Aseptic meningitis in adults

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INTRODUCTION

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 and often present soon after symptom onset. 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 fever, headache, stiff neck, nausea, and photophobia. In contrast to bacterial meningitis, patients do not present with altered mental status and the onset may be less acute. 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 [4].

  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, coccidioidal 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) or by human parechovirus [5]. 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.

- **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. (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 [6]. (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) [7,8]. (See "Cerebrospinal fluid: Physiology and utility of an examination 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 [9,10]. A rapid multiplex PCR that detects 14 etiologies in one hour is available and can identify the most common viral, bacterial, and fungal causes of meningitis [11]. However, this test should not be routinely performed because of concerns of false-positive results (eg, cytomegalovirus [CMV] and human herpesvirus 6 [HHV6]) in patients without a compatible disease and 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", section on 'Types of tests'.)
- A West Nile virus immunoglobulin (Ig)M in the CSF or serum should be sent in all patients that present between June and October in the United States [12]. (See "Clinical manifestations and diagnosis of West Nile virus infection", section on 'Serologic tests'.)
- 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 [13]. 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 and utility of an examination 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 x10^9/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) [14]. This risk score had a 99.6 to 100 percent sensitivity in identifying a low-risk subgroup [14,15]. 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 culture [9]. A delay in performing the LP is associated with an increase in the cost of hospitalization [16].

  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 of 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]) [5,9].

Enteroviruses and parechoviruses — 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 [5]. 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 [17,18].

Enteroviral meningitis has a subacute presentation with a median duration of symptoms of three days before presentation. Signs and symptoms typically include headache, fever, nausea or vomiting, malaise, photophobia, and meningismus [19,20]. Rash, diarrhea, and upper respiratory symptoms may also be present [9].

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) [21], 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 [9,22,23]. 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 [11].

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 [23].

- **Meningitis due to HSV** – HSV is a leading cause of aseptic meningitis [22]. In contrast to HSV encephalitis, which is almost exclusively due to HSV-1, viral meningitis in immunocompetent adults is generally caused by HSV-2 [9]. 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 [5,24]. However, in a large prospective study of 205 patients with HSV meningitis, only 8 percent had genital mucocutaneous lesions [24]. 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".)

  For patients who present with HSV meningitis, we administer antiviral therapy. There is no standard approach to treatment of HSV meningitis [25]. 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 Lexicomp 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 [24]. 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 [25]. By contrast, this benefit was not seen in a study of 60 immunocompetent patients with HSV meningitis [26].

- **Meningitis due to varicella-zoster virus** – VZV can cause aseptic meningitis in patients with or without typical skin lesions [23,26]; the latter are known as zoster sine herpete. VZV is likely an underdiagnosed etiology, as only 1.2 percent of patients with aseptic meningitis undergo a CSF VZV PCR [22]. 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 [23]. 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 [9]. These are discussed in detail separately. (See "Epidemiology, clinical manifestations, and diagnosis of herpes zoster", section on 'Aseptic meningitis' and "Human herpesvirus 6 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 infection", 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 [22]. 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. Patients with meningitis typically present with fever, headache, nausea, vomiting, stiff neck, photophobia, and occasionally with a maculopapular rash [22]. The CSF profile resembles enteroviral meningitis, sometimes presenting with a neutrophilic pleocytosis [7]. Patients may have persistent headaches, memory impairment, and chronic fatigue years after infection [6]. (See "Epidemiology and pathogenesis of West Nile virus infection" and "St. Louis encephalitis" and "Viral encephalitis in adults".)

HIV — 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 [9]. 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 [27]. 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 are observed in 20 to 30 percent of patients with LCMV meningitis and CSF WBC counts of greater than 1000/microL are not unusual [27]. 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 [27]. 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 [10,23].

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 [28]; 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 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 and 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 outbreaks — Health care-associated outbreaks due to *Fusarium* species have been reported. This includes an outbreak in Durango, Mexico in November of 2022 [29] and an ongoing 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 [30,31]. The 2023 outbreak was first reported in May, and as of June 14, 2023 18 suspected, 10 probable, and 6 confirmed cases have been reported [32]; four of these patients have died. The presumed pathogen has been identified as *Fusarium solani* species complex.

