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AHC Media

Meningitis Update

Missed meningitis is every emergency physician's worst nightmare, especially in a child. We all know the explanations of why it may be missed. First of all, it is uncommon; how many lumbar punctures (LPs) have you done that were "negative"? Second, there are much more common causes of fever, headache, and irritability. And third, performing an LP in a combative patient is not easy. So, it is easy to talk yourself out of doing one. This issue of EM Reports *should provide you with enough reasons to stick with your first instinct and do the LP.*

—J. Stephan Stapczynski, MD, Editor

Introduction

Meningitis is inflammation of the meninges lining the brain, that if allowed to progress, causes impaired absorption and distribution of cerebrospinal fluid (CSF), vasodilation, and disruption of the blood-brain barrier, ultimately leading to increased intracranial pressure.[1] Infectious organisms gain access to this space either through hematologic spread, usually from the upper respiratory tract, or directly through infections of adjoining structures such as otitis media, mastoiditis, or sinusitis. Encephalitis, defined as inflammation of the brain parenchyma, causes alterations in mental status or other neurologic pathologies, whereas these features are technically absent in meningitis. These disease processes often coexist in the entity sometimes called meningoencephalitis. This update will refer to the term meningitis in the broad sense, with the implication that concomitant encephalitis may or may not be present.

Meningitis is usually classified as either bacterial or aseptic. Aseptic meningitis is defined as meningitis with CSF cultures that produce no growth with routine bacterial culture; it includes viral, fungal, tuberculous, and neoplastic meningitides. Other rare etiologies of meningitis, such as drug-induced and autoimmune meningitides, are diagnoses of exclusion and less pertinent to the practice of emergency medicine, and so they will not be part of this discussion.

Bacterial Meningitis

Epidemiology

The epidemiology of bacterial meningitis has drastically changed due to vaccines against the most common bacterial pathogens.[2] Cases of meningitis due to *H. influenzae* type b have decreased by more than 90% in the United States after the introduction of the conjugate vaccine in 1990. In developing countries, where few patients have access to this vaccine, it continues to be a major cause of pediatric meningitis, causing more than 100 cases per 100,000 children per year in some countries.[2] Vaccines against *Streptococcus pneumoniae* have led to a 59% reduction in pediatric meningitis in the United States due to that pathogen.[2] One of the most common bacterial causes of meningitis

EXECUTIVE SUMMARY

- Almost all cases of bacterial meningitis present with some combination of fever, headache, neck stiffness, and altered mental status — the absence of all four makes the diagnosis highly unlikely.
- If the LP is delayed for any reason, initiate empiric antibiotics.
- In patients with suspected meningitis, add acyclovir to the initial empiric antibiotic regimen if there are new-onset seizures or focal neurologic findings.
- Administer dexamethasone prior to or simultaneously with the first dose of antibiotics in adults and children older than 1 month of age with suspected bacterial meningitis in high-income countries.

in neonates is group B streptococcus (GBS) or *Streptococcus agalactiae*, usually transmitted to the child during the birthing process. Beginning in the 1990s, the screening of pregnant women for the colonization of rectovaginal group B streptococcus at 35 to 37 weeks gestation, and the subsequent administration of penicillin to carriers, has led to a decrease in meningitis due to group B streptococcus, from 2 cases per 1000 live births in 1990 to 0.3 cases per 1000 live births in 2004.[2] There is a quadrivalent meningococcal vaccine (MCV4) against *Neisseria meningitidis* strains AC, W135, and Y, and there has been a decline in bacterial meningitis due to *N. meningitidis* by more than 50% from 1998-1999 to 2006-2007. The overall effect of these immunizations resulted in approximately 4100 cases per year of bacterial meningitis in the United States from 2003 to 2007, with 500 fatalities annually.[3]

The most common bacterial producing meningitis in the United States varies according to age and risk factors (*see Table 1*). Overall, 61% of bacterial meningitis cases in the United States are due to *Streptococcus pneumoniae*, followed by *Neisseria mengingitidis* (16%), *Streptococcus agalactiae* (14%), *Haemophilus influenzae* (7%), and *Listeria monocytogenes* (2%).[1] Worldwide, across all age groups, the most common bacteria causing meningitis is *S. pneumoniae*.

Clinical Features

The classic combination of fever, headache, neck stiffness, and altered mental status is not always present. The reported incidence of all four findings is 21-66%. Fever is the most common of these features, present in 84-97% of adult patients with bacterial meningitis.[4] Two or more of these features were found in 95% of adults with acute bacterial meningitis, according to one analysis.[4] Although individually these signs and symptoms are neither sensitive nor specific, the absence of all of the features of the classic triad (fever, stiff neck, and altered mental status) is 99-100% sensitive in excluding bacterial meningitis, according to one meta-analysis.[5] Conversely, at least one of these signs and symptoms is present in nearly all patients with bacterial meningitis.[4,6]

The classic Kernig's and Brudzinski's signs were developed more than 100 years ago to aid in the physical examination of patients suspected of having meningitis. Kernig's sign, defined as resistance of knee extension with the hips flexed, and Brudzinski's sign, defined as hip and knee flexion in response to forward flexion of the neck, increases the likelihood of meningitis when found to be positive.[7] However, according to one meta-analysis, the sensitivities of Kernig's and Brudzinski's signs were 53% and 66%, respectively, so clinicians should not use the absence of these signs to exclude meningitis.[8,9]

The clinical presentations of the very young, very old, and the immunocompromised are even more variable. Infants with bacterial meningitis often present with nonspecific signs and symptoms, such as fever, irritability, and poor feeding. Neck stiffness and meningismus are seldom present and can be difficult to assess in this age group, so the absence of these signs should not be used to exclude meningitis.[2,10] Older children are more likely to present with signs and symptoms more commonly associated with bacterial meningitis, such as neck stiffness, photophobia, and vomiting.[2] The elderly more frequently present with altered mental status and focal neurologic deficits, and less often have headache and neck stiffness.[2]
In HIV-positive patients, the clinical presentation is similar to age-matched cohorts, but seizures are significantly more common in patients with HIV (22%) in contrast to those without HIV (3%).[11]

Diagnosis

Lumbar puncture (LP) is required to both diagnose bacterial meningitis and to exclude its presence. Because of the consequences of untreated bacterial meningitis, emergency physicians have had a low threshold for performing this procedure. The risk of an adverse event from an LP is low, but can occur even in experienced hands. The most serious complication of lumbar puncture is cerebral herniation, but other risks associated with the procedure include post-LP headache, bleeding, infection, and radicular pain.

