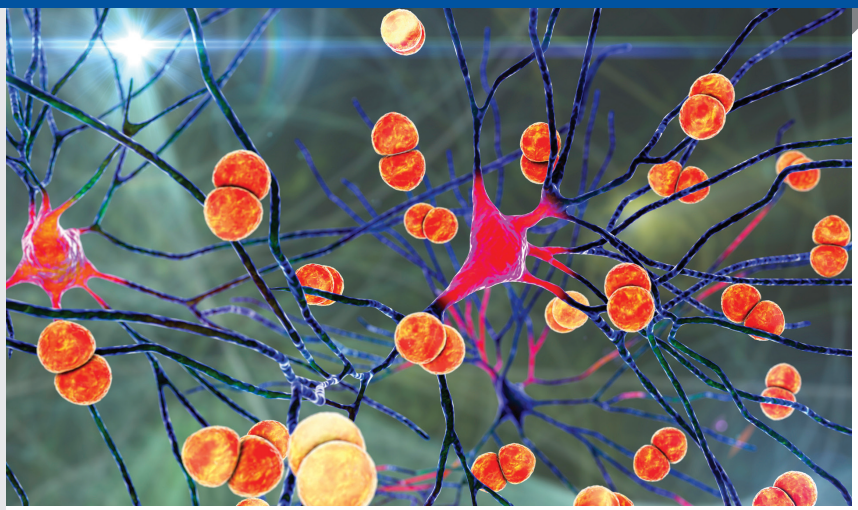
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Emergency Medicine Practice
Evidence-Based Education • Practical Application

CLINICAL CHALLENGES:

- **What are the elements of the history and physical examination** for meningitis and encephalitis?
- **What are the key findings** in cerebrospinal fluid and blood testing?
- **What are recommendations on antimicrobial therapies?**



Emergency Department Management of Adults With Infectious Meningitis and Encephalitis

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Prior to beginning this activity, see "CME Information" on page 22.

Abstract

Infectious meningitis and encephalitis are often life-threatening illnesses, though prompt workup and targeted treatment can greatly reduce morbidity and mortality. Although presentation of central nervous system infection can sometimes be subtle, this issue focuses on evidence-based strategies for identifying combinations of signs and symptoms to narrow the diagnosis. Identifying meningitis versus encephalitis; bacterial versus viral, fungal, or iatrogenic causes; and providing prompt empiric antimicrobials and appropriate diagnostic testing are key to management. Cerebrospinal fluid testing findings are outlined to help determine a potential cause for symptoms, along with blood and serum testing options. International society guidelines and evidence regarding the need for computed tomography prior to lumbar puncture are presented, which can help reduce unnecessary imaging. Disposition criteria are expanded to help determine whether a patient can go home, or the level of hospital care that will be required for those admitted.

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Case Presentations

CASE 1

A 24-year-old woman with a history of migraine presents to the ED with a "splitting" headache…

- The patient says this headache is more severe than any migraine she has had before.
- She is noted to have a temperature of 38.3°C, a heart rate of 115 beats/min, and a blood pressure of 105/70 mm Hg.
- You wonder whether this episode is simply another migraine or something else entirely…

CASE 2

A 62-year-old man with a history of heart transplant presents by EMS as a possible code stroke, with facial droop and partial hemiparesis….

- On arrival, the patient is noted to be febrile to 38.8°C with a heart rate of 112 beats/min and blood pressure of 131/64 mm Hg.
- His wife informs you by telephone that he has been developing the symptoms over several days and has also been prone to bizarre fits of laughter and angry outbursts.
- You wonder whether the patient's change in behavior is related to the fever, and if so, why?…

CASE 3

A 36-year-old man with a history of IV heroin use and HIV presents to your ED with 2 weeks of worsening headache, neck stiffness, and malaise. Your institution's sepsis alert is triggered…

- He admits to poor adherence to his antiretroviral medications for "a long time."
- His temperature is 38.5°C; his heart rate, 121 beats/min; and his blood pressure, 95/48 mm Hg.
- Manipulation of his neck elicits guarding.
- You order broad-spectrum antibiotics according to a sepsis order set, but you wonder whether these antimicrobials are sufficient to cover for potential causative agents…

Introduction

Infectious meningitis and encephalitis are etiologies on the differential diagnosis of several common emergency department (ED) complaints that include headache, neck pain, altered mental status, and sepsis. Bacterial meningitis and herpes encephalitis are severe neurological conditions with very high rates of morbidity and mortality, especially when left untreated. Early in the disease course of these central nervous system (CNS) infections, symptoms may be nonspecific. Classic symptoms and pathognomonic findings may be absent or subtle. Management of these conditions is time-sensitive, and emergency clinicians are well-positioned to ensure that workup and treatment proceed in a timely manner. Unfortunately, recognition of the possibility of meningitis or encephalitis is often delayed when presentations are not overt and multiple diagnoses are under consideration. Overreliance on the physical examination, failure to obtain appropriate laboratory tests, excessive neuroimaging, and incorrect timing of antimicrobial therapy all contribute to suboptimal results when managing these patients. This issue of *Emergency Medicine Practice* focuses on strategies to address the many potential pitfalls of managing meningitis and encephalitis in the ED setting.

Critical Appraisal of the Literature

A search of the PubMed and EMBASE databases was performed using the search terms *bacterial meningitis, viral meningitis, aseptic meningitis, fungal meningitis,* and *viral encephalitis.* Results were filtered to exclude items published before January 2000 and to include only narrative reviews, systematic reviews, research studies, and meta-analyses. This search generated a preliminary list of 4727 articles. These results were supplemented by a search of the Cochrane Database of Systematic Reviews using similar search terms. The preliminary list was narrowed by excluding the majority of articles focused on pediatric populations or noninfectious causes of meningitis and encephalitis. When possible, higher-level sources (eg, meta-analyses and controlled trials) were utilized. Review articles were preferentially selected based on recency of publication, comprehensiveness, and applicability to the emergency care setting. Several international guideline documents were included. Additional impactful sources—some of which were published prior to 2000—were identified as citations within other articles reviewed.

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Etiology and Pathophysiology

The term *meningitis* refers to inflammation of the meninges and subarachnoid space, while *encephalitis* refers to inflammation of the brain parenchyma itself. Although either process may cause systemic infectious symptoms, the presence of focal neurological signs indicates involvement of brain tissue and encephalitis. For the emergency clinician, infection by micro-organisms is the most common and important cause of these syndromes. Subtypes such as acute bacterial meningitis (ABM) and herpes simplex encephalitis cause very high morbidity and mortality that can be reduced by early recognition and antimicrobial treatment.[1]

The skull and the blood-brain barrier provide the CNS with increased protection against infection, compared to other organ systems. Infection occurs when a pathogen breaches these defenses due to specific virulence factors or environmental conditions and gains access to the subarachnoid space. Invasion of meningeal tissues leads to release of cytokines and other inflammatory mediators and can precipitate classic clinical signs of meningeal irritation and systemic infection. This inflammatory response causes further compromise of the blood-brain barrier, influx of immune cells from the systemic circulation, cerebral edema, and increased intracranial pressure (ICP). Increased ICP accounts for symptoms such as headache and altered mental status. As inflammation in the subarachnoid space persists, microvascular damage occurs to cerebral tissue, leading to neurological deficits. In cases of encephalitis, ICP increases and vascular injury is magnified when cerebral tissue itself is infected. Seizures and pronounced focal neurological deficits—some of which are irreversible, even with treatment—subsequently develop.

Bacterial Infections

ABM occurs with an incidence of approximately 0.9 cases per 100,000 persons per year in industrialized countries such as the United States, the United Kingdom, and the Netherlands.[2] Developing areas such as sub-Saharan Africa have a higher incidence of bacterial meningitis (10-40 per 100,000), most likely resulting from limited access to healthcare. Mortality from untreated ABM approaches 100%.[3] Even with appropriate therapeutics, mortality remains substantial. A prospective cohort study performed in the Netherlands of 1412 episodes of community-acquired bacterial meningitis in adults between 2006 and 2014 determined an overall mortality rate of 17%.[4] Other high-quality observational studies have reported similar mortality rates between 14% and 25%.[3,5,6]

Worldwide, *Streptococcus pneumoniae* is the most common cause of ABM, followed by *Neisseria meningitidis*. *Listeria monocytogenes, Haemophilus influenzae,* and *Mycobacterium tuberculosis* are other less common but notable causes affecting susceptible populations in developed nations.[2] In developing areas with higher rates of immunocompromise due to HIV, *M tuberculosis* is an important etiology of bacterial meningitis.[7] In recent decades, vaccination efforts have substantially reduced rates of *N meningitidis* and *H influenzae* meningitis. In contrast, *S pneumoniae* vaccines have had a negligible impact on the burden of pneumococcal disease because the prevalence of non–vaccine serotypes has increased in proportion to vaccination rates.[8] **Table 1** summarizes features of and risk factors for the most common etiologies of ABM.