In response to the 2023 outbreak, the United States CDC has provided recommendations for evaluation and management of individuals who are at risk for fungal meningitis following epidural anesthesia at one of the two clinics listed below [30]. Updated information on this outbreak, which should be reviewed prior to the evaluation and management of such patients, can be found on the CDC website. These patients should be managed in consultation with public health officials.

- **Evaluation/diagnosis** – Persons who received epidural anesthesia at River Side Surgical Center or Clinica K-3 between January 1 to May 13, 2023 should be evaluated for

meningitis, regardless of symptoms [32].

- A lumbar puncture (LP) should be performed in all patients if there are no contraindications (eg, skin infection over the puncture site, brain mass causing increased intracranial pressure). Cerebrospinal fluid (CSF) should be sent for beta-D-glucan, fungal culture, and pan-fungal PCR testing or metagenomic testing, in addition to routine studies. A serum beta-d-glucan should be performed as well. (See 'Diagnostic testing' above.)

- In patients with an abnormal LP (eg, >5 WBC/microL), an MRI with and without contrast should be obtained to assess for meningeal enhancement, vasculitis, stenosis, hemorrhage, or ischemia.

- **Management** – Management of individuals with a potential exposure during the outbreak depends upon the CSF findings:

  - For patients who have >5 WBC/microL in the CSF, empiric therapy should be initiated as soon as possible after CSF is obtained, regardless of whether they have symptoms.

    Treatment should include liposomal amphotericin B (5 mg/kg IV daily) plus voriconazole (eg, 6 mg/kg IV every 12 hours for two doses, then 4 mg/kg IV every 12 hours thereafter) [33]. Patients can transition to oral voriconazole when they are clinically stable. Dual therapy is recommended for initial treatment because of the high case-fatality rate seen during previous outbreaks of fungal meningitis involving *Fusarium*. During a similar outbreak that was reported following epidural anesthesia in Durango, Mexico in 2022, the mortality rate was >40 percent [34].

    Empiric therapy should be continued while awaiting the results of CSF beta-D-glucan, fungal culture, and pan-fungal PCR testing or metagenomic testing. Given the evolving nature of this outbreak, clinicians should refer to the CDC website and the fungus education hub for information on the subsequent management of those with a CSF pleocytosis or confirmed/probable meningitis due to *Fusarium*.

  - For individuals with ≤5 WBC/microL in the CSF, empiric therapy is not needed, even if symptoms were present. However, such patients should continue to be monitored. An LP can be repeated after two weeks in patients with persistent symptoms. In those who were asymptomatic, an LP should be repeated if symptoms develop. The approach to monitoring is discussed in greater detail on the CDC website and the fungus education hub.

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 [35]. (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 [36].

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. (See "Clinical features and diagnosis of acute bacterial meningitis in adults".)

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 [37]. (See "Spinal epidural abscess" and "Intracranial epidural abscess" and "Acute sinusitis and rhinosinusitis in adults: Clinical manifestations and diagnosis" and "Acute otitis media 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 [38]. Two mechanisms have been proposed for drug-induced meningitis, a delayed hypersensitivity type reaction and direct meningeal irritation [38].

In a study of 329 patients with drug-induced meningitis [39], 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 [22,40]. 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; some patients may have evidence of genital lesions at the time of presentation [22]. HSV-1 and Epstein Barr virus can rarely be the cause of RBLM [22]. 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 [41].

