

Aseptic meningitis in adults

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INTRODUCTION

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The term aseptic meningitis syndrome was initially described in 1925 by Wallgren as an acute community-acquired meningitis with a negative cerebrospinal fluid (CSF) Gram stain and culture, absence of a systemic illness or parameningeal focus, and a benign clinical outcome. The most common etiologies are viruses (enteroviruses, arboviruses, herpes simplex virus type 2) [1]. However, this term also includes more than 100 causes, such as other infections (mycobacteria, fungi, spirochetes), parameningeal infections, medications, and malignancies (table 1) [2]. In many patients with aseptic meningitis, this diagnostic uncertainty has fostered hospital admissions and unnecessary cranial imaging and empirical antibiotic therapy.

This topic will provide an overview of the diagnostic approach to patients who present with presumed aseptic meningitis, as well as a review of the most common etiologies. The approach to diagnosis and management of patients with suspected bacterial meningitis is presented elsewhere. (See "[Clinical features and diagnosis of acute bacterial meningitis in adults](#)".)

INITIAL EVALUATION

Clinical evaluation

History

— In patients who present with suspected meningitis, the initial history provides important information that impacts diagnostic testing and empiric treatment. (See '[Diagnostic testing](#)' below and '[Antimicrobial therapy](#)' below.)

It is important to assess for underlying conditions, especially those that may result in some degree of immune compromise. In addition, clinicians should evaluate for:

- **Features consistent with bacterial meningitis** – Patients with bacterial meningitis are usually quite ill, with approximately 50 percent presenting in the first 24 hours [3]. The classic triad of acute bacterial meningitis consists of fever, nuchal rigidity, and a change in mental status but is only present in 41 percent of patients [3]. Patients with aseptic meningitis often present with a few-day history of headache, stiff neck, nausea, photophobia, and with normal mental status [4]. Fever is only present in about one-fourth of adults with aseptic meningitis.

A detailed discussion of the clinical features of bacterial meningitis are presented elsewhere. (See "[Clinical features and diagnosis of acute bacterial meningitis in adults](#)", section on '[Clinical features](#)'.)

- **Features consistent with encephalitis** – The presence or absence of normal brain function is the important distinguishing feature between encephalitis and aseptic meningitis.
 - Patients with aseptic meningitis may be transiently lethargic but their cerebral function remains normal.
 - By contrast, patients with encephalitis commonly have altered mental status. A consensus statement of the international encephalitis consortium developed the following case definition for encephalitis: altered mental status for more than 24 hours without an alternative diagnosis (major criteria) with at least two (possible) or three or more (probable or confirmed) of the following six criteria: 1) fever >38°C (100.4°F); 2) generalized or partial seizures not attributed to a pre-existing seizure disorder; 3) new onset focal neurologic findings; 4) cerebrospinal fluid (CSF) white blood cell (WBC) count ≥5/microL; 5) new or acute neuroimaging abnormalities; and 6) abnormal electroencephalogram consistent with encephalitis [5]. Up to one fourth of patients with encephalitis lack CSF pleocytosis [6].

However, the distinction between the two entities can sometimes be blurred since some patients may have both a parenchymal and meningeal process with clinical features of both. The patient is usually labeled as having meningitis or encephalitis based upon which features predominate in the illness although meningoencephalitis is also a common term that recognizes the overlap. (See "[Viral encephalitis in adults](#)".)

- **Clues to help identify etiology** — Clinicians should bear in mind the following points:
 - **Travel and exposure history** – A travel and exposure history can provide important clues. Clinicians should assess for exposures to mosquitoes (arboviruses), rodents (lymphocytic choriomeningitis virus [LCMV]), and ticks (*Borrelia burgdorferi*), as well as travel to certain areas (tuberculosis, coccidioid infection), sexual activity (herpes simplex virus [HSV]-2, human immunodeficiency virus [HIV], *Treponema pallidum*), and contact with other individuals with similar symptoms or viral exanthems (enteroviruses). (See "[Evaluation of fever in the returning traveler](#)" and "[Skin lesions in the returning traveler](#)" and "[Approach to illness associated with travel to Latin America and the Caribbean](#)" and "[Approach to illness associated with travel to South Asia](#)".)

- **Season** – Certain infections have a seasonal distribution. As an example, aseptic meningitis occurring during the summer or fall is most likely to be caused by enteroviruses (eg, Coxsackievirus, echovirus, other nonpoliovirus enteroviruses), flaviviruses (eg, West Nile virus), or by human parechovirus [7]. Other infections that occur during this time frame include arboviral and Lyme meningitis. However, infections due to other pathogens (eg, herpes viruses) can occur at any time. (See "[Enterovirus and parechovirus infections: Clinical features, laboratory diagnosis, treatment, and prevention](#)" and "[Nervous system Lyme disease](#)" and "[Clinical manifestations and diagnosis of West Nile virus infection](#)".)
- **New medications** – Patients should be specifically questioned about use of drugs associated with meningitis (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], intravenous [immune globulin](#), trimethoprim-sulfamethoxazole). (See '[Drug-induced meningitis](#)' below.)