In immunocompromised individuals, very rarely, bacterial species such as *Bartonella henselae, Borrelia burgdorferi,* or *Mycoplasma pneumoniae* can invade cerebral tissue and cause encephalitis.[10] Although viral causes of encephalitis still predominate in the immunocompromised population, testing for bacterial etiologies should still be performed.[10,11]

Viral Infections

Viral Meningitis

Viral meningitis is more common than bacterial meningitis and has an estimated incidence in the United States of 8 to 10 cases per 100,000 persons.[12] The term *aseptic meningitis* is sometimes used in place of *viral meningitis*, and is based on a case definition from the 1950s describing a meningitis syndrome without evidence of bacteria in the cerebrospinal fluid.[12] Noninfectious causes of aseptic meningitis (eg, drug toxicity, autoimmune disease) have since been identified, so the more precise term,

Table 1. Common and Notable Causes of Acute Bacterial Meningitis[9]

Pathogen	Features
Streptococcus pneumoniae	• Most common community-acquired cause
Neisseria meningitidis	• Second most common community-acquired cause
Listeria monocytogenes	• Third most common community-acquired cause • Risk factors: elderly age, pregnancy, immunocompromise
Haemophilus influenzae	• Rare in United States due to herd immunity from childhood immunizations • Risk factors: not immunized
Gram-negative bacilli (eg, *Pseudomonas aeruginosa, Acinetobacter baumannii,* Enterobacteriaceae)	• Multidrug-resistant strains are an emerging threat • Risk factors: neurosurgical procedures, head trauma, immunocompromise
Staphylococcus aureus	• Healthcare-associated infection • Methicillin resistance is an increasing threat
Mycobacterium tuberculosis	• Risk factors: immunocompromise (eg, HIV), malnutrition

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viral meningitis, is used throughout this review. Among cases in the United States with an identified causative pathogen, non–polio enteroviruses represent 23% to 61% of sporadic viral meningitis cases.[12] Herpes simplex virus 2 (HSV-2) is a less common but notable cause in developed countries.[12] Arthropod-borne viruses, such as West Nile virus in North America, Japanese encephalitis virus in Asia, and Chikungunya in South America frequently lead to regional epidemics. Over the last 2 decades, cases of meningitis due to numerous emerging viruses have been identified.[12] Viral meningitis generally has a less severe clinical course, lower rates of mortality, and fewer long-term complications compared to cases caused by bacterial pathogens.[13]

Viral Encephalitis

In contrast to viral meningitis, viral encephalitis causes a much more severe clinical syndrome and leads to much higher morbidity and mortality. Herpes simplex encephalitis is caused by herpes simplex virus 1 (HSV-1), and is the most important endemic cause of viral encephalitis in the Western world, accounting for most of the sporadic cases in which a pathogen is identified.[11] Prior to the advent of effective antiviral agents, mortality from herpes simplex encephalitis was as high as 70%.[14] Contemporary data show herpes simplex encephalitis mortality is now around 9% when appropriately treated with antiviral therapy and intensive care.[15,16] Varicella zoster virus (VZV) infection occurs more frequently among immunocompromised patients. Arthropod-borne and emerging viruses account for many focal outbreaks of encephalitis around the world, although cases occur at a lower rate than viral meningitis.[17] **Table 2** summarizes the features of common and uncommon viral etiologies of meningitis and encephalitis.

COVID-19

The ongoing global COVID-19 pandemic has placed a spotlight on the far-reaching implications of infection with SARS-CoV-2. Although several cases of meningitis due to SARS-CoV-2 have been reported, this agent (along with other coronaviruses) is not considered to be a significant source of CNS infections.[18] In a 2021 review of 166 patients with altered mental status in the setting of SARS-CoV-2 infection, only 0.6% of cases were attributed to possible encephalitis.[19]

Fungal Infections

Fungal meningitis is primarily a disease of immunocompromised and immunosuppressed populations. Most cases present subacutely, with weeks of slowly evolving symptoms, although acute meningitis syndromes are possible.[17] HIV/AIDS, solid organ transplant, and autoimmune disorders are prominent risk factors. *Cryptococcus neoformans* causes an estimated 1 million cases of meningitis worldwide among patients with HIV/AIDS every year. Annually, approximately 600,000 of these affected individuals die.[21] In addition to *C neoformans, Histoplasma capsulatum, Coccidioides* species, and *Candida* species may also cause fungal meningitis.

Differential Diagnosis

A "classic" triad of fever, neck stiffness, and altered mental status has been described for acute meningitis.[22] Headache is another common feature in cases of meningitis,[6] and patients with encephalitis often have seizures or exhibit focal neurological deficits.[17] These signs and symptoms are variably present and inadequately sensitive for diagnosing meningitis or encephalitis based on clinical evaluation alone.[6]

In isolation, symptoms such as fever, altered mental status, or headache have expansive differential diagnoses. For example, a sepsis syndrome caused by a non-CNS infection (eg, pyelonephritis) could display these same features.[23] When several symptoms suggestive of acute meningitis or encephalitis are present, however, the working differential diagnosis is narrower and more easily evaluated. A variety of

Table 2. Viral Causes of Encephalitis and Meningitis[20]

Common Causes	Uncommon Causes

• Nonseasonal
  ◦ Herpes simplex virus type 1
  ◦ Herpes simplex virus type 2
• Seasonal: summer and fall–arboviruses (arthropod-borne)
  ◦ West Nile virus
  ◦ St. Louis encephalitis virus
  ◦ Eastern/western equine encephalitis virus
  ◦ La Crosse/California encephalitis virus
• Seasonal: non–arthropod-borne
  ◦ Summer and fall: enteroviruses (including coxsackie viruses, echoviruses, polioviruses, enterovirus 71)
  ◦ Winter: influenza virus
• Immunosuppressed patients
  ◦ Human immunodeficiency virus
  ◦ Varicella zoster virus
  ◦ Cytomegalovirus
  ◦ Human herpesvirus 6
  ◦ Epstein-Barr virus
  ◦ John Cunningham (JC) virus
	• Causes originating within the United States
	  ◦ Measles
	  ◦ Mumps
	  ◦ Rubella
	  ◦ Adenovirus
	  ◦ Jamestown Canyon virus
	  ◦ Cache Valley virus
	  ◦ Lymphotropic choriomeningitis virus
	  ◦ Rabies
	  ◦ Variegated squirrel bornavirus
	  ◦ Herpes B virus (monkeys)
	  ◦ Zika virus*
	  ◦ Chikungunya virus*
	  ◦ Powassan encephalitis virus*
	• Causes originating outside the United States
	  ◦ Japanese encephalitis virus
	  ◦ Tick-borne encephalitis virus
	  ◦ Venezuelan equine encephalitis virus
	  ◦ Dengue virus
	  ◦ Rift Valley fever virus
	  ◦ Murray Valley encephalitis virus
	  ◦ Nipah virus

*Causes also originating outside the United States.

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vascular, neoplastic, and inflammatory etiologies may cause symptoms similar to CNS infection. **Table 3** lists important differential diagnoses to consider based on prominence of specific symptoms.

Prehospital Care

Many patients with acute meningitis and encephalitis are critically ill and access the healthcare system by calling emergency medical services (EMS). EMS professionals must recognize the possibility of an infectious etiology in the appropriate clinical setting. Because many of the causative agents behind these syndromes are contagious, EMS professionals should don personal protective equipment, including particulate respirators for potentially airborne pathogens such as VZV or tuberculosis.

Obtaining a point-of-care glucose level is essential to rule out hypoglycemia in patients with altered mental status or focal neurological abnormalities. For patients with evidence of sepsis, initiating prehospital peripheral venous access and intravenous (IV) isotonic fluid resuscitation is indicated and has been shown to reduce mortality.[24] Altered patients with inadequate respirations or inability to maintain protective airway reflexes may require advanced airway management.

Some EMS systems have implemented prehospital sepsis protocols that include administration of empiric broad-spectrum antibiotics. Some patients with acute meningitis or encephalitis may meet inclusion criteria for these protocols. Administering antibiotics before obtaining cerebrospinal fluid (CSF) for analysis, however, reduces the sensitivity of some diagnostic studies for identifying causative pathogens in these patients.[25-27] The benefit of early antibiotics for septic patients or those facing long transport times, however, may outweigh the risk of compromising CSF tests.

Table 3. Differential Diagnoses, by Symptom, for Meningitis and Encephalitis

Neck Stiffness
- Subarachnoid hemorrhage
- Torticollis (eg, adverse effect of dopaminergic medication)

Seizure
- Primary seizure disorder
- Medication or illicit drug toxicity
- Mass lesion (eg, tumor, arteriovenous malformation, abscess)
- Cerebral venous thrombosis
- Hypoglycemia

Focal Neurological Deficit
- Acute ischemic stroke
- Intraparenchymal hemorrhage
- Mass lesion
- Cerebral venous thrombosis
- Thrombotic thrombocytopenic purpura
- Hypoglycemia

EMS agencies with prehospital protocols for antibiotic administration should consider involving online medical control in the decision-making process in cases of suspected CNS infection.

Postexposure Prophylaxis Recommendations for Prehospital Clinicians

Providing appropriate postexposure prophylaxis for EMS professionals is necessary when unanticipated exposures to certain pathogens occur. Individuals exposed to *N meningitidis* should receive for chemoprophylaxis a single dose of intramuscular ceftriaxone or a single dose of oral ciprofloxacin or 2 days of oral rifampin. Adults exposed to *H influenzae* should receive rifampin postexposure prophylaxis if they live in a household with incompletely vaccinated children aged <4 years or immunocompromised children aged <18 years, regardless of vaccination status.[28] Options and regimens for postexposure prophylaxis are summarized in **Table 4**. Administration of varicella zoster immunoglobulin may be considered for high-risk individuals (eg, immunocompromised, pregnant) without evidence of immunity who have unprotected exposure to VZV, but this should be administered in consultation with an infectious disease specialist.[29]

Table 4. Postexposure Prophylaxis Regimens for Exposure to Bacterial Pathogens[28,30]

Pathogen	Indications	Recommended Regimen
Neisseria meningitidis	• Close contact with an affected individual in the 7 days before the onset of symptoms, without adequate personal protective equipment (droplet precautions) • Unprotected exposure to secretions	Rifampin 600 mg PO every 12 hours for 2 days (contraindicated during pregnancy; alternative contraceptive use necessary while on rifampin) **OR** Ceftriaxone, 250 mg IM once (preferred agent during pregnancy) **OR** Ciprofloxacin, 500 mg PO once (avoid during pregnancy or in patients aged <18 years)
Haemophilus influenzae	• Unprotected exposure of individual residing in a household with incompletely vaccinated children aged <4 years or immunocompromised children aged <18 years, regardless of vaccination status	Rifampin, 20 mg/kg (max 600 mg) PO daily for 4 days (contraindicated during pregnancy; alternative contraceptive use necessary while on rifampin)

Abbreviations: IM, intramuscular; PO, orally.

