Central Nervous System Infections

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Infectious Diseases & Clinical Microbiology
CNS Infections

- Acute bacterial meningitis
- Viral meningitis
- Encephalitis
- Focal infections: Brain abscess, subdural empyema
- Infectious thrombophlebitis
**Meningitis**
- Inflammatory disease of the leptomeninges (the tissues surrounding the brain and spinal cord).

**Encephalitis**
- Evidence of either generalized or focal involvement of brain tissue in the cerebral hemispheres, cerebellum, or brainstem brain tissue is directly injured by a viral infection.

**Cerebritis/abscess**
- Focal bacterial, fungal, or parasitic infections involving brain tissue are classified as either cerebritis or abscess, depending on the presence or absence of a capsule.
ACUTE BACTERIAL MENINGITIS

The meninges consist of three parts: the pia, arachnoid, and dura mater.

Meningitis is the inflammatory disease of the leptomeninges (the tissues surrounding the brain and spinal cord---arachnoid + pia mater).

The infection predominantly involves the subarachnoid space (Arachnoid mater, CSF)
Brain surrounded by pus (the yellow-greyish coat around the brain, under the dura lifted by the forceps), the result of bacterial meningitis.

Underneath the dura mater are the leptomeninges, which appear to be edematous and have multiple small hemorrhagic foci (red).

http://nurseslabs.com/bacterial-meningitis/
Meningitis is associated with a CNS inflammatory reaction that may result in **decreased consciousness, seizures, raised intracranial pressure (ICP) and stroke.**

The **meninges, the subarachnoid space, and the brain parenchyma** are all frequently involved in the inflammatory reaction (**meningoencephalitis**)
Bacterial meningitis can be **community acquired or healthcare associated**

The major causes of community-acquired bacterial meningitis in adults in developed countries are *Streptococcus pneumoniae, Neisseria meningitidis*, and, primarily primarily in patients over age 50 to 60 years or those who have deficiencies in cell-mediated immunity, *Listeria monocytogenes*

The major causes of **healthcare-associated bacterial meningitis** are different (usually *staphylococci* and aerobic gram-negative bacilli).

Healthcare-associated bacterial meningitis may also occur in patients with **internal or external ventricular drains or following cranial trauma**
• Most commonly responsible for community acquired bacterial meningitis are:

  – *Streptococcus pneumoniae* (∼50%),
  – *N. meningitidis* (∼25%),
  – *Group B streptococci* (∼15%),
  – *Listeria monocytogenes* (∼10%).

*H. Influenzae* now accounts for <10% of cases of bacterial meningitis in most series.

*N. meningitidis* meningitis can be contagious and the health care providers are needed prophylaxis
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns</td>
<td>Group B Streptococcus, Escherichia coli, Listeria monocytogenes</td>
</tr>
<tr>
<td>Infants and Children</td>
<td>Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae type b</td>
</tr>
<tr>
<td>Adolescents and Young Adults</td>
<td>Neisseria meningitidis, Streptococcus pneumoniae</td>
</tr>
<tr>
<td>Older Adults</td>
<td>Streptococcus pneumoniae, Neisseria meningitidis, Listeria monocytogenes</td>
</tr>
</tbody>
</table>
PATHOGENESIS

Invasion of SAS by meningeal pathogens

- Multiplication of organisms and lysis of organisms by bactericidal antibiotics
- Release of bacterial cell wall components (endotoxin, teichoic acid)

Production of inflammatory cytokines

- Altered blood-brain barrier permeability
- Adherence of leukocytes to cerebral capillary endothelial cells
- Alterations in cerebral blood flow
- Production of excitatory amino acids and reactive oxygen and nitrogen species

† Permeability of blood vessels with leakage of plasma proteins into CSF
- Leukocytes migrate into CSF, degranulate, and release toxic metabolites
- Cell injury and death
CLINICAL FEATURES

• Presenting manifestations

• The classic triad of acute bacterial meningitis consists of **fever, nuchal rigidity, and a change in mental status.**

• **Headache** is also common. The headache is typically described as severe and generalized.
In a 2004 review of 696 cases of community-acquired bacterial meningitis, only 44 percent had the clinical triad of fever, neck stiffness, and altered mental status! Almost all patients (95 percent) presented with at least two of four symptoms (i.e., headache, fever, stiff neck, and altered mental status).
Signs of Meningeal Irritation

- Nuchal Rigidity
- Kernig’s
- Brudzinski’s
**Nuchal rigidity** ("stiff neck")

The pathognomonic sign of meningeal irritation and is present when the neck resists passive flexion.