Cerebral herniation due to lumbar puncture most often occurs in patients with space occupying lesions such as abscesses, tumors, and infarctions. Imaging may be performed to help identify space occupying lesions, but determining who needs a computed tomography (CT) scan prior to LP is a dilemma. Obtaining a CT scan usually leads to a significant delay in both lumbar puncture and the initiation of antibiotic therapy, and CT scans expose the patient to a significant amount of radiation.[8] Expert opinion has identified clinical characteristics in which the CT should be done prior to LP (*see Table 2*); if none of these are present, LP can be done without prior CT. It is notable that cerebral herniation following lumbar puncture is a controversial subject; several experts point to case reports of cerebral herniation occurring in patients with bacterial meningitis even without a preceding lumbar puncture. One study from Sweden calls into question the recommendation that moderate to severe impairment of consciousness be a

Table 1. Common Bacterial Causes of Meningitis and Empiric Antibiotic Therapy Based on Patient Age and Clinical Risk Factors[1,2,4,15,23]

Patient Characteristics	Most Common Bacterial Agents	Empiric Antibiotic Therapy
Neonates (0-42 days)	Group B *Streptococcus* *Listeria monocytogenes* *E. coli* and other Gram-negative rods	Ampicillin + cefotaxime or Ampicillin + gentamicin
Infants and Children	*Streptococcus pneumoniae* *Neisseria meningitidis*	Vancomycin Ceftriaxone or cefotaxime
Adults	*Streptococcus pneumoniae* *Neisseria meningitidis*	Vancomycin Ceftriaxone
Elderly (50 years and older)	*Streptococcus pneumoniae* *Neisseria meningitidis* *Listeria monocytogenes* Aerobic Gram-negative rods	Vancomycin Ceftriaxone Ampicillin
Immunocompromised, alcohol abuse, pregnancy	*Streptococcus pneumoniae* *Neisseria meningitidis* *Listeria monocytogenes* *E. coli* *Salmonella* *Staphylococcus aureus*	Vancomycin Ceftriaxone Ampicillin
Neurosurgery patients (patients with ventriculoperitoneal shunts, recent craniotomy or cranioplasty)	*Streptococcus pneumoniae* *Staphylococcus aureus* *Staphylococcus epidermidis* *Pseudomonas aeruginosa* and other aerobic Gram-negative rods	Vancomycin Cefepime, ceftazidime, or meropenem
Patients with basilar skull fracture or head trauma causing CSF leak	*Streptococcus pneumoniae* *Haemophilus influenzae* Group B *Streptococcus* Group A β-hemolytic *Streptococcus*	Vancomycin ceftriaxone or cefotaxime

contraindication to lumbar puncture. In that study, following revision of Swedish guidelines regarding CT scan before LP, there was a significant decrease in time to treatment, morbidity, and mortality.[12] **If a head CT is ordered, empiric antibiotics should be started prior to the imaging.** To prevent serious bleeding, LP is relatively contraindicated in the setting of therapeutic anticoagulation, disseminated intravascular coagulation, or significant thrombocytopenia in patients with hematologic disorders or those receiving chemotherapy.[8]

After performing the lumbar puncture, the following CSF studies should be obtained: cell count and differential, glucose, protein, Gram stain, culture, and antibiotic susceptibility. The gold standard for diagnosis of bacterial meningitis is CSF culture, but it can be negative in up to 20% of cases depending on the etiologic agent, and results of the culture will rarely be available with the patient still in the emergency department, so other tests must be utilized to guide initial therapy.[2] Classic CSF characteristics in acute bacterial meningitis include elevated white blood cell count with a polymorphonucleocyte (PMN) predominance, decreased glucose concentration, and increased protein concentration (*see Table 3*).[8] Greater than 92% of adults with bacterial meningitis will have a CSF white blood cell count of 100 cells per mm^3 or more, and 78% will have 1000 or more.[4] Immunosuppressed patients are a notable exception; they often present with a lower CSF white blood cell count.[8] The CSF protein concentration is elevated in 90% of adults with acute bacterial meningitis.[8] The sensitivity of CSF Gram stain depends on the species, ranging from 10-35% with *Listeria monocytogenes* to 69-93% with *Streptococcus pneumoniae*.[2]

The majority of patients with bacterial meningitis will have typical CSF results, but some will not. Early viral meningitis or tuberculous meningitis may result in similar CSF characteristics to bacterial meningitis; in early aseptic meningitis, the majority of white cells in the CSF may be neutrophils, but usually less than 80%, in contrast to bacterial causes.[8] If antibiotics are given to patients with bacterial meningitis before lumbar puncture, a CSF mononuclear predominance, suggesting an aseptic meningitis, may be found.[13] Rigid application of these characteristics may lead to the inappropriate withholding of antibiotics from patients with bacterial meningitis. If antibiotics are started before LP, the sensitivity of all CSF studies decreases, so LP should precede treatment if it can be performed within a reasonable amount of time. No definite time threshold has been determined to guide recommendations, but if it seems unlikely that LP will be performed within a few hours of the patient's presentation, empiric antibiotics should be given before lumbar puncture. For instance, if the patient requires a CT scan or transfer to another facility prior to LP, antibiotics should be given before those events. However, even if antibiotic therapy has been started, lumbar puncture should still be performed when possible; most CSF studies will yield positive results 4 hours after the first dose of antibiotics.[2,8,14-16]

Clinical prediction rules have been developed to aid in the assessment of possible meningitis cases. Oostenbrink and others developed a diagnostic decision rule for the management of children aged one month to 15 years with suspected bacterial meningitis. The authors developed a scoring system to determine which patients should undergo lumbar puncture. Points were assigned based on duration of symptoms, serum C-reactive protein (CRP) level, and the presence or absence of vomiting, meningeal irritation, petechiae, cyanosis, and disturbed consciousness; the higher the score the greater

Table 2. Indications for Head CT Prior to LP[8]

Head CT is indicated prior to LP if one or more of the following are present:

