imaging; *PCR,* polymerase chain reaction; *PMN,* polymorphonuclear leukocyte; *TB,* tuberculosis; *VDRL,* Venereal Disease Research Laboratory; *VZV,* varicella zoster virus; *WNV,* West Nile virus. Tier 1 evaluation described. See text for subsequent evaluation based on exposures.

abnormalities or specific patterns of dysfunction that are rarely seen in encephalopathy (see later).

AUTOIMMUNE ENCEPHALITIS

Antibody-mediated autoimmune encephalitis is an important cause of encephalitis and should be considered in the differential diagnosis of patients with encephalitis. In addition to traditional paraneoplastic autoimmune etiologies of encephalitis (e.g., anti-Ma, anti-Yo, anti-Hu), neuronal antigen targeting by antibodies in the CNS is increasingly identified as an important cause of encephalitis and was recently reviewed.[9] About 70% of patients develop prodromal symptoms including headache, fever, nausea, vomiting, diarrhea, or upper respiratory tract symptoms. Within a few days to 2 weeks, patients can develop psychological symptoms including anxiety, insomnia, delusions, mania, or paranoia. Short-term memory loss is common but may be underrecognized owing to rapid disintegration of language and reduction in verbal output, which can progress to frank mutism. In more advanced stages of disease, patients develop decreased responsiveness, autonomic instability, dyskinesias, dystonia, rigidity, and opisthotonic postures.

In an analysis of patients younger than 30 years and enrolled in the CEP, anti–*N*-methyl-D-aspartate (NMDA) receptor encephalitis and viral encephalitis were noted to be equally important etiologies of encephalitis.[10] CSF in patients with anti–NMDA receptor encephalitis was characterized by a mild pleocytosis (median white blood cell count, 23 cells/mL) in the CSF with normal protein and glucose levels. The findings of neuroimaging with magnetic resonance imaging (MRI) were often abnormal but nonspecific, with no characteristic pattern or defining imaging results. When brain MRI findings were abnormal (50%), changes included T2 and fluid-attenuated inversion recovery (FLAIR) signal hyperintensity in the hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, brainstem, and rarely the spinal cord. EEGs in patients with anti-NMDA receptor encephalitis were often abnormal, most commonly due to diffuse or focal slowing patterns with occasional superimposed epileptic activity.

Autoimmune encephalitis is diagnosed by demonstrating the presence of specific antineuronal antibodies in the serum and/or the CSF in a patient with characteristic features of autoimmune encephalitis and negative findings on evaluation for infectious etiologies. Guidelines have been established to facilitate diagnosis of autoimmune limbic encephalitis in the absence of detectable autoantibodies.[9] Studies have also shown that viral causes of encephalitis such as HSV may be associated with production of autoreactive antibodies.[11] It is important to remember that the diagnoses of autoimmune encephalitis and viral encephalitis are not mutually exclusive; patients with HSV and other viral encephalitides may also have or develop autoantibodies and patients in whom autoantibodies are detected may also have an associated viral encephalitis. The list of autoantibodies associated with autoimmune encephalitis is rapidly expanding; the most commonly identified antibodies are those against the NMDA receptor; leucine-rich, glioma-inactivated 1 (LGI-1) protein; α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (AMPAR); and γ-aminobutyric acid B receptor ($GABA_BR1$). Although patients with autoimmune encephalitis generally have antibodies present in serum, in the case of anti-NMDA receptor encephalitis, CSF autoantibodies may be present in the absence of serum antibodies.

Treatment of autoimmune encephalitis is largely based on immunosuppressive regimens. Response to treatment for autoimmune encephalitis is variable, and relapse can occur in up to 24% of patients.[12] In female patients with NMDA receptor encephalitis, evaluation for an underlying ovarian teratoma and removal, if a tumor is found, is indicated. First-line immunotherapy consists of corticosteroids, intravenous immunoglobulins (IVIGs), or plasma exchange. In patients without a tumor, delayed diagnosis, or poor response to first-line therapy, second-line immunotherapy with rituximab, cyclophosphamide, or both is indicated. Despite the difficulty in treating these patients, the mortality rate is low, yet long-term neurologic outcomes are variable with potential for severe, fixed neurologic impairment.

It is also important to consider postinfectious encephalomyelitis or ADEM when evaluating patients with possible encephalitis. ADEM is an inflammatory demyelinating disease of the CNS that follows an infection or vaccination, typically after a delay of 1 to 4 weeks.[13] Most cases are monophasic and associated with MRI findings of diffuse or multifocal subcortical and central white matter lesions with increased signal on T2-weighted and FLAIR sequences.[14,15] A preceding infection or vaccination is found in about two-thirds of pediatric cases and half of adult cases.[14,16] Studies have stressed the importance of antecedent infections caused by influenza A and B, hepatitis viruses, nonspecific flu-like upper respiratory tract infections, and nonviral infectious agents including *Mycoplasma*.[16] Postvaccination cases of ADEM are rare with the vaccines in general use now.

GENERAL CLINICAL APPROACH

When an infection of the CNS is considered in the differential diagnosis, the evaluation should progress efficiently to rule out important reversible causes of disease (see Fig. 89.1). Diagnostic algorithms have been developed to help standardize the clinical approach to these complex patients.[8] In cases of bacterial meningitis and herpes simplex encephalitis (HSE), studies have shown that delay in therapy increases morbidity and mortality.[17–19] When evaluating a patient with possible encephalitis, the initial diagnostic goals are to obtain CSF for appropriate studies and to perform neuroimaging, preferably MRI, unless contraindicated. In patients who are older than 60; are immunocompromised; have a history of known CNS disease; or have recent seizures, altered consciousness, focal neurologic deficits, or other signs suggestive of increased intracranial pressure (ICP), neuroimaging should be completed before lumbar puncture.[18,20] In patients with suspected bacterial meningitis, empirical antibiotic therapy should be initiated after blood cultures are performed if lumbar puncture is delayed for neuroimaging (see Chapter 87).[18] Empirical acyclovir therapy should be initiated in patients with suspected encephalitis, pending results of diagnostic studies.[7]

MRI is more sensitive and provides more detailed diagnostic information than computed tomography (CT) in patients with suspected CNS infections, including encephalitis, and is the procedure of choice.[21,22] Neuroimaging studies can provide valuable clues that can assist in specific diagnosis of encephalitis. The most common abnormalities include areas of increased signal on T2 and FLAIR sequences. Diffusion-weighted imaging sequences may show abnormalities before, or that are more extensive than those seen in, T2 and FLAIR sequences.[21–26]

CSF examination is part of basic testing in all patients with suspected encephalitis or meningitis.[7,18] The most common CSF profile in patients with viral encephalitis is a lymphocytic pleocytosis with a normal glucose concentration and an elevated protein concentration. This pattern is similar to that seen in most cases of autoimmune encephalitis, ADEM, and several other causes of noninfectious encephalitis. The presence of neutrophils rather than lymphocytes as the predominant cell type occurs frequently in patients with WNV neuroinvasive disease or tick-borne encephalitis virus and can occur with eastern equine encephalitis and some enteroviruses (see specific virus sections for details).

Suggested CSF diagnostic studies in immunocompetent adults in the United States with suspected encephalitis include a CSF opening pressure, cell count and differential, protein and glucose concentrations, Gram stain, and bacterial cultures (see Fig. 89.1, tier 1 studies). Initial viral studies of the CSF should include polymerase chain reaction (PCR) studies for HSV, VZV, and enteroviruses, and WNV immunoglobulin M (IgM) serology (in the appropriate season). Routine testing should also include HIV testing, CSF Venereal Disease Research Laboratory (VDRL) test with serum treponemal assessment, and cryptococcal antigen testing. Additional diagnostic tests, or tier 2 tests, are guided by and prioritized according to the clinical and epidemiologic clues obtained during evaluation of the patient (Table 89.2). Diagnostic algorithms for patients with encephalitis have been proposed.[8]

In immunocompromised patients, CSF PCR for CMV, human herpesvirus type 6 (HHV-6), and in specific settings JC virus can be included in the initial evaluation depending on the underlying risk factors. A second tier of CSF diagnostic studies in immunocompetent patients might include PCR studies of the CSF for HIV, *Mycoplasma pneumoniae,* and *Mycobacterium tuberculosis*; IgM serologies for specific viruses such as WNV, Powassan virus, La Crosse virus (California encephalitis), St. Louis encephalitis virus, and eastern equine encephalitis virus, and Lyme disease (as geographically appropriate); acid-fast bacillus smear and culture; tuberculosis PCR; fungal cultures; *Coccidioides*

TABLE 89.2 Possible Etiologic Agents of Encephalitis Based on Epidemiology and Risk Factors

EPIDEMIOLOGY OR RISK FACTOR	POSSIBLE INFECTIOUS AGENTS
Travel	
Caribbean islands, Central America, South America	Rabies virus; eastern equine encephalitis virus; western equine encephalitis virus; Venezuelan equine encephalitis virus; St. Louis encephalitis virus; Rocio virus; Zika virus; chikungunya virus; Dengue virus
Australia	Murray Valley encephalitis virus; Japanese encephalitis virus; Hendra virus
Southeast Asia, China	Japanese encephalitis virus; tick-borne encephalitis; Nipah virus; Me Tri virus; Semliki Forest virus
India, Nepal	Rabies virus; Japanese encephalitis virus; chikungunya virus
Africa	Rabies virus; WNV; Rift Valley fever virus
Middle East	WNV
Europe	WNV; tick-borne encephalitis; louping ill virus; Toscana virus
Russia	Tick-borne encephalitis; Powassan virus
Insect Contact	
Mosquitoes	WNV; Zika virus; Eastern equine encephalitis virus; Venezuelan equine encephalitis virus; St. Louis encephalitis virus; Murray Valley encephalitis virus; Japanese encephalitis virus; California encephalitis group; chikungunya virus
Ticks	Tick-borne encephalitis; Powassan virus; louping ill virus
Animal Contact	
Old World monkeys	Herpesvirus B
Birds	WNV; eastern equine encephalitis virus; Venezuelan equine encephalitis virus; St. Louis encephalitis virus; Murray Valley encephalitis virus; Japanese encephalitis virus
Rodents	Eastern equine encephalitis virus (South America); Venezuelan equine encephalitis virus; tick-borne encephalitis; Powassan virus; La Crosse virus (chipmunks and squirrels); LCMV; monkeypox
Horses	Eastern equine encephalitis virus; western equine encephalitis virus; Venezuelan equine encephalitis virus; Hendra virus
Swine	Japanese encephalitis virus; Nipah virus
Dogs	Rabies virus
Bats	Rabies virus; Nipah virus
Raccoons	Rabies virus
Skunks	Rabies virus
Sheep and goats	Louping ill virus
Human Contact	
Person-to-person transmission	HSV (neonatal); VZV; Venezuelan equine encephalitis virus (rare); poliovirus; enteroviruses; measles virus; mumps virus; rubella virus; EBV; HHV-6; herpesvirus B; WNV (transfusion, transplantation, breast-feeding); HIV; rabies virus (transplantation); influenza virus
Season	
Late summer, early fall	All agents transmitted by mosquitoes and ticks (see above); enteroviruses
Winter	Influenza virus; LCMV
Recreational Activities	
Sexual contact	HIV; Zika virus
Swimming	Enteroviruses
Camping, hunting	All agents transmitted by mosquitoes and ticks (see above)
Spelunking	Rabies virus
Occupation	
Physicians and health care workers	VZV; HIV; influenza virus
Veterinarians	Rabies virus
Laboratory workers	WNV; HIV
Workers exposed to Old World primates	Herpesvirus B
Workers exposed to horses	Hendra virus
Ingestions	
Unpasteurized milk	Tick-borne encephalitis
Age	
Neonates	HSV-2; CMV; rubella virus; Zika virus
Infants and children	Eastern equine encephalitis virus; Murray Valley encephalitis virus (rapid in infants); influenza virus; La Crosse virus
Elderly	Eastern equine encephalitis virus; St. Louis encephalitis virus; WNV

Continued

TABLE 89.2 Possible Etiologic Agents of Encephalitis Based on Epidemiology and Risk Factors—cont'd

EPIDEMIOLOGY OR RISK FACTOR	POSSIBLE INFECTIOUS AGENTS
Other	
Unvaccinated	VZV; Japanese encephalitis virus; poliovirus; measles virus; mumps virus; rubella virus
Recent vaccination	ADEM
Transfusion and transplantation	CMV; EBV; WNV; HIV; tick-borne encephalitis virus; rabies virus; LCMV
Immunocompromised	VZV; CMV; HHV-6; WNV; HIV; JC virus
Agammaglobulinemia	Enteroviruses

ADEM, Acute disseminated encephalomyelitis; *CMV,* cytomegalovirus; *EBV,* Epstein-Barr virus; *HHV,* human herpesvirus; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus; *LCMV,* lymphocytic choriomeningitis virus; *VZV,* varicella-zoster virus; *WNV,* West Nile virus.
Modified from Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Disease Society of America. Clin Infect Dis. *2008;47:303–327.*

complement fixation titer; and antibody titer. Other studies to consider based on epidemiologic risk profiles include PCR studies of the CSF for *Rickettsia, Ehrlichia,* and *Anaplasma*; CSF *Histoplasma* antigen; and CSF enzyme-linked immunosorbent assay (ELISA) and Western blot for *Borrelia burgdorferi.* Such tests are appropriate in areas where these agents are endemic or with potential exposure history.

CSF studies should be supplemented with serum diagnostic studies. Common tests include HIV serology and plasma HIV RNA viral load; EBV serologies (IgG and IgM antibodies against viral capsid antigen and IgG antibodies against early and nuclear antigens); *Mycoplasma* serologies; syphilis serology; *Borrelia* serologies[a]; *Rickettsia, Ehrlichia,*[a] and *Anaplasma* serologies[a]; serum cryptococcal antigen[a]; serum antibodies against *Coccidioides*[a]; and urine *Histoplasma* antigen.[a]

An EEG can be helpful in evaluating the type and frequency of seizures and the presence of nonconvulsive status epilepticus. The degree and severity of slowing is a sensitive indicator of the presence and severity of metabolic encephalopathies. Specific EEG patterns may suggest an increased likelihood of specific diagnoses (see "Diagnostic Tests").