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 [41]. 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 recurrences 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 [42]. 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)")

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 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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Topic 1296 Version 28.0

GRAPHICS

Differential diagnosis of selected causes of aseptic meningitis

Viral

- Adenovirus
- Arboviruses
- Coxsackieviruses types A and B
- Cytomegalovirus
- Echoviruses
- Encephalomyocarditis virus
- Epstein-Barr virus
- Herpes simplex virus types 1 and 2
- Human herpes virus 6 (in children)
- Human Parechovirus
- Human immunodeficiency virus
- Influenza A and B
- Lymphocytic choriomeningitis virus
- Measles
- Mumps
- Parainfluenza
- Poliovirus
- Rotavirus
- Rubella
- Toscana virus
- Varicella-zoster virus

Bacterial

- *Actinomyces* spp
- Bacterial endocarditis
- *Borrelia burgdorferi* (Lyme disease)
- *Borrelia recurrentis* (relapsing fever)
- *Brucella* spp
- *Chlamydia* spp
- *Leptospira* spp
- *Mycobacterium tuberculosis*
- *Mycoplasma hominis*
- *Mycoplasma pneumoniae*
- *Nocardia* spp
- Parameningeal bacterial infection (epidural, subdural abscess)
- Partially treated bacterial meningitis
- *Rickettsia* spp
- *Spirillum minor* (rat bite fever)
- *Treponema pallidum* (syphilis)
- *Ureoplasma ureolyticum*

Fungal

- *Aspergillus* spp
- *Blastomyces dermatitidis*
- *Candida* spp
- *Coccidioides immitis*
- *Cryptococcus neoformans*
- *Histoplasma capsulatum*
- *Sporothrix schenckii*

Parasitic

- *Angiostrongylus cantonensis*
- *Taenia solium* (cysticercosis)

- *Toxoplasma gondii*
- *Trichinella spiralis*

Drug

- Anti-CD3 monoclonal antibody
- Azathioprine
- lbuprofen
- Other NSAIDs
- Pyridium (phenazopyridine)
- Trimethoprim-sulfamethoxazole

Malignancy

- Leukemia
- Lymphoma
- Metatstatic carcinomas and adenocarcinomas

Autoimmune

- Behçet disease
- Sarcoidosis
- Systemic lupus erythematosus
- Vogt-Koyanagi-Harada syndrome

Other

- Epidermoid cyst
- Postvaccination

NSAIDs: nonsteroidal anti-inflammatory drugs.

Modified from Connolly KJ, Hammer SM. The acute aseptic meningitis syndrome. Infect Dis Clin North Am 1990; 4:599.

Graphic 79745 Version 5.0

Signs of meningeal irritation

Signs of meningeal irritation	Maneuver	Positive test
Kernig sign	Place patient supine with hip flexed at 90 degrees. Attempt to extend the leg at the knee.	The test is positive when there is resistance to extension at the knee to >135 degrees or pain in the lower back or posterior thigh
Brudzinski sign	Place patient in the supine position and passively flex the head toward the chest.	The test is positive when there is flexion of the knees and hips of the patient.
Jolt accentuation of headache	Patient rotates his/her head horizontally two to three times per second.	The test is positive if the patient reports exacerbation of his/her headache with this maneuver.

Graphic 82677 Version 4.0

Typical cerebrospinal fluid findings in central nervous system infections*

	Glucose (mg/dL)		Protein (mg/dL)		Total white blood cell (cells/microL)		
	<10¶	10 to 40Δ	100 to 500◇	50 to 300§	>1000	100 to 1000	
More common	Bacterial meningitis	Bacterial meningitis	Bacterial meningitis	Viral meningitis Nervous system Lyme disease (neuroborreliosis) Encephalitis Neurosyphilis TB meningitis¥	Bacterial meningitis	Bacterial or viral meningitis TB meningitis	Ea ba me Vir me Ne TB me
Less common	TB meningitis Fungal meningitis	Neurosyphilis Some viral infections (such as mumps and LCMV)		Early bacterial meningitis	Some cases of mumps and LCMV	Encephalitis	En

TB: tuberculosis; LCMV: lymphocytic choriomeningitis virus.

* It is important to note that the spectrum of cerebrospinal fluid values in bacterial meningitis is so wide that the absence of one or more of these findings is of little value. Refer to the UpToDate topic reviews on bacterial meningitis for additional details.

¶ <0.6 mmol/L.

Δ 0.6 to 2.2 mmol/L.

◇ 1 to 5 g/L.