Physical examination

- **General findings** – Patients with meningitis typically present with fever and signs of meningeal irritation (eg, nuchal rigidity and photophobia). Tests to illustrate meningismus, such as Kernig and Brudzinski signs ([table 2](#)), may be positive but were originally developed and tested in patients with severe, late-stage untreated bacterial and tuberculous (TB) meningitis in the preantibiotic era. Nuchal rigidity is seen in less than 30 percent of patients with aseptic meningitis [4].
- **Findings concerning for bacterial meningitis** – It can be difficult to distinguish aseptic and bacterial meningitis on clinical exam alone. However, one distinguishing feature may be the presence of altered mental status and focal neurologic signs in patients with bacterial meningitis. In addition, although rash can be associated with many types of meningitis, the presence of petechiae and palpable purpura would be suggestive of meningococcal disease. (See "[Clinical features and diagnosis of acute bacterial meningitis in adults](#)", [section on 'Clinical features'](#).)
- **Findings suggestive of a specific agent** – Certain exam findings may be suggestive of a specific etiology:
 - A diffuse maculopapular exanthem in a mildly ill patient may be consistent with enteroviral infection, West Nile virus, HIV seroconversion, or syphilis.
 - Parotitis suggests mumps meningitis, particularly in an unvaccinated patient. (See '[Mumps](#)' below.)
 - Dermatomal vesicular lesions suggest varicella-zoster virus (VZV) infection, but the absence should not preclude testing (zoster sine herpete). (See '[Herpes virus meningitis](#)' below.)
 - Painful ulcerative genital lesions suggest a primary episode of HSV-2 infection (although many patients do not present with ulcers [8]). (See '[Herpes virus meningitis](#)' below.)
 - Oropharyngeal thrush and cervical lymphadenopathy are consistent with primary HIV infection. (See '[HIV](#)' below.)
 - Asymmetric flaccid paralysis strongly suggests the possibility of West Nile virus meningitis or Enterovirus D68 or 71 [9]. (See '[Arboviruses](#)' below.)

Laboratory testing

— Patients with aseptic meningitis can have a wide range of laboratory findings (WBC count, platelet count, liver function). The specific pattern depends upon the etiologic agent. (See '[Infections due to specific pathogens](#)' below.)

The typical CSF profile of patients with aseptic meningitis is described in the table ([table 3](#)). However, patients with viral meningitis can present with a neutrophilic pleocytosis in up to 25 percent of cases that can switch to a lymphocytic predominance if a repeat lumbar puncture (LP) is done and with mild hypoglycorrhachia (CSF glucose between 30 and 45 mg/dL) [10,11]. (See "[Cerebrospinal fluid: Physiology, composition, and findings in disease states](#)".)

Diagnostic testing

— For patients with suspected meningitis, blood cultures and CSF testing should be performed. Serologies (eg, Lyme, arboviruses) and polymerase chain reaction (PCR) testing may also be helpful in identifying the etiology.

Blood cultures

— All patients with suspected meningitis should have blood cultures obtained. This is particularly helpful to identify an organism in the setting of bacterial meningitis or a parameningeal focus. (See "[Clinical features and diagnosis of acute bacterial meningitis in adults](#)", [section on 'Blood tests'](#) and "[Pathogenesis, clinical manifestations, and diagnosis of brain abscess](#)", [section on 'Laboratory studies'](#).)

Cerebrospinal fluid

— An LP should be promptly performed in all patients with suspected meningitis. The decision to perform imaging (eg, computed tomography [CT] scan) prior to LP is discussed elsewhere. (See "[Clinical features and diagnosis of acute bacterial meningitis in adults](#)", [section on 'Indications for CT scan before LP'](#).)

- The opening CSF pressure should be noted and CSF should be sent for cell count, glucose, protein, and bacterial culture.
- Molecular tests for the most common etiologies (eg, enteroviruses, herpes viruses) should routinely be done to decrease the use of antimicrobial therapy, avoid or decrease length of stay for viral pathogens, and reduce the use of cranial imaging [12,13]. There are two FDA-approved rapid multiplex PCR that detect 14 and 16 etiologies, respectively. The results of these tests are available in one hour and can identify the most common viral, bacterial, and fungal causes of meningitis [14]. However, there are some concerns with false-negative (eg, *Cryptococcus neoformans*, herpes simplex virus) and false-positive (eg, *Streptococcus pneumoniae*, *Escherichia coli*, and human herpesvirus 6 [HHV-6]) results with these tests. In patients without a compatible disease, it is best utilized with infectious diseases consultation. More detailed information on molecular testing is presented in a separate topic review. (See "[Molecular diagnosis of central nervous system infections](#)".)

- A West Nile virus (WNV) immunoglobulin (Ig)M in the CSF or serum should be sent in all patients that present between June and October in the United States [15]. Immunocompromised individuals (eg, solid organ transplant recipients) may have false negative serologies and a CSF WNV PCR should be sent [16]. (See "[Clinical manifestations and diagnosis of West Nile virus infection](#)", section on 'Diagnosis'.)
- Additional CSF testing depends upon the concern for a specific pathogen, as discussed below. (See '[Infections due to specific pathogens](#)' below.)

Other types of testing

— Other types of testing can be performed to help determine the etiology in patients with aseptic meningitis. As examples:

- Disease-specific serology testing should be performed if certain conditions are suspected (eg, syphilis, Lyme disease). (See "[Syphilis: Screening and diagnostic testing](#)", section on 'Approach to testing' and "[Diagnosis of Lyme disease](#)", section on 'Early disseminated and late Lyme disease'.)
- HIV antibody testing should be done in all patients with meningitis [17]. If acute HIV is being considered, blood testing for HIV RNA should be performed. (See "[Acute and early HIV infection: Clinical manifestations and diagnosis](#)".)
- If aseptic meningitis due to HSV is suspected, the patient should be evaluated for concomitant genital lesions, and any active lesions should be swabbed. (See "[Epidemiology, clinical manifestations, and diagnosis of genital herpes simplex virus infection](#)".)