Clinical Manifestations

The clinical presentation of patients with viral encephalitis can be heterogeneous, necessitating a high index of suspicion in any patient with signs of infection and CNS dysfunction. The syndrome of acute viral encephalitis is characterized by fever, headache, and altered mental status.[7] These may be combined with focal neurologic deficits corresponding to areas of the CNS that are infected and injured, which vary with specific pathogens. This constellation of signs and symptoms is not unique for encephalitis and can occur in various other diseases, including viral and bacterial meningitis, brain abscess, cerebritis, subdural and epidural empyema, and septic cerebral venous or sinus thrombosis. The frequency of specific signs and symptoms varies among different types of encephalitis and is discussed more completely in the sections on individual viral pathogens.

The presence of specific sets of neurologic signs and symptoms by themselves does not allow unequivocal diagnosis of a specific cause of encephalitis. Findings of neurologic examination can increase the likelihood of some etiologic agents and reduce the likelihood of other pathogens, facilitating and guiding confirmatory diagnostic testing. The most common focal neurologic signs associated with encephalitis include hemiparesis, aphasia, ataxia, cranial nerve (CN) palsies, myoclonus, and seizures. Other important neurologic findings include loss of temperature and vasomotor control because of autonomic dysfunction and either diabetes insipidus or the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) resulting from hypothalamic dysfunction.

Signs of parkinsonism (bradykinesia, rigidity, rest tremor) may suggest infection with a flavivirus (e.g., WNV, St. Louis encephalitis virus, Japanese encephalitis virus [JEV]), and frontotemporal signs such as aphasia, memory impairment, and personality changes may suggest limbic encephalitis from HSV, HHV-6 infection, a paraneoplastic etiology, or autoimmune limbic encephalitis. Seizures occur most frequently in encephalitides that involve the cortex (e.g., HSV encephalitis) and less commonly with flavivirus infections (e.g., WNV, St. Louis encephalitis virus, JEV) that involve predominantly deep gray matter structures such as the basal ganglia and thalamus. Brainstem involvement can occur with HSV, enterovirus 71 infections, and flaviviruses (e.g., WNV), whereas cerebellitis is associated with EBV, VZV, mumps, and flavivirus (e.g., WNV, St. Louis encephalitis virus) infections. Flaviviruses (e.g., WNV, JEV), enteroviruses D-68 and 71, and poliovirus can cause disease in the anterior horn of the spinal cord, resulting in a poliomyelitis and the clinical syndrome of acute flaccid paralysis.

The frequency of CN palsies varies greatly in patients with encephalitis. CN palsies are common in several nonviral infections that can mimic viral encephalitis (e.g., Lyme disease, syphilis, tuberculosis, fungal infections) and most commonly produce peripheral facial palsy (CN VII), vestibular or cochlear dysfunction (CN VIII), or paralysis of extraocular movements (CN III, IV, or VI). CN palsies are generally infrequent in viral encephalitis, unless there is concomitant brainstem involvement. However, WNV infection and VZV vasculopathy have been associated with palsies of various CNs (see specific sections).

The epidemiologic features of different neurotropic viruses vary widely and often help guide diagnostic testing (see Table 89.2). Immunocompromised patients are at increased risk for neuroinvasive viral infections resulting from VZV, CMV, HHV-6, JC virus (PML), and WNV. Similarly, older individuals have an increased risk of neuroinvasive disease after infection with many arboviruses (*ar*thropod-*bo*rne *viruses*), including WNV, St. Louis encephalitis virus, and eastern equine encephalitis virus, and have an increased incidence of HSV encephalitis. Prenatal infection with subsequent pregnancy loss or devastating postnatal complications including microcephaly, intracranial calcifications, ventriculomegaly, and developmental abnormalities frequently occurs after infection with CMV and Zika virus (ZIKV).

Seasonal incidence is characteristic of all arbovirus infections in the United States. Most arboviruses are transmitted by a mosquito vector during summer and early fall months in patients living in areas of epizootic transmission of virus. By contrast, infection with some viruses, including lymphocytic choriomeningitis virus (LCMV) and influenza, are more frequent during late fall and winter months. Many arboviruses are geographically restricted, and residence or a recent travel history can provide important clues to potential exposures. WNV is now endemic throughout the United States and causes sporadic seasonal epidemics (www.cdc.gov/ncidod/dvbid/westnile/). Other arboviruses are also geographically restricted in the United States, and Powassan virus has emerged as an increasingly common cause of encephalitis (Fig. 89.2). A history of travel to specific foreign countries where other arboviruses are endemic should be specifically sought, and diagnostic studies should be adjusted appropriately.

The general physical examination also provides important clues that assist in the diagnosis of encephalitis. Skin rashes are common and characteristic for VZV, WNV, ZIKV, some enteroviruses, measles, and rubella and may occur with various nonviral infections, including Lyme

[a]Based on geographic setting and exposure history.

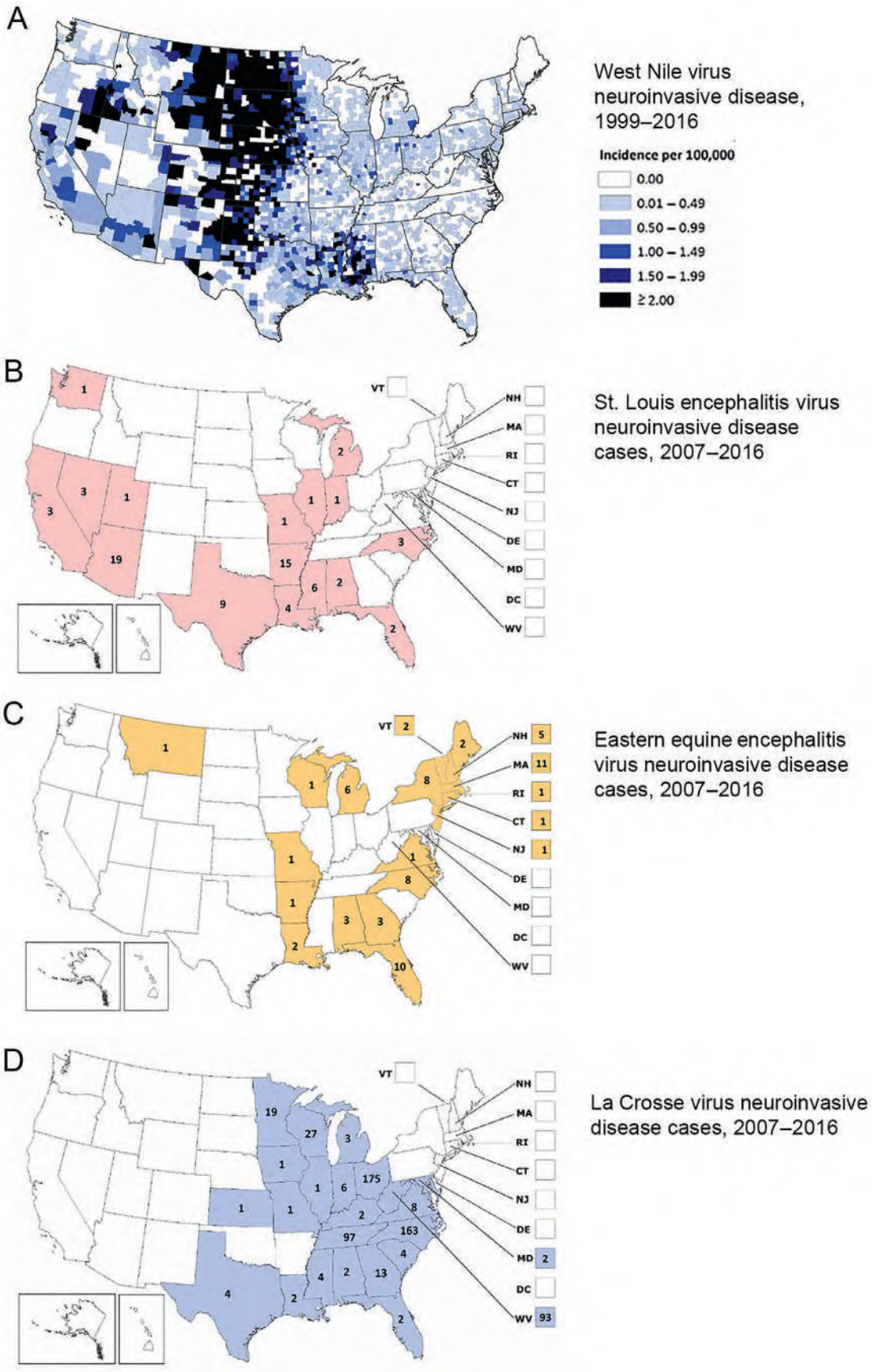

FIG. 89.2 **Incidence of select arboviruses in the United States.** (A) Annual incidence of West Nile virus neuroinvasive cases by county from 1999 to 2016. Number of neuroinvasive cases of (B) St. Louis encephalitis virus, (C) eastern equine encephalitis virus, and (D) La Cross virus reported to the Centers for Disease Control and Prevention from 2007 to 2016. *(Modified from Centers for Disease Control and Prevention.* www.cdc.gov/westnile, www.cdc.gov/sle, www.cdc.gov/easternequineencephalitis, www.cdc.gov/lac.*)*

disease, syphilis, mycoplasmosis, rickettsiosis, anaplasmosis, and ehrlichiosis. Oral mucosal ulcerations may suggest herpangina and an enterovirus. Ocular findings including chorioretinitis occur with WNV, CMV, and *Bartonella* infection (cat-scratch disease). Parotitis, orchitis, and oophoritis can occur with mumps and LCMV infections.

Diagnostic Tests

When a patient develops encephalitis, specific diagnosis is usually based on CSF studies. Diagnostic studies obtained from samples outside the CNS, including serum serologies, serum nucleic acid amplification tests, serum or urine antigen tests, and cultures of body fluids (blood, nasopharyngeal swab, sputum, and urine), may be useful in establishing the presence of a particular infectious process. Despite the presence of a systemic infection, additional testing may be required to establish a definitive cause of CNS disease. General diagnostic studies such as a complete blood count and markers of inflammation (e.g., erythrocyte sedimentation rate, C-reactive protein) may support the presence of an infectious or inflammatory process but do not help determine a specific etiology. Chest radiography may suggest an infectious cause, such as influenza, mycoplasmosis, tuberculosis, or coccidioidomycosis. It may also suggest the presence of cancer or other noninfectious causes of encephalitis.

Neuroimaging

Unless specifically contraindicated, all patients with suspected encephalitis should undergo MRI. The sensitivity and specificity of different patterns of neuroimaging abnormalities for the diagnosis of specific forms of encephalitis have not been formally defined. Different forms of encephalitis may produce distinctive MRI patterns that can provide clues suggestive of particular agents, which can guide more definitive confirmatory tests.

Temporal lobe and limbic abnormalities are seen in HSV, HHV-6, and autoimmune encephalitis, whereas subependymal enhancement occurs with CMV ventriculitis. MRI often reveals multifocal hemorrhagic infarctions and demyelinating lesions in cases of VZV vasculopathy.[27] Predominant demyelination on MRI studies suggests PML caused by JC virus infection, ADEM, or encephalitis mimics such as multiple sclerosis or other noninfectious CNS inflammatory diseases. PML lesions typically do not enhance or do so faintly at lesion margins, whereas MRI lesions associated with ADEM typically uniformly enhance acutely and become nonenhancing over time.

In HSV encephalitis, MRI is significantly more sensitive than CT, revealing temporal lobe abnormalities in 90% of PCR-proven HSV cases (Fig. 89.3).[28] In one study, 79% of patients with HSV encephalitis had abnormalities on their initial CT scan, but 100% of the 17 patients whose CT scan was initially normal and who had repeat scans had abnormalities an average of 5 days later.[28] MRI abnormalities of the temporal lobe were shown in 89% of patients with HSV; 36% also had frontal lobe involvement. Only 9% of adult patients with HSV encephalitis had MRI with abnormalities exclusively outside the frontotemporal area, although patterns in infants and children may be more variable. In 57% of HSV encephalitis patients, the abnormalities were predominantly unilateral.[17] Characteristic MRI changes occur early in the course of HSV encephalitis and include high–signal intensity lesions on T2-weighted and FLAIR images involving the medial and inferior temporal lobes with extension into the insula. MRI abnormalities can also include the orbitofrontal gyri and inferomedial frontal lobes.[29,30] Diffusion-weighted imaging abnormalities may antedate and be more extensive than abnormalities seen on T2 and FLAIR sequences.[21–26]

CT scans are almost invariably normal early in WNV infection. MRI abnormalities are less frequent in cases of WNV than in cases of HSV encephalitis. In two series involving 34 patients, initial MRI studies were normal in approximately one-third of patients. MRI abnormalities associated with WNV encephalitis included areas of increased T2 and FLAIR and low T1 signal that involved the basal ganglia, thalamus, and brainstem.[31,32] The MRI abnormalities in WNV infection are generally distinct from the abnormalities seen in HSV encephalitis, although in one series about 20% of patients with WNV encephalitis had abnormalities limited to the mesial temporal lobes.[32] Some patients with WNV infection have only meningeal enhancement or abnormalities seen only on diffusion-weighted images.

Patients with JEV and St. Louis encephalitis virus have MRI abnormalities similar to those reported for WNV. In one study, MRI was more sensitive than CT for JEV infections, showing abnormalities in more than 90% of adults and children.[33] The most commonly involved areas were the thalamus (88%), basal ganglia (41%–54%), and brainstem,[33,34] but some patients can have medial temporal lesions resembling those seen in HSV encephalitis.[35] Patients infected with enterovirus 71 may show increased T2 and FLAIR signal intensity in the midbrain, pons, and medulla. Congenital and neonatal ZIKV infection can result in a wide spectrum of abnormalities including microcephaly, intracranial calcifications, ventriculomegaly, and developmental abnormalities.