- New-onset seizures
- HIV/AIDS
- Immunosuppressive therapy
- History of organ transplantation
- History of focal central nervous system (CNS) lesion (tumor, stroke, abscess)
- Papilledema
- Focal neurologic deficits
- Moderate to severe altered mental status
- Evolving signs of herniation

the likelihood of bacterial meningitis. If patients were below the threshold score, lumbar puncture could be safely excluded. If patients were above the threshold score, they underwent lumbar puncture, and a second scoring system, the CSF score, was used to determine which patients should receive antibiotic therapy. The CSF score was based on the CSF white blood cell count and the ratio of CSF to blood glucose concentration. The authors contend that the clinical decision rule can identify children at very low risk of bacterial meningitis and prevent unnecessary lumbar punctures, hospital admissions, and antibiotic therapy in those patients without missing any cases of bacterial meningitis.[17]

A meta-analysis of eight studies of 5312 patients aged 29 days to 19 years conducted between 2002 and 2012 was utilized to derive and validate a Bacterial Meningitis Score to identify children with CSF pleocytosis at very low risk of bacterial meningitis. Patients were assigned two points for positive CSF Gram stain and one point each for CSF protein concentration of 80 mg/dL or greater, peripheral absolute neutrophil count (ANC) of 10,000 cells/mm^3 or more, seizure at or before presentation, and CSF ANC of 1000 cells/mm^3 or more. Patients with a score of 0 were classified as having low risk of bacterial meningitis and could be deemed appropriate for outpatient management after starting treatment with a long-acting parenteral antibiotic. The decision tool was found to be 99.3% sensitive and 62.1% specific for bacterial meningitis. The few cases of bacterial meningitis that were missed using the Bacterial Meningitis Score were all due to meningococci that were present without CSF pleocytosis. To avoid missing any cases of bacterial meningitis, the authors recommend that the Bacterial Meningitis Score only be applied to well-appearing children, children 2 months of age or older, and those without physical examination findings of meningococcemia such as purpura or petechiae.[18,19]

Additional studies may increase the diagnostic yield in cases in which LP is contraindicated, delayed until after initiation of antibiotic therapy, or when initial CSF studies are negative. CSF lactate has been shown in two meta-analyses to differentiate bacterial from aseptic meningitis with a sensitivity of 93-97% and a specificity of 94-96%, suggesting that CSF lactate may be a better diagnostic predictor of bacterial meningitis than cerebrospinal fluid white blood cell count and protein and glucose concentrations.[8,20,21] Blood cultures are positive in 50-80% of cases of bacterial meningitis depending on the causative species.[2,8] Polymerase chain reaction (PCR) to detect common bacterial pathogens is expensive and not widely available, but the technology is advancing rapidly, so it may become more useful in the near future. It has good sensitivity (67-100%) and excellent specificity (95-100%), but studies show conflicting results regarding its incremental value when all other CSF studies are negative.[2,8] Serum inflammatory markers such as C-reactive protein (CRP) and procalcitonin have been shown to be elevated in bacterial meningitis; a CRP of 20 mg/L or greater and procalcitonin of 0.5 ng/mL or greater suggests but does not confirm bacterial instead of aseptic meningitis.[2] In cases of suspected meningitis due to *Neisseria meningitidis*, Gram stain and culture of skin lesions was shown to be 36% sensitive in one study.[2] Latex agglutination has been shown to have low sensitivity by several studies and is not widely available.[2] Other CSF markers of bacterial meningitis have recently been proposed, including complement factor 3, complement factor B, heparin-binding protein, cortisol, soluble triggering receptor expressed on myeloid cells 1 (sTREM1), interleukins 1β, 6 and 12, and tumor necrosis factor alpha. However, neither marker has been validated for general use.[8]

Treatment

Acute bacterial meningitis is a medical emergency with a mortality of 13-27% despite treatment. Timely and appropriate therapy is essential to prevent death and significant neurologic impairment, with studies showing increasing mortality and morbidity in proportion to length of time from patient arrival to the hospital to the first dose of antibiotics.[14] Some experts have recommended specific timelines for initiation of antibiotics — for instance, within three hours of the patient's arrival to the hospital. However, others believe an arbitrary timeline is less helpful than the general recommendation that antibiotics be started as soon as possible and that the patient's disease severity should be taken into consideration.[4] Initial therapy should consist of broad spectrum antibiotics; antibiotic therapy can be subsequently tailored to the bacteria that are identified via Gram stain or culture of the cerebrospinal fluid. Initial antibiotic therapy should also take into consideration the patient's age and clinical scenario to cover the most likely pathogens (*see Table 1*). A third-generation cephalosporin such as ceftriaxone or cefotaxime is recommended, as it has a broad spectrum of coverage and because of its ability to penetrate the cerebrospinal fluid.[2,4] Cefotaxime as opposed to ceftriaxone is recommended in children due ceftriaxone-associated cholelitihiasis and biliary sludge, which has a higher incidence in children.[22] Vancomycin is

Table 3. Classic CSF Findings in Normal Patients and Those with Various Types of Meningitis[1,4,13,15,35]

	Normal	Bacterial	Viral	Neoplastic	Fungal	Tuberculous
Opening pressure (mm H2O)	< 170	> 300	< 300	200	300	> 250
WBC count (per mm^3)	< 5	> 1000	< 1000	< 500	< 500	50-1000
Neutrophils	0%	> 80%	< 20%	1-50%	1-50%	< 80-90% in adults < 50% in children
Glucose (mg/dL)	> 40	< 40	> 40	< 40	< 40	< 40
Protein (mg/dL)	< 50	> 200	< 200	> 200	> 200	50-250
Gram stain	negative	positive	negative	negative	negative	negative

recommended for all patients other than neonates to cover for multiple drug-resistant *Streptococcus pneumoniae*, shown to be increasing in prevalence in many regions.[4] Ampicillin should be given to neonates, immunocompromised patients (including pregnant patients and those with a history of alcohol abuse), and those age 50 years or older to cover for *Listeria monocytogenes*, which has higher rates of incidence in those groups.[2,4] The use of gentamicin in neonates to cover Gram-negative bacteria is controversial primarily based on data that show synergistic activity with other antibacterial agents, but these data come from in vitro studies, and gentamicin has poor cerebrospinal fluid penetration.[2,23] Neurosurgery patients have a higher risk of *Pseudomonas aeruginosa* meningitis, so empiric therapy should include a broad spectrum agent such as meropenem or an advanced generation cephalosporin with activity against *Pseudomonas* such as cefepime or ceftazidime.[2]