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Emergency Department Evaluation

ED management of meningitis and encephalitis depends upon recognizing the potential presence of these infections through high clinical suspicion, then gathering the data needed to confirm the diagnosis and guide treatment.

History

No single symptom can differentiate meningitis from other disease processes. While headache is the most consistently encountered symptom, it is reported in only 84% to 87% of cases. Other common symptoms include fever, neck stiffness, and altered mental status (Glasgow Coma Scale [GCS] score <14). These 3 symptoms are present in 78%, 73% to 83%, and 79% to 80% of patients, respectively.[6] Nausea, vomiting, and myalgias are also common in CNS infections, but these nonspecific symptoms are less helpful in making a diagnosis.

Combinations of symptoms are more useful in making a diagnosis, but they remain nondiagnostic. The classic triad of meningitis—fever, neck stiffness, and altered mental status—is found in only 44% to 66% of patients with bacterial meningitis.[3,6] When headache is added to the triad, 2 out of the 4 symptoms have been found to be present in 95% of cases.[6] The presence of at least 1 of these symptoms has a sensitivity of 99% to 100%.[6] Stated another way, absence of all 4 of these symptoms effectively rules out meningitis or encephalitis.[22]

Poorly controlled HIV, the use of immunosuppressive medications (eg, after solid organ transplant or for rheumatologic disease), and recent neurosurgical procedures may predispose a patient to developing meningitis or encephalitis.[22,31] Clinicians should carefully elicit patient risk factors for immunocompromise or iatrogenic exposure to CNS infection, since all of these symptoms may be less apparent in these populations. This may be due to a less vigorous immune response or, if the infection occurred as a complication of a neurosurgical procedure, as a result of CSF leakage preventing buildup of ICP.[31]

History of recent otitis media, sinusitis, or recent contact with another person displaying symptoms of a viral syndrome can raise suspicion for meningitis or encephalitis in the appropriate clinical setting. Prior or recent oral or genital herpes infection may raise suspicion for HSV-2 meningitis or HSV-1 encephalitis.[12] Other pertinent historical findings, particularly in cases of viral encephalitis, include geographic location, travel history, occupational exposure history, contact with animals or insects, and other activities that would confer higher risk.[32,33]

Physical Examination

The Kernig and Brudzinski signs are classically taught as pathognomonic findings for meningeal irritation suggestive of CNS infection. The Kernig test is usually performed by passively extending the knee of a supine patient with the hip flexed to 90°. It is considered positive when it provokes pain in the lower back or posterior thigh.[34] The Brudzinski sign is present (positive) when passive flexion of the neck in a supine patient elicits spontaneous flexion of the knees and hips. A 2014 study in emergency patients found the Kernig sign to have a sensitivity of only 2%, but a specificity of 97%, and the Brudzinski sign similarly had a sensitivity of 2% and specificity of 98%.[35]

Another physical examination sign, jolt accentuation of headache, was originally thought to outperform both the Kernig and Brudzinski signs, with a sensitivity of 65% to 97% and specificity of 60% to 70% for identifying meningitis.[35-37] Testing for this finding is performed on a patient in a seated position by actively turning their head from side to side at a rate of 2 to 3 rotations per second. Jolt accentuation is considered present if the maneuver causes the patient's baseline headache to worsen.[36,38] Further study has found this to be less useful, with a sensitivity of just 21% and specificity of 82%, making this finding inadequate to confirm or refute the diagnosis of meningitis or encephalitis.

The clinical presentations of encephalitis may be very similar to severe meningitis. Few data have been published on the prevalence of specific clinical features in patients with encephalitis. Cranial nerve palsies may occur in bacterial meningitis due to increased ICP and meningeal inflammation without involvement of cerebral tissue.[22] More advanced focal neurological deficits, however, indicate involvement of brain parenchyma and the presence of encephalitis.[17] Neurological findings may include motor weakness (including hemiparesis), aphasia, neuropsychiatric symptoms (eg, personality changes, hallucinations, or psychosis), or dysautonomia. Symptoms generally correlate with the specific affected cerebral territory.

Physical examination findings from other body systems may provide evidence for specific etiologies of CNS infection. Diffuse, petechial rash involving the palms and soles is classically associated with meningitis caused by *N meningitidis* but can be seen less frequently with other common community-acquired bacterial etiologies. Recent dermatomal, vesicular rash consistent with shingles should raise suspicion of VZV as the causative agent of meningitis or encephalitis.[12] Swollen parotid glands, particularly in individuals who did not receive common childhood immunizations, suggest mumps as an underlying etiology.[12]

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Diagnostic Studies

Cerebrospinal Fluid Analysis

Lumbar puncture with CSF analysis is the mainstay of diagnosis for meningitis and encephalitis. Lumbar puncture should be performed with the patient in the lateral decubitus position if measurement of opening pressure is desired, but for some patients, it may be performed more easily in an upright position.

Four tubes of CSF should be collected. Tubes 1 and 4 are used for red blood cell (RBC) and white blood cell (WBC) counts. This allows for differentiating traumatic tap from subarachnoid hemorrhage, which will be on the differential diagnosis of many of these patients. Protein, glucose, and lactic acid concentrations as well as polymerase chain reaction (PCR) tests are conducted on fluid from tube 2. Tube 3 is used for Gram stain, specific antigen tests, and cultures. Tube 3 can also be used for additional PCR tests.[23] Collecting larger volumes of CSF increases the sensitivity of several diagnostic CSF tests and ensures an adequate supply in case additional tests are needed at a later time.[23] CSF is produced at a rate of 22 mL/hr, and 15 mL or more can be taken safely.[38,39]

Normal Cerebrospinal Fluid Findings

Normal CSF should contain zero RBCs, <5 WBCs, a CSF to serum glucose ratio >0.67, protein concentration <50 mg/dL, and no visible organisms on Gram stain.[23] Abnormal CSF findings are detected in 88% of cases of all-cause bacterial meningitis, but can also appear deceptively normal. Normal or near-normal findings in some or all of the measured values have been found in 25% of cases of infection with *L monocytogenes* and 2% of other adult cases.[1,11,39]

Measurement of Opening Pressure

Opening pressure can be measured if lumbar puncture is performed with the patient in the lateral decubitus position. While opening pressure is usually normal in viral meningitis (<20 mm H_2O), it is often elevated in bacterial meningitis, and is >40 cm H_2O in 39% of cases.[6,40]

Cerebrospinal Fluid Cell Counts

ABM typically presents with elevated CSF WBC count, often in the range of 10 to 10,000 cells/mcL, usually >100.[23,41] Cell differential usually shows a predominance of neutrophils, particularly after the first 24 hours of infection, but may be normal in early disease or in immunodeficient states. Lymphocytes may predominate in infections partially treated with antibiotics and in cases caused by *L monocytogenes*.[42] Importantly, 6% of patients with culture-proven ABM do not have elevated CSF WBC counts, and 10% have lymphocyte-predominant differentials.[1,43] In viral meningitis, WBC count is generally <250 cells/mcL and typically ranges between 5 cells/mcL and 1000 cells/mcL, with a large proportion of lymphocytes.[41,44]

A traumatic lumbar puncture can complicate CSF cell count interpretation, as WBCs from outside the CSF will contaminate the sample. Traditionally, corrected cell counts are derived by subtracting 1 WBC for every 500 to 1500 RBCs in the sample.[40] However, multiplying CSF RBCs by the ratio of blood WBCs and blood RBCs yields a more accurate corrected result. The formula for predicting CSF WBCs after traumatic puncture is:[45]

Predicted CSF WBCs = CSF RBCs × (blood WBCs / blood RBCs)

Cerebrospinal Fluid Protein Level

Normal CSF protein concentration is 45 to 50 mg/dL. Nearly all patients with bacterial meningitis have an elevated CSF protein level, with a mean value of 135 mg/dL.[25,43] Normal to mildly elevated levels are seen in viral meningitis, with a mean of 56 mg/dL.[25,46]

Cerebrospinal Fluid to Serum Glucose Ratio

The ratio of CSF to serum glucose levels has diagnostic value in acute meningitis when samples are measured simultaneously. The normal CSF to serum glucose ratio is >0.67. In bacterial meningitis, this value ranges from normal to significantly decreased, depending on the type of pathogen, the time since infection onset, and presence of dextrose in any intravenous (IV) fluids administered.[46] One study found that using a cutoff point of <0.36 yielded a sensitivity and specificity of 93% for ABM, although the clinical utility of this very low value is unclear.[47] Viral meningitis usually has a normal to mildly decreased ratio.[43]

Cerebrospinal Fluid Gram Stain

Gram stain of the CSF has shown a sensitivity of 60% to 99% for bacterial meningitis, with a specificity of 97% to 100%.[6,43] Sensitivity is negatively impacted if lumbar puncture is performed after antibiotic administration. Thus, a negative Gram stain cannot be used to exclude bacterial meningitis.