Cerebrospinal Fluid Analysis

Cerebrospinal Fluid Profile

CSF examination is an essential part of the diagnosis of encephalitis and should be performed in all patients unless absolutely contraindicated.[7] The most typical CSF profile in patients with viral encephalitis is a CSF pleocytosis with a predominance of lymphocytes, a normal glucose level, and an elevated protein level. In cases of flavivirus infection, particularly WNV, neutrophils may predominate,[36] a finding also associated with eastern equine encephalitis. In one large series, the median percentage of neutrophils in patients with WNV encephalitis was 45%, and 37% of cases had a neutrophil predominance.[36] By contrast, patients with HSV encephalitis typically have 5% to 24% neutrophils.[17,37]

The magnitude of CSF pleocytosis varies greatly in different forms of encephalitis. In the classic studies of biopsy-proven HSV encephalitis by the Collaborative Antiviral Study Group (CASG), patients had a median CSF white blood cell count of 130 cells/mm^3; 68% of patients had 50 to 500 cells/mm^3. Only 4% of patients had fewer than 5 cells/mm^3, and only 8% had more than 500 cells/mm^3.[38] Similar CSF profiles were noted in a study of HSV encephalitis confirmed with CSF PCR. In that study, no patient with HSV encephalitis had fewer than 5 cells/mm^3, and 69% of HSV encephalitis patients had 50 to 500 cells/mm^3.[28] Two later PCR-based studies reported that patients had a mean of 202 to 237 leukocytes/mm^3.[17,37] In a large series of cases with serologically proven WNV encephalitis, the mean CSF cell count was 227 cells/mm^3 (95% confidence interval [CI], 133–321).[36] Patients with mumps meningoencephalitis had higher mean cell counts compared with WNV patients, with a mean of 540 ± 460 cells/mm^3 and an average of 56% lymphocytes.[39]

Although pathologic evaluation of HSV encephalitis often shows the presence of hemorrhagic necrosis, CSF red blood cell counts do not differ significantly between patients with biopsy-proven HSV encephalitis and nonherpetic encephalitis.[38,40] Glucose concentrations are normal in more than 95% of patients with encephalitis caused by HSV and flaviviruses (WNV, St. Louis encephalitis virus) but may be low in some cases of CMV, mumps, and eastern equine encephalitis infection.[38,39,41,42]

Polymerase Chain Reaction and Antibody Studies

For some neuroinvasive viruses, PCR of the CSF has high sensitivity and specificity, making it the diagnostic study of choice for identifying a specific viral etiology.[43] HSV PCR of the CSF has a sensitivity of 98% and a specificity of 94%.[30,44] The sensitivity of PCR for detection of HSV encephalitis varies with the timing of the study. In the CEP, three patients with negative CSF HSV PCR test results performed within 72 hours of symptom onset had positive test results 4 to 7 days later.[45] By contrast, in a study using nested PCR to detect HSV DNA in CSF, 100% (18 of 18) of patients tested within 72 hours of onset of neurologic symptoms had amplifiable DNA.[46] CSF HSV PCR sensitivity declines as a function of duration of antiviral therapy; 98% of studies remain positive in patients treated for 7 days or less, followed by a decrease in sensitivity with ongoing treatment to 47% at 8 to 14 days and 21% after 15 days of antiviral treatment.[44] These results reflect the progressive decline in CSF viral load that occurs as a function of duration of acyclovir therapy. With use of quantitative PCR, acyclovir-treated patients had negative PCR results 19 ± 6 days (range, 9–28 days) after initiation of acyclovir

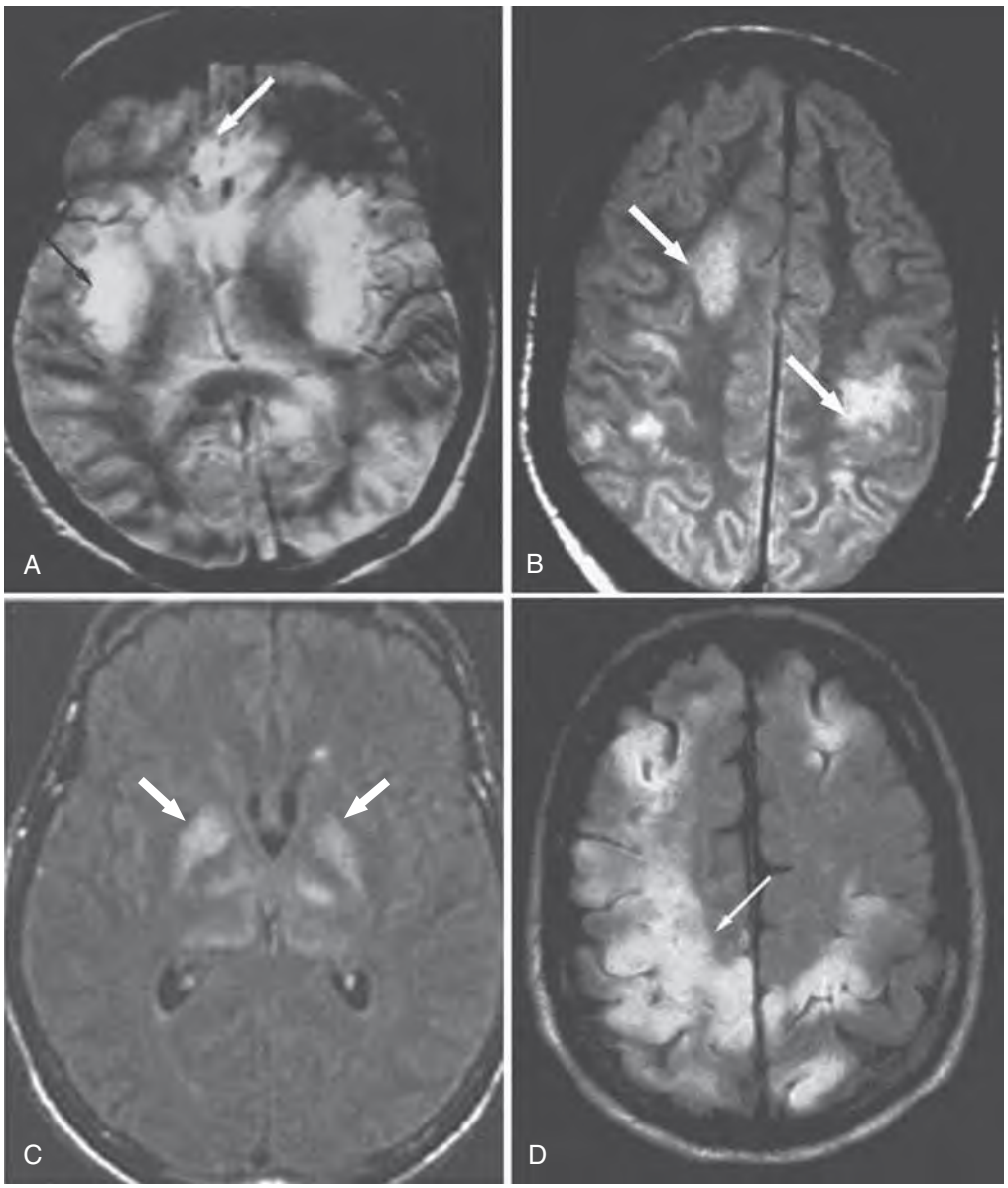

FIG. 89.3 Typical magnetic resonance imaging (MRI) changes associated with viral encephalitis. (A) Herpes simplex virus type 1 encephalitis with increased T2-weighted signal in bilateral temporal lobes. Increased signal does not extend beyond the insular cortex *(black arrow)* but does involve the cingulate gyrus *(white arrow).* (B), Varicella-zoster virus vasculopathy on proton-density MRI scan with multiple areas of infarction in both hemispheres *(arrows).* (C) West Nile virus encephalitis with increased signal on FLAIR MRI image of the basal ganglia *(arrows).* (D) Enterovirus encephalitis with increased signal intensity on FLAIR MRI image in both hemispheres, greater on the right, in the posterior cerebral hemisphere *(arrow). (Modified from Gilden DH, Mahalingam R, Cohrs RJ, Tyler KL. Herpesvirus infections of the nervous system.* Nat Clin Pract Neurol. *2007;3:83; and Debiasi RL, Tyler KL. West Nile virus meningoencephalitis.* Nat Clin Pract Neurol. *2006;2:264.)*

therapy.[47] Neither the initial CSF HSV viral load nor its maximal level predicts outcome[47,48]; however, one study found that patients with extremely high copy number (>100,000 copies HSV DNA per milliliter) were more likely to have a reduced level of consciousness, CT scan lesions, and poor outcomes compared with patients with less than 100,000 DNA copies/mL.[49]

The results of HSV PCR should be interpreted in the context of the timing of the study and the pretest probability of disease. In patients with a high pretest probability of HSV encephalitis (e.g., 60%), a positive PCR result increases the posttest probability to 99%, and a negative study result reduces it to 6%. In patients with a moderate pretest probability of HSV (e.g., 35%), the posttest probability for a positive test result is 98%, and probability for a negative test result decreases to 2%. In patients with low pretest probability of HSV encephalitis (e.g., 5%), the posttest probabilities are 84% for a positive test result and 0.2% for a negative test result.[50]

HSV-specific CSF antibody testing to detect intrathecal synthesis of antibody can complement PCR testing when specimens are obtained later in the course of illness. After the first week of disease, the sensitivity of CSF HSV PCR declines (see earlier), whereas the sensitivity of CSF antibody testing increases. In one series of patients with HSV encephalitis, none of 36 CSF samples taken later than 30 days after onset of neurologic symptoms had amplifiable DNA, but all had detectable HSV antibody.[46]

PCR detection of VZV DNA in the CSF has a specificity of greater than 95%, but sensitivity can decrease after 2 to 3 weeks following presentation. In cases of VZV CNS vasculopathy, CSF should also be tested for intrathecal synthesis of VZV-specific antibody (CSF–to–serum IgG ratio) because these studies are complementary to PCR.[51]

PCR for EBV or HHV-6 DNA in the CSF can be a valuable addition to the evaluation of a patient with viral encephalitis.[52,53] However, the

results must be interpreted with caution and correlated with the clinical presentation, imaging, and serology results because latently infected, HHV-6– or EBV-positive mononuclear cells in the CSF can produce false-positive results.

CSF PCR is extremely specific (>95%) for diagnosis of PML in immunocompromised patients with appropriate clinical and radiographic findings. The sensitivity of CSF JC virus PCR is quite variable in different settings (50%–80%). For example, patients with PML associated with use of immunomodulatory drugs such as natalizumab frequently have a low JC virus CSF copy number and those with HIV-associated PML a higher copy number, with assay sensitivity paralleling copy number. Higher CSF JC viral loads correlate with worse outcomes in patients with HIV-associated PML.[54] A positive JC virus serum antibody finding is of limited diagnostic use because approximately 55% to 85% of individuals are seropositive in serum by adult life, although the absence of detectable anti–JC virus antibodies may decrease the likelihood of PML in the differential diagnosis unless a patient is severely immunocompromised and unable to mount an antibody response. In some studies, increasing titers of CSF or serum JC virus antibodies have immediately preceded the onset of PML.

In the case of flaviviruses including WNV, CSF PCR is less sensitive (57%–70%) compared with detection of CSF IgM antibodies for diagnosis of neuroinvasive disease.[55] An exception may occur in immunocompromised patients, such as bone marrow and solid organ transplant recipients, who have a prolonged, high-titer viremia, and can have positive serum or CSF PCR studies, or both, when antibody tests are negative or seroconversion is delayed.[56,57]

In a study of blood donors with asymptomatic WNV infection detected with positive results of serum nucleic acid amplification testing, peak serum RNA levels occurred at 5 to 6 days after an infected mosquito bite, IgM seroconversion occurred 3.9 days after RNA detection (95% CI, 3.4–4.4), and IgG seroconversion occurred at 7.7 days after RNA detection (95% CI, 6.9–8.5).[58] CSF IgM WNV antibodies are diagnostic of acute WNV infection and neuroinvasive disease; their presence is indicative of intrathecal synthesis because IgM molecules cross the blood-brain barrier poorly owing to their large size. CSF IgM antibodies are found in approximately 80% of patients with WNV neuroinvasive disease within 1 week of onset of symptoms, increasing at a rate of about 10% per day after symptom onset.[59] It is unclear how long CSF WNV IgM antibodies persist. In one small study, 60% of patients with WNV encephalitis had persisting CSF IgM antibody for as long as 500 days.[60]

Future diagnostic approaches. Recent advances in nested PCR testing using film-array technology now allow for multiplex testing of patient samples against a panel of pathogens. Clinical laboratories are increasingly using multiplex PCR testing for multiple clinical samples including respiratory samples, stool samples, and CSF samples. A multicenter study of a multiplex diagnostic CSF panel found that the assay exhibited high specificity for all tested pathogens but exhibited variable sensitivity for several that ranged from 0% to 100%.[61] Some variability in sensitivity was due to low numbers of pathogens in the study groups. Also, inclusion of targets such as HHV-6 that can produce positive test results in situations that are not likely due to HHV-associated disease may create problems with interpretation. The current commercially available CSF arrays are more applicable for pediatric populations, and further development of these arrays will likely provide new diagnostic approaches for cases of adult encephalitis. In addition to multiplexed assays, next-generation sequencing (NGS) assays of CSF samples are being evaluated and applied to clinical samples.[62] As the cost for sequencing technology continues to decrease and processes are simplified, future diagnostic approaches may include routine metagenomic NGS for unbiased detection of pathogens. To date this technology has proven to be most useful in immunocompromised patients rather than as a global diagnostic tool. It is important to recognize that the major advantage of this approach is its "unbiased" nature—meaning its ability to enable detection of a wide variety of pathogens. Conversely, NGS may be less sensitive than individually targeted PCR assays for specific pathogens and requires meticulous attention to technique to avoid contamination from reagents or other ambient sources.