Adjunctive treatment with dexamethasone to reduce inflammatory effects is recommended for some patients.[15] A meta-analysis of 25 studies with more than 4000 adult and pediatric patients showed that dexamethasone does not decrease overall mortality, but can reduce morbidity and mortality in some groups.[24] It has been shown to decrease hearing loss in children in high-income but not low-income countries, and it has been shown to reduce mortality in bacterial meningitis due to *Streptococcus pneumoniae*, but not due to *Neisseria meningitidis* or *Haemophilus influenzae*. Some experts have raised the theoretical concern that corticosteroids may limit the penetration of antibiotics into the cerebrospinal fluid; however, the only significant adverse event associated with dexamethasone identified by this analysis was recurrent fever.[4,24] There is insufficient evidence of benefit in neonates to recommend the use of dexamethasone in this age group.[2,23] Based on this evidence, dexamethasone is recommended in adults and children older than 1 month of age in high-income countries. It should be administered just prior to or at the same time as the first dose of antibiotics.[2,15]

A few experimental models and case reports have suggested that daptomycin, linezolid, tigecycline, and fluoroquinolones such as moxifloxacin may be useful as adjunctive or alternative antibiotic therapy in bacterial meningitis, but definitive evidence is lacking, and they are not recommended for empiric therapy at this time.[23] Other novel adjunctive therapies, including glycerol to reduce intracranial pressure and induced hypothermia, are being studied, but there is currently insufficient evidence to support their use.[23,25] In addition to definitive therapy, patients with bacterial meningitis should receive supportive care, including anticonvulsant medications if seizures occur, and maintenance of normoglycemia and normovolemia.[23]

Viral Meningitis

Epidemiology

In adults, 80-85% of viral meningitis cases are due to non-polio enteroviruses such as Coxsackie A and B viruses and echovirus, with the remaining cases due to other viruses (*see Table 4*).[1,13] After enteroviruses, herpes simplex viruses are the second most common cause of aseptic meningitis in adolescents and young adults in high-income countries. Mumps, once the most common cause of viral meningitis in children prior to the measles, mumps, and rubella (MMR) vaccine, still frequently causes meningitis, but much less frequently than do the enteroviruses. Overall, viral meningitis is more common than bacterial meningitis, and it is probably underreported, so the incidence may be even higher. Seasonal variation in the incidence of viral meningitis is notable, peaking in the summer in temperate climates. No such seasonal variation is seen in warmer climates. The incidence of viral meningitis decreases significantly with age, with the vast majority of cases occurring in infants. In infants younger than 1 year of age, the annual incidence of viral meningitis is as high as 219 per 100,000.[13] In contrast, the annual incidence of bacterial meningitis in the United States in children younger than age 2 years is approximately 90 per 100,000.[26] In adults, the annual incidence of viral meningitis is slightly greater than that of bacterial meningitis (7.6 vs 5.3 per 100,000, respectively).[3,13]

Clinical Features

Importantly, aseptic meningitis cannot be distinguished from bacterial meningitis based on clinical signs and symptoms. Viral meningitis presents with the same symptoms of fever, headache, and neck stiffness found in bacterial meningitis. Infants with viral and bacterial meningitis present similarly, with irritability and fever, and rarely exhibit meningeal signs.[13] Laboratory testing, discussed above, is essential for excluding bacterial meningitis, but there are some findings that may suggest a viral as opposed to a bacterial etiology. Skin and mucous membrane vesicles are often found in infections due to enteroviruses, herpes simplex viruses,

Table 4. Etiologies of Viral Meningitis

- Enteroviruses (poliovirus, Coxsackie viruses A and B, Enterovirus 71, echoviruses)
- Varicella zoster virus (VZV)
- Herpes simplex viruses 1 and 2 (HSV-1 and HSV-2)
- Epstein-Barr virus (EBV)
- Human immunodeficiency virus (HIV)
- Cytomegalovirus (CMV)
- Mumps
- West Nile virus
- St. Louis encephalitis
- Lymphocytic choriomeningitis virus (LCMV)

or varicella zoster virus. Mumps should be suspected in a patient with a history of lack of or incomplete vaccination. Oral thrush should raise concern for HIV infection. Tick exposure and/or travel history increases the likelihood of infection with West Nile and St. Louis viruses in North America and tick-borne encephalitis viruses in Eastern Europe. Contact with rodents may suggest lymphocytic choriomeningitis virus meningitis.[13] However, none of these features is sufficient to exclude bacterial meningitis.

Some experts consider herpes simplex virus encephalitis and meningitis to be separate entities as opposed to points on a continuum. Encephalitis should be suspected in a patient presenting with seizures, altered mental status, or focal neurologic deficits. Appropriate antiviral therapy should be initiated. Herpes simplex virus 1 primarily causes oral lesions, whereas herpes simplex virus 2 tends to cause genital lesions, although a substantial percentage of patients with HSV-1 infections will present with lesions suggestive of HSV-2 infection and vice versa. Herpes simplex virus meningitis can be caused by either strain and is usually associated with a primary infection; between 13-26% of patients with a primary genital herpes infection have symptoms of meningitis. Herpes simplex virus meningitis may also occur in patients without a history of genital herpes or without genital lesions on physical examination.[13]

Diagnosis

Diagnosis of viral meningitis is approached in a similar manner to that of bacterial meningitis, discussed above. Head CT should be performed prior to LP if the features noted in Table 2 are present. Lumbar puncture should be performed as soon as possible, and cerebrospinal fluid sent for testing. The classic laboratory findings of viral meningitis are elevated CSF white blood cell count with a mononuclear predominance, a CSF to serum glucose concentration ratio of greater than 0.5, and an elevated CSF protein concentration. The CSF white blood cell count and protein concentration are not as markedly elevated in viral meningitis as in acute bacterial meningitis. A polymorphonuclear pleocytosis may be found in early viral meningitis, and a mononuclear predominance may be found in bacterial meningitis if the CSF is obtained after antibiotics have been administered. In addition to the tests for bacterial meningitis discussed above, viral PCR for detection of enteroviruses, herpes simplex virus, and varicella zoster virus should be performed. In the case of herpes simplex virus encephalitis, brain magnetic resonance imaging (MRI) may show temporal lobe abnormalities, although this is unlikely to change management in the emergency department. Other tests that may be useful include the monospot test or serology for EBV, HIV, or mumps. The benefits of identifying a specific viral etiology lie in decreasing hospitalizations and the use of antibiotics.[13]