The high prevalence of cervical spine disease in older individuals may result in false-positive tests for nuchal rigidity.
Kernig’s sign is elicited with the patient in the supine position. The thigh is flexed on the abdomen with the knee flexed; attempts to passively extend the knee elicit pain when meningeal irritation is present.
Brudzinski’s sign is elicited with the patient in the supine position and is positive when passive flexion of the neck results in spontaneous flexion of the hips and knees.
Headache, Fever, ± Nuchal Rigidity

Altered mental status?

Yes

Meningoencephalitis, ADEM, encephalopathy, or mass lesion

Obtain blood culture and start empirical antimicrobial therapy

Imaging: Head CT or MRI (preferred)

Mass lesion

No mass lesion

No

Meningitis

Papilledema and/or focal neurologic deficit? Immunocompromised?

History of recent head trauma, known cancer, sinusitis?

Yes

No
Mass lesion
  ➔ Abscess or tumor
    ➔ Appropriate medical and/or surgical interventions

No mass lesion
  ➔ Focal or generalized gray matter abnormalities or normal
    ➔ Encephalitis
      ➔ Pleocytosis with PMNs
         ➔ Elevated protein
         ➔ Decreased glucose
         ➔ Gram’s stain positive
          ➔ Bacterial process

  ➔ White matter abnormalities
    ➔ ADEM
      ➔ Immediate blood culture and lumbar puncture

  ➔ Pleocytosis with MNCs
    ➔ Normal or increased protein
    ➔ Normal or decreased glucose
    ➔ Gram’s stain negative

Tier 1 Eval (no unusual historic points or exposures):
- Viral: CSF PCR for enterovirus, HSV, VZV
- CSF IgM for WNV
- Viral culture: CSF, throat, stool
- If skin lesions DFA for HSV, VZV
- HIV serology
- Serology for enteroviruses and arthropod-borne viruses
- Fungal: CSF cryptococcal Ag, fungal cultures
- Bacterial: VDRL and bacterial culture
- Mycobacterial: CSF AFB stain and TB PCR, TB culture, CXR, PPD
Tier 2 Evaluation (if above negative):  
- EBV: Serum serology, CSF PCR  
- Mycoplasma: Serum serology, CSF PCR  
- Influenza A, B: Serology, respiratory culture, CSF PCR  
- Adenovirus: Serology, throat swab. CSF PCR  
- Fungal: CSF & serum coccidioidal antibody, *Histoplasma* antigen & antibody

Tier 3 Evaluation (based on epidemiology):

- Mosquito or tick exposure:
  - CTFV  
  - Arbovirus  
  - Rickettsial  
  - *Borrelia*  
  - *Ehrlichia*
- Recent exanthemal illness:
  - Measles  
  - Rubella  
  - HHV-6
- Diarrhea (infant/child):
  - Rotavirus
- Hepatitis
  - Hepatitis C
In addition to the classic findings, a number of other manifestations, both neurologic and nonneurologic, can occur in patients with bacterial meningitis.

**Neurologic complications**
- seizures,
- focal neurologic deficits (including cranial nerve palsies), papilledema

Hearing loss is a late complication.
**Arthritis** occurs in some patients with bacterial meningitis. In a case series of 696 episodes of community-acquired bacterial meningitis, arthritis was diagnosed in 48 (7 percent) of the episodes, with *N. meningitidis* the etiologic agent in two-thirds of these joint infections.

Patients with *Listeria meningitis* have an increased tendency to have seizures and focal neurologic deficits early in the course of infection, and some patients may present with a syndrome of rhombencephalitis (manifested as ataxia, cranial nerve palsies, and/or nystagmus).
MENAGEMENT & DIAGNOSIS

(1) Empirical therapy!!!Urgent
(2) CT or MRI
(3) lumbar puncture (LP)
Indications of CT

CT scan of the head before LP should be performed in adult patients with:

- Immunocompromised state (e.g., HIV infection, immunosuppressive therapy, solid organ or hematopoietic stem cell transplantation)
- History of CNS disease (mass lesion, stroke, or focal infection)
- New onset seizure (within one week of presentation)
- Papilledema
- Abnormal level of consciousness
- Focal neurologic deficit

Based upon Infectious Diseases Society of America (IDSA) guidelines
Although there are no absolute contraindications to performing the procedure, caution should be used in patients with:

- Possible raised intracranial pressure
- Thrombocytopenia or other bleeding diathesis (including ongoing anticoagulant therapy)
- Suspected spinal epidural abscess
COMPLICATIONS of LP