§ 0.5 to 3 g/L.

¥ Cerebrospinal fluid protein concentrations may be higher in some patients with tuberculous meningitis; concentrations >500 mg/dL are an indication of blood-brain barrier disruption or increased intracerebral production of immunoglobulins, and extremely high concentrations, in the range of 2 to 6 g/dL, may be found in association with subarachnoid block.

Graphic 76324 Version 11.0

Recommendations for empiric antimicrobial therapy for purulent meningitis based on patient age and specific predisposing condition*

Predisposing factor	Common bacterial pathogens	Antimicrobial therapy
Age		
<1 month	*Streptococcus agalactiae*, *Escherichia coli*, *Listeria monocytogenes*	Ampicillin plus cefotaxime; OR ampicillin plus an aminoglycoside
1 to 23 months	*Streptococcus pneumoniae*, *Neisseria meningitidis*, *S. agalactiae*, *Haemophilus influenzae*, *E. coli*	Vancomycin plus a third-generation cephalosporin¶ Δ ◇
2 to 50 years	*N. meningitidis*, *S. pneumoniae*	Vancomycin plus a third-generation cephalosporin¶ Δ ◇
>50 years	*S. pneumoniae*, *N. meningitidis*, *L. monocytogenes*, aerobic gram-negative bacilli	Vancomycin plus ampicillin plus a third-generation cephalosporin¶ Δ
Head trauma		
Basilar skull fracture	*S. pneumoniae*, *H. influenzae*, group A beta-hemolytic streptococci	Vancomycin plus a third-generation cephalosporin¶ Δ
Penetrating trauma	*Staphylococcus aureus*, coagulase-negative staphylococci (especially *Staphylococcus epidermidis*), aerobic gram-negative bacilli (including *Pseudomonas aeruginosa*)	Vancomycin plus cefepime; OR vancomycin plus ceftazidime; OR vancomycin plus meropenem
Postneurosurgery	Aerobic gram-negative bacilli (including *P. aeruginosa*), *S. aureus*, coagulase-negative staphylococci (especially *S. epidermidis*)	Vancomycin plus cefepime; OR vancomycin plus ceftazidime; OR vancomycin plus meropenem
Immunocompromised state	*S. pneumoniae*, *N. meningitidis*, *L. monocytogenes*, aerobic gram-negative bacilli (including *P. aeruginosa*)	Vancomycin plus ampicillin plus cefepime; OR vancomycin plus meropenem§

* For recommended doses, refer to the UpToDate content on treatment of bacterial meningitis in children and adults.

¶ Ceftriaxone or cefotaxime.

Δ Some experts would add rifampin if dexamethasone is also given.

◇ Add ampicillin if meningitis caused by *Listeria monocytogenes* is suspected.

§ Meropenem provides sufficient coverage for *Listeria* when used as part of an initial regimen. However, if *Listeria* is identified, the patient should generally be switched to a regimen that includes ampicillin. Refer

to the UpToDate topic that discusses treatment of *Listeria* for a discussion of regimen selection.

Graphic 71968 Version 12.0

Estimated per-act risk for acquisition of HIV, by exposure route

Exposure route		Risk per 10,000 exposures to an infected source (risk)
Blood-borne exposure	Blood transfusion	9000 (9/10)
	Needle-sharing injection drug use	67 (1/150)
	Percutaneous needle stick	23 (1/435)
	Mucous membrane exposure to blood (eg, splash to eye)	10 (1/1000)
Sexual exposure	Receptive anal intercourse	138 (1/72)
	Insertive anal intercourse	11 (1/900)
	Receptive penile-vaginal intercourse	8 (1/1250)
	Insertive penile-vaginal intercourse	4 (1/2500)
	Receptive or insertive penile-oral intercourse	0-4
Other	Biting, spitting, throwing body fluids (including semen and saliva), sharing sex toys	Negligible

There are scant empiric data on per contact risk of exposure. This table lists the estimated risk by exposure type in the absence of antiretroviral treatment of the HIV-infected source and in the absence of amplifying factors. Most of these estimates are derived through modeling studies of different cohorts. Clinicians need to be aware that estimates of sexual risk are often based on studies of monogamous couples among whom amplifying factors have been treated and repeated exposure may offer as yet unexplained protection from infection. Using a single value for assessing risk of HIV transmission based on route of sexual exposure fails to reflect the variation associated with important cofactors. A variety of amplifying factors and conditions have been identified, and these factors can be expected to increase transmission probability.