Electroencephalography

EEGs in patients with viral encephalitis are frequently abnormal, but the results only rarely provide a clue to a specific etiologic diagnosis. The most common abnormality is the presence of generalized slowing.[63] Focal EEG abnormalities, most commonly involving the temporal lobes, are seen in 75% to 80% of patients with HSV encephalitis.[28,38] Common abnormalities include the presence of frontotemporal slowing, temporal sharp or spike activity, and periodic lateralizing epileptiform discharges at a rate of 2 to 3 Hz.[38] None of these patterns is diagnostic of HSV encephalitis. Periodic lateralizing epileptiform discharges, previously considered characteristic of HSV encephalitis, can also be seen in other types of encephalitis (e.g., La Crosse/California virus encephalitis).[64] Appearance and resolution of EEG abnormalities do not correlate well with clinical presentation or resolution of disease.[30,65]

EEG abnormalities have been reported in approximately 60% to 90% of patients with WNV encephalitis. The most common finding is the presence of diffuse irregular slow waves, although the presence of anteriorly predominant slowing may suggest the diagnosis.[66] Triphasic slow waves, generally considered more characteristic of metabolic encephalopathies, have also been reported in WNV encephalitis.[67]

Other Diagnostic Studies

In general, CSF culture is of limited value in cases of viral encephalitis and is not recommended for routine clinical application.[7] Occasionally, acute and convalescent serum studies suggest a viral etiology and may be required in rare cases when CSF evaluation is impossible. Additional studies, such as PCR assay of gastrointestinal samples for enteroviruses, have been used as supportive diagnostic tests for viral encephalitis.[63] Other supportive tests include PCR or antigen detection of respiratory secretions for adenoviruses, parainfluenza, or influenza viruses. Fluid from skin vesicles should be examined with PCR for evidence of enteroviruses, VZV, or HSV. Brain biopsy is rarely used today because of the availability and accuracy of PCR and antibody tests. Brain biopsy still serves a diagnostically useful function, however, in unexplained cases of encephalitis associated with progressive neurologic deterioration.[7]

Management

The clinical status of patients with encephalitis can deteriorate rapidly; patients should be closely monitored in an intensive care unit or equivalent setting. Viral encephalitis caused by arboviruses or herpesviruses does not require patient isolation for infection control. Respiratory or contact isolation should be considered in cases of encephalitis of unknown etiology or in patients with possible bacterial meningitis or a skin rash. Universal precautions should be applied to handling all body fluids, including CSF, blood, saliva, respiratory secretions, stool, and urine because their potential infectivity varies with the inciting pathogen.

Patients with encephalitis may develop increased ICP. Patients with potential signs of increased ICP, such as decreased level of consciousness, papilledema, or cerebral edema, often require continuous ICP monitoring. Clinical trials studying the role of corticosteroids in encephalitis patients have been inconclusive, and further studies are necessary; however, in cases of encephalitis with increased ICP, corticosteroids may be used to treat cerebral edema.[63,68,69] Additional measures to reduce increased ICP acutely include hyperventilation and administration of intravenous (IV) mannitol.

Patients with certain types of encephalitis are likely to be at increased risk of seizures, and seizures can contribute to transiently increased ICP. There is no proven clinical value for primary prophylactic anticonvulsant therapy in patients with encephalitis. Patients with seizures are generally treated urgently with lorazepam or diazepam followed by maintenance therapy with IV fosphenytoin. Patients may require continuous EEG monitoring because clinical observation in obtunded patients may not reliably detect seizures.

Patients with encephalitis can experience autonomic dysfunction resulting in hypotension or cardiac arrhythmias and should undergo close monitoring of blood pressure and electrocardiogram until clinically stable. If the airway is compromised because of alterations in

consciousness, intubation should be considered to protect the airway and prevent aspiration. If clinically indicated, empirical antimicrobial agents should be initiated in patients with suspected bacterial infection or bacterial meningitis.

Few randomized controlled trials have assessed the efficacy of antiviral treatments or immunomodulatory therapy in patients with viral encephalitis, other than acyclovir therapy in patients with HSV encephalitis. Current recommended treatments for viral encephalitis are largely based on case reports or small clinical case series. (See the Herpesviruses section later for more information on acyclovir therapy.)

VIRAL ETIOLOGY OF ENCEPHALITIS

General features of the basic biology, pathogenesis, clinical features, epidemiology, diagnosis, and treatment of particular agents are discussed in the individual chapters devoted to these agents and have been reviewed.[70] Brief summaries of relevant issues related to encephalitis are provided in the subsequent sections, and additional encephalitis viruses not discussed in the text are summarized in Table 89.3. Table 89.4 presents the Infectious Diseases Society of America (IDSA)–US Public Health Service (USPHS) grading system for ranking recommendations.

TABLE 89.3 Other Important and Emerging Causes of Viral Encephalitis

VIRAL ETIOLOGY	EPIDEMIOLOGY	CLINICAL FEATURES	DIAGNOSIS	TREATMENT
Adenovirus	Children and immunocompromised patients	Associated pneumonia	PCR or culture of brain biopsy specimen or CSF	Supportive
Chikungunya virus	Epidemic setting; India and Southeast Asia; mosquito vector	Febrile syndrome with rash and arthralgias	CSF and serum IgM and PCR	Supportive
Hendra virus	Australia; fruit bat reservoir; humans infected by secretions of bats	Fever, drowsiness, seizures, and coma associated with a flulike prodrome	Contact Special Pathogens Branch at CDC	Supportive
HIV	Worldwide epidemic; recent high-risk behavior	Fever, headache-associated acute retroviral syndrome; commonly associated with HIV dementia	HIV serology testing and HIV quantitative PCR of CSF; MRI may reveal T2 or FLAIR hyperintense lesions in periventricular regions and centrum semiovale	Combination antiretroviral therapy
Influenza	Fall and winter seasonal predilection; worldwide distribution; rare complication in children	Associated febrile syndrome, myalgias, respiratory prodrome; may be associated with bilateral thalamic necrosis	Viral culture, antigen detection, and PCR in respiratory secretions	Oseltamivir (III-C); poor outcomes
Japanese encephalitis	Mosquito vector, swine and bird reservoirs; most common cause of epidemic viral encephalitis throughout Southeast Asia and Australia	Seizures and parkinsonian features common; acute flaccid paralysis; case-fatality rate of 20%–30%	Serum IgM or acute/convalescent IgG; CSF IgM or antigen; MRI can show T2 and FLAIR hyperintense lesions at basal ganglia, thalami, and midbrain	Supportive; formalin-inactivated mouse brain–derived vaccine available for prevention
JC virus	Cell-mediated immunodeficiencies (AIDS) and immunomodulating therapy (e.g., natalizumab)	Cognitive dysfunction, limb weakness, gait disturbance, visual loss, focal neurologic findings	CSF PCR (sensitivity 50%–70% for PML); MRI shows ≥1 nonenhancing, confluent subcortical white matter hyperintensity on T2 and FLAIR sequences	Combination antiretroviral therapy in AIDS patients or reversal of immunosuppression
Louping ill virus	Tick-borne disease; found in Ireland, Scotland, and England; associated with livestock	Usually mild febrile illness with associated confusion and stupor in some; deaths are rare	Serum IgM ELISA or a fourfold increase in IgG antibody in paired acute and convalescent sera	Supportive
LCMV (see Chapter 167)	Rodent-borne virus infects humans with exposure to infected urine, feces, saliva, or blood; severe disease in immunocompromised patients	Fever, headache, leukopenia, and thrombocytopenia; encephalitis characterized by personality changes, increased ICP, paraplegia, and cranial nerve and sensory dysfunction	CSF and serum IgM ELISA	Supportive
Me Tri virus	Mosquito-borne; Southeast Asia; transmitted among livestock	Fever, rash, seizures, lethargy, and meningismus	CSF PCR and IgM ELISA, serology	Supportive
Monkeypox	Prairie dog exposure	Vesiculopustular rash on head, extremities, palms, and soles; adenopathy; encephalitis is rare, with confusion, somnolence, and diminished reflexes	Skin biopsy, CSF, and serum IgM, serology; MRI showing T2 and FLAIR hyperintense lesions of the pons, thalamus, and subparietal cortex	Supportive care; consider cidofovir or vaccinia immune globulin (III-C)
Mumps virus	Unvaccinated	Previous parotitis followed by headaches, vomiting, seizures, altered consciousness, and sensorineural hearing loss	Fourfold IgG increase in paired acute and convalescent sera, culture of saliva, CSF culture and PCR	Supportive
Murray Valley encephalitis virus	Mosquito vector; bird reservoir; Australia and New Guinea	Rapid onset in infants with case-fatality rate of 15%–30%	IgG antibody testing with fourfold increase in paired acute and convalescent sera	Supportive
Nipah virus	Exposure to infected pigs; pteropid bat reservoir; exposure to infected bats or bat roosting sites; close contact to infected humans; South Asia	Fever, headache, altered consciousness, dizziness, vomiting, myoclonus, dystonia, areflexia, hypotonia; pneumonitis	Fourfold IgG increase in paired acute and convalescent sera; CSF culture; MRI may show T2 focal hyperintensity of subcortical and deep white matter of cerebral hemispheres; contact Special Pathogens Branch at CDC	Supportive; ribavirin (III-C)

Continued

TABLE 89.3 Other Important and Emerging Causes of Viral Encephalitis—cont'd

VIRAL ETIOLOGY	EPIDEMIOLOGY	CLINICAL FEATURES	DIAGNOSIS	TREATMENT
Powassan virus	Tick vector; rodent reservoir; New England states, Canada, and Asia	Case-fatality rate of 10%–15% and focal neurologic findings in >50% of patients	Serum and CSF IgM; IgG antibody fourfold increase in acute and convalescent paired sera	Supportive
Rift Valley fever virus	Sub-Saharan Africa, Egypt, Saudi Arabia, Yemen; mosquito vector and livestock reservoir; humans infected via exposure to infected animal secretions	1% of infected humans develop encephalitis with headache, meningismus, and altered consciousness	ELISA antigen detection or culture from serum and PCR; contact Special Pathogens Branch at CDC	Supportive
Rocio virus	Cause of epidemic encephalitis in Brazil; mosquito vector	Fever, headache, confusion, motor impairment, and cerebellar syndrome; sequelae include ataxia, dysphagia, incontinence, and memory problems	Fourfold IgG increase in acute and convalescent sera	Supportive
Rubella virus	Unvaccinated adults	Rash followed by headache, dizziness, behavioral changes, and seizures	CSF IgM; fourfold IgG increase in paired acute and convalescent sera	Supportive
Snowshoe hare virus	Mosquito-borne; North America; children predominantly affected by encephalitis	Fever, headache, confusion, and lethargy; low mortality and rare long-term neurologic sequelae	CSF and serum IgM ELISA or fourfold increase in IgG acute and convalescent sera	Supportive
Tick-borne encephalitis virus	Tick vector; rodent reservoir; unpasteurized milk; Eastern Russia, central Europe, Far East	Acute encephalitis; acute flaccid paralysis	Serum IgM or fourfold increase in IgG antibody in paired acute and convalescent sera	Supportive
Toscana virus	Sandfly vector; infection during summer months in Mediterranean countries	Fever, headache, meningismus, and meningoencephalitis with coma, lethargy, hydrocephalus, and hepatosplenomegaly	CSF PCR; serum and CSF IgM; fourfold increase in IgG acute and convalescent sera	Supportive
Vaccinia	Most cases are postinfectious; rare event after vaccination	Abrupt encephalopathy with focal neurologic signs 2–30 days postvaccination	CSF PCR or IgM	Supportive; corticosteroids if postvaccination (III-C); consider cidofovir or vaccinia immune globulin
Zika virus	Mosquito-borne, epidemic febrile rash	Fever, rash, congenital infection	PCR of serum and ZIKV-specific IgM	Supportive

AIDS, Acquired immunodeficiency syndrome; *CDC,* Centers for Disease Control and Prevention; *CSF,* cerebrospinal fluid; *ELISA,* enzyme-linked immunosorbent assay; *FLAIR,* fluid-attenuated inversion recovery; *HIV,* human immunodeficiency virus; *ICP,* intracranial pressure; *LCMV,* lymphocytic choriomeningitis virus; *MRI,* magnetic resonance imaging; *PCR,* polymerase chain reaction; *PML,* progressive multifocal leukoencephalopathy.
Modified from Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Disease Society of America. Clin Infect Dis. *2008;47:303–327.*

TABLE 89.4 Infectious Diseases Society of America–US Public Health Service Grading System for Ranking Recommendations

CATEGORY, GRADE	DEFINITION
Strength of Recommendation	
A	Good evidence to support recommendation for use
B	Moderate evidence to support recommendation for use
C	Poor evidence to support recommendation for use
Quality of Evidence	
I	Evidence from ≥1 randomized, controlled trial
II	Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-control 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

Modified from Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Disease Society of America. Clin Infect Dis. *2008;47:303–327.*

Herpesviruses

The Herpesviridae are ubiquitous viruses found in multiple animal species. Herpesviruses that cause neuroinvasive disease in humans include HSV-1, HSV-2, VZV, CMV, EBV, HHV-6, HHV-7, HHV-8, and simian herpesvirus B.

Herpes Simplex Virus Types 1 and 2

Herpes Simplex Virus Pathogenesis

The exact mechanism by which HSV-1 and HSV-2 invade the CNS is unknown. Primary HSV-1 infection frequently causes gingivostomatitis, which is followed by axoplasmic transport of virus to the trigeminal sensory ganglion, where latency can be detected in virtually all seropositive individuals.[30,71] Trigeminal ganglion reactivation of HSV-1 usually results in retrograde axonal transport and the development of herpes labialis, but rarely reactivation may result in spread via the tentorial nerves to the anterior and medial cranial fossa.[72] It has been suggested, on the basis of animal inoculation studies, that the olfactory tract could also provide a potential route of neuroinvasion for HSV-1. In the case of primary infection, virus could invade the olfactory bulbs through the nose and spread via olfactory pathways to the orbitofrontal and medial temporal lobes.[30] At autopsy, approximately one-third of HSV-seropositive individuals with no known neurologic illness have PCR-amplifiable HSV DNA in the CNS, including the olfactory bulbs, hippocampus, and brainstem.[73] If this represents latent virus, which has not yet been convincingly established, reactivation from CNS sites could provide another mechanism for development of HSV encephalitis.