Cerebrospinal Fluid Culture

CSF culture provides definitive diagnosis and antibiotic sensitivities, but if it is obtained after antibiotics are started, positive yield is negatively impacted. When lumbar puncture is performed >4 hours after antibiotic initiation, culture sensitivity is reduced >30%.[38] Cultures may be sterile within 2 hours of antibiotic administration in infections caused by *N meningitidis*.[48]

Cerebrospinal Fluid Lactate Concentration

CSF lactate concentration can be helpful in the diagnosis of bacterial meningitis. In bacterial meningitis, this end product of cellular anaerobic metabolism increases due to bacterial production, cerebral edema, vascular inflammation, and cerebral ischemia.[25] Because lactate crosses the blood-brain barrier very

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slowly, the CSF concentration is independent of the serum level.[49] The normal CSF lactate level is <35 mg/dL.[25] A level >35.1 mg/dL has demonstrated sensitivity of 93% and specificity of 97% for bacterial meningitis when obtained prior to administration of antibiotics.[26] Accuracy of this test is negatively affected by antibiotics.[25] The CSF lactate level is particularly useful in neurosurgery-related infections, as normal postoperative inflammation can alter the findings of many of the conventional markers, but does not affect lactate.[50] CSF lactate may be elevated in fungal meningitis or viral encephalitis, although reliable diagnostic cutoff points have not been reported.[1,49] CSF lactate can also be elevated due to seizure, ischemia, and hemorrhage.[49,51]

Cerebrospinal Fluid Nucleic Acid Amplification Tests

CSF nucleic acid amplification tests (NAATs) are increasingly being used to detect viral or bacterial DNA and RNA in CSF. In the case of bacterial meningitis, polymerase chain reaction (PCR) testing can detect bacterial DNA even several days after antibiotic therapy has begun, with a sensitivity of 87% to 100% and specificity of 98% to 100%.[27] For identification of specific etiologies of viral meningitis, PCR has become the gold standard (although this information is not essential for management of most viral cases).[52]

Other advanced NAATs are increasingly used for rapid diagnosis of causative pathogens in CNS infections, although their value remains unsettled. Regarding cases of tubercular meningitis, traditional smear microscopy has very poor sensitivity (10%-15%).[53] Although culture for tuberculosis has a better sensitivity at 50%, it requires 10 days to 8 weeks to result.[53] Newer NAATs, such as the Xpert® MTB/RIF assay detect *M tuberculosis* with much greater speed and sensitivity.[54] While tubercular meningitis testing has traditionally been the purview of inpatient medicine, the Xpert® MTB/RIF assay has a 2-hour turnaround time and could potentially be useful in EDs, where available.

Blood Tests

While crucial for many other types of infection, there are no blood or serum studies that can substitute for CSF sampling in the diagnosis of CNS infection. Several different tests, however, may serve as useful adjuncts in the evaluation of these pathologies.

Complete Blood Cell Count

Complete blood cell count (CBC), while commonly obtained, provides little diagnostic value in the setting of suspected meningitis or encephalitis. The average WBC count in adults with ABM is 17,500 cells/mcL, and 11,096 cells/mcL in viral meningitis.[55] Neutrophilia may be seen in bacterial meningitis with systemic manifestations, but this finding is nonspecific. A normal or only mildly elevated WBC count should not be reassuring, however, and may occur early in the disease course or in elderly and immunocompromised patients. As such, WBC count has very low predictive power among relevant diagnostic tests.[25]

Liver Enzymes and Disseminated Intravascular Coagulation Panel

Liver enzymes and a disseminated intravascular coagulation panel may be helpful for differentiating a possible meningococcal rash from noninfectious hematological etiologies such as thrombotic thrombocytopenia purpura, which also may also present with fever or focal neurological signs. These tests do not provide any added benefit in diagnosing meningitis or differentiating between bacterial, viral, or other forms.

C-Reactive Protein

C-reactive protein (CRP) is an acute-phase protein that is synthesized in the presence of infections and other inflammatory processes. This test may have some value as an adjunct in situations where CSF cultures are not diagnostic. At a cutoff point of 37 mg/L, CRP demonstrates sensitivity of 85% and specificity of 84% for distinguishing bacterial from viral meningitis when other first-line studies are inconclusive.[55] Similar to WBC count, the diagnostic utility of CRP is lessened in elderly and immunocompromised patients, due to decreased synthesis.

Serum Procalcitonin

Serum procalcitonin (PCT) is another biomarker of interest in the workup of possible CNS infections. In healthy persons under normal conditions, PCT is almost undetectable. Its production greatly increases in many tissues in response to inflammatory cytokines in the setting of bacterial infection.[56] Early in the course of ABM, PCT levels have been shown to rise after 4 hours, peak at 6 hours, and remain elevated for more than 24 hours. In contrast, PCT values do not rise significantly in viral infections.[57] When trying to distinguish bacterial from viral meningitis, PCT concentrations >0.25-0.5 ng/mL yield a sensitivity of 90% to 95% and specificity of 98% to 100%.[25,55,57] Values in this range are more sensitive for this purpose than any CSF marker. Although PCT is potentially useful to distinguish bacterial from viral meningitis or alternative diagnoses, lack of availability in many EDs limits its role.

Blood Cultures

Blood cultures have a yield as high as 66% in bacterial meningitis.[6] While results and associated antibiotic sensitivities help guide treatment, slow turnaround times render blood cultures unhelpful in the ED evaluation and decision-making for CNS infections. Nevertheless, these samples should be

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collected in the ED to maximize their utility during the downstream care of patients.

Serum Polymerase Chain Reaction Testing

Serum PCR testing has shown higher sensitivity than blood cultures, especially when patients have received empiric antibiotic therapy prior to blood sampling.[58] Again, usefulness of PCR is limited by availability and timing.

Blood Lactate Testing

Blood lactate values may be elevated in both viral and bacterial CNS infections; however, levels also rise in many other infectious and noninfectious systemic inflammatory conditions. Thus, elevations are nonspecific and minimally helpful in early evaluation for meningitis and encephalitis.[25]

Serum Cryptococcal Antigen Testing

Serum cryptococcal antigen testing is 99.7% sensitive and 94.1% specific in the specific setting of cryptococcal meningitis.[59]

Imaging Studies

Computed Tomography

Computed tomography (CT) of the brain is not sensitive for detecting meningitis or encephalitis.[60] CT may be useful for excluding other pathologies on the working differential diagnosis.

Performing Computed Tomography Prior to Lumbar Puncture

Lumbar puncture is essential to the workup of CNS infections, but the procedure is potentially contraindicated in some conditions that cause increased ICP, such as space-occupying masses, as the brain shift that occurs due to the increased pressure can be increased by the removal of CSF at the lumbar level, leading to herniation.[1] Unfortunately, several of these conditions are on the differential diagnosis of meningitis and encephalitis. **(See Table 3, page 5.)**

Over the last 2 decades, the question of which patients with suspected CNS infection should undergo CT prior to lumbar puncture has been debated extensively. In 2004, the Infectious Diseases Society of America (IDSA) guideline for bacterial meningitis recommended CT prior to lumbar puncture in selected patients. To decrease delays to lumbar puncture and antimicrobial therapy for patients with suspected bacterial meningitis, 2009 Swedish guidelines eliminated altered mental status and self-limited seizures from its criteria for CT before lumbar puncture. Subsequent evidence has suggested these 2 findings are not independent risk factors for herniation.[61] The 2016 United Kingdom joint specialist societies guideline recommended CT prior to lumbar puncture if focal neurologic signs were present, or with the presence of papilledema, continuous or uncontrolled seizures, GCS score ≤12, or rapidly declining level of consciousness.[27] The criteria from these societies are summarized in **Table 5**.

Despite the potential for severe complications, herniation following lumbar puncture is rare. One prospective cohort study found that only 3.1% of patients had deterioration that could possibly have been caused by lumbar puncture, without proving causality. Only 0.1% of patients who deteriorated did so within 1 hour of the lumbar puncture. Of

Table 5. Comparison of Society Guideline Recommendations on Indications for Computed Tomography Before Lumbar Puncture

Infectious Diseases Society of America (2004)[43]	Revised Swedish National Guideline for Acute Bacterial Meningitis (2009)[61]	United Kingdom Joint Specialist Societies (2016)[27]	European Society for Clinical Microbiology and Infectious Diseases (2016)[1]
• Abnormal level of consciousness • Unable to answer 2 consecutive questions • Unable to follow 2 consecutive commands • Seizure ≤1 week prior to presentation • Known central nervous system disease (mass lesion, stroke, or focal infection) • Gaze palsy • Abnormal visual fields • Facial palsy • Arm/leg drift • Abnormal language • Age ≥60 years • Immunocompromised state	• Focal neurological deficit (excluding cranial nerve palsy) • New-onset seizure (only if clinical picture does not correlate with acute bacterial meningitis) • Ongoing seizures • Ongoing or impending herniation • Papilledema • Severe coagulopathy • Infection at lumbar puncture site	• Focal neurological signs • Continuous or uncontrolled seizures • Glasgow Coma Scale score ≤12 • Rapidly declining level of consciousness • Papilledema	• Focal neurologic deficits (excluding cranial nerve palsy) • New-onset seizure • Glasgow Coma Scale score <10 • Immunocompromised state

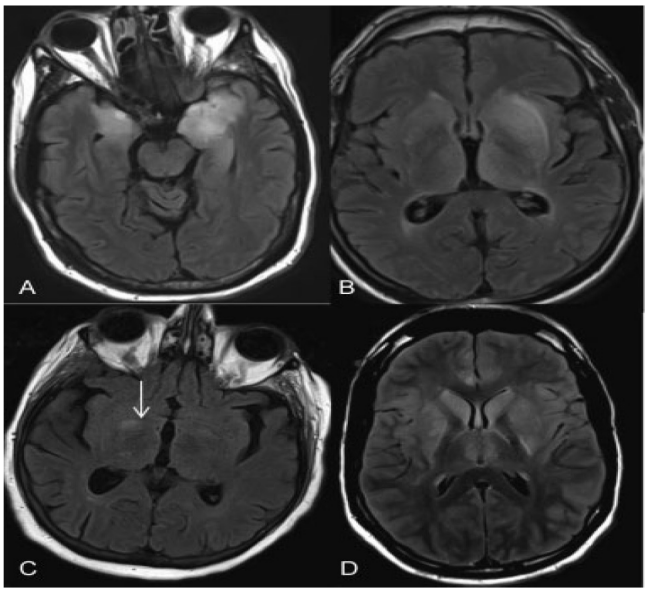
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the patients who deteriorated, 91% underwent CT prior to lumbar puncture that did not identify a contraindication.[62] Furthermore, while studies exist that identify risks associated with abnormal findings on CT, no study has directly identified features directly associated with increased risk for herniation after lumbar puncture.[27]

Magnetic Resonance Imaging

Although it is not useful for detecting meningitis, magnetic resonance imaging (MRI) demonstrates unique radiographic findings in the setting of encephalitis.[63] MRI can also distinguish between various subtypes of encephalitis.[63] Characteristic MRI suggestive of specific etiologies of encephalitis are demonstrated in **Figure 1**. Nonetheless, the length of time required to obtain MRI, in addition to inconsistent availability in many EDs limits its utility during early patient management.