Data from:

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Graphic 60145 Version 6.0

Treatment of Lyme disease*

	Drug	Adult dose	Pediatric dose	Comment
Erythema migrans (early disease)				
	Doxycycline[¶ Δ ◇]	100 mg orally twice daily for 10 days	4.4 mg/kg/day orally divided twice daily (maximum 100 mg per dose) for 10 days	▪ Patients with early disseminated disease who present with multiple erythema migrans lesions are treated the same way as those with a single erythema migrans lesion. ▪ For patients unable to tolerate the preferred regimens, alternative treatments include: • Azithromycin (in adults: 500 mg orally once daily; in children: 10 mg/kg/day [maximum 500 mg per dose]) for 7 days (range 5 to 10 days); **or** • Clarithromycin (in adults: 500 mg orally twice daily; in children: 15 mg/kg/day divided twice daily [maximum 500 mg per dose]) for 14 to 21 days.
	or Amoxicillin	500 mg orally 3 times daily for 14 days	50 mg/kg/day orally divided 3 times daily (maximum 500 mg per dose) for 14 days	
	or Cefuroxime axetil	500 mg orally twice daily for 14 days	30 mg/kg/day orally divided twice daily (maximum 500 mg per dose) for 14 days	
Neurologic disease[§]				
Acute neurologic disease, such as: ▪ Cranial nerve palsy (eg, facial nerve palsy)	Doxycycline[¶ Δ ◇]	100 mg orally twice daily for 14 to 21 days	4.4 mg/kg/day orally divided twice daily (maximum	▪ For patients with isolated facial nerve palsy (eg, no evidence of meningitis or radiculoneuropathy),

▪ Meningitis ▪ Radiculoneuropathy (early disseminated disease)			100 mg per dose) for 14 to 21 days	amoxicillin or cefuroxime is an alternative in patients with contraindications to doxycycline. For patients with other forms of acute neurologic disease, most experts would initiate IV therapy (eg, ceftriaxone) if doxycycline cannot be used. ▪ In the United States, most practitioners favor using longer courses of antibiotics (eg, 28 days) for those with evidence of severe neurologic disease.
Severe neurologic disease, including encephalitis	Ceftriaxone[¥ ‡]	2 g IV once daily for 14 to 28 days	50 to 75 mg/kg IV once daily (maximum 2 g per dose) for 14 to 28 days	
Carditis				
Mild (eg, asymptomatic patients with first-degree atrioventricular block and PR interval <300 milliseconds)	Doxycycline[¶ Δ ◇]	100 mg orally twice daily for 14 to 21 days	4.4 mg/kg/day orally divided twice daily (maximum 100 mg per dose) for 14 to 21 days	
	or Amoxicillin	500 mg orally 3 times daily for 14 to 21 days	50 mg/kg/day orally divided 3 times daily (maximum 500 mg per dose) for 14 to 21 days	
	or Cefuroxime axetil	500 mg orally twice daily for 14 to 21 days	30 mg/kg/day orally divided twice daily (maximum 500 mg per	