ANTIMICROBIAL THERAPY

Role of empiric therapy

— The decision to administer empiric antimicrobial therapy in a patient with possible aseptic meningitis depends upon the concern for bacterial meningitis based on the history, physical examination, and cerebrospinal fluid (CSF) findings (table 3). (See "[Cerebrospinal fluid: Physiology, composition, and findings in disease states](#)".)

- **Antimicrobial therapy for bacterial meningitis** – Antibiotics should be initiated promptly in those with suspected bacterial meningitis. In patients with a CSF leukocytosis and a negative Gram stain, factors predictive of bacterial meningitis include serum leukocytes $>10.0 \times 10^9/L$, CSF leukocytes >2000 per mm^3 , CSF granulocytes >1180 per mm^3 , CSF protein >2.2 g/L, CSF glucose <1.9 mmol/L, and/or fever on admission. In one study, these factors were included in a risk score, which was dichotomized in "low-risk" (zero variables present) and "high-risk" (>0 variables present) [18]. This risk score had a 99.6 to 100 percent sensitivity in identifying a low-risk subgroup [18,19]. Regimen selection is summarized in the table (table 4) and discussed in detail in a separate topic review. (See "[Initial therapy and prognosis of community-acquired bacterial meningitis in adults](#)".)

When it is not clear whether the patient has a viral or bacterial process, the treating physician can choose empiric antibiotics for 48 hours while awaiting culture results. The lumbar puncture (LP) should be done in the emergency department before the initiation of antibiotic therapy to avoid impacting the sensitivity of the CSF gram stain and culture [13]. A delay in performing the LP is also associated with an increase in the cost of hospitalization [20].

If the patient is symptomatically improved and culture results are negative, clinicians should assess if the patient may have had bacterial meningitis that has been partially treated with previous antibiotics. If there is no concern for partially treated meningitis, or if it is confirmed to have a viral etiology, then antibiotics can generally be stopped. A repeat LP off antibiotics may be indicated in patients with persistent symptoms who do not have a clear diagnosis. (See "[Approach to the patient with chronic meningitis](#)".)

- **Antiviral therapy** – Empiric therapy with intravenous [acyclovir](#) should be initiated if there is a concern for herpes simplex virus (HSV) or varicella-zoster virus (VZV) encephalitis. (See "[Herpes simplex virus type 1 encephalitis](#)" and "[Treatment of herpes zoster](#)", section on 'Neurologic complications'.)

Empiric therapy with intravenous [acyclovir](#) is also reasonable if clinical findings (eg, vesicular skin lesions) are suggestive of HSV or VZV. (See '[Herpes virus meningitis](#)' below and "[Epidemiology, clinical manifestations, and diagnosis of genital herpes simplex virus infection](#)" and "[Epidemiology, clinical manifestations, and diagnosis of herpes zoster](#)".)

Tailored therapy

— If an infectious agent is identified and is amenable to therapy (eg, spirochetal infection such as Lyme disease or syphilis), therapy should be tailored to the best possible treatment option. (See '[Infections due to specific pathogens](#)' below.)

INFECTIONS DUE TO SPECIFIC PATHOGENS

Viral meningitis

— A number of viruses produce aseptic meningitis, with some typically presenting during the summer and fall (eg, enteroviruses, parechoviruses, arboviruses, Toscana in the Mediterranean), and others presenting year round (eg, herpes simplex virus [HSV], HIV, varicella-zoster virus [VZV]) [7,13].

Enteroviruses and parechoviruses

— Enteroviruses are the most common cause of viral meningitis in adults, accounting for 40 percent of cases [21,22]. Aseptic meningitis occurring during the summer or fall is most likely to be caused by enteroviruses (eg, Coxsackievirus, echovirus, other nonpoliovirus enteroviruses) or by human parechovirus, the most common causes of viral meningitis [7]. However, seasonal variation of certain central nervous system (CNS) viral infections is relative and not absolute. Enteroviruses continue to cause 6 to 10 percent of cases of viral meningitis in the winter and spring despite their predilection for inciting illness in the late summer and fall [23,24].

Enteroviral meningitis has a subacute presentation with a median duration of symptoms of two days before presentation [21]. Signs and symptoms typically include headache, fever, nausea or vomiting, malaise, photophobia, and meningismus [25,26]. Rash, diarrhea, and upper respiratory symptoms may also be present [13].

Cerebrospinal fluid (CSF) findings are typical of other viral meningitides and include a white blood cell (WBC) count that is generally less than 250 cells/microL with a lymphocytic pleocytosis, a modest elevation in CSF protein concentration (generally less than 100 mg/dL) [27], and a normal glucose concentration (table 3).

Polymerase chain reaction (PCR) testing for enteroviruses should be done in patients presenting with aseptic meningitis to confirm the diagnosis, as this can decrease the economic burden on health systems by decreasing the use of unnecessary antimicrobial therapy, cranial imaging, and frequency/duration of hospital admissions [4,13,28]. CSF nucleic acid amplification tests (NAATs) for enteroviruses yield sensitivities that range from 86 to 100 percent and specificities that range from 92 to 100 percent. NAAT testing is included in multiplex PCR tests that can be performed in one hour [14].