Cell death and tissue injury in HSV encephalitis likely result from direct viral killing of neurons and immune-mediated mechanisms of cell death. Several studies have shown that apoptosis plays a role in

neuronal cell death in human HSV encephalitis.[74,75] Studies in humans and mice have shown that the host's immune response may contribute to HSV-induced neuronal injury and death during encephalitis.[76–78] Genetic defects in TLR3-interferon and interferon responses have been shown to predispose to HSV encephalitis in several studies and may be particularly important in individuals with recurrent disease or in families with multiple cases of herpetic encephalitis.

HSV is the most common cause of sporadic encephalitis in the United States, with an incidence of hospitalization ranging from 1 to 1.2 per 100,000 population per year; it accounted for approximately 3300 hospitalizations per year from 1998 to 2010.[4] A recent multinational study in immunocompetent adults found that HSV-1 accounted for 92% of HSV encephalitis cases, with the remainder caused by HSV-2.[79] In patients with HSV in the CNS without evidence of encephalitis, largely meningitis cases, HSV-1 accounted for 45% of cases and HSV-2 accounted for the remainder. Although HSV encephalitis is the most commonly identified specific cause of viral encephalitis, it still accounts for only approximately 10% of all encephalitis cases.[30,80,81] HSV encephalitis has no seasonal or gender predilection. Cases occur in a bimodal age distribution with approximately one-third of individuals affected at younger than 20 years, and half of cases occur in individuals older than 50 years.[30]

Herpes Simplex Virus Encephalitis: Clinical Presentation

Patients with HSV encephalitis present with fever (90%–100%), altered consciousness (97%–100%), and headache (70%–81%).[17,38,82] Other common clinical features of HSV encephalitis include disorientation (70%–76%), seizures (40%–68%), behavior or personality change (41%–87%), memory disturbance (24%–45%), motor deficit (30%–40%), and speech disturbances (31%–59%).[17,28,38,40] A more recent multinational study of patients with HSV neuroinvasive disease found that fever (83%), change in consciousness (80.2%), headache (59.9%) and disorientation (58.3%) were the most common symptoms associated with encephalitis.[79] Mild or otherwise atypical presentations of HSV encephalitis have been reported in 14% to 17% of PCR-proven cases. These patients typically have mild alteration in level of consciousness and an absence of focal features at neurologic examination (although focal features may be present on EEG or neuroimaging studies).[28,83,84] A "normal" initial neurologic examination has been reported in less than 6% of patients.[17] In the original CASG trial comparing vidarabine and acyclovir, 29% of patients had a Glasgow Coma Scale (GCS) score of 6 or less, 41% had a GCS score of 7 to 10, and 30% had a GCS score of 10 or greater.[40] In later studies using CSF HSV PCR rather than brain biopsy for diagnosis, the level of consciousness of patients has been higher because of earlier detection. In the study by Domingues and associates,[28] 78% of patients had a GCS score of 12 or greater, including 28% with a GCS score of 15.

Herpes Simplex Virus Encephalitis: Diagnosis

PCR of HSV DNA in the CSF is the procedure of choice for diagnosis of HSV encephalitis[44,46] (see earlier for full discussion). Compared with brain biopsy, CSF HSV PCR has a sensitivity of 98% and a specificity of 94%, and more recent PCR tests for HSV exhibit sensitivity >95% and specificity >99%.[44,79] PCR results need to be evaluated in light of the timing of test performance. False-negative PCR results may also occur in bloody CSF specimens as a result of the presence of porphyrin compounds derived from degradation of heme in erythrocytes or during early stages of presentation, notably the first 48 hours after symptom onset.[46]

The results of diagnostic tests including CSF examination, neuroimaging, and EEG in HSV encephalitis were discussed in earlier sections. As noted, 96% to 100% of patients have a CSF pleocytosis (>5 white blood cells/mm^3) with a lymphocytic predominance. The protein is usually elevated (mean and median, 80–85 mg/dL), and the glucose level is normal in 95% of cases.[17,28,40] Initial CT scan can be abnormal in 40% to 79% of patients.[17] The most commonly observed abnormalities have been found to occur in the temporal (53%) or temporal and frontal lobes (36%).[17] MRI is more sensitive than CT and reveals abnormalities of the temporal lobes in 89% of cases confirmed with CSF HSV PCR (see Fig. 89.3A).[28] EEG patterns are not specific for HSV encephalitis, but as noted earlier, focal EEG abnormalities have been reported in 81% of biopsy-proven HSV encephalitis cases[38] and temporal lobe abnormalities occur in 75% of PCR-proven cases.[28] A more recent study found that MRI was abnormal in 84% of HSV encephalitis patients, and 91% of patients had an abnormal EEG.[79]

Herpes Simplex Virus Encephalitis: Treatment and Outcomes

The treatment and factors influencing prognosis for HSV encephalitis were discussed earlier. IV acyclovir (10 mg/kg every 8 hours) is the drug of choice for treatment of HSV encephalitis. The recommended duration of acyclovir therapy is 14 to 21 days according to the IDSA guidelines, and the mean duration of therapy in many studies is 21 days.[7] In the original CASG trial of adenine arabinoside for treatment of HSV encephalitis, the mortality in the 10 placebo-treated patients was 70%. Of the 3 survivors, 1 had minor, 1 had moderate, and 1 had severe sequelae.[85] A randomized placebo-controlled phase III clinical trial comparing long-term oral valacyclovir with placebo after completion of standard IV acyclovir treatment for HSE found no benefit to ongoing oral antiviral therapy for HSE.[86] Similarly, there is no proven benefit of adjunctive steroid therapy for treatment of HSV encephalitis, although uncontrolled studies and some experimental animal models suggest possible benefit.

Guidelines from IDSA advise that acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies (level III-A recommendation; see Table 89.4).[7] The goal of empirical treatment before diagnosis is to increase the likelihood of initiating treatment at an earlier stage in patients who ultimately prove to have HSV encephalitis. There is no proven benefit of acyclovir therapy in patients with non-HSV encephalitis (see discussion of specific herpesviruses for virus-specific details). The benefit of "empirical" use of acyclovir in patients with suspected encephalitis, rather than in patients with established HSV encephalitis, has not yet been established in a randomized controlled clinical trial.[40] Several studies have now shown that initiation of acyclovir within 2 days of hospitalization is associated with more favorable outcomes in patients with HSV encephalitis.[17,87,88] Multiple factors contribute to unfavorable outcomes, including advanced age, comorbid conditions, symptom duration before hospitalization, severely depressed consciousness, extent of brain involvement at MRI, and duration of hospitalization.[17,87–89]

A retrospective study found that only 29% of patients meeting specified criteria for suspected encephalitis (fever, neuropsychiatric abnormality, CSF pleocytosis, and negative Gram stain) received empirical acyclovir in the emergency department (median time to administration, 1.5 hours; 95% CI, 0–31.1 hours). The remaining 71% received acyclovir after inpatient admission (median time, 16 hours; 95% CI, 7.5–44 hours).[90] Five of 24 patients studied were eventually diagnosed with HSV encephalitis; only 2 of the 5 diagnosed with HSV encephalitis received acyclovir in the emergency department. In a large French study, a mean delay of 2 days ± 2.7 occurred between hospital admission and initiation of acyclovir therapy, and a mean of 5.5 days ± 2.9 lapsed between reported onset of symptoms and initiation of treatment.[17] These studies suggest that delays in administration of empirical antiviral therapy are common.

Several factors influence the prognosis of HSV encephalitis, including patient age, level of consciousness, immune suppression, and duration of clinical encephalitis before initiation of acyclovir therapy (measured by day of symptom onset or day of hospitalization). In the CASG trials of vidarabine versus acyclovir, age was stratified into patients younger than 30 years and patients 30 years of age or older.[40] Mortality was 6% (1 of 18) in acyclovir-treated patients younger than age 30 years but increased to 36% (5 of 14) in the older age group. It was subsequently reported that mortality in acyclovir-treated patients increased in a stepwise fashion from 11% (<2 years old) to 22% (22–59 years old) to 62% (≥60 years old).[91]

Similarly, level of consciousness at presentation, as evaluated according to GCS score, influenced mortality. In the original trial comparing vidarabine and acyclovir, mortality was 25% (2 of 8) in patients with a GCS score less than 6 compared with 17% (4 of 24) in patients with

a GCS score greater than 6.[40] It was subsequently noted that mortality was 0% in acyclovir-treated patients with a GCS score greater than 10 compared with 25% in patients with GCS score of 10 or less.[91] Patients with a GCS score of 7 to 10 and early institution of acyclovir therapy have improved outcomes compared with patients with lower GCS scores or late institution of acyclovir therapy.[91] In one large study, patients treated more than 2 days after hospital admission had a 3.1-fold (95% CI, 1.1–9.1) greater likelihood of a poor outcome compared with patients treated earlier.[17] In the vidarabine and acyclovir comparative study, the mortality rate in patients treated within 4 days of onset of fever, headache, and focal neurologic findings was 0% compared with a mortality of 35% in patients with symptoms of disease for more than 4 days.[40] Additional factors reported to influence prognosis include the Simplified Applied Physiology Score (SAPS II),[17] presence of lesions on an initial CT scan, and immunocompromised state.[92] Studies have indicated that the absolute value of the HSV PCR viral load in the CSF has no prognostic implications.[93,94] The role of management of increased ICP in HSV encephalitis has not been studied systematically, but use of aggressive medical and surgical therapy has been reported to be beneficial.[95]

HSV-2 Central Nervous System Disease

When evaluating patients with HSV neuroinvasive infections, the clinician must remember that HSV can also cause recurrent meningitis and myelitis. Although HSV-1 is the most common cause of sporadic, viral encephalitis, HSV-2 is the most common cause of recurrent, benign lymphocytic meningitis.[96] Patients with recurrent HSV-2 meningitis are more likely to be female (69%) and have a mean age of 38 years.[96,97] Patients present with acute onset of headache, fever, photophobia, and meningismus. Episodes last for a mean of 6 days, and patients have an average of four recurrences.[96,97] CSF is remarkable for lymphocytic pleocytosis (range, 86–1800), mildly elevated protein (range, 60–258), and normal glucose.[98] Diagnosis is made with HSV PCR of the CSF and is positive in 85% of patients with recurrent meningitis.[97] Neuroimaging is normal in the majority of patients (83%), although some patients develop nonspecific changes (14%) or meningeal changes (3%).[98] Of patients with CSF that was positive for HSV with PCR, 95% of cases are caused by HSV-2. Although recurrent HSV meningitis is a benign, self-limiting illness, acyclovir was used in the past for suppression of recurrences.[96] However, a double-blind, randomized trial demonstrated that suppressive therapy with valacyclovir was equivalent to placebo in suppressing HSV meningitis recurrences.[99] After 1 year of study drug exposure, patients were followed for an additional year off study drug, and patients exposed to valacyclovir had a significantly elevated risk (hazard ratio, 3.29) of recurrent HSV meningitis compared with the placebo group.

Herpes Simplex Virus Myelitis

HSV-1 and HSV-2 cause myelitis, but HSV-2 most commonly causes myelitis in adults. Most cases manifest as a monophasic illness (about 20% are recurrent) associated with acute onset of paralysis in the legs or less commonly the arms, reduced or absent reflexes, hyperreflexia with extensor-plantar responses, decreased sensation, and decreased anal tone or urinary incontinence with sacral dermatome involvement.[100–102] Severe forms of HSV myelitis include acute necrotizing myelopathy, which occurs in patients with underlying disease such as HIV, diabetes, or malignancy. CSF examination shows lymphocytic pleocytosis, elevated protein, and normal glucose concentration.[100,101] MRI typically exhibits intramedullary fusiform or spindle-shaped areas of increased T2-weighted signal.[100,101] Diagnosis is made with HSV PCR in the CSF, but measuring intrathecal synthesis of HSV-specific immunoglobulins may be helpful in the diagnosis of recurrent cases.[101] There are no controlled trials of antiviral therapy for HSV myelitis; however, there are anecdotal reports of success with IV acyclovir (10 mg/kg every 8 hours) for at least 14 days followed by oral antiviral drugs (valacyclovir, 1 g three times daily) until symptoms resolve. Despite therapy, the prognosis is extremely variable. In one small study of nine patients with HSV myelitis, one-third (three patients) made a complete recovery, whereas the remaining patients had residual sequelae including paraplegia and tetraplegia.[101]

Varicella-Zoster Virus

Varicella-Zoster Virus Pathogenesis and Central Nervous System Disease

Primary VZV infection (chickenpox) occurs mainly in children 1 to 9 years old, and seroprevalence by adult life is greater than 95%. After primary infection, the virus establishes latency in dorsal root ganglia. Reactivation results in herpes zoster (shingles). VZV CNS infection (encephalitis or vasculopathy) can occur during primary infection or after viral reactivation from latency.