Treatment

In contrast to acute bacterial meningitis, most cases of viral meningitis are self-limited and probably portend a good prognosis. Treatment is supportive and includes antipyretics, analgesia, and judicious fluid management; patients can be managed on an outpatient basis if symptoms are not severe.[27] However, herpes simplex virus encephalitis is a medical emergency that requires admission for intravenous antiviral medications such as acyclovir. If seizures, altered mental status, or focal neurologic deficits are found in a patient suspected of having meningitis, acyclovir should be considered along with empiric antibacterial therapy. There is no clear mortality benefit to antiviral therapy in herpes simplex meningitis, but agents such as acyclovir, famciclovir, or valaciclovir may be considered, as they theoretically reduce recurrence risk and duration and severity of symptoms.[13]

Fungal Meningitis

Epidemiology and Risk Factors

Fungal pathogens are common causes of meningitis for immunocompromised patients, but they can also cause disease in immunocompetent hosts. Fungal species are classified as primary or secondary pathogens. Primary pathogens are those that can cause disease in immunocompetent patients. Secondary pathogens (also known as opportunistic pathogens) affect immunocompromised patients.[28] The most common primary fungal pathogens are *Cryptococcus neoformans* and *Coccidioides immitis*. *Histoplasma capsulatum* and *Blastomyces dermatitidis* are less common primary fungal pathogens, and when they affect immunocompetent patients they are more likely to cause other central nervous system (CNS) infections such as brain abscesses as opposed to meningitis. The most common opportunistic pathogens are *Candida albicans* and *Aspergillus fumigatus*. Some of these pathogens have very specific geographic distributions. *Coccidioides* is endemic to Mexico and the southwestern United States. *Histoplasma* causes disease in the Ohio and Mississippi River valleys. *Blastomyces* is found in the Mississippi Valley and the North Central and Mid-Atlantic regions of the United States. *Cryptococcus*, *Candida*, and *Aspergillus* are found worldwide.[28]

The epidemiology of cryptococcal meningitis reflects the rise of the

AIDS epidemic and the subsequent introduction of antiretroviral therapy. A significant increase in the incidence of cryptococcal meningitis was observed during the rise of the AIDS epidemic. Subsequently, antiretroviral drugs led to a decrease in its incidence. Among non-HIV infected patients, the rate of fungal meningitis has remained more or less constant during the past few decades.[28,29] The populations with highest risk for cryptococcal meningitis are AIDS patients with CD4 counts of 100 or less and chronic immunosuppressant use in transplant patients and those with autoimmune disease.[28] HIV-negative and non-transplant patients with cryptococcal meningitis most often have risk factors for fungal disease such as cancer or immunologic or autoimmune disorders.[30]

Risk factors for candidal meningitis include neurosurgery patients, presence of a ventriculostomy or ventriculoperitoneal shunt, neutropenia, intravenous drug use, and systemic candidiasis. *Candida* species are by far the most common fungal pathogens to infect CNS shunts; patients usually present weeks to months after placement of the device and are at particularly high risk of contracting candidal meningitis if they have received antibiotics for a bacterial infection. Neonates, especially premature infants and those receiving antibiotics for a bacterial infection, are at increased risk of meningitis due to *Candida*.[28] Meningitis due to *Aspergillus* is rare and has been considered to occur primarily in patients with severe chronic neutropenia or immunosuppressed transplant patients, especially those experiencing graft rejection and therefore receiving aggressive immunosuppressive regimens.[28] However, in one review of 93 cases, more than half of patients (55.9%) were immunocompetent.[31] *Coccidioides* and *Histoplasma* most often cause subclinical or self-limited respiratory illness, but can cause disseminated disease. In one-third to one-half of patients with disseminated coccidioidal disease, meningitis develops. Only 2% of patients with coccidioidal meningitis are HIV-positive or on immunosuppressive drugs.[28] Disseminated disease and meningitis in histoplasmosis is much more common in immunocompromised hosts.[28]

Clinical Manifestations

The clinical manifestations of fungal meningitis are variable and depend on the causative fungi, but much variability exists even within one type of fungal meningitis. As in bacterial meningitis, neck stiffness is not a reliable sign in neonates with fungal meningitis, who usually present with fever and nonspecific signs and symptoms.[32] Cryptococcal meningitis most commonly presents with gradual onset headache and confusion. Patients may present with cranial nerve palsies, seizures, and visual loss as a result of increased intracranial pressure. Fewer than one out of every five patients with cryptococcal meningitis present with the classic signs of meningitis such as fever and neck stiffness. Symptoms are usually less acute than with bacterial and viral meningitis, with patients sometimes reporting weeks of symptoms.[28,30] Candidal meningitis most commonly presents with headache and fever; symptoms may be acute or chronic in onset.[28,32] Patients with CNS shunts are more susceptible to candidal than other fungal infections; they most often present with fever and signs and symptoms of increased intracranial pressure such as headache, vomiting, and altered mental status.[32] Most patients with aspergillus meningitis present with altered mental status, seizures, or focal neurologic deficits. Neck stiffness is found in a minority (19%); symptoms are usually acute in onset but may also be chronic or subacute.[28,31] Patients with meningitis due to *Coccidioides*, *Blastomyces,* and *Histoplasma* almost always present with symptoms of chronic meningitis.[28]