			dose) for 14 to 21 days	
More serious disease (eg, symptomatic, second- or third-degree atrioventricular block, first-degree atrioventricular block with PR interval ≥300 milliseconds)	Ceftriaxone[¥ ‡]	2 g IV once daily for 14 to 21 days	50 to 75 mg/kg IV once daily (maximum 2 g per dose) for 14 to 21 days	▪ A parenteral antibioti regimen is recommended for initial treatment for hospitalized patients. IV antibiotics should be continued until high-grade atrioventricular block has resolved and the PR interval has become less than 300 milliseconds. The patient may then be switched to oral therapy to complete a 14- to 21-day course. ▪ A temporary pacemaker may be necessary for some patients with carditis.
Arthritis				
Initial treatment[†]	Doxycycline[¶ ◇]	100 mg orally twice daily for 28 days	≥8 years: 4.4 mg/kg/day orally divided twice daily (maximum 100 mg per dose) for 28 days[◇]	▪ Cefuroxime is a suitable alternative in patients with contraindications to doxycycline and amoxicillin, although it has not been assessed in clinical studies for this indication.
	or Amoxicillin	500 mg orally 3 times daily for 28 days	50 mg/kg/day orally divided 3 times daily (maximum 500 mg per dose) for 28 days	
Persistent arthritis with little or no response to oral antibiotics (despite	Ceftriaxone[¥]	2 g IV once daily for 14 to 28 days	50 to 75 mg/kg IV once daily	▪ IV therapy should be administered to patients who

adequate prior oral therapy)			(maximum 2 g per dose) for 14 to 28 days	presented with moderate-to-severe arthritis and had minimal or no response to oral therapy. ▪ Retreatment with a second course of oral therapy can be used for those with persistent arthritis who initially presented with mild arthritis (even if there is a minimal response to therapy) as well as those with moderate-to-severe disease who had a partial response to oral therapy. If there is an incomplete response after the second course of oral treatment, then IV therapy should be administered. ▪ For patients who fail to respond to oral and IV therapy, the use of disease-modifying antirheumatic drugs or arthroscopic synovectomy may be indicated.
	or Doxycycline¶ ◇	100 mg orally twice daily for 28 days	≥8 years: 4.4 mg/kg/day orally divided twice daily (maximum 100 mg per dose) for 28 days◇	
	or Amoxicillin	500 mg orally 3 times daily for 28 days	50 mg/kg/day orally divided 3 times daily (maximum 500 mg per dose) for 28 days	
Acrodermatitis chronica atrophicans				
	Doxycycline¶ ◇	100 mg orally twice daily for 21 to 28 days	4.4 mg/kg/day orally divided twice daily (maximum 100 mg per dose) for 21 to 28 days◇	
	or Amoxicillin	500 mg orally 3	50 mg/kg/day	

		times daily for 21 to 28 days	orally divided 3 times daily (maximum 500 mg per dose) for 21 to 28 days	
	or Cefuroxime	500 mg orally twice daily for 21 to 28 days	30 mg/kg/day orally divided twice daily (maximum 500 mg per dose) for 21 to 28 days	

This table is meant for use with UpToDate content on Lyme disease. Refer to UpToDate content for additional details on management of special populations (eg, pediatric and pregnant patients) and management of those with persistent symptoms after treatment.

IV: intravenous.

* A complete response to treatment may be delayed beyond the treatment duration, regardless of the clinical manifestation of Lyme disease. However, in most patients with persistent symptoms the duration of treatment should not be extended.

¶ For pregnant and lactating patients, tetracyclines are generally avoided in favor of a beta-lactam (eg, amoxicillin, cefuroxime). In the setting of neurologic disease or contraindication to a beta-lactam, the decision to use doxycycline must be decided on a case-by-case basis. Although most tetracyclines are contraindicated in pregnancy because of the risk of hepatotoxicity in the mother and potential adverse effects on fetal bone and teeth, limited data suggest these events are extremely rare with doxycycline when short courses are used.

Δ Doxycycline also has activity against coinfections such as *Anaplasma phagocytophilum* and *Borrelia miyamotoi* but not against *Babesia microti*.

◇ The American Academy of Pediatrics supports the use of doxycycline for children <8 years of age if it is administered for ≤21 days. However, the data on safety of doxycycline in this population are limited, and some providers still prefer a beta-lactam rather than doxycycline unless there is evidence of neurologic disease or infection with *Anaplasma*. Studies have not evaluated the safety of doxycycline in children <8 years of age when the duration of treatment is >21 days (eg, Lyme arthritis).