During primary infection with VZV, acute cerebellar ataxia develops in 1 in 400 children younger than 15 years old.[103] It is unknown whether this clinical presentation is due to direct viral infection in the CNS[104] or represents a postinfectious immune-mediated state.[105] The clinical presentation is characterized by onset of gait ataxia, tremor, vomiting, and headache occurring 1 to 3 weeks after onset of chickenpox. CSF shows a lymphocytic pleocytosis with elevated protein. Imaging findings are often normal, and patients tend to have a full recovery. A study of VZV encephalitis cases found that a variety of VZV genotypes still cause neuroinvasive disease despite introduction of varicella vaccine, and vaccine genotypes are rarely associated with neuroinvasive infection in the CNS.[106]

VZV infection can cause myelitis associated with shingles or, more rarely, in the absence of rash ("zoster sine herpete"). In immunocompetent patients, myelitis is focal and typically manifests as weakness in myotomes corresponding to the dermatomes of the associated shingles outbreak (segmental zoster paresis). Immunocompetent and immunocompromised patients may develop more severe zoster myelitis.[107] In these cases, myelitis follows the rash by a median of 12 days, with maximal deficit being reached an additional 10.5 days later. The most common neurologic manifestations are weakness (75%), usually involving the leg ipsilateral to the rash, and less commonly paraparesis or paraplegia. Sensory abnormalities are common (approximately 50%) and can include dysesthesias, paresthesias, loss of pain-temperature or position-vibration sense or less commonly a sensory level to all modalities, or Brown-Séquard syndrome. Sphincter disturbances occur in approximately 25%. Some patients may have recurrent episodes of myelitis.[108] About 75% of patients have a lymphocytic CSF pleocytosis with elevated protein (approximately 70%) and normal glucose (approximately 95%) levels. MRI may show increased T2 signal lesions in the cord in association with cord swelling.[108] Diagnosis can be confirmed with demonstration of VZV DNA in CSF with PCR, or intrathecal anti-VZV antibody synthesis (increased CSF–to–serum IgG ratio).[108]

Varicella-Zoster Virus Vasculopathy

Modern studies suggest that most cases of VZV "encephalitis" are actually caused by VZV CNS vasculopathy, which most commonly involves large vessels (granulomatous arteritis) in immunocompetent patients and small vessels in immunocompromised patients.[108–113] However, a case series found that only 4 of 20 patients with VZV encephalitis developed a vasculopathy, and 14 of the 20 patients had nonvascular, nonspecific, or normal neuroimaging results.[114] In elderly immunocompetent patients, large vessel vasculopathy follows an episode of trigeminal herpes zoster by a few weeks to months with an average time to onset of 4 months, resulting in a mortality rate of 25%.[115] Most cases are monophasic, but relapses can occur. Patients develop myriad symptoms and acute focal deficits that vary with the location of the lesions. MRI findings are abnormal in 97%, with multifocal hyperintense lesions on T2-weighted FLAIR images (see Fig. 89.3B).[115] Lesions are typically located in the white matter or at the gray-white matter junction. Typical CSF findings include lymphocytic pleocytosis (67%), elevated protein level, and normal glucose level.

Small vessel VZV vasculopathy classically occurs in immunocompromised patients, resulting in a clinical syndrome of altered mental status changes, headache, focal deficits, and seizures.[115] The typical rash of herpes zoster is often absent. Neuroimaging shows evidence of multifocal infarcts, and CSF analysis reveals mild pleocytosis and a normal-to-mild elevation in CSF protein. In a retrospective study of VZV vasculopathy, 70% of patients had abnormalities at magnetic resonance angiography or traditional angiography.[115] Fifty percent had

evidence of small vessel and large vessel involvement. Angiography reveals focal narrowing or occlusion of involved vessels.

Diagnosis of VZV vasculopathy can be made by demonstration of intrathecal synthesis of VZV-specific antibody or by demonstration of VZV DNA in CSF with PCR.[115] Because VZV can cause a vasculopathy, some studies suggest that serum VZV PCR assay is sensitive and can help support a potential diagnosis of VZV CNS vasculopathy. At autopsy, involved vessels show focal inflammation with multinucleated giant cells, VZV antigen in endothelial cells, and Cowdry type A inclusion bodies in infiltrating histiocytes.[116]

Varicella-Zoster Virus Meningitis

VZV can produce an aseptic meningitis that can occur in the absence of rash. The frequency of VZV meningitis is uncertain; however, in one large series it accounted for 8% of cases. Patients typically have a lymphocytic pleocytosis in the CSF with elevated protein and normal glucose.[117] Neuroimaging findings are usually normal. Diagnosis can be made by showing VZV DNA in CSF with PCR. It has been reported that VZV viral loads are lower in patients with meningitis (mean, 4000 copies/mL) compared with patients with encephalitis (mean, 72,000 copies/mL).[118] It has been suggested that the severity of VZV CNS disease may correlate with CSF viral load. Patients with fewer than 10,000 VZV DNA copies/mL have a milder course compared with patients with higher viral loads.[118]

Varicella-Zoster Virus Central Nervous System Disease Treatment

No randomized controlled clinical trials are available to guide therapy for VZV CNS infection, but treatment with high-dose IV acyclovir (10–15 mg/kg every 8 hours for 10–14 days) has been recommended for severe disease.[7,111,112] Some experts also recommend a short course of adjunctive corticosteroid therapy (e.g., prednisone, 60–80 mg/day for 3–5 days).[109,111] In a noncontrolled retrospective review of VZV vasculopathies, 66% of patients who received acyclovir alone and 75% who received acyclovir and steroids improved or stabilized.[115] IDSA guidelines[7] indicate that acyclovir therapy is recommended (category III-B), that ganciclovir can be considered an alternative (category III-C), and that adjunctive corticosteroids can be considered (category III-B).

Cytomegalovirus

CMV is a ubiquitous human virus, with a 90% to 100% antibody seroprevalence in adults. It is transmitted through various routes, including body fluids such as saliva and genital secretions, blood transfusions, and organ transplants. CMV transmission typically occurs during childhood or early adulthood owing to common transmission via body fluid exposure. CMV causes acute infection and reactivation disease from latent virus. Primary infection with CMV is often clinically silent but may produce a mononucleosis-like syndrome. Neurologic complications from CMV infection in adults include retinitis, encephalitis, polyradiculomyelopathy, and neuropathy, all of which occur predominantly in immunocompromised hosts. CMV is also an important cause of congenital infections (see Chapter 137).

CMV encephalitis most commonly occurs in patients with a compromised immune system because of acquired immunodeficiency syndrome (AIDS) or organ transplantation; however, CMV neuroinvasive infections can infrequently occur in immunocompetent patients.[119] In patients with AIDS, CMV encephalitis occurs when the $CD4^+$ cell count is less than 50 cells/mm^3. Patients may develop a nonspecific febrile encephalopathy with or without focal signs. Some patients present with acutely altered mental status, and others present with a slowly progressive ventriculoencephalitis with CN palsies. Findings at MRI of the brain in AIDS patients with CMV encephalitis are variable, but hyperintense signal in the periventricular white matter is often seen on T2-weighted images and ependymal enhancement on contrast-enhanced T1-weighted images.[120] The CSF in patients with CMV encephalitis is nonspecific with mild lymphocytic pleocytosis and mild elevation in CSF protein level. In patients with CMV polyradiculopathy, the CSF profile is distinctive, with neutrophilic pleocytosis, low glucose, and elevated protein. Diagnosis is confirmed through amplification of CMV DNA from CSF by PCR. CMV PCR in the CSF of AIDS patients with CMV encephalitis has a reported sensitivity of 62% to 100% and specificity of 89% to 100%.[121]

Patients with HIV-associated CMV ventriculoencephalitis have a median survival of 42 days.[122] In a prospective study of 146 HIV patients with neurologic symptoms, the median survival was 50 days in patients with a positive CMV CSF PCR result compared with 205 days in patients with a negative CMV CSF PCR result ($P < .001$).[123]

Recommended initial treatment for CMV neuroinvasive disease includes the combination of ganciclovir (5 mg/kg IV every 12 hours) and foscarnet (60 mg/kg IV every 8 hours or 90 mg/kg IV every 12 hours) (category III-B).[7] Initial therapy is generally maintained for 2 to 3 weeks and is often followed by lower-dose maintenance therapy. Efforts should be made to reduce the degree of host immunosuppression whenever possible.

Epstein-Barr Virus

Primary EBV infection can be asymptomatic or can result in a mononucleosis syndrome characterized by cervical lymphadenopathy, exudative pharyngitis, and splenomegaly. Significant CNS disease occurs in less than 1% of acute EBV infectious mononucleosis cases and can manifest with myriad CNS syndromes, including meningitis, encephalitis, transverse myelitis, and Guillain-Barré syndrome.[124] The frequency of EBV as a cause of encephalitis is unknown.

Patients with EBV encephalitis present with altered consciousness, seizures, and focal neurologic deficits. In a study of 21 children (<17 years old) with EBV CNS infection, only 1 patient had concomitant infectious mononucleosis.[124] Other patients had a nonspecific presentation with fever (81%), headache (66%), and seizures (48%). CSF shows a pleocytosis (mean, 58 cells/mm^3) with mildly elevated protein (mean, 48 mg/dL) and normal glucose levels. In one series, 60% of patients had a neutrophil predominance.[124] About 80% of patients have MRI abnormalities, which can take the form of increased signal on T2 and FLAIR sequences that most commonly involve the basal ganglia and thalamus, temporal lobes, and subcortical white matter. In some patients, lesions are consistent with the lesions seen in ADEM or acute hemorrhagic leukoencephalitis. EEG abnormalities occur in approximately 75% of patients, most commonly in the form of generalized slowing, although patients may also have focal slowing, frequent intermittent rhythmic delta-wave activity, or epileptiform discharges.

Diagnosis of EBV CNS disease includes serology testing including IgM and IgG antibodies to viral capsid antigens and antibodies against Epstein-Barr early antigen (EA) and Epstein-Barr nuclear antigen (EBNA), and CSF PCR testing. Diagnosis of neuroinvasive disease is typically made with EBV PCR of the CSF or demonstration of intrathecal antibody synthesis (CSF EBV viral capsid antigen IgM or elevated EBV viral capsid antigen IgG CSF-to-serum ratio). PCR testing in the CSF needs to be interpreted with caution because false-positive results due to presence of EBV DNA in CSF mononuclear cells resulting from other conditions may occur. A study of patients with EBV DNA in the CSF at PCR found evidence of EBV encephalitis in patients with stem cell transplantation, but positive EBV DNA in the CSF of other patients did not appear to be causally related and was often associated with another infection in the CNS.[125] EBV serology consistent with acute infection (e.g., EBV viral capsid antigen IgM in the absence of IgG, elevated IgG antibody titers against early antigen but not nuclear antigen) supports, but does not definitively establish, the presence of EBV CNS disease. A study of 28 patients with CNS EBV infection found that patients with encephalitis had a high EBV PCR copy number (4.2 $\log_{10}$ copies/mL) and high leukocyte counts (143 cells/mm^3) in the CSF.[52]

There are no controlled trials evaluating therapy in patients with EBV CNS infection; however, some case reports suggest that ganciclovir treatment improved outcomes in patients with EBV meningoencephalitis.[126] Steroids have shown benefit in uncontrolled trials in some patients, including patients with evidence of increased ICP (category III-C).[7] Mortality of EBV encephalitis is 10% or less. Prognosis for survivors is excellent; 90% return to normal function, and the remaining 10% have only mild residual deficits.[124]

Human Herpesvirus 6

HHV-6 is a ubiquitous viral infection of lymphocytes that causes a spectrum of disease on primary infection, including exanthem subitum (roseola) in infants, febrile seizures, and lymphadenopathy syndromes. Virus then becomes latent and can periodically reactivate to cause disease.

HHV-6 is increasingly recognized as a cause of encephalitis in immunocompromised adults,[127,128] particularly patients with allogeneic bone marrow transplants (hematopoietic stem cell transplants).[129,130] The predominant amount of data in hematopoietic stem cell transplant patients, which consists of small case series, case reports, and small cohort studies, supports a diagnosis of HHV-6 encephalitis in hematopoietic stem cell transplant patients with encephalitis, without other causes of neurologic disease, and CSF positive for HHV-6 with PCR assay.[131] In hematopoietic stem cell transplant patients, HHV-6 causes limbic encephalitis, characterized by short-term memory loss, insomnia, and seizures.[132] MRI exhibits characteristic increased hyperintense signal on T2 images of the medial temporal lobe.[133] Diagnosis is made through demonstration of HHV-6 DNA in the CSF. In a case-control study, HHV-6 PCR from the CSF of 22 bone-marrow transplant patients with neurologic symptoms was compared with 107 immunocompromised controls without neurologic symptoms.[134] Because HHV-6 is latent in lymphocytes, interpretation of PCR-positive samples in blood and in the CSF can be complicated by confounding detection of latent HHV-6 DNA in lymphocytes. Thus interpretation of PCR results should be placed in the context of the disease presentation and the degree of host immune suppression.

HHV-6 is most commonly associated with focal encephalitis in bone marrow transplant patients. Estimates of its frequency have ranged from 6.5% in specimens from the CASG HSV encephalitis treatment trials[135] to 0.4% (4 per 1000) in the CEP.[127] Patients typically have CSF lymphocytic pleocytosis, elevated protein level, and normal glucose level. MRI may be normal or may show temporal lobe abnormalities. Diagnosis is typically made with CSF PCR or serum serology. Sensitivity and specificity of these tests are unknown. It has been suggested that high CSF viral loads support the diagnosis.[127] The possibility that latent HHV-6 DNA in mononuclear cells may result in false-positive PCR test results may complicate diagnosis.

Treatment of HHV-6 encephalitis is similar to that of CMV CNS infections. In general, HHV-6 is not responsive to acyclovir therapy but is responsive to ganciclovir and foscarnet. Although HHV-6 is sensitive to cidofovir therapy, this drug is not recommended for treatment of HHV-6 CNS disease because of the high risk of adverse events and uncertainty about its degree of CNS penetration. There are no controlled clinical trials studying antiviral therapy for HHV-6 limbic encephalitis. Case studies have suggested that therapy with ganciclovir or foscarnet can be successful in bone marrow transplant recipients.[136,137] Other reports have found that antiviral treatments do not prevent death and do not reduce CSF HHV-6 DNA viral load.[138,139] IDSA guidelines recommend use of ganciclovir or foscarnet in immunocompromised patients (category III-B) and indicate that these agents can be considered in immunocompetent patients, although data on efficacy are lacking (category III-C).[7]

Herpesvirus B

Herpesvirus B infects Old World monkeys and is the only nonhuman herpesvirus that also infects humans, resulting in a high mortality.[140] Monkeys of the genus *Macaca* (macaques) are lifelong viral carriers and asymptomatically shed virus. Humans develop disease after a monkey bite or scratch or mucosal contact with infected body fluid. Vesicles develop at the site of exposure, followed by onset of a flulike syndrome characterized by fever, chills, myalgias, and headache.[140] When the virus invades the CNS, the patient develops diplopia, ataxia, hyperesthesias, agitation, and ascending paralysis.