Additional discussions of enterovirus infections are found elsewhere. (See "[Enterovirus and parechovirus infections: Clinical features, laboratory diagnosis, treatment, and prevention](#)" and "[Enterovirus and parechovirus infections: Epidemiology and pathogenesis](#)".)

Herpes virus meningitis

— The two most common herpes viruses causing aseptic meningitis are HSV and VZV, each accounting for about 15 percent of all viral meningitis cases in adults [21,28].

- **Meningitis due to HSV** – HSV is a leading cause of aseptic meningitis [4]. In contrast to HSV encephalitis, which is almost exclusively due to HSV-1, viral meningitis in immunocompetent adults is generally caused by HSV-2 [13]. The typical CSF profile includes a pleocytosis with a predominance of lymphocytes and a normal CSF glucose concentration (table 3).

HSV-2 meningitis is more commonly seen in young females with 50 percent of them having a history of genital herpes and 30 percent having a history of previous viral meningitis [7,8]. However, in a large prospective study of 205 patients with HSV meningitis, only 8 percent had genital mucocutaneous lesions [8]. Thus, the absence of genital lesions should not deter the clinician from testing for HSV-2 infection in a patient with aseptic meningitis. (See "[PCR testing for the diagnosis of herpes simplex virus in patients with encephalitis or meningitis](#)".)

There is no standard approach to treatment of HSV meningitis [29]. For patients who present with HSV meningitis, antiviral therapy is given to about 95 percent of patients [21]. For hospitalized patients, we administer intravenous **acyclovir** (10 mg/kg every eight hours). The dose should be adjusted for individuals with reduced kidney function; recommendations are provided in the drug information topic on acyclovir within UpToDate. Patients can be switched to oral **valacyclovir** (1 g every eight hours) on discharge for a total of 10 days of treatment. Oral acyclovir should not be used as it has poor oral bioavailability (15 to 35 percent). Considerations for management of recurrent HSV meningitis are discussed below. (See '[Recurrent \(Mollaret\) meningitis](#)' below.)

Most patients with HSV meningitis have a good prognosis; however, in a prospective study of 205 adults, one-third had unfavorable outcomes (neuropsychological and neurocognitive) at the time of discharge with 11 percent having sequelae at six-month follow-up [8]. Although antiviral therapy is typically administered given the low risk of treatment, the benefit of antiviral therapy for HSV meningitis remains unclear, especially in immunocompetent hosts. As an example, in a retrospective observational study that evaluated forty-two patient episodes of HSV meningitis, immunocompromised patients had fewer neurologic sequelae when treated with a short course of antiviral therapy [29]. By contrast, this benefit was not seen in a study of 60 immunocompetent patients with HSV meningitis [30].

- **Meningitis due to varicella-zoster virus** – VZV can cause aseptic meningitis in patients with or without typical skin lesions [28,30]; the latter are known as zoster sine herpette. VZV is likely an underdiagnosed etiology, as only 1.2 percent of patients with aseptic meningitis undergo a CSF VZV PCR in some centers [4]. In a study of 1126 patients in the United Kingdom with suspected meningitis, in which a VZV PCR was routinely done, VZV was the third most common cause of viral meningitis [28]. Similarly in a study from Denmark, where CSF VZV PCR was done routinely, VZV accounted for 15 percent (162 of 1066) of adults with viral meningitis [21]. The treatment of VZV meningitis is presented elsewhere. (See "[Treatment of herpes zoster](#)", section on '[Neurologic complications](#)'.)
- **Meningitis due to other herpes viruses** – Aseptic meningitis may be due to herpes viruses other than HSV and VZV. Cytomegalovirus (CMV), Epstein-Barr virus, and human herpesvirus 6 (HHV6) have all been reported to cause aseptic meningitis [13]. These are discussed in detail separately. (See "[Epidemiology, clinical manifestations, and diagnosis of herpes zoster](#)", section on '[Aseptic meningitis](#)' and "[Human herpesvirus 6B infection in children: Clinical manifestations, diagnosis, and treatment](#)", section on '[Less common manifestations](#)' and "[Epidemiology, clinical manifestations, and treatment of cytomegalovirus infection in immunocompetent adults](#)", section on '[Neurologic manifestations](#)' and "[Pathogenesis, epidemiology, and clinical manifestations of adenovirus infections](#)", section on '[Nervous system](#)'.)

Arboviruses

— Arboviruses (arthropod-borne viruses) are an important cause of aseptic meningitis that can be transmitted by mosquitos, ticks, or sandflies [4]. Many of these also present as encephalitis. (See "[Arthropod-borne encephalitides](#)".)

The most common arbovirus in the United States is West Nile virus, a flavivirus. Neuroinvasive disease, which develops in about one percent of patients with West Nile virus infection, typically occurs during the summer and fall and presents as aseptic meningitis, encephalitis, retinopathy, or acute flaccid paralysis/myelitis. The most common presenting symptoms include fever, nausea/vomiting, fatigue, headache, altered mental status, and focal neurological deficits [4]. The CSF profile resembles enteroviral meningitis, sometimes presenting with a neutrophilic pleocytosis [10]. Patients may have persistent headaches, memory impairment, and chronic fatigue years after infection [9]. A detailed discussion of the clinical manifestations and diagnosis of West Nile virus is presented separately. (See "[Clinical manifestations and diagnosis of West Nile virus infection](#)".)