Diagnosis

Diagnosis of suspected fungal meningitis includes analysis of the cerebrospinal fluid with India ink and fungal cultures in addition to the studies discussed for bacterial meningitis. The CSF will usually have a white blood cell count of 20 to 500 cells per mm^3 and have a mononuclear predominance, although *Aspergillus* and *Blastomyces* have been known to give a polymorphonuclear pleocytosis in some cases. *Coccidioides* tends to cause an increased CSF eosinophil count. Diagnosis of coccidioidal meningitis can be augmented with examination of the CSF for complement fixation antibodies (CFA).[28] It is important to note that in immunosuppressed patients most susceptible to fungal infections, the CSF white blood cell count may not be elevated. CSF protein concentration is usually elevated, and CSF glucose concentration is usually depressed. The gold standard for diagnosis of fungal meningitis is CSF culture, but many of the pathogens causing fungal meningitis are difficult to culture and are unlikely to change management in the emergency department. India ink stain of the CSF is positive in most cases of cryptococcal meningitis. Latex agglutination and enzyme-linked immunosorbent assay (ELISA) tests for *Cryptococcus* are more than 90% sensitive and specific.[28] *Candida* is difficult to detect in the CSF; only 17% of cases are detected with staining and 44% with routine culture.[28] Confirmation of the diagnosis is therefore unlikely in the emergency department. Other assays to detect components of the fungal cell wall or metabolic products have been proposed, but there are few data to support their use.[32] The diagnosis of meningitis due to *Aspergillus*, *Histoplasma*, and *Blastomyces* is extremely difficult and unlikely to be made in the emergency department. In one case review of *Aspergillus* meningitis, it was not diagnosed until autopsy for almost half of patients.[31] CSF culture is insensitive; PCR or detection of aspergillus-specific antigens may be useful, but the sensitivity of these tests is unknown.[28] Meningitis due to *Histoplasma* is likely to depend on detection of complement fixation antibodies in the CSF.[28] *Blastomyces* meningitis is unlikely to be diagnosed unless the patient has evidence of disseminated infection. It is frequently detected on imaging as basilar meningitis with obstructive hydrocephalus.[28]

Treatment

Cryptococcal meningitis is almost always fatal if left untreated; even with treatment, mortality has been reported to be 20-50%.[28,33] Antifungal treatment should be initiated in the emergency department if the diagnosis is established. First-line treatment consists of combination therapy of amphotericin

B and flucytosine. Flucytosine, unavailable throughout most of Africa, Asia, and low-income countries, has been shown to improve outcomes when given in combination with amphotericin B. Fluconazole plus amphotericin B is an acceptable second-line alternative if flucytosine is unavailable.[28,30,33,34] Liposomal amphotericin B may be substituted for amphotericin B for patients with renal dysfunction.[33] Patients should remain on these medications for two weeks or longer, depending on clinical response and risk factors.[28,33]

Candidal meningitis has high rates of mortality, ranging from 11% in neurosurgery patients, to 31% in HIV-positive patients, to 60% in neonates. Treatment is similar to that for cryptococcal meningitis, consisting of combination therapy with amphotericin B plus flucytosine.[32,33] Treatment of aspergillus meningitis has not been studied as well as that for cryptococcal or candidal meningitis. If the diagnosis is made in the emergency department, initiating treatment with amphotericin B and flucytosine is reasonable.[28] Meningitis due to *Coccidioides*, *Histoplasma*, and *Blastomyces* is usually treated with amphotericin B without flucytosine.[28]

Tuberculous Meningitis

Epidemiology and Risk Factors

Tuberculous meningitis complicates about 1% of all cases of tuberculosis and more commonly occurs in children ages 2 to 4 years and HIV-positive patients not receiving highly active antiretroviral therapy (HAART). Overall, the incidence of and mortality rates due to tuberculous meningitis have been declining since the 1990s, but certain regions have experienced an increase. Prevention has been attributed to the Bacillus Calmette-Guerin (BCG) vaccine, which has been shown to provide protection against disseminated childhood tuberculosis including tuberculous meningitis. In addition, advances in identification of patients exposed to tuberculosis and prophylactic treatment with isoniazid has contributed to the decline in numbers of new cases and deaths due to tuberculous meningitis. Several vaccines now being studied have the potential for improved prevention of pulmonary tuberculosis and, therefore, disseminated forms of the disease. With the decline of bacterial meningitis after introduction of widespread vaccination programs, tuberculous meningitis is now the most common cause of pediatric meningitis in some countries, most notably in sub-Saharan Africa.[35]

Clinical Manifestations

Just as in bacterial meningitis, a delay in diagnosis and administration of appropriate therapy for tuberculous meningitis is associated with increased morbidity and mortality, but diagnosis of tuberculous meningitis is difficult.[8,35] The clinical presentation of tuberculous meningitis tends to be nonspecific in all age groups in the early stages of the illness. In children and adults, signs and symptoms include fever, malaise, weight loss, cough, and vomiting. The prodrome of tuberculous meningitis is difficult to distinguish from many common viral syndromes. In adults, headache develops and worsens over one to two weeks, often accompanied by vomiting and confusion. Neck stiffness and focal neurologic deficits such as cranial nerve palsies and hemiplegia eventually develop. In children, the prodrome eventually gives way to meningeal signs, but these are variably present.[35,36] Signs of decreased responsiveness and increased intracranial pressure (manifesting as a bulging anterior fontanelle, cranial nerve palsies, and focal neurologic deficits) may also be seen.[35,36] Once the disease progresses beyond the prodromal phase and meningeal signs are present, the prognosis is poor.[35,37] Researchers have developed clinical prediction tools for tuberculous meningitis similar to the Bacterial Meningitis Score discussed above. One such tool developed in Vietnam and validated in other populations has been reported to be 86% sensitive and 79% specific for adult tuberculous meningitis. Features suggestive of tuberculous meningitis in that study include age younger than 36 years, white blood cell count of less than 15,000 per mm^3, history of illness of 6 days or more, CSF white blood cell count of less than 750 per mm^3, and CSF neutrophils less than 90% of total white blood cells. The feature most predictive of tuberculous meningitis in this study was history of illness of 6 days or more.[35,36] In HIV-positive patients, tuberculous meningitis can be difficult to differentiate from cryptococcal meningitis. The following features have been found to be more likely in tuberculous as opposed to cryptococcal meningitis: greater neck stiffness, altered mental status, higher body temperature, lower CSF opening pressure, a CD4 count of less than 200 cells per mm^3, a CSF to plasma glucose concentration ratio of 0.2 or less, a CSF lymphocyte count of greater than 200 cells per mm^3, and a negative CSF cryptococcal antigen test.[35]

Diagnosis

CSF characteristics in tuberculous meningitis are listed in Table 3. The classic Ziehl-Nielsen stain for acid-fast bacilli in the CSF is only 60-80% sensitive.[35,36] Nucleic acid amplification techniques (NAATs) are highly specific for tuberculous meningitis, but poorly sensitive, so they may be useful to confirm but not to exclude the disease.[35,37] Real-time PCR is showing some potential for improved sensitivity for tuberculous meningitis, but it is expensive, not widely available, and therefore of little utility in resource-poor settings where tuberculosis is most prevalent. Additional studies are still required to prove its incremental value over existing tests.[35,37]