Figure 1. MRI Patterns in Patients With Viral Encephalitides



A: Patient with herpes simplex virus encephalitis. Asymmetric T2/fluid-attenuated inversion-recovery (FLAIR) hyperintensities and edema involving the bilateral mesial temporal lobes are seen.
B: Patient with eastern equine encephalitis virus. Abnormal T2/FLAIR hyperintensities of the bilateral basal ganglia and thalami, left greater than right are seen. Additionally, there is T2 prolongation in the midbrain and mesial temporal lobes (not shown here).
C: Patient with West Nile virus encephalitis. There is a small area of T2/FLAIR hyperintensity in the right basal ganglia (white arrow).
D: Patient with Powassan encephalitis. Seen are T2/FLAIR hyperintensities involving the bilateral insula, opercula, perisylvian temporal lobes, medial thalami, caudate nuclei, and putamina.

Abbreviation: MRI, magnetic resonance imaging.

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Treatment

The treatment of bacterial meningitis and all forms of encephalitis is time-sensitive. A retrospective study of 269 episodes of bacterial meningitis over 25 years demonstrated that delayed initiation of antibiotics in the ED correlated with progression of clinical disease severity and increased patient mortality.[64] Another well-designed retrospective study of 119 patients with ABM admitted to a tertiary care hospital system over a 12-year period demonstrated an incremental association between longer delays to antimicrobials and mortality.[65] Because of these time-dependent effects, prophylactic antimicrobial treatment should be initiated prior to identification of the specific causative agent. Guidelines recommend administering broad-spectrum IV antimicrobials within 1 hour of the time at which possible bacterial meningitis is first suspected.[1] Specific empiric regimens are chosen based on the patient's age, immune status, and historical factors (eg, geographic location). **(See Table 6.)** Once an organism is identified, further treatment may then be tailored

Table 6. Empiric Antimicrobial Therapy for Acute Meningitis and Encephalitis[23,43,50,66]

Patient Characteristics	Recommended Regimen and Dosage
Immunocompetent (age <50 years)	• A third-generation cephalosporin: ○ Ceftriaxone 2 g IV every 12 hours ○ Cefotaxime 2 g IV every 4-6 hours ○ Ceftazidime 2 g IV every 8 hours **PLUS** • Vancomycin 15-20 mg/kg IV every 8 to 12 hours
Immunocompromised (HIV infection or AIDS, receiving immunosuppressive therapy, or after transplantation) **OR** Relative immunocompromise (age >50 years or pregnant)	• A third-generation cephalosporin: ○ Ceftriaxone 2 g IV every 12 hours ○ Cefotaxime 2 g IV every 4-6 hours ○ Ceftazidime 2 g IV every 8 hours **PLUS** • Vancomycin 15-20 mg/kg IV every 8 to 12 hours **PLUS** • Ampicillin 2 g IV every 4 hours
Healthcare-associated infections	• Vancomycin 15 to 20 mg/kg IV every 8 to 12 hours **PLUS** • An antipseudomonal beta-lactam: ○ Cefepime 2 g IV every 12 hours ○ Meropenem 2 g IV every 8 hours ○ Ceftazidime 2 g IV every 8 hours
Fungal meningitis suspected (eg, cryptococcal)	**ADD** Amphotericin B liposomal IV **PLUS** flucytosine IV (only in consultation with an infectious disease specialist for guidance on formulations and dosing)
Viral encephalitis (eg, HSV-1, VZV)	**ADD** Acyclovir 10 mg/kg IV every 8 hours

Abbreviations: HSV-1, herpes simplex virus 1; IV, intravenous; VZV, varicella zoster virus.

according to results of CSF studies, imaging findings, and antibiotic susceptibilities.

Immunocompetent Individuals With Bacterial Meningitis

S pneumoniae and *N meningitidis* are the 2 most common pathogens causing bacterial meningitis in immunocompetent adults, followed less commonly by *H influenzae* and skin flora. The empiric antibiotic regimen of choice for community-acquired ABM in these patients includes a third-generation cephalosporin (eg, ceftriaxone or cefotaxime) at higher doses than for other indications to achieve consistent CNS penetration.[9] These agents have potent activity against the major pathogens of ABM, with the exceptions of *L monocytogenes* and some resistant strains of *S pneumoniae.* Given the increasing prevalence of penicillin-resistant pneumococci, vancomycin should be administered in locations where the ceftriaxone resistance rate is >1%, which includes essentially all developed nations.[9] Meropenem can also be used in cases of cephalosporin-resistant bacterial meningitis, especially if concern exists for infection with multidrug-resistant organisms.[31] While there are currently minimal data regarding the efficacy of rifampin in patients with pneumococcal meningitis, some experts recommend its use in areas with high resistance to cephalosporins.[1] Institution-specific antibiograms or antibiotic sensitivity results from an individual patient's recent cultures may inform the decision to select this agent.

Immunocompromised Individuals With Bacterial Meningitis

Individuals with immunocompromising conditions (eg, HIV infection or AIDS, receiving immunosuppressive therapy, or after transplantation) are at increased risk from opportunistic pathogens. For these patients, antibacterial coverage should be expanded with an agent directed against *L monocytogenes.* Ampicillin is widely available and effective for this purpose.[9] Although it is not reflected in major guidelines, some experts recommend using an antimicrobial agent active against *P aeruginosa* in immunocompromised patients.[67] Cefepime, a fourth-generation cephalosporin, or an antipseudomonal carbapenem, such as meropenem, can replace ceftriaxone for this purpose. Meropenem also has activity against *L monocytogenes*; therefore, addition of ampicillin is not required if this agent is used.[9]

Individuals aged >50 years and pregnant women are at increased risk for contracting meningitis caused by *L monocytogenes,* due to relative immunosuppression. In older adults, immunosenescence develops with advancing age and increases susceptibility to neuro-invasive listeriosis. Likewise, pregnant women are 10 to 20 times more likely to contract listerial infections (including meningitis) than the general population, although the specific immunological underpinnings of this increased risk are poorly understood.[68] Mortality from listerial meningitis is relatively high, on par with pneumococcal disease and ranging between 17% and 30%.[69] Infection with this pathogen during pregnancy is often devastating for the fetus.[68] In patients at high risk for CNS infection due to *L monocytogenes*, ampicillin should be added to empiric treatment regimens.

Patients With Suspected Cryptococcal Meningitis

C neoformans is another notable cause of meningitis in immunocompromised hosts. Cryptococcal meningitis remains the second highest cause of mortality in patients with HIV/AIDS, with the highest burden of disease in sub-Saharan Africa, where more than 75% of all deaths occur.[70] Multiple different antifungal regimens for cryptococcal meningitis have been examined. A Cochrane review that included 13 studies and 2426 participants concluded that 1 week of amphotericin B plus flucytosine therapy (followed by 1 week of fluconazole) was most effective and led to the lowest mortality rates.[71] If high suspicion exists for cryptococcal CNS infection, empiric administration of amphotericin B liposomal and flucytosine are indicated.[66] Due to the significant toxicity profiles of these medications, they should be initiated only after consultation with an infectious disease specialist.

Patients With Viral Infections

For most cases of viral meningitis, the course is usually self-limited, and no directed therapy has proven to affect patient-oriented outcomes. Supportive care is the mainstay of management in patients with a presentation and workup clearly suggestive of a mild viral etiology.[11] Patients with severe symptoms or equivocal test results in the ED should be empirically treated for bacterial meningitis, using previously described regimens, and admitted.

All patients with clinical signs of acute encephalitis should empirically receive acyclovir pending PCR results.[23] In a randomized controlled trial of 208 patients with encephalitis due to HSV-1, patients who received acyclovir had a reduced mortality rate of 28% compared to a rate of 70% in the placebo group.[14] If PCR for HSV-1 is negative but high suspicion remains for herpes simplex encephalitis based on risk factors or MRI findings, antiviral therapy should be continued. Because false-negative PCR is possible during the first 72 hours of herpes simplex encephalitis, PCR testing should be repeated after 3 to 7 days.[72]

Varicella zoster infection causes a disproportionate number of cases of viral encephalitis in immunocompromised patients. If VZV is identified as the cause of viral encephalitis, guidelines recommend continuing empiric acyclovir therapy despite less

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robust supporting evidence for this medication than in HSV-1 infection.[73]

Corticosteroids

Corticosteroids have been studied extensively as an adjunct to the treatment of meningitis and encephalitis. These medications are the only adjunctive therapy that has been shown to impact outcomes—such as mortality and hearing loss—in patients with bacterial meningitis.[9] The most common guideline-recommended treatment regimen is administration of 0.15 mg/kg dexamethasone IV every 6 hours for 2 to 4 days.[43] Bactericidal antibiotics, including cephalosporins and vancomycin, are critical for treating bacterial meningitis, but they cause a vigorous inflammatory response in the subarachnoid space that can lead to negative neurological sequelae. In a 2015 Cochrane meta-analysis of 25 studies involving 4121 participants, adjunctive corticosteroids were associated with a nonsignificant reduction in mortality (17.8% vs 19.9%) in cases of bacterial meningitis from all causes.[74] In the subgroup of patients with pneumococcal meningitis in high-income countries, however, corticosteroids significantly reduced mortality.[74] For meningitis caused by *M tuberculosis*, a Cochrane analysis of 9 trials including 1337 total patients found that use of adjunctive corticosteroids reduced mortality by almost one-quarter after 18 months.[75]

International society guidelines vary on timing of administration of corticosteroids, but initiation at the same time as antimicrobial therapy (or up to 15-20 minutes before) is generally recommended.[1,43] Corticosteroids should be discontinued if the causative agent of meningitis is found not to be *S pneumoniae* or *M tuberculosis*. This is especially important for meningitis caused by *L monocytogenes* or *C neoformans*, as corticosteroids in these cases are associated with worsened outcomes.[1] A Swedish registry study over a 19-year period of 1746 adults treated for ABM showed a nonsignificant trend toward worse outcomes in patients with listerial meningitis treated with corticosteroids.[76]

At present, major guidelines suggest empiric administration of dexamethasone as a component of initial empiric treatment of suspected bacterial meningitis.[1] Because identification of a causative pathogen is essentially impossible within 1 hour of presentation, it is possible that some patients with listerial or cryptococcal infections will be harmed by this therapy.