HIV

— An HIV test should be done in all patients presenting with meningitis as it can help with the differential diagnosis, and acute HIV seroconversion syndrome can present with aseptic meningitis [17]. (See "[Screening and diagnostic testing for HIV infection in adults](#)", section on '[Testing algorithm](#)'.)

Primary infection with HIV frequently presents as a mononucleosis-like syndrome, manifested by fever, malaise, lymphadenopathy, rash, and pharyngitis. A subset of these patients will develop meningitis or meningoencephalitis, with headache, confusion, seizures, or cranial nerve palsies. (See "[Acute and early HIV infection: Pathogenesis and epidemiology](#)".)

In patients with acute HIV, the CSF profile characteristically has a lymphocytic pleocytosis, an elevated protein concentration, and a normal glucose concentration ([table 3](#)). Documentation of primary HIV infection is accomplished by demonstrating HIV-1 viremia with or without HIV antibody. (See "[Acute and early HIV infection: Clinical manifestations and diagnosis](#)", [section on 'Diagnosis'](#).)

Clinicians should have a high index of suspicion for primary HIV infection in patients with risk factors for HIV transmission ([table 5](#)). In most patients with HIV-1 meningitis, the clinical findings resolve without treatment, and patients may be erroneously assumed to have a benign cause of viral meningitis (eg, enterovirus). Identifying patients with acute HIV infection is important so that antiretroviral therapy can be instituted. (See "[Acute and early HIV infection: Treatment](#)".)

Lymphocytic choriomeningitis virus

— Lymphocytic choriomeningitis virus (LCMV) is a human zoonosis caused by a rodent-borne arenavirus. LCMV is excreted in the urine and feces of rodents, including mice, rats, and hamsters, and is transmitted to humans by exposure to secretions or excretions (by direct contact or aerosol) of infected animals or contaminated environmental surfaces [[13](#)]. Infection is more common during winter months.

Affected patients generally present with an influenza-like systemic illness accompanied by headache and meningismus. Although LCMV is rarely documented as a cause of aseptic meningitis, a seroprevalence of 5 percent was documented in a study of 400 patients with neurologic infections in Finland [[31](#)]. A minority of patients with LCMV develop orchitis, parotitis, myopericarditis, or arthritis.

CSF findings are typical of other causes of viral meningitis except that low glucose concentrations can be observed in patients with LCMV meningitis and CSF WBC counts of greater than 1000/microL are not unusual [[32,33](#)]. The diagnosis is established by serologic testing, documenting seroconversion in paired serum samples two to four weeks apart. There is no specific antiviral therapy for LCMV.

Mumps

— Aseptic meningitis is the most frequent extra-salivary complication of mumps virus infection. Prior to the introduction of the mumps vaccine in 1967, this paramyxovirus was a relatively common cause of viral meningitis, accounting for between 10 and 20 percent of all cases [[31](#)]. With the introduction of the measles, mumps, and rubella (MMR) vaccine, the incidence of meningitis caused by mumps is <1 percent of all cases of meningitis and encephalitis in the United Kingdom and United States [[12,28](#)].

The most frequent manifestations are headache, low-grade fever, and mild nuchal rigidity. The onset of meningitis is variable and can occur before, during, or after an episode of mumps parotitis; however, salivary gland enlargement is only present in about 50 percent of patients with mumps CNS disease. (See "[Mumps](#)".)

The CSF profile typically reveals fewer than 500 WBC/microL with a lymphocytic predominance, but more than 1000 WBC/microL and an early neutrophil predominance can occasionally be seen. The CSF total protein is generally normal or mildly elevated and the CSF glucose levels may be mildly depressed.

Spirochetes

— The two major spirochetes that should be considered in the differential diagnosis of aseptic meningitis are *T. pallidum*, the causative agent of syphilis, and *B. burgdorferi*, the spirochete that causes Lyme disease. Leptospirosis can also cause an aseptic meningitis syndrome. (See "[Leptospirosis: Epidemiology, microbiology, clinical manifestations, and diagnosis](#)", [section on 'Clinical manifestations'](#).)

Syphilis

— *T. pallidum*, the causative agent of syphilis, disseminates to the CNS during early infection. Syphilitic meningitis can present in the setting of early syphilis with headache, malaise, and disseminated rash. (See "[Syphilis: Epidemiology, pathophysiology, and clinical manifestations in patients without HIV](#)", [section on 'Neurologic findings'](#).)

CSF findings include a lymphocytic pleocytosis with an elevated protein concentration; occasionally a depressed glucose concentration may also be seen. Specific serum treponemal tests are almost always positive. The CSF venereal disease research laboratory (VDRL) test is often negative (sensitivity of 30 to 70 percent) but is highly specific in the absence of visible blood contamination. A more detailed discussion of how to diagnose neurosyphilis is presented elsewhere. (See "[Neurosyphilis](#)", [section on 'Diagnosis'](#).)

Lyme disease

— Lyme meningitis typically occurs in the late summer and early fall, the same time as the peak incidence of enteroviral meningitis. Meningitis usually occurs several weeks to a few months after the tick bite and may be the first manifestation of Lyme disease. Clinically, Lyme disease is largely indistinguishable from viral meningitis, with headache, fever (which is usually mild), photosensitivity, and neck stiffness. In one study, children were unlikely to have Lyme meningitis if all of the following were absent: ≥7 days of headache, any cranial neuritis, or ≥70 percent CSF mononuclear cells [[34](#)]; this rule of 7's classifies children as low-risk for Lyme meningitis with a 98 percent sensitivity and a 100 percent negative predictive value. (See "[Nervous system Lyme disease](#)", [section on 'Meningitis'](#).)