Imaging can be used to augment laboratory studies in the diagnosis of tuberculous meningitis and is also necessary for detecting complications of the disease such as tuberculomas and hydrocephalus.[35,36] About half of patients with tuberculous meningitis will have evidence of pulmonary tuberculosis on chest X-ray.[36] Neuroimaging findings suggestive of tuberculous meningitis are basal hyperdense exudates on noncontrast head CT, basal meningeal enhancement, hydrocephalus, infarcts, and tuberculomas on head CT with contrast, and meningeal tubercles on MRI. MRI is 90% specific in children and 70% specific in adults with tuberculous meningitis.[35]

Treatment

Early treatment with a combination of rifampicin, isoniazid, and pyrazinamide is the cornerstone of treatment for tuberculous meningitis.[35-37] An additional agent such as ethambutol, streptomycin, or ethionamide is

usually recommended, with some differences in published guidelines.[35,36] Fluoroquinolones such as moxifloxacin and levofloxacin are being investigated as possible alternatives to ethambutol, streptomycin, and ethionamide; they are also key agents in treatment of multiple-drug resistant tuberculous meningitis.[35] If a multiple-drug resistant strain happens to be detected quickly via NAATs, starting the patient on a fluoroquinolone is recommended.[35] Adjunctive treatment with corticosteroids (prednisolone or dexamethasone) has been shown to reduce morbidity and mortality by 30% and is therefore recommended for all patients with tuberculous meningitis.[35,37]

If communicating hydrocephalus is found on neuroimaging, patients should be started on acetazolamide and furosemide.[35,36] If hydrocephalus is non-communicating, neurosurgery should be consulted for placement of a ventriculoperitoneal shunt. If imaging reveals optochiasmatic arachnoiditis, urgent treatment with thalidomide is recommended to prevent blindness.[35] Tuberculomas detected on neuroimaging may also benefit from treatment with thalidomide.[35,36]

Neoplastic Meningitis

Neoplastic meningitis is found in 5-25% of cancer patients and the incidence is increasing along with improved cancer survival rates. Breast and lung cancers, melanoma, and acute lymphocytic leukemia (ALL) are the most common malignancies to metastasize to the meninges. The condition is underdiagnosed due to the nonspecific presentation; patients may be asymptomatic or present with headache, altered mental status, dizziness, nausea, vomiting, radiculopathy, cranial nerve palsies, or a combination of these. In addition, the patient may have concomitant brain metastases, to which the clinical presentation may be attributed. The historical gold standard test for diagnosis of neoplastic meningitis is cytologic analysis of the cerebrospinal fluid, but this is only 50% sensitive. The sensitivity can be improved by repeating lumbar puncture if initial testing is negative, placing samples on ice to prevent lysis of malignant cells, and assessing for the presence of tumor markers. MRI is increasingly being utilized for diagnosis, as it is 88-93% sensitive for detecting lesions. Neoplastic meningitis has a poor prognosis, with survival rates of four to six weeks if untreated. Treatment consists of radiation therapy and intrathecal or systemic chemotherapy and is focused on preventing further decompensation and prolonging survival, which rarely exceeds six months.[38]

Conclusion

There are several etiologies of meningitis, but it is most often due to an infectious process. It must be considered in any patient presenting with fever, headache, or neck stiffness. Bacterial and aseptic meningitis present similarly and cannot be reliably distinguished based on clinical features. Whereas bacterial meningitis is a medical emergency, viral meningitis is most often self-limited. Diagnosis and treatment should be pursued expeditiously in the emergency department and focused on evaluation for bacterial meningitis. Delays in diagnosis and treatment have been shown to increase morbidity and mortality. Ideally, lumbar puncture should be performed as soon as the diagnosis is suspected, followed immediately by initiation of empiric broad spectrum antibiotics. Other forms of aseptic meningitis include fungal, tuberculous, and neoplastic meningitis. Fungal meningitis should be suspected in immunocompromised patients. Tuberculous meningitis should be suspected in immunocompromised patients and in regions with a high prevalence of tuberculosis. Just as in bacterial meningitis, early detection and treatment of tuberculous meningitis are crucial to reduce the risk of morbidity and mortality. Neoplastic meningitis is common in cancer patients but should be considered a diagnosis of exclusion.

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CME Questions

1. A 26-day-old female born at term at an outside hospital presents to the emergency department with fever, irritability, and poor feeding for the past two days. Her 2-year-old brother was reportedly diagnosed with a viral upper respiratory infection a few days ago. Physical examination reveals fever of 101.0, mild tachycardia and tachypnea, irritability, flat fontanelles, normal lung sounds, but is otherwise unremarkable. Preliminary work-up including chest X-ray, urinalysis, CBC, and BMP reveal no source of infection. What is the next most appropriate step?
   A. antibiotics followed by dexamethasone to treat empirically for presumed bacterial meningitis
   B. CT head to exclude intracranial mass
   C. discharge home with diagnosis of viral syndrome with urgent follow-up with pediatrician tomorrow morning
   D. lumbar puncture to evaluate for bacterial meningitis
2. Head CT prior to lumbar puncture is indicated for all of the following *except*:
   A. focal neurologic deficits
   B. history of ischemic stroke
   C. history of tuberculosis
   D. moderate to severe alterations in mental status
3. Why is vancomycin recommended in the treatment of most patients with suspected bacterial meningitis?
   A. A significant percentage of *Streptococcus pneumoniae* has been shown to be resistant to penicillins.
   B. It covers for methicillin-resistant *Staphylococcus aureus*, a less common etiologic agent in bacterial agent but with high rates of morbidity and mortality.
   C. Lower doses and hence less toxic doses of cephalosporins are required when used in combination with vancomycin due to synergistic activity.
   D. The CSF penetration of cephalosporins is improved when used in combination with vancomycin.
4. Dexamethasone should be administered as adjunctive treatment in which of the following patients with suspected bacterial meningitis?
   A. 6-year-old HIV-positive female in Malawi
   B. 14-day-old male to an untreated GBS-positive mother in Canada
   C. 42-year-old male in Vietnam
   D. 62-year-old female with type 2 diabetes mellitus and alcohol abuse in the United States
5. Which of the following CSF findings is most suggestive of bacterial as opposed to aseptic meningitis?
   A. CSF glucose concentration of 40 mg/dL