Diagnosis is made through wound or contact site culture and demonstration of an antibody response with acute and convalescent sera.[140] Culture must occur in a Biosafety Level 4 facility, so local health authorities should be notified if herpesvirus B is suspected. Because mortality approaches 100% after CNS symptoms develop, treatment should be initiated at exposure rather than delayed until onset of symptomatic disease.

There are no controlled clinical trials studying regimens for post-exposure prophylaxis (PEP), treatment of symptomatic individuals who have not yet developed CNS symptoms, or treatment of patients with CNS disease. PEP refers to administration of antiviral drugs in individuals who have been potentially exposed to virus but who are not known to be infected. The regimen recommended for PEP in asymptomatic individuals is oral valacyclovir (1 g orally three times a day for 14 days).[141] In patients with symptomatic disease who do not have CNS signs or symptoms, either acyclovir (12.5–15 mg/kg every 8 hours) or IV ganciclovir (5 mg/kg every 12 hours) is recommended. In individuals with CNS symptoms, it has been suggested that ganciclovir treatment is preferable.[141] Therapy is generally continued for a minimum of 14 days and is extended if symptoms have not resolved or cultures remain positive. When IV therapy is discontinued, patients should be monitored for viral shedding (cultures of conjunctivae and oral mucosa) initially at weekly intervals and later less frequently (one to two times a year). Lifelong suppressive therapy with oral valacyclovir is usually recommended.[141]

Vector-Borne Viral Infections

Vector-borne viral infections are important causes of viral encephalitis in the United States as a result of the endemic establishment of WNV circulation. With the emergence of ZIKV in the Americas, close monitoring for continued emergence and spread of new neuroinvasive arthropod-borne viruses needs to be a priority. For example, the upper Midwest and Northeast of the United States have seen a significant increase in Powassan virus infections. Powassan virus is a member of the genus *Flavivirus* and related to WNV. This virus is spread by *Ixodes* ticks and causes disease similar to WNV (see later). The most common vectors that transmit encephalitic viruses in the United States are mosquito species[142] and tick species.[143] These arthropods and the viruses they transmit constitute a common group of viruses called *ar*thropod-*bo*rne viruses, or *arbo*viruses. Viruses included in this group belong to four families: Togaviridae, Flaviviridae, Bunyaviridae, and Reoviridae; each specific arbovirus within a family is commonly transmitted by a specific species of mosquito or tick.

Encephalitic Arbovirus Pathogenesis

Many encephalitic arboviruses maintain an enzootic (animal) cycle that does not involve human infection. However, some arboviruses, such as ZIKV, can establish an urban or epizootic cycle of transmission that involves humans as an amplifying host. After a bite from an infected mosquito, the virus replicates in dendritic cells and macrophages in local tissue and lymph nodes, resulting in a primary viremia that disseminates virus to end organs including the CNS. The ability of an arbovirus to invade the CNS (neuroinvasiveness) is determined by multiple viral and host factors.[144] Proposed routes of arboviral CNS entry include penetration of the cerebral microvasculature after infection of endothelial cells, diapedesis of infected leukocytes, penetration of fenestrated capillaries in structures such as the choroid plexus, and transneuronal spread of virus.

When the virus has penetrated the blood-brain barrier, arboviruses can directly infect and cause death of neurons. Several studies have shown that apoptosis is an important mechanism of WNV neuron cell death and CNS injury.[145–147] Immune responses also contribute to clearance of virus and immunopathologically mediated neuronal cell death.

West Nile Virus (Also See Chapter 153)

WNV is an arbovirus in the family Flaviviridae, genus *Flavivirus,* along with other important human viral pathogens including dengue virus, ZIKV, yellow fever virus, JEV, and many others. WNV infection is endemic in the United States and is the second most common cause of viral encephalitis in the United States after HSV (see Fig. 89.2A). Since its emergence in New York City in 1999 and through 2016, approximately 50,000 cases of WNV infection have been reported in the United States, including 18,810 cases (42%) of neuroinvasive disease and 1765 (4%) deaths (www.cdc.gov/ncidod/dvbid/westnile). The

epidemics of WNV in 2003 and 2012 were the largest outbreaks of neuroinvasive viral infections ever reported in the Western Hemisphere.[148]

West Nile Virus Pathogenesis

WNV is transmitted via a mosquito bite from an infected *Culex* mosquito. Transmission also can occur after organ transplantation of WNV-infected organs,[149] breastfeeding,[150,151] and blood transfusions.[152] Most (80%) infections are asymptomatic. Approximately 20% of infected individuals develop an acute febrile flulike illness (West Nile fever) characterized by fever, headache, fatigue, anorexia, nausea, myalgia, and lymphadenopathy. A maculopapular rash involving the trunk and limbs occurs in 25% to 50%.[153] Less than 1% of WNV-infected individuals develop neuroinvasive disease, including meningitis, encephalitis, and acute flaccid paralysis.[148,154–156] It has been estimated that 30% to 40% of patients with neuroinvasive WNV infection develop meningitis, 50% to 60% develop encephalitis, and 5% to 10% develop acute flaccid paralysis.[157,158] Other reported syndromes include rhabdomyolysis,[159] chorioretinitis,[160] myositis,[161] and autonomic nerve dysfunction.[162]

Neuroinvasive disease most commonly occurs in older individuals (>60 years old). In one study, the odds ratio of developing encephalitis was 2.2 (95% CI, 1.6–3.1) in individuals older than 64 years.[163] Additional identified risk factors for encephalitis include hypertension and diabetes.[154,163,164] Immunocompromised patients, including organ transplant recipients, are at high risk of developing severe WNV disease. Specific genetic factors in humans shown to enhance susceptibility to serious WNV disease include single nucleotide polymorphisms in the oligoadenylate synthetase gene, which encodes an interferon inducible enzyme involved in antiviral innate immunity,[165] and a genetic deficiency of the chemokine receptor CCR5, which may inhibit trafficking of WNV-specific $CD8^+$ T cells into the CNS.[166]

West Nile Virus: Infection Clinical Features

WNV meningitis is characterized by the abrupt onset of fever, headache, meningeal signs, photophobia, and phonophobia. Patients have lymphocytic CSF pleocytosis with an average of 226 cells/mm^3, mildly elevated protein, and normal glucose. Neutrophils, rather than lymphocytes, predominate in the CSF in approximately 50% of patients with WNV meningitis.[36] Neuroimaging studies are unremarkable, and the EEG is usually normal.

WNV encephalitis is distinguished from meningitis by the presence of signs and symptoms of brain parenchymal involvement or abnormalities at neuroimaging or on EEG indicative of brain parenchymal involvement. Patients with WNV encephalitis present with fever (70%–100%), headache (50%–100%), and altered mental status (45%–100%). Common signs unusual in other forms of viral encephalitis that may suggest the diagnosis of WNV or flavivirus infection include tremor, parkinsonism, and myoclonus (20%–40%).[156,157] Weakness is common and may be generalized or of a lower motor neuron type associated with hypotonia and areflexia with preserved sensation. Cranial neuropathies, most commonly involving unilateral or bilateral peripheral facial palsy, occur in approximately 20%.

The prevalence of tremors ranges from 12% to nearly 100% in different studies.[155] It is often coarse, typically involves the arms, and has postural and kinetic components.[167] Parkinsonian features also occur with variable frequency and include signs such as bradykinesia, hypomimia, and postural instability.[155,167] Myoclonus can resemble that seen in prion diseases and usually involves the upper extremities and face. Cerebellar abnormalities including incoordination and gait ataxia occur in a variable percentage of cases.[154,157,164,168]

Patients with WNV infection have a normal complete blood count or mild leukocytosis.[3] The CSF findings in patients with encephalitis are almost identical to the findings with meningitis, including pleocytosis (mean, 227 cells/mm^3), elevated protein level, and normal glucose level. There is a predominance of neutrophils rather than lymphocytes in 37% of cases.[36] MRI is abnormal in approximately 50% to 70% of WNV encephalitis cases, which is somewhat less frequent than in HSV encephalitis, and the frequency depends on the timing of the studies and the imaging sequences used. CT considerably less sensitive than MRI, and CT scans are usually normal. When present, MRI abnormalities typically involve the thalamus, basal ganglia, and brainstem. Less commonly, they involve the deep white matter (see Fig. 89.3C).

WNV can produce a poliomyelitis-like acute flaccid paralysis that results from viral injury to motor neurons in the anterior horns of the spinal cord. Patients typically develop acute onset of asymmetrical limb paralysis associated with decreased or absent reflexes and preserved sensation. Weakness may be associated with respiratory impairment from diaphragm or intercostal muscle paralysis. Electrophysiology studies obtained acutely show reduction in amplitude or absence of compound muscle action potentials with relatively preserved sensory nerve action potentials. Electromyographic studies obtained 2 to 3 weeks after onset show characteristic features of denervation, including increased insertional activity and fasciculations. In contrast to Guillain-Barré syndrome, there is no evidence of significant demyelination (slowed conduction velocities or conduction block). In most, but not all, cases of WNV, acute flaccid paralysis is associated with clinical signs and symptoms of systemic infection, and the syndrome may occur in association with meningitis or encephalitis. Patients typically have CSF features similar to the features seen in meningoencephalitis. MRI of the spinal cord may show increased signal in the anterior horns on T2 and FLAIR sequences.

West Nile Virus Infection: Diagnosis

WNV neuroinvasive disease is usually diagnosed through demonstration of WNV-specific IgM in CSF with ELISA.[169] In some patients, CSF WNV IgM may persist for 1 year or longer, and it may be necessary to perform serial studies of serum and CSF IgG and IgM to definitively distinguish acute from remote infection. CSF PCR for WNV is highly specific but less sensitive than serologic studies. CSF PCR may be particularly useful early in infection, however, before antibody responses have fully evolved, and in immunocompromised individuals who may have delayed or absent seroconversion.[169] Antibodies reacting with WNV antigens in ELISA tests may occur as a result of heterologous cross-reactions induced by infection with or vaccination against other flaviviruses, including St. Louis encephalitis virus, yellow fever virus, and JEV. In some cases, it may be necessary to confirm ELISA results with plaque reduction neutralization assays. Neutralization antibody titers are typically highest against the inciting virus compared with cross-reacting species.

West Nile Virus: Prevention and Treatment

There is no specific therapy of proven benefit for WNV infection. Thus prevention of mosquito bites remains the best strategy for WNV infection. This includes avoiding outdoor exposure during dawn and dusk time periods when *Culex* mosquito activity increases, wearing long sleeves and pants, and using *N,N*-diethyl-meta-toluamide (DEET)-containing insect repellent on exposed skin when outdoors. A study was able to show that a live-attenuated chimeric WNV vaccine (rWN/DEN4delta30) was immunogenic and well tolerated in a cohort of flavivirus-naïve adults aged 50 to 65 years.[170] Targeted development of a vaccine for older adults may be a cost-effective approach to deploy in regions of high endemic WNV circulation or during new epidemics. Isolated case reports and small series have revealed both benefit and lack of effect from treatment with IVIG-containing high-titer anti-WNV antibodies (Omr-IgG-am) and with interferon-α. A phase I/II trial to evaluate the safety and efficacy of a humanized monoclonal antibody (MGAWN1) directed against an epitope on the WNV envelope glycoprotein was closed owing to low enrollment (NCT00515385). Isolated reports of corticosteroid use in patients with WNV acute flaccid paralysis and brainstem disease do not permit any conclusions about efficacy.[171]

West Nile Virus: Infection Outcome

Mortality from WNV neuroinvasive disease is approximately 12% and occurs almost exclusively in the subsets of patients with severe encephalitis or severe acute flaccid paralysis. The frequency and severity of sequelae are still not well understood.[172] Six months after the acute infection, 40% of patients with movement disorders such as myoclonus, parkinsonism, or tremors have residual symptoms, and 20% have ongoing symptoms at 18 months of follow-up.[172] More recent studies have also suggested that 50% of WNV encephalitis survivors report cognitive

problems, decreased motor speed, and diminished dexterity 3 months after the initial infection.[172] Long-term follow-up of patients with WNV infection found that about 31% of participants experienced more than 6 months of fatigue symptoms after infection, with an average duration of 5 years.[173] However, it is not clear how different the infected cohort is from prospective, age-matched community control subjects.

St. Louis Encephalitis

St. Louis encephalitis virus has been an important cause of arbovirus encephalitis in the United States since the 1930s and was the most important neuroinvasive flavivirus in North America until the emergence of WNV.[3] St. Louis encephalitis virus is found in a broad range from Canada and the United States to Central and South America (see Fig. 89.2B). Transmission to humans in the western United States is primarily via *Culex tarsalis*; in the eastern United States, it is through *Culex pipiens, Culex quinquefasciatus,* and *Culex nigripalpus.* The incidence rates for St. Louis encephalitis virus in the United States range from 0.003 to 0.752 per 100,000, with a median of 35 cases per year.[174] In 1975 the largest outbreak recorded in the United States involved 2800 cases in 31 states. In 2015 and 2016, 19 and 7 respective cases of St. Louis encephalitis virus infection, mainly in Arizona and the Mississippi river basin, were reported to the Centers for Disease Control and Prevention (CDC) (www.cdc.gov/ncidod/dvbid/sle/index.html). Thus St. Louis encephalitis continues to circulate in the continental United States.