§ For patients with neurologic disease, there are no studies to help guide length of therapy within the range suggested by the guidelines, and there are no diagnostic tests to determine clearance of infection or predict the success of therapy.

¥ Alternative IV agents include cefotaxime 2 g IV every 8 hours for 14 to 28 days for adults and 150 to 200 mg/kg/day in 3 divided doses (maximum 6 g per day) for children, or penicillin G 18 to 24 million units per day divided into doses given every 4 hours in adults and 200,000 to 400,000 units/kg/day divided every 4 hours (maximum 18 to 24 million units per day) in children.

‡ Doxycycline can be used in patients intolerant of beta-lactam antibiotics.

† On rare occasion, patients may present with late-stage neurologic disease and arthritis. In this setting, IV therapy is usually preferred for initial treatment.

Adapted from:

1. *Lantos PM, Rumbaugh J, Bockenstedt LK, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis, and Treatment of Lyme Disease. Arthritis Rheumatol 2021; 73:12.*
2. *Sanchez E, Vannier E, Wormser GP, Hu LT, et al. Diagnosis, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: a review. JAMA 2016; 315:1767.*
3. *American Academy of Pediatrics. Lyme disease. In: Red Book: 2018 Report of the Committee on Infectious Diseases, 31st ed, Kimberlin DW, Brady MT, Jackson MA, Long SS (Eds), American Academy of Pediatrics, 2018. p.515.*

Graphic 59949 Version 12.0

First-line antituberculosis drugs for treatment of CNS tuberculosis

Drug	Adult dose*	Pediatric dose[¶]
Isoniazid[Δ]	5 mg/kg (usual maximum dose 300 mg)	10 to 15 mg/kg per day
Rifampin (rifampicin)[◇]	10 mg/kg (usual maximum dose 600 mg)	20 to 30 mg/kg per day
Rifabutin[◇]	5 mg/kg (usual maximum dose 300 mg)	--
Pyrazinamide[§]	Patient weight 40 to 55 kg[¥]: ▪ 1000 mg (18.2 to 25 mg/kg)	30 to 40 mg/kg per day
	Patient weight 56 to 75 kg[¥]: ▪ 1500 mg (20 to 26.8 mg/kg)	
	Patient weight 76 to 90 kg[¥ ‡]: ▪ 2000 mg[†] (22.2 to 26.3 mg/kg)	
Ethambutol**	Patient weight 40 to 55 kg[¥]: ▪ 800 mg (14.5 to 20 mg/kg)	15 to 25 mg/kg per day
	Patient weight 56 to 75 kg[¥]: ▪ 1200 mg (16 to 21.4 mg/kg)	
	Patient weight 76 to 90 kg[¥]: ▪ 1600 mg[†] (17.8 to 21.1 mg/kg)	
Ethionamide	--	15 to 20 mg/kg per day in 2 or 3 divided doses
Amikacin	--	15 to 20 mg/kg per day
Levofloxacin		15 to 20 mg/kg per day

Antituberculous agents are used in multidrug combination regimens of varying duration, which are described in detail in a separate table (refer to the UpToDate table on regimens for treatment of drug-susceptible tuberculosis) and in the accompanying text.

CNS: central nervous system.

* Adult dosing listed in this table is used in patients ≥15 years old or >40 kg. Dosing based on actual weight is acceptable in patients who are not obese. For obese patients (>20% above ideal body weight [IBW]), dosing based on IBW may be preferred for initial doses. Some clinicians prefer a modified IBW (IBW + [0.40 × (actual weight − IBW)]) as is done for initial aminoglycoside doses. Because tuberculosis

drug dosing for obese patients has not been established, therapeutic drug monitoring may be considered for such patients.

¶ For empiric treatment of CNS TB (not known or suspected to be drug resistant) in children, we are in agreement with the American Academy of Pediatrics, which recommends treatment with an intensive phase 4-drug regimen consisting of isoniazid, rifampin, pyrazinamide, and ethionamide or levofloxacin (in place of ethambutol, given its poor CNS penetration) administered daily for 2 months.