Additionally, patients who receive corticosteroids for pneumococcal disease and initially recover from acute illness face increased risk for delayed cerebral thrombosis over subsequent weeks.[8] Ultimately, the risk-benefit balance skews in favor of empiric administration of corticosteroids when bacterial meningitis or acute encephalitis are suspected in immunocompetent patients. Because pneumococcus is the most common cause of ABM, the likelihood of appropriately treating pneumococcal meningitis likely outweighs the chance that a patient has cryptococcal or listerial disease. In situations where clinical evidence strongly favors those pathogens, however, withholding corticosteroids should be considered. If either is definitively identified, subsequent doses of corticosteroids should be discontinued immediately.

Special Populations

Patients With Autoimmune Encephalitis

Rarely, patients who recover from viral meningitis or encephalitis infections experience recurrent or more severe neurological symptoms within the next several weeks.[77] Symptoms may include neuropsychiatric manifestations, severe focal neurological deficits, or seizures. Such cases were traditionally believed to occur due to reactivation of the pathogen responsible for the initial infection, especially after cases of HSV-1 encephalitis.[77] In most instances, however, viral material could not be detected on CSF analysis during these relapses.[77] Subsequently, newer evidence has revealed autoimmune mechanisms underlying these biphasic syndromes. Autoantibodies against numerous neuronal antigens—most prominently the N-methyl-D-aspartate receptor (NMDAR)—have been identified and linked to these syndromes.[78] Certain HLA haplotypes and genetic factors may predispose individuals to developing autoimmune encephalitis.[77] Emergency clinicians managing cases of suspected autoimmune encephalitis should involve neurological specialists in patient care.

Individuals Without Childhood Immunizations

The mumps virus is a less common but important cause of viral CNS infection, accounting for 7% to 16% of cases of viral meningitis.[12] A subset of patients with mumps meningitis progress to a syndrome of encephalitis with focal neurological deficits. Individuals who are not vaccinated against mumps are susceptible to such infections. In contrast, receiving 2 doses of the measles-mumps-rubella (MMR) vaccine, as recommended by standard childhood vaccination schedules, is 88% effective at preventing mumps infection.[79] Cases of mumps encephalitis are virtually nonexistent among fully vaccinated individuals.[10]

The measles virus, which is also a target of routine and effective childhood immunization, does not generally cause acute meningitis, but childhood infection may lead to a serious, delayed complication known as subacute sclerosing panencephalitis after several years (9.5 on average).[80]

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Healthcare-Associated Infections

Individuals with iatrogenic or traumatic violation of the subarachnoid space are predisposed to infection of the CNS by a different set of pathogens, compared to community-acquired cases. Major risk factors for these healthcare-associated infections include neurosurgical procedures, presence of foreign bodies (eg, shunts or drains), CSF leaks, and basilar skull fractures.[50] CSF lactate level is particularly useful in diagnosis of these infections, as normal postoperative inflammation can alter the findings of many of the conventional markers, but it does not affect lactate.[50] Healthcare-associated CNS infections most commonly involve gram-negative bacilli such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* or gram-positive skin flora such as *Staphylococcus* species.[31] Multidrug-resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenem-resistant *Acinetobacter baumannii* (CRAB) represent a growing barrier to treatment of these infections. Overall mortality is estimated in the 16% to 41% range.[31] Empiric antibiotics administered in the ED for at-risk patients should have broad-spectrum coverage and activity against likely resistant organisms. Use of second- or third-line antimicrobials such as linezolid and involvement of infectious disease specialists may be necessary during later care.

Controversies and Cutting-Edge

Other Adjunctive Therapies

Osmotic agents and therapeutic hypothermia have been investigated as potentially beneficial adjuncts aimed at reducing ICP due to cerebral edema in CNS infections. Osmotic agents reduce ICP by drawing extracellular fluid into the intravascular space. Induced hypothermia reduces cerebral oxygen demand, decreasing the effect of hypoperfusion on edema. Limited data exist for these therapies in adult patients. Studies of both adjunctive osmotic agents and therapeutic hypothermia in adult patients have been stopped early due to concerns for increased mortality in treatment groups compared to controls.[81,82] At this time, neither of these therapies is recommended for the treatment of CNS infections.

Role of Newer Diagnostic Modalities

Since patients with CNS infections may present with a heterogeneous collection of signs and symptoms, CSF collection remains essential for diagnosing and guiding treatment. Traditional CSF cell count, protein, and glucose patterns can suggest a class of causative organism (eg, viral vs bacterial), but they are variably sensitive and unable to identify individual pathogens in the same class (eg, pneumococcal vs meningococcal, enterovirus vs West Nile virus). Regarding this first limitation, recent studies have shown a possible role for the biomarkers, serum PCT and CSF lactate, to help discriminate between bacterial and viral CNS infections with high sensitivity.[25] Although CSF lactate can be measured using commonly available laboratory analyzers, availability of PCT testing is more limited. CSF culture is the gold standard for pathogen identification but requires considerable time to produce results (up to 8 weeks for some cases of tubercular meningitis).[7]

Newer NAATs, such as the loop-mediated isothermal amplification (LAMP) assay for common bacteria, FilmArray® panels (eg, BioFire®) for viral and bacterial pathogens, and the Xpert® MTB/RIF Ultra test for *M tuberculosis* have demonstrated very good sensitivities and specificities in meta-analyses.[54,83,84] While these NAATs show promising diagnostic accuracy, none has yet to demonstrate a significant impact on patient-centered outcomes in a controlled trial. More studies on this topic are needed.

Disposition

In general, most cases of meningitis and encephalitis will be admitted due to the possibility of a bacterial cause and the need for symptom control. Clinicians must then decide which hospital unit is most appropriate. Patients who are alert enough to maintain their airways, have stable vital signs, are not receiving titratable medications, and do not require close monitoring can be admitted to the general medical ward. There, patients can receive antibiotics while awaiting results of CSF analysis. Once these results are available, antimicrobial therapy can be further tailored to specific causative agents.

In some cases of acute meningitis and most instances of encephalitis, however, patients have a more critical systemic illness. Any patient who presents with severely depressed mental status (such as indicated by a GCS score ≤8) requires admission to an intensive care unit, as well as possible advanced airway management.[11] For patients with seizure-like activity or focal neurological deficits, admission to a unit capable of conducting continuous electroencephalographic measurement, monitoring ICP, and performing frequent reassessment of neurological status is indicated.

Can Some Patients be Discharged Safely?

Although most patients with meningitis are hospitalized, a subgroup of those with viral meningitis may be treated safely in the outpatient setting. Absolute criteria for discharge from the ED have not been established or validated in adults, but investigations in children suggest that some patients can be discharged without significant adverse outcomes. Criteria to support disposition decisions are summarized in **Table 7, page 14**, although they are extrapolated from pediatric data and should not replace the emergency clinician's clinical judgment.

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Data suggest that patients aged >1 year who have a nontoxic clinical appearance, normal serum WBC count, mild CSF pleocytosis, negative CSF Gram stain, adequate control of symptoms (eg, headache, nausea, vomiting), and a reliable support system at home are potential candidates for discharge.[85] Similar criteria for the disposition of adult patients are reasonable. Strict and detailed indications for return to the ED—such as worsening headaches, vomiting, confusion, or seizures—must be discussed thoroughly prior to releasing any patient. Patients with likely viral meningitis who are discharged from the ED should ideally follow up with a primary care provider within a short period of time (eg, 3 days) for reassessment.

Summary

Management of acute meningitis and encephalitis hinges upon early consideration of CNS infection on the differential diagnosis, followed by rapid administration of empiric antimicrobials tailored to patient risk factors, and prompt collection of CSF for identification of causative pathogens. Clinicians should recognize that antibiotics must not be delayed for lumbar puncture or CT scanning, and that lumbar puncture must be performed at the earliest opportunity to maximize sensitivity of diagnostic studies. Clinicians must be facile with interpretation of CSF patterns as well as newer useful biomarkers such as CSF lactate and serum PCT. Corticosteroids represent an important adjunctive treatment, and ED physicians must know when to initiate this therapy. After diagnosing the category of CNS infection underlying their patient's clinical picture, clinicians must decide which patients are safe for discharge and which patients require inpatient or intensive care admission.

Table 7. Proposed Criteria for Disposition Decisions[11,85]

Potential Discharge	Medical Ward	Intensive Care Unit
• Clinical picture of viral (aseptic) meningitis • No history of seizures • Negative CSF Gram stain • CSF WBC <1000 cells/mcL • CSF protein <80 mg/dL • Peripheral WBC <10,000 cells/mcL • Reliable support system	• GCS score >8 • No known seizures • Hemodynamically stable • Concern for bacterial meningitis	• GCS score ≤8 • Multiple or continuous seizures • Focal neurologic deficits consistent with encephalitis • Requirement for vasopressors • Signs of elevated ICP • Behavioral disturbance preventing ward admission

Abbreviations: GCS, Glasgow Coma Scale; CSF, cerebrospinal fluid; ICP, intracranial pressure; WBC, white blood cell.