St. Louis Encephalitis Virus Infection: Clinical Features

After the bite of an infected mosquito, an incubation period of 4 to 21 days precedes the onset of clinical symptoms. In adults, symptomatic infection occurs in 1 of 300 individuals exposed to virus.[3] These patients develop a flulike illness characterized by fever, myalgias, headaches, and other nonspecific symptoms including nausea, vomiting, cough, and sore throat. In patients younger than 20 years, 40% develop meningitis and 50% develop encephalitis.[175] In patients older than 60 years, more than 90% of patients develop encephalitis. Common manifestations of St. Louis encephalitis virus include reduced level of consciousness with lethargy, coma, tremors, myoclonic jerks, opsoclonus, nystagmus, and ataxia. Mortality of St. Louis encephalitis virus infections ranges from 4% to 27%,[175] seizures develop in 47% of patients, and acute flaccid paralysis has been associated with 6% of encephalitis cases.[176,177]

St. Louis Encephalitis Virus Infection: Diagnosis

MRI findings are often normal, but images may show high T2 signal intensity of the substantia nigra. In a case series of 11 patients, CSF studies revealed a lymphocytic pleocytosis in all patients (mean, 107 cells/mm^3; range, 5–446 cells/mm^3), elevated protein level (mean, 67 mg/dL) in 7 patients, and normal CSF glucose level.[177] EEG is almost invariably abnormal, with the most common finding being generalized slowing. Severely affected patients may have seizures or periodic lateralizing epileptiform discharges. General laboratory studies reveal a peripheral leukocytosis, hyponatremia, mild transaminitis, and sterile pyuria.[176] Diagnosis is based on demonstration of anti–St. Louis encephalitis virus IgM antibodies in the serum or CSF.[178] A fourfold increase in neutralizing antibody titers in the serum during the acute and convalescent phases of disease can also be used to establish a diagnosis. There is no therapy of proven efficacy for St. Louis encephalitis virus, although therapy with interferon-α2 may be considered (III-C).[7] An open-label, nonrandomized study of interferon-α2b suggested that therapy may improve outcome.[179]

Zika Virus (Also See Chapter 153)

ZIKV is an arbovirus in the flavivirus genus and shares many features with both dengue virus and WNV in terms of molecular structure and clinical features. Like dengue, ZIKV can be spread by *Aedes aegypti* mosquitos in an urban cycle that involves humans as an amplifying host. Like WNV, ZIKV is neuroinvasive, but ZIKV is the first flavivirus known to cause severe neurologic disease in human fetuses when a pregnant mother is acutely infected. ZIKV transmission in the Americas peaked in the summer and early fall of 2016. There have been 5590 reported symptomatic infections in the continental United States and 37,086 cases of symptomatic infection in US territories. This has resulted in possible ZIKV infections in 2311 and 4621 pregnant women in the US states and US territories, respectively (www.cdc.gov/zika/reporting).

Zika Virus Clinical Features

The pathogenesis in adults is likely similar to that of other flaviviruses described earlier and results in asymptomatic infection in up to 80% of adults exposed to infection.[180] In adult patients who develop disease, symptoms are characterized by fever, rash, myalgias, arthralgias, headache, and nonpurulent conjunctivitis that usually resolves in 7 days. Hospitalization and severe disease following acute ZIKV infection in adults are rare. During the ZIKV outbreak in Brazil, a prospective cohort of adult patients with neurologic complications was evaluated during a 3-month period of enrollment in the summer.[181] Of the 40 patients included in the study, 68% had Guillain-Barré syndrome, 13% had encephalitis, and 5% had transverse myelitis.

Despite relatively uncomplicated disease in adults, ZIKV complications can be clinically severe when pregnant women are acutely infected, resulting in infection in the fetus and congenital defects. Birth defects due to ZIKV are broadly categorized as congenital ZIKV syndrome and include chorioretinal atrophy and scarring, optic nerve abnormalities, microcephaly, developmental delay, arthrogryposis, hearing loss, and a variety of brain developmental abnormalities. Fetal abnormalities in the brain after ZIKV infection are directly related to virus infection of neuronal progenitor cells and astrocytes in the brain and other developing nervous system structures.

Zika Virus: Transmission

The major mode of ZIKV transmission remains mosquito-borne transmission from the bite of an infected *A. aegypti* mosquito. However, ZIKV is the first known arbovirus that can also be spread through sexual transmission. Because of the risk of sexual transmission, the CDC has published recommendations on prevention of ZIKV by sexual contact (www.cdc.gov/pregnancy/zika). ZIKV can also be spread through blood transfusion and organ transplantation, similar to WNV.

Zika Virus Infection: Diagnosis and Management

In suspected cases of ZIKV disease, diagnosis requires a compatible clinical syndrome and recent travel to an endemic area with ongoing ZIKV transmission.[180] Women who are pregnant and have traveled to endemic areas should be evaluated by health professionals with expertise in evaluation and monitoring of high-risk pregnancies associated with ZIKV. Suspected cases of ZIKV disease can be diagnosed through molecular detection of ZIKV RNA with reverse-transcriptase polymerase chain reaction (RT-PCR) testing in serum, CSF, and urine samples or serologic testing for ZIKV-specific IgM antibodies and ZIKV-specific neutralizing antibodies in serum or CSF. Serologic detection of ZIKV IgM and neutralizing antibodies is sensitive for infection after 1 week of symptoms but lacks specificity owing to antibody cross-reactivity among all related flaviviruses. However, ZIKV PCR testing is sensitive in the first week of symptoms and has a specificity of >95%.

There are no approved therapies for ZIKV infection. Prevention of infection is based on prevention of mosquito bites and avoidance of travel to an area of ongoing mosquito transmission of ZIKV. ZIKV may be shed for prolonged periods in semen, and sexual transmission of ZIKV has been described (see Chapter 153).

Multiple candidate ZIKV vaccines have shown efficacy in animal models, and have demonstrated immunogenicity in phase I clinical trials (see Chapter 153).

Eastern Equine Encephalitis Virus

Eastern equine encephalitis virus is an alphavirus that causes a sporadic, mosquito-borne viral infection endemic in the eastern United States and the Caribbean. There are four lineages of eastern equine encephalitis virus: group I causes most disease in humans, and groups IIA, IIB, and III cause primarily equine disease in Central and South America. Eastern equine encephalitis virus is maintained in an enzootic cycle with avian species after a bite from a mosquito vector, *Culiseta melanura*.[182] Birds serve as the primary reservoir host and amplifying hosts, and humans are incidentally infected by various mosquito bridging vectors, including

Culex and *Aedes* spp.[183] In the United States, most cases occur along the eastern seaboard. Cases are found sporadically along the Gulf Coast and upper Midwest, typically within 5 miles of swamplands or marshlands (see Fig. 89.2C). Approximately 1 in 30 individuals exposed to eastern equine encephalitis virus develops disease.[184] Eastern equine encephalitis virus causes sporadic infections in human populations during the summer months and occasional epidemic outbreaks.

Patients with eastern equine encephalitis virus develop nonspecific symptoms common to other causes of viral encephalitis, including fever, chills, malaise, and myalgias.[41] The prodrome is followed by either recovery without neurologic illness or the onset of encephalitis characterized by severe headache, confusion, nausea, and vomiting. Seizures, focal neurologic deficits such as CN palsies or focal weakness, and meningismus are common findings.[41] Brainstem involvement is common and is associated with gaze palsies, nystagmus, and pupillary abnormalities. Mortality is about 33% but increases to 50% in patients older than 60 years. Moderate-to-severe sequelae occur in one-third of survivors.[41]

In one study CT was reported to show findings suggestive of diffuse cerebral edema in 40% of cases.[185] Similar to the flaviviruses, in eastern equine encephalitis MRI abnormalities occur predominantly in the thalamus, basal ganglia, and brainstem.[41] EEG is typically diffusely slow, with some severely ill patients having burst suppression or diffuse high-voltage delta-wave slowing.[185] Laboratory studies may show a leukocytosis with a neutrophil predominance and hyponatremia in 60% of patients.[41] CSF typically shows a significant pleocytosis; two studies demonstrated a mean cell count of 370 leukocytes/mm^3 and 940 leukocytes/mm^3, respectively.[41,185] Two-thirds of eastern equine encephalitis virus cases display a neutrophil predominance, with a median neutrophil proportion of 70% of cells.[41,185] CSF protein is often elevated (median, 97 mg/dL), and 90% of patients have CSF glucose concentrations less than 60% of coincident serum values.[41,185] CSF red blood cells are common, reflecting the necrotic and hemorrhagic features of the encephalitis pathologically.

Diagnosis is typically made through demonstration of IgM antibodies in CSF with capture ELISA, demonstration of serum IgM antibodies, or a fourfold increase in IgG antibodies between acute and convalescent sera. No proven antiviral therapy exists for eastern equine encephalitis virus. Treatment is focused on supportive care and managing complications such as seizures and increased ICP. There is no commercial vaccine for eastern equine encephalitis virus, but standard precautions to prevent mosquito bites may help to prevent infection. In evaluating laboratory and imaging studies for prognostic value, one study found that CSF leukocytosis greater than 500 cells/mm^3 and hyponatremia less than 130 mEq/L were predictive of a poor outcome,[41] but a longer prodromal period was associated with a better prognosis. Overall mortality is approximately 30%, although higher mortality rates have been reported in older individuals. Sequelae are more common and generally more severe in children.[185]

Western Equine Encephalitis

Western equine encephalitis virus is an alphavirus that was originally isolated from the brains of horses in an epizootic outbreak in the San Joaquin Valley of California in 1930.[186] There have been 639 cases of western equine encephalitis virus in the United States since 1964 but none since 1994.[186a] A single case of probable western equine encephalitis was reported from Uruguay in 2009.[187]

Venezuelan Equine Encephalitis

Venezuelan equine encephalitis virus is an alphavirus that was originally isolated from the brains of dead horses.[188] Venezuelan equine encephalitis virus circulates between a mosquito vector, *Culex (Melanoconion),* and forest-dwelling small mammals and birds in Central and South America. It emerges during epizootic outbreaks to infect horses and humans via bridge vectors such as *Aedes taeniorhynchus.* Epidemics typically occur in northern South America but have extended as far north as Mexico and Texas.[189] In areas of sylvatic (forest) activity, seroprevalence can be 50%. During an outbreak of Venezuelan equine encephalitis virus in Venezuela and Colombia in 1995, approximately 3000 cases of neurologic disease were reported, resulting in 300 deaths.[190,191] In contrast to other arbovirus infections in humans, viremia in humans is sufficient to transmit virus to mosquitoes. Forty percent of patients with Venezuelan equine encephalitis virus have virus in the pharynx, suggesting that direct spread between humans may be possible, although this has never been shown.[190,192]

Symptomatic Venezuelan equine encephalitis virus results in neurologic disease in a few cases after a viral prodrome of fever, headache, photophobia, conjunctival injection, myalgia, arthralgia, nausea, and dizziness. Pharyngeal inflammation, painful cervical lymphadenopathy, somnolence, and tremulousness may occur.[193,194] CSF analysis reveals lymphocytic pleocytosis, elevated protein, and in some cases an elevated glucose ratio. There are few reports of neuroimaging studies. CT scans are usually normal. EEG typically shows diffuse slowing, although some cases have focal temporal slowing similar to that seen in HSV encephalitis. General laboratory abnormalities include leukopenia and elevated transaminase levels.[193]

Venezuelan equine encephalitis virus is diagnosed by detection of specific IgM antibody in the CSF or serum. Venezuelan equine encephalitis virus nucleic acid can also be amplified with PCR from the blood or pharynx on the eighth day of illness.[192] Fatality rates range from 0.2% to 1% of symptomatic Venezuelan equine encephalitis virus patients and 10% to 25% of patients with encephalitis. There is no antiviral therapy of proven benefit.

Chikungunya

Chikungunya virus (CHIKV) is an Old World alphavirus that reemerged as a cause of a major epidemic in Africa in 2004, then spread to the island of Réunion in the Indian Ocean in 2006 and to Southeast India itself. As of late July 2014, CHIKV had spread extensively into Caribbean islands and to multiple Central and South American countries (see Chapter 151). CHIKV generally causes an acute infection consisting of fever, rash, and polyarthritis that can be severe and prolonged (see Chapter 151). CNS involvement has been reported but appears to be uncommon.[226,227195–199]

The large outbreak of CHIKV infection in Réunion enabled a detailed study of CHIKV-associated encephalitis to be carried out.[200] CHIKV-associated encephalitis was defined by the presence of CHIKV RNA or anti-CHIKV IgM, along with clinical criteria of the International Encephalitis Consortium. Twenty-four cases of encephalitis were reported for a cumulative incidence rate of 8.6 per 100,000 persons. Incidence rates were highest in patients younger than 1 year and in those older than 65 years. The case-fatality rate of CHIKV-associated encephalitis was 16.6%, and the proportion of children diagnosed with persisting disabilities was between 30% and 45%. Poor prognoses (death or sequelae) were more frequent in adults (53.6%) than in children (18.2%).[200]

California Encephalitis Group

California encephalitis virus, La Crosse virus, Jamestown Canyon virus, and Tahyna virus are the major causes of encephalitis in the California encephalitis group within the family of Bunyaviridae and genus *Bunyavirus.* Of these viruses, La Crosse virus, California encephalitis virus, and Jamestown Canyon virus are causes of disease in the United States, and Tahyna virus is predominantly a cause of encephalitis in Russia. La Crosse virus is the most common cause of disease in the California encephalitis group. It was originally described in 1965 after a postmortem examination of a child who died of encephalitis in La Crosse, Wisconsin.[201] La Crosse virus is transmitted in an enzootic pattern between squirrels and chipmunks by the mosquito *Aedes triseriatus* in areas of the Mississippi and Ohio river basins (see Fig. 89.2D).[202,203] Recent outbreaks of La Crosse virus have demonstrated a shift in incidence to the Appalachian region and West Virginia.[204] Human exposure is often associated with camping or other recreational activities in wooded areas in endemic regions.

California encephalitis virus was originally isolated in 1941,[205] but it is rare. Most human cases occur in the western United States and Canada. The ratio of asymptomatic to symptomatic infections is 1000 : 1.[206]

Although La Crosse and California encephalitis viruses cause most disease in children, Jamestown Canyon virus affects predominantly elderly individuals in regions of the northern United States, with