B. CSF protein concentration of 200 mg/dL
C. CSF WBC count of 1000 cells per mm^3
D. neutrophils composing 95% of total CSF white blood cells

6. Which of the following would be the most appropriate regimen in the corresponding patient for tuberculous meningitis?
   A. rifampicin, isoniazid, and ethambutol for an HIV-positive 24-year-old female
   B. rifampicin, isoniazid, ethambutol, and aspirin for a 29-year-old male with multiple tuberculomas and infarcts visible on head CT
   C. rifampicin, isoniazid, ethambutol, pyrazinamide, and moxifloxacin for a 4-year-old male in South Africa
   D. rifampicin, isoniazid, ethambutol, pyrazinamide, moxifloxacin, and dexamethasone for a 33-year-old male with multi-drug resistant strain of *Mycobacterium tuberculosis*
7. Which of the following statements regarding fungal meningitis is true?
   A. Cryptococcal meningitis most often presents with acute onset fever, headache, and neck stiffness.
   B. *Histoplasma* meningitis is likely in an HIV-positive patient from Arizona presenting with gradual onset fever and headache.
   C. Initial first-line therapy of most types of fungal meningitis includes amphotericin B and fluconazole.
   D. Neurosurgery patients are at greater risk of meningitis due to *Candida albicans* than other fungi.
8. A 26-year-old male with no significant past medical history presents to an emergency department with acute onset of fever, headache, and confusion. On examination, the patient has a fever of 101.7, GCS of 12 (opens eyes to command, confused speech, localizes to pain), and oral mucous membrane ulcers are visualized. The patient is not cooperative with a neurologic examination, but no focal deficits are appreciated. What is the most appropriate empiric therapy for this patient?
   A. dexamethasone given simultaneously with vancomycin and ceftriaxone
   B. dexamethasone followed immediately by vancomycin, ceftriaxone, and acyclovir
   C. dexamethasone followed immediately by vancomycin, ceftriaxone, and moxifloxacin
   D. vancomycin, ceftriaxone, and acyclovir
9. Ampicillin should be administered for coverage against *Listeria monocytogenes* in all of the following patients with suspected bacterial meningitis *except*:
   A. 55-year-old female with no significant past medical history
   B. 14-year-old female receiving immunosuppressive therapy for liver transplant
   C. 8-week-old male with no significant past medical history
   D. 25-year-old G1P0 female at 22 weeks of pregnancy
10. A 29-year-old male with history of untreated HIV infection presents to an emergency department in the United States with fever, headache, and neck stiffness. While in the waiting room, the patient has a seizure. Of the following choices, what is the most appropriate sequence of action to take in managing this patient?
    A. CT head, empiric antibiotic therapy, lumbar puncture
    B. empiric antibiotic therapy, CT head, lumbar puncture
    C. lumbar puncture, CT head, empiric antibiotic therapy
    D. lumbar puncture, empiric antibiotic therapy

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Meningitis Update

Common Bacterial Causes of Meningitis and Empiric Antibiotic Therapy Based on Patient Age and Clinical Risk Factors

Patient Characteristics	Most Common Bacterial Agents	Empiric Antibiotic Therapy
Neonates (0-42 days)	Group B *Streptococcus* *Listeria monocytogenes* *E. coli* and other Gram-negative rods	Ampicillin + cefotaxime or Ampicillin + gentamicin
Infants and Children	*Streptococcus pneumoniae* *Neisseria meningitidis*	Vancomycin Ceftriaxone or cefotaxime
Adults	*Streptococcus pneumoniae* *Neisseria meningitidis*	Vancomycin Ceftriaxone
Elderly (50 years and older)	*Streptococcus pneumoniae* *Neisseria meningitidis* *Listeria monocytogenes* Aerobic Gram-negative rods	Vancomycin Ceftriaxone Ampicillin
Immunocompromised, alcohol abuse, pregnancy	*Streptococcus pneumoniae* *Neisseria meningitidis* *Listeria monocytogenes* *E. coli* *Salmonella* *Staphylococcus aureus*	Vancomycin Ceftriaxone Ampicillin
Neurosurgery patients (patients with ventriculoperitoneal shunts, recent craniotomy or cranioplasty)	*Streptococcus pneumoniae* *Staphylococcus aureus* *Staphylococcus epidermidis* *Pseudomonas aeruginosa* and other aerobic Gram-negative rods	Vancomycin Cefepime, ceftazidime, or meropenem
Patients with basilar skull fracture or head trauma causing CSF leak	*Streptococcus pneumoniae* *Haemophilus influenzae* Group B *Streptococcus* Group A β-hemolytic *Streptococcus*	Vancomycin ceftriaxone or cefotaxime

Indications for Head CT Prior to LP

Head CT is indicated prior to LP if one or more of the following are present:

- New-onset seizures
- HIV/AIDS
- Immunosuppressive therapy
- History of organ transplantation
- History of focal central nervous system (CNS) lesion (tumor, stroke, abscess)
- Papilledema
- Focal neurologic deficits
- Moderate to severe altered mental status
- Evolving signs of herniation

Classic CSF Findings in Normal Patients and Those With Various Types of Meningitis

	Normal	Bacterial	Viral	Neoplastic	Fungal	Tuberculous
Opening pressure (mm H2O)	< 170	> 300	< 300	200	300	> 250
WBC count (per mm^3)	< 5	> 1000	< 1000	< 500	< 500	50-1000
Neutrophils	0%	> 80%	< 20%	1-50%	1-50%	< 80-90% in adults < 50% in children
Glucose (mg/dL)	> 40	< 40	> 40	< 40	< 40	< 40
Protein (mg/dL)	< 50	> 200	< 200	> 200	> 200	50-250
Gram stain	negative	positive	negative	negative	negative	negative

Etiologies of Viral Meningitis

- Enteroviruses (poliovirus, Coxsackie viruses A and B, Enterovirus 71, echoviruses)
- Varicella zoster virus (VZV)
- Herpes simplex viruses 1 and 2 (HSV-1 and HSV-2)
- Epstein-Barr virus (EBV)
- Human immunodeficiency virus (HIV)
- Cytomegalovirus (CMV)
- Mumps
- West Nile virus
- St. Louis encephalitis
- Lymphocytic choriomeningitis virus (LCMV)

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