Time- and Cost-Effective Strategies

- Measuring CSF lactate (which can be interpreted by standard laboratory analyzers) enhances the overall sensitivity for distinguishing bacterial meningitis from viral meningitis.
- Familiarity with guidelines for CT before lumbar puncture can reduce unnecessary neurological imaging and delays to lumbar puncture and administration of antibiotics.
- Barring extenuating circumstances, healthy, immunocompetent patients aged <50 years do not need ampicillin or acyclovir as part of empiric therapy for suspected bacterial meningitis.
- Some patients with viral meningitis who are clinically assessed to be at low risk may be appropriate for discharge, sparing the patient hospital admission.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study is included in bold type following the references, where available. The most informative references cited in this paper, as determined by the authors, are noted by an asterisk (*) next to the number of the reference.

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Case Conclusions

CASE 1

For the 24-year-old woman with a history of migraine who presented with a splitting headache…

Noting her fever and headache, meningitis immediately jumped to the top of your differential diagnosis. Your examination did not reveal focal deficits, but flexion of the patient's neck did elicit discomfort. She reported ongoing nausea and that she vomited en route to the ED. These symptoms improved somewhat with IV antiemetics. She had no contraindications to lumbar puncture or indications for CT, so lumbar puncture was performed immediately in the lateral decubitus position. Empiric IV vancomycin, ceftriaxone, and dexamethasone were subsequently administered. CSF analysis showed opening pressure of 18 cm H_2O, 29 WBCs, 2 RBCs, protein of 61 mg/dL, and CSF to blood glucose ratio of 0.63. She remained very nauseated, and her headache was minimally improved after IV ketorolac and metoclopramide. You suspected viral meningitis, but recognized that her CSF results were borderline. You continued antibiotics and admitted her to the medical ward. Several hours later, CSF PCR results identified enterovirus as the causative agent.

CASE 2

For the ill-appearing 62-year-old man with a history of heart transplant who presented as a possible code stroke from the field…

You recognized that this patient may have had an infectious cause for his symptoms rather than a primary acute ischemic stroke. Due to his focal neurologic deficits, he was taken emergently to the CT scanner according to your stroke protocol, where imaging did not show evidence of mass occupying lesions or an intracranial bleed. You and your consulting neurologist agreed that the patient should be treated for infectious encephalitis rather than ischemic stroke. Broad-spectrum IV antimicrobials were started emergently. You added IV acyclovir to his treatment regimen since you recalled that the vast majority of encephalitis cases result from viral causes. Review of the EMR revealed he had a history of cold sores and shingles within the last year, so you suspected that HSV-1 or VZV may be the causative agent. IV sedation was considered to facilitate lumbar puncture, but he was calm, and the procedure was safely accomplished with gentle redirection. CSF analysis revealed a pattern suggestive of herpes encephalitis. You optimized your patient's hemodynamics, consulted the on-call neurologist, and admitted your patient to the ICU.

CASE 3

For the 36-year-old man with a history of IV heroin use and HIV who presented with sepsis, headache, and neck stiffness…

Your clinical evaluation suggested acute meningitis in the setting of severe immunocompromise due to AIDS. You recognized the need for both rapid treatment of his sepsis with antibiotics as well as lumbar puncture. You quickly consented the patient for lumbar puncture and performed the procedure while nurses established IV access and administered broad-spectrum antibiotics and isotonic fluids. IV dexamethasone was added to treat a presumptive bacterial etiology. CSF was sent for analysis and culture. Given the patient's severe immunocompromise, you considered the possibility of a fungal meningitis. You added a cryptococcal antigen test to your workup and empirically administered IV amphotericin B liposomal after discussion with the on-call infectious disease physician. Several hours later, the patient's hemodynamics had improved, and he was boarding in the ED until a bed was available on the ward. You noted that CSF tests returned positive for *Cryptococcus neoformans*. You canceled additional scheduled doses of dexamethasone due to the risk for adverse outcomes with this pathogen.

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Risk Management Pitfalls for Meningitis and Encephalitis in the Emergency Department

1. **"It's probably just a migraine. She's just being dramatic."** Failing to consider CNS infection on the differential diagnosis leads to delayed diagnosis, delayed treatment, and increased mortality for ABM and herpes simplex encephalitis.

2. **"She's febrile and has a bad headache, but her neck is supple on examination and her GCS score is 15. Meningitis is ruled out."** Physical examination findings alone cannot rule out meningitis. Conversely, in 95% of cases, at least 2 of the 4 findings (which include headache, fever, neck stiffness, and altered mental status) are present. This patient has 2 of 4.

3. **"Kernig and Brudzinski signs are negative, so he probably just has musculoskeletal strain."** While these classic examination findings show high specificity (nearly 100%) for meningitis when present, neither is sensitive enough to rule out meningitis (<5% for both).

4. **"He's old and has sepsis. He's probably just has a urinary tract infection and is confused due to metabolic encephalopathy. We don't need to do a lumbar puncture."** Lumbar puncture can be a time-consuming procedure in a busy ED, and older individuals (especially with dementia) may not cooperate well with the procedure. However, failing to obtain CSF early for possible meningitis—especially when antibiotics are given—greatly impairs identification of causative pathogens.

5. **"She has a fever and maybe some neck stiffness, so meningitis is on my differential, but let's just wait for the head CT results before we convince her to get a lumbar puncture."** Meningitis cannot be ruled out without CSF analysis. Blood tests and CT are not sensitive for detecting meningitis or encephalitis. Delaying antibiotics leads to worsened outcomes. Antibiotics before delayed lumbar puncture impairs identification of causative pathogens. Finally, CT is not needed before lumbar puncture unless there are findings suggestive of an intracranial mass lesion.

6. **"This patient is coming from his nursing facility with fever, headache, and left-sided weakness. I started vancomycin and piperacillin-tazobactam, so he's covered for infection. Get him to the scanner."** The overwhelming majority of encephalitis cases are caused by viral pathogens. HSV-1 is the most common cause in industrialized countries, and elderly patients are at increased risk of VZV encephalitis. Acyclovir must be included in empiric treatment regimens for encephalitis.

7. **"Let's wait for the CSF results before we load this patient with antibiotics. I think it's probably just a viral infection."** Due to the time-dependency of poor outcomes in ABM, guidelines recommend administration of antibiotics within 1 hour of initial suspicion for meningitis.

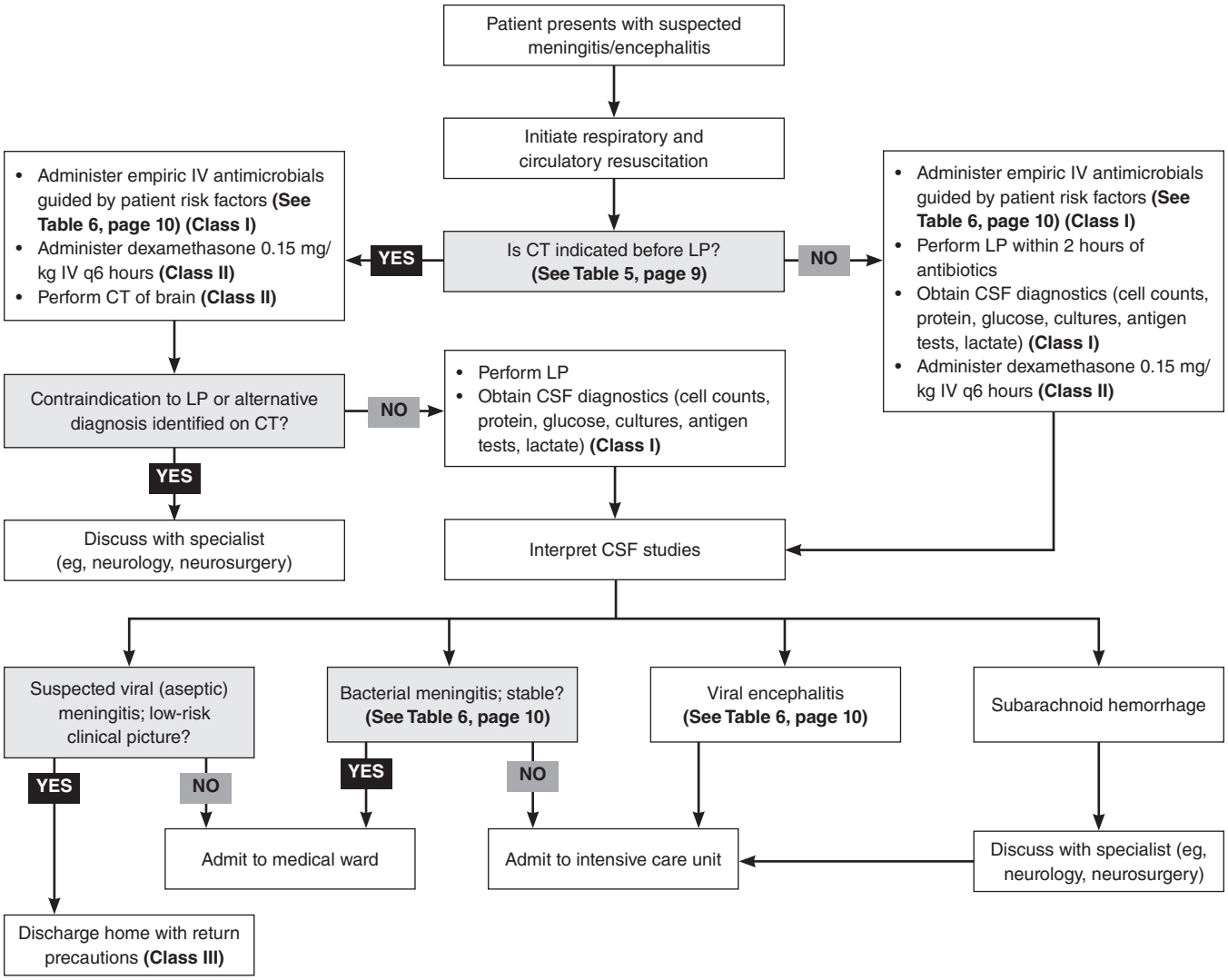
8. **"The CSF was flowing slowly. A few drops in each tube should be OK. I have other patients waiting."** Larger volumes of CSF increase the sensitivity of many important diagnostic tests. Up to 15 mL (3-4 mL per tube) can be safely collected in most patients.