The diagnosis of Lyme disease meningitis is facilitated when other characteristic findings are present, such as erythema migrans. When Lyme meningitis occurs alone, the diagnosis can be missed unless the clinician considers other risk factors, such as potential exposure to ticks or travel history. The diagnosis of Lyme meningitis is generally made through serologic testing. (See "[Epidemiology of Lyme disease](#)" and "[Diagnosis of Lyme disease](#)".)

Antibiotic regimens for the treatment of Lyme meningitis are summarized in the table ([table 6](#)) and discussed in detail separately. (See "[Treatment of Lyme disease](#)", [section on 'Acute neurologic manifestations'](#).)

Fungal infections

— *Cryptococcus* and *coccidioidomycosis* are the two major fungal infections that should be considered in the differential diagnosis of aseptic meningitis.

Cryptococcal infection

— *Cryptococcus neoformans* produces infection following inhalation through the respiratory tract. The organism disseminates hematogenously and has a propensity to localize to the CNS, particularly in patients with severe deficiencies in cell-mediated immunity. (See "[Clinical manifestations and diagnosis of *Cryptococcus neoformans* meningoencephalitis in patients without HIV](#)" and "[Epidemiology, clinical manifestations, and diagnosis of *Cryptococcus neoformans* meningoencephalitis in patients with HIV](#)".)

Symptoms typically begin in a subacute presentation, usually over a period of one to two weeks. The three most common symptoms are fever, malaise, and headache. Stiff neck, photophobia, and vomiting are seen in one-fourth to one-third of patients.

The CSF WBC count is typically low (<50/microL) with a mononuclear predominance and the protein and glucose concentrations are usually only slightly abnormal.

A definitive diagnosis of cryptococcal meningoencephalitis is made by culturing the organism from the CSF. In immunocompromised persons at risk for cryptococcal meningitis, a positive cryptococcal polysaccharide antigen in the CSF or serum strongly suggests the presence of infection before the cultures become positive. (See "[Clinical manifestations and diagnosis of *Cryptococcus neoformans* meningoencephalitis in patients without HIV](#)" and "[Epidemiology, clinical manifestations, and diagnosis of *Cryptococcus neoformans* meningoencephalitis in patients with HIV](#)".)

Treatment typically includes induction therapy with amphotericin plus [flucytosine](#), followed by consolidation and maintenance therapy with [fluconazole](#). (See "[Cryptococcus neoformans: Treatment and prevention of meningoencephalitis and disseminated infection in patients without HIV](#)" and "[Cryptococcus neoformans meningoencephalitis in persons with HIV: Treatment and prevention](#)".)

Coccidioidal infection

— *Coccidioides immitis* is endemic in desert regions of the southwestern United States, Mexico, Central, and South America. This infection has protean manifestations, and primary infection is frequently unrecognized. Meningitis is the most lethal complication of coccidioidomycosis and is therefore crucial to recognize.

Symptoms of meningitis, including persistent and severe headache, usually develop within several months of the initial infection. Abnormal neurologic findings on physical examination are frequently absent early in the course of coccidioidal meningitis.

The CSF WBC counts range from one to several hundred cells. A significant number of eosinophils may be present, but this finding is not specific for coccidioidal meningitis. The CSF glucose concentration may be depressed and is occasionally profoundly low in association with an elevation of the CSF protein concentration.

A definitive diagnosis of coccidioidal meningitis is supported by isolating *Coccidioides* species from CSF or other CNS specimens; however, most cases are presumptively diagnosed by identifying anticoccidioidal antibodies in the CSF and/or a CSF coccidioidal antigen. For most patients with coccidioidal meningitis, [fluconazole](#) is the treatment of choice and has to be continued for life.

Coccidioidal meningitis is discussed in detail in a separate topic review. (See "[Coccidioidal meningitis](#)".)

Fusarium infection

— Health care-associated outbreaks due to *Fusarium* species have been reported. This includes an outbreak in Durango, Mexico in November of 2022 [35] and an outbreak in 2023 involving patients from Mexico and the United States who underwent cosmetic procedures under epidural anesthesia in the city of Matamoros, Tamaulipas, Mexico [36,37]. The pathogen has been identified as *Fusarium solani* species complex. More detailed information on the epidemiology, clinical manifestations, and treatment of meningitis due to *Fusarium* is presented separately. (See "[Clinical manifestations and diagnosis of Fusarium infection](#)", section on '[Outbreaks of meningitis](#)' and "[Treatment and prevention of Fusarium infection](#)".)

Tuberculous meningitis

— Patients with tuberculous (TB) meningitis typically present with a subacute to chronic presentation, with protracted headache, vomiting, confusion, and varying degrees of cranial nerve signs with basilar involvement on magnetic resonance imaging (MRI) of the brain. Mental status changes can occur, leading to coma, seizures, and, at times, hemiparesis. Although signs of disseminated TB are of diagnostic importance, they are often absent. The Lancet consensus criteria can be useful to differentiate TB meningitis from bacterial meningitis but is not able to differentiate it from other types of chronic meningitis, such as neurobrucellosis or fungal meningitis [38]. (See "[Clinical features and diagnosis of acute bacterial meningitis in adults](#)" and "[Approach to the patient with chronic meningitis](#)".)