Δ Pyridoxine (vitamin B6; 25 to 50 mg/day) is given with isoniazid to individuals at risk for neuropathy (eg, pregnant women, breastfeeding infants, and individuals with HIV infection, diabetes, alcoholism, malnutrition, chronic renal failure, or advanced age). For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/day.

◇ Rifabutin dose may need to be adjusted when there is concomitant use of protease inhibitors or nonnucleoside reverse transcriptase inhibitors. Refer to the UpToDate topic on treatment of pulmonary tuberculosis in HIV-infected adults for specific dose adjustments.

§ For patients with creatinine clearance <30 mL/min (by Cockroft-Gault equation) or for patients receiving intermittent hemodialysis, pyrazinamide dosing consists of 25 to 35 mg/kg (ideal body weight) per dose orally 3 times per week (**not** daily); max 2.5 g per dose. On the day of hemodialysis, medications should be administered after hemodialysis. Monitoring of serum drug concentrations should be considered to ensure adequate drug absorption without excessive accumulation and to assist in avoiding toxicity.

¥ Based on estimated lean body weight.

‡ Patients >90 kg should have serum concentration monitoring. In obese patients, weight-based dosing is likely best based on measurements of ideal (versus total) body weight.

† Maximum dose regardless of weight.

** For patients with creatinine clearance <30 mL/min (by Cockroft-Gault equation) or for patients receiving intermittent hemodialysis, ethambutol dosing consists of 20 to 25 mg/kg (ideal body weight) per dose orally 3 times per week (**not** daily); max 1.6 g per dose. On the day of hemodialysis, medications should be administered after hemodialysis. Monitoring of serum drug concentrations should be considered to ensure adequate drug absorption without excessive accumulation and to assist in avoiding toxicity.

Data adapted from:

1. *Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of American clinical practice guidelines: Treatment of drug-susceptible tuberculosis. Clin Infect Dis 2016; 63:e147.*
2. *Curry International Tuberculosis Center and California Department of Public Health, 2016: Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, Third Edition.*

Graphic 127916 Version 2.0

Potential causes of chronic meningitis

Infections	Noninfectious conditions	Drugs
Mycobacterial ▪ *Mycobacterium tuberculosis* **Spirochetal** ▪ *Borrelia burgdorferi* ▪ *Treponema pallidum* ▪ *Leptospira* species **Bacterial** ▪ *Brucella* species ▪ *Francisella tularensis* ▪ *Actinomyces* species ▪ *Listeria monocytogenes* ▪ *Ehrlichia chaffeensis* ▪ *Nocardia* species ▪ *Tropheryma whipplei* (Whipple disease) **Viral** ▪ Human immunodeficiency virus ▪ Cytomegalovirus ▪ Epstein-Barr virus ▪ Human T cell lymphotrophic virus I and II ▪ Enterovirus ▪ Herpes simplex virus ▪ Varicella-zoster virus ▪ Cache Valley virus **Fungal** ▪ *Cryptococcus neoformans/gattii* ▪ *Sporothrix* ▪ *Histoplasma* ▪ *Blastomyces* ▪ *Coccidioides* ▪ Other (eg, *Scedosporium apiospermum*, *Paracoccidioides*, dematiaceous molds)	▪ Neoplastic ▪ Sarcoidosis ▪ Systemic lupus erythematosus ▪ Granulomatosis with polyangiitis (Wegener's) ▪ Behçet syndrome ▪ Fabry disease ▪ Central nervous system vasculitis ▪ Vogt-Koyanagi-Harada disease ▪ Chemical or drug-induced meningitis ▪ Idiopathic (up to one-third of cases) ▪ Rheumatoid arthritis	▪ Nonsteroidal anti-inflammatory drugs ▪ Intravenous immunoglobulin ▪ Intrathecal agents

Parasitic ▪ *Taenia solium* (cysticercosis) ▪ *Angiostrongylus* ▪ *Schistosoma* ▪ *Toxoplasma* ▪ *Acanthamoeba* ▪ *Balamuthia mandrillaris*		

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