9. **"CSF analysis looks like a viral pattern. The patient still has a headache and is vomiting. We'll admit her, but she doesn't need antibiotics."** The pattern of CSF studies early in the course of bacterial meningitis may be similar to the pattern in viral infections. Empiric antibiotics should not be delayed for CSF analysis, and should likely be continued for admitted patients, pending clinical improvement.

10. **"CSF analysis shows a clear viral pattern. The patient still has a headache and is vomiting, but his viral meningitis can be managed at home with NSAIDs and antiemetics."** Patients with severe symptoms, even with viral causes of meningitis, may still require admission for symptomatic treatment.

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Clinical Pathway for Emergency Department Management of Meningitis and Encephalitis



Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; IV, intravenous; q, every; LP, lumbar puncture.

Class of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.
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1. **A paramedic who works for your local EMS agency presents to your ED as a patient with a syndrome of meningitis. Which of the following pathogens could he have received postexposure prophylaxis for, if appropriately recognized at the time?**
   a. HSV-1
   b. *Listeria monocytogenes*
   c. *Streptococcus pneumoniae*
   d. *Neisseria meningitidis*

2. **When _____ is added to the "classic triad" of fever, neck stiffness, and altered mental status, a patient with 2 of these 4 symptoms has a 95% sensitivity for meningitis.**
   a. Photophobia b. Nausea and vomiting
   c. Headache d. Cranial nerve palsy

3. **Which of the following physical examination findings is most sensitive for the presence of meningitis?**
   a. Brudzinski sign (nape-of-the-neck sign)
   b. Jolt accentuation of headache
   c. Petechial rash
   d. Parotid gland swelling

4. **Which criterion would indicate a need for CT before lumbar puncture, based on any of the major society guidelines?**
   a. New-onset seizure
   b. Motor weakness of the arm
   c. Glasgow Coma Scale score 14
   d. Cranial nerve palsy

5. **Which of the following symptoms does NOT result from physiological changes from meningitis?**
   a. Headache b. Cranial nerve palsies
   c. Aphasia d. Altered mental status

6. **What cerebrospinal fluid (CSF) study, when elevated, is most sensitive and specific for bacterial (vs viral) meningitis?**
   a. Lactate
   b. White blood cell count
   c. Procalcitonin
   d. CSF to serum glucose ratio

7. **Administering adjunctive corticosteroids would most benefit a patient diagnosed with which infection?**
   a. Pneumococcal meningitis
   b. Meningococcal meningitis
   c. Herpes simplex encephalitis
   d. Listerial meningitis

8. **A 42-year-old woman develops a severe headache, altered mental status, personality changes, and seizures several weeks after recovering from a severe case of viral meningitis. What process most likely accounts for her recurrent symptoms?**
   a. Bacterial superinfection
   b. Reactivation of viral particles
   c. Autoimmune attack on neurotransmitter receptors
   d. Incomplete clearance of prior infection

9. **Vaccination efforts have significantly decreased the prevalence of meningitis caused by which 2 pathogens?**
   a. *S pneumoniae*; mumps
   b. *N meningitidis; S pneumoniae*
   c. *Haemophilus influenzae; S pneumoniae*
   d. *H influenzae;* mumps

10. **A 27-year-old woman is brought in with fever, splitting headache, drowsiness (GCSE3V5M6), and subjectively stiff neck. Her 2-year-old son had gastroenteritis last week. CSF analysis suggests a viral pattern. She feels considerably better after receiving IV fluids, IV ketorolac, and IV ondansetron. She passes an oral challenge, and her vital signs are in the normal range. What is the most appropriate disposition for this patient?**
    a. Consider discharge home now into the care of her husband with prescriptions for symptom control medications.
    b. Admit to the general medical ward while bacterial cultures result.
    c. Observe in the ED another 6 hours, then discharge if she is stable.
    d. Admit to the ICU for encephalitis because her GCS on presentation was <15.

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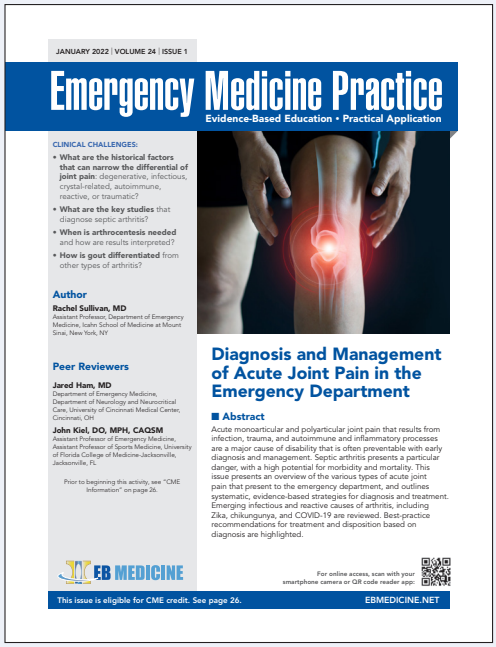
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Needs Assessment: The need for this educational activity was determined by a practice gap analysis; a survey of medical staff, including the editorial board of this publication; review of morbidity and mortality data from the CDC, AHA, NCHS, and ACEP; and evaluation responses from prior educational activities for emergency physicians.

Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

Goals: Upon completion of this activity, you should be able to: (1) identify areas in practice that require modification to be consistent with current evidence in order to improve competence and performance; (2) develop strategies to accurately diagnose and treat both common and critical ED presentations; and (3) demonstrate informed medical decision-making based on the strongest clinical evidence.

CME Objectives: Upon completion of this activity, you should be able to: (1) list the strengths and weaknesses of history and physical examination findings in the management of meningitis and encephalitis; (2) describe the role of cerebrospinal fluid (CSF) sampling for meningitis/encephalitis and select diagnostic tests; and (3) select empiric treatments and appropriate dispositions for patients with meningitis or encephalitis.

Discussion of Investigational Information: As part of the activity, faculty may be presenting investigational information about pharmaceutical products that is outside Food and Drug Administration approved labeling. Information presented as part of this activity is intended solely as continuing medical education and is not intended to promote off-label use of any pharmaceutical product.

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QUICK READ

Points & Pearls

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Emergency Department Management of Adults With Infectious Meningitis and Encephalitis

Points

- *Meningitis* refers to inflammation of the meninges; *encephalitis* refers to inflammation of the brain parenchyma.
- The presence of focal neurological signs (seizure, motor weakness, aphasia, neuropsychiatric symptoms, or dysautonomia) indicates involvement of brain tissue and encephalitis.
- Prehospital providers exposed to bacterial pathogens should receive postexposure prophylaxis. **See Table 4** for recommended regimens.
- No single symptom can differentiate meningitis from other disease processes.
- Kernig and Brudzinski signs have a sensitivity of 2%, and specificity of 97% and 98%, respectively.
- The history (travel, or animal or insect contact) may point to a viral cause, including varicella zoster virus infection or herpes infection. **See Table 2** for potential viral causes.
- The most common pathogens causing bacterial meningitis in immunocompetent adults are *Streptococcus pneumonia* and *Neisseria meningitidis*.
- Petechial rash; dermatomal, vesicular rash; or recent oral/genital herpes may point to a specific etiology of CNS infection.
- CNS infection can also occur following neurosurgical procedures or injury with CSF leakage.
- MRI does not detect meningitis, but it can help distinguish between various subtypes of encephalitis. **(See Figure 1.)**
- CT is not sensitive for detecting meningitis or encephalitis,[60] but may be helpful for excluding other pathologies or making a diagnosis
- Lumbar puncture may be contraindicated in some conditions that cause increased intracranial pressure, though recommendations on indications for CT vary. **Table 5** summarizes 4 different society guidelines on indications for CT.
- Empiric antimicrobial regimens should be chosen based on patient age, immune status, and historical factors (eg, local resistance patterns). **See Table 6** for antimicrobial regimens.
- In immunocompromised adults, antibacterial coverage should include *Listeria monocytogenes* and *Pseudomonas aeruginosa*.

Pearls

- The "classic" triad of signs—fever, neck stiffness, and altered mental status—may be absent or subtle, particularly in the elderly or immunosuppressed. It has been shown to be present in only 44%-66% of patients with bacterial meningitis.[3,6] Adding a fourth sign, headache, improves sensitivity/specificity.
- Herpes simplex encephalitis carries a mortality rate of around 9%. Patients with clinical signs of this should empirically receive acyclovir pending PCR results.
- Antimicrobial treatment should be initiated within 1 hour of the time that bacterial meningitis is suspected.[1]
- Lumbar puncture with CSF analysis is the mainstay of diagnosis. See the "Cerebrospinal Fluid Analysis"section for findings that may be seen in normal, bacterial, and viral fluid.
- Corticosteroids are the only adjunctive therapy shown to impact outcomes in patients with bacterial meningitis from *S pneumoniae* or *M tuberculosis*, and should be initiated within 1 hour. However, they should be discontinued if the causative agent is not suspected or determined to be caused by these 2 pathogens, as its use is associated with worse outcomes.[1,74]
- Pregnant women are at particular risk from listerial infection.
- Most cases of viral meningitis are self-limited and require no directed therapy.
- False-negative PCR results are possible during the first 72 hours of herpes simplex encephalitis; PCR testing should be repeated after 3-7 days.[70]
- Neuropsychiatric manifestations and seizures, can be caused by autoimmune responses following CNS infection. Seek neurologic specialist care in these cases.
- **See Table 7** for recommendations on the disposition of patients: discharge, medical ward, or ICU.

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