CSF analysis typically shows elevated protein and lowered glucose concentrations with a mononuclear pleocytosis ([table 3](#)). The diagnosis may be definitively established in the setting of CSF with positive smear for acid-fast bacilli, CSF culture positive for *Mycobacterium tuberculosis*, or CSF with positive NAAT. However, definitive diagnosis can be challenging, and a presumptive diagnosis of TB meningitis may be made in the setting of relevant clinical and epidemiologic factors and typical CSF findings. (See "[Tuberculous meningitis: Clinical manifestations and diagnosis](#)".)

Patients with tuberculosis meningitis are typically treated for 9 to 12 months ([table 7](#)). (See "[Central nervous system tuberculosis: Treatment and prognosis](#)".)

Angiostrongylus infection

— *Angiostrongylus cantonensis*, the rat lungworm, is a parasite that is endemic in Southeast Asia and the Pacific and can cause aseptic meningitis. Symptoms include severe headache, stiff neck, paresthesias, and uncommon facial nerve palsy [39].

The diagnosis of cerebral angiostrongyliasis is generally based upon the clinical presentation, CSF eosinophilia, and an epidemiologic history of known or possible exposure to infective *A. cantonensis* larvae. The CSF protein concentration is usually elevated, but the glucose concentration is normal or only minimally reduced. Peripheral blood and CSF eosinophilia frequently occur. (See "[Eosinophilic meningitis](#)", [section on 'Angiostrongylus cantonensis'](#).)

ADDITIONAL CONSIDERATIONS

Bacterial central nervous system infections

— When evaluating a patient with aseptic meningitis it is important to assess for prior antibiotic use. A lymphocytic cerebrospinal fluid (CSF) profile and sterile cultures may be seen in partially treated bacterial meningitis. Bacterial PCR may be helpful to document a bacterial etiology in this setting since it can remain positive even after nine days of intravenous antibiotic therapy [40]. (See "[Clinical features and diagnosis of acute bacterial meningitis in adults](#)" and "[Molecular diagnosis of central nervous system infections](#)".)

There are other ways in which bacterial infections can lead to a clinical picture of aseptic meningitis with a CSF pleocytosis. As an example, parameningeal sources, such as an epidural abscess or subdural empyema, sinus, or ear infection can occasionally lead to meningitis with negative CSF cultures [41]. (See "[Spinal epidural abscess](#)" and "[Intracranial epidural abscess](#)" and "[Acute sinusitis and rhinosinusitis in adults: Clinical manifestations and diagnosis](#)" and "[Acute otitis media \(AOM\) in children: Epidemiology, microbiology, and complications](#)", [section on 'Complications and sequelae'](#).)

Bacterial endocarditis can also lead to brain abscesses and seeding of the CSF via hematogenous seeding. (See "[Complications and outcome of infective endocarditis](#)", [section on 'Neurologic complications'](#).)

Neoplasms of the leptomeninges

— Several neoplasms involve the leptomeninges. Hematologic malignancies have a particular propensity to seed the central nervous system (CNS), especially large cell lymphomas and acute leukemias. Solid tumors frequently causing carcinomatous meningitis include breast cancer, lung cancer, melanoma, gastrointestinal malignancies, and cancers of unknown primary origin. (See "[Treatment of leptomeningeal disease from solid tumors](#)".)

Meningeal signs caused by tumor invasion of the leptomeninges and secondary inflammation are common. In such patients, headache, nausea, and vomiting may be the presenting symptoms of increased intracranial pressure.

The CSF profile may include an elevated protein concentration and a lymphocytic pleocytosis; a very high protein concentration suggests a CSF block. There may be a low glucose concentration, sometimes close to zero. CSF eosinophilia can be seen in Hodgkin lymphoma.

The diagnosis of neoplastic meningitis is the cytologic identification of malignant cells within the CSF.

Drug-induced meningitis

— Drug-induced meningitis is an unusual adverse reaction that is usually a diagnosis of exclusion [42]. Two mechanisms have been proposed for drug-induced meningitis, a delayed hypersensitivity type reaction and direct meningeal irritation [42].

In a study of 329 patients with drug-induced meningitis [43], the CSF profile was either purulent (45 percent) or lymphocytic (33 percent). The majority of patients (96 percent) had complete resolution of symptoms after drug discontinuation.

The most commonly implicated medications are nonsteroidal anti-inflammatory drugs (NSAIDs), certain antibiotics (eg, [trimethoprim-sulfamethoxazole](#)), intravenous [immune globulin](#), vaccines, intrathecal antimetabolites, corticosteroids, and anaesthetics.

Recurrent/chronic meningitis

Recurrent (Mollaret) meningitis

— Mollaret meningitis is a form of recurrent benign lymphocytic meningitis (RBLM), an uncommon illness characterized by greater than three episodes of fever and meningismus lasting two to five days, followed by spontaneous resolution [4,44]. There is large patient-to-patient variation in the time course to recurrence, which can vary from weeks to years. One-half of patients can also exhibit transient neurological manifestations, including seizures, hallucinations, diplopia, cranial nerve palsies, or altered consciousness.

The most common etiologic agent of Mollaret meningitis is herpes simplex virus (HSV)-2. Although some patients may have evidence of genital lesions at the time of presentation [45], many do not [8]. In a study that compared 47 patients with RBLM associated with herpes simplex virus type 2 with patients who had one episode of HSV-2 meningitis, patients with RBLM were older, were less likely to present with fever, and had a lower CSF pleocytosis [46]. HSV-1 and Epstein Barr virus can rarely be the cause of RBLM [47]. The management of HSV meningitis is discussed above. (See '[Herpes virus meningitis](#)' above.)

In patients with recurrent meningitis due to HSV-2, the use of suppressive therapy should be determined on a case-by-case basis. Although suppressive therapy can lead to a decrease in genital outbreaks and possibly recurrent meningitis outbreaks, available data does not support the use of suppressive antiviral therapy for preventing recurrent meningitis [48].

Only one small, randomized trial has evaluated whether suppressive therapy with [valacyclovir](#) (500 mg twice daily for one year) was more effective than placebo in preventing recurrent HSV-2-related recurrent meningitis [48]. Study participants had been diagnosed with acute meningitis related to primary HSV-2 infection or had a history of recurrent meningitis in the past. During the first year of follow-up, suppressive valacyclovir did not have an effect on the number of episodes of meningitis,

although genital HSV-2 meningitis were lower in the treatment arm. However, during the second year, when patients were without study drug, the risk of recurrence of verified and probable HSV-2 meningitis was higher among patients who had been exposed to valacyclovir (hazard ratio, 3.29; 95% CI, 10.06-10.21). This trial was limited by several factors, including inclusion of patients without a clear etiologic diagnosis at study entry, use of symptoms alone for the diagnosis of recurrent meningitis, and small sample size.

Noninfectious etiologies for Mollaret meningitis have also been proposed. As an example, patients with an intracranial epidermoid cyst or other cystic abnormalities in the brain can develop meningeal irritation due to intermittent leakage of irritating squamous material into the CSF [49]. This may be detected by polarizing microscopy of CSF. Imaging studies should be performed subsequently when the patient is asymptomatic, since the epidermoid cyst is often collapsed immediately after leaking its contents. (See "Uncommon brain tumors", section on 'Epidermoid cyst'.)

Other forms of chronic meningitis

— Chronic meningitis is defined as meningitis lasting for four weeks or more and is a complex entity with both infectious and noninfectious causes (table 8). The symptoms can remain static, fluctuate, and/or slowly worsen. Despite extensive testing, an etiologic diagnosis may not be determined in up to one-third of patients. The approach to patients with chronic meningitis is presented in a separate topic review. (See "Approach to the patient with chronic meningitis".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Viral meningitis (The Basics)" and "Patient education: Viral meningitis in adults – Discharge instructions (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Definition and etiologies** – The term aseptic meningitis typically describes an acute community-acquired meningitis with a negative cerebrospinal fluid (CSF) Gram stain and culture. (See 'Introduction' above.)

The most common etiologies are viruses. However, this term also includes more than 100 causes, such as other infections (mycobacteria, fungi, spirochetes), parameningeal infections, medications, and malignancies (table 1). (See 'Infections due to specific pathogens' above.)

- **Initial evaluation** – The initial evaluation of a patient with presumed meningitis includes a careful clinical evaluation as well as specific diagnostic testing. This evaluation informs the use of empiric antimicrobial therapy.
 - **Clinical evaluation** – Clinicians should evaluate patients for features consistent with bacterial meningitis or encephalitis, as well as historical clues or physical exam findings that may support a specific etiology. This includes the presence of underlying conditions, especially those that may result in some degree of immune compromise. (See 'Clinical evaluation' above.)
 - **Diagnostic testing** – For patients with suspected meningitis, blood cultures should be obtained, and a lumbar puncture (LP) should be promptly performed. The decision to perform imaging (eg, CT scan) prior to LP is discussed elsewhere. (See "Clinical features and diagnosis of acute bacterial meningitis in adults", section on 'Indications for CT scan before LP'.)

CSF should be sent for cell count, glucose, protein, and bacterial culture. In addition, when aseptic meningitis is being considered, molecular tests for the most common etiologies (eg, enterovirus, herpes viruses) should be performed. (See 'Cerebrospinal fluid' above.)

Additional types of serum and CSF testing depend upon the concern for a specific pathogen. (See 'Infections due to specific pathogens' above.)

- **Antimicrobial therapy**
 - **Role of empiric therapy** – The decision to administer empiric antimicrobial therapy in a patient with possible aseptic meningitis depends primarily upon the concern for bacterial meningitis, which is based on the history, physical examination, and CSF findings (table 3). (See 'Role of empiric therapy' above.)

When it is not clear whether the patient has a viral or bacterial process, the treating physician can choose empiric antibiotics for 48 hours while awaiting culture results (table 4).

Empiric therapy with intravenous **acyclovir** should be initiated if there is a concern for herpes simplex virus (HSV) or varicella-zoster virus (VZV) encephalitis or if clinical findings (eg, vesicular skin lesions) are suggestive of herpes virus infection.
 - **Tailored therapy** – If an infectious agent is identified and is amenable to therapy (eg, spirochetal infection such as Lyme disease or syphilis), therapy should be tailored to the best possible treatment option. (See 'Infections due to specific pathogens' above.)

- If no source identified – A repeat LP off of antibiotics may be indicated in patients with persistent symptoms who do not have a clear diagnosis. (See 'Additional considerations' above.)

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