- Post-LP headache
- Infection
- Bleeding
- Cerebral herniation
- Minor neurologic symptoms such as radicular pain or numbness
- Late onset of epidermoid tumors of the thecal sac
- Back pain
<table>
<thead>
<tr>
<th>CEREBROSPINAL FLUID (CSF) ABNORMALITIES IN BACTERIAL MENINGITIS</th>
</tr>
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<tbody>
<tr>
<td>Opening pressure</td>
</tr>
<tr>
<td>White blood cells</td>
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<tr>
<td>Red blood cells</td>
</tr>
<tr>
<td>Glucose</td>
</tr>
<tr>
<td>CSF-serum glucose</td>
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<tr>
<td>Protein</td>
</tr>
<tr>
<td>Gram’s stain</td>
</tr>
<tr>
<td>Culture</td>
</tr>
<tr>
<td>Latex agglutination</td>
</tr>
<tr>
<td>Limulus lysate</td>
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<tr>
<td>PCR</td>
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</tbody>
</table>

*Note: PCR, polymerase chain reaction.*
**Streptococcus pneumoniae in cerebrospinal fluid**

Gram stain of cerebrospinal fluid (x1000) shows inflammatory cells and gram-positive diplococci. *Streptococcus pneumoniae* grew from this specimen.

*Courtesy of Harriet Provine.*
Neisseria meningitidis in cerebrospinal fluid

Gram stain of cerebrospinal fluid (×1000) shows inflammatory cells and kidney-shaped, gram-negative diplococci (arrows). Neisseria meningitidis grew from this specimen. 

Courtesy of Harriet Provine.
Haemophilus influenzae in cerebrospinal fluid

Gram stain of cerebrospinal fluid (x1000) shows inflammatory cells and small, pleomorphic, gram-negative coccobacilli. *Haemophilus influenzae* grew from this specimen.

*Courtesy of Harriet Provine.*
Gram stain of cerebrospinal fluid (x1000) shows inflammatory cells and small, gram-positive rods and coccobacilli. Culture of this specimen revealed moderate sized, beta-hemolytic colonies composed of small, motile gram-positive rods, confirmed to be Listeria monocytogenes.

Courtesy of Harriet Provine.
Listeria monocytogenes on blood agar

The clear areas around each colony of *Listeria monocytogenes* are characteristic small zones of beta-hemolysis.

*Courtesy of Harriet Provine.*
<table>
<thead>
<tr>
<th>Glucose (mg/dL)</th>
<th>Protein (mg/dL)</th>
<th>Total white blood cell count (cells/microL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10*</td>
<td>&gt;250Δ</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>10 to 45*</td>
<td>50 to 250</td>
<td>100 to 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 to 100</td>
</tr>
</tbody>
</table>

**More common**
- Bacterial meningitis
- Bacterial meningitis
- Bacterial meningitis
- Viral meningitis
- Nervous system Lyme disease (neuroborreliosis)
- Neurosyphilis
- Bacterial meningitis
- Bacterial or viral meningitis
- TB meningitis
- Early bacterial meningitis
- Viral meningitis
- Neurosyphilis
- TB meningitis

**Less common**
- TB meningitis
- Fungal meningitis
- Neurosyphilis
- Some viral infections (such as mumps and LCMV)
- TB meningitis
- Some cases of mumps and LCMV
- Encephalitis
- Encephalitis

LCMV: lymphocytic choriomeningitis virus; TB: tuberculosis.
* <0.6 mmol/L.
• 0.6 to 2.5 mmol/L.
Δ >2.5 g/L.
◊ 0.5 to 2.5 g/L.
If possible, crucial historical information (eg, serious drug allergies, recent exposure to an individual with meningitis) should be obtained before antibiotic treatment of presumed bacterial meningitis is instituted.

Initial blood tests should include a complete blood count with differential and two sets of blood cultures. The initial approach to management in a patient with suspected bacterial meningitis includes performance of a lumbar puncture (LP) to determine whether the cerebrospinal fluid (CSF) findings are consistent with the diagnosis.

There are three general requirements of antimicrobial therapy for bacterial meningitis: use of bactericidal drugs effective against the infecting organism, use of drugs that enter the CSF, and use of drugs with optimal pharmacodynamics.
Adjunctive **dexamethasone** should be given shortly before or at the same time as the first dose of antibiotics, when indicated.

For adults in the developed world with suspected bacterial meningitis in whom the organism is unknown or *Streptococcus pneumoniae* is confirmed, administration of dexamethasone is recommended.

**Dexamethasone should be continued if the CSF Gram stain and/or the CSF or blood cultures reveal** *S. pneumoniae*. Rifampin is added to the regimen in patients receiving dexamethasone under certain circumstances.
Once the CSF Gram stain results are available, the antimicrobial regimen should be tailored to cover the most likely pathogen.

If the CSF findings are consistent with the diagnosis of acute bacterial meningitis but the Gram stain is negative, empiric antibiotic therapy should be continued.

The antibiotic regimen should be modified further, when indicated, based on the CSF culture and susceptibility results.
### Antibiotics Used in Empirical Therapy of Bacterial Meningitis and Focal CNS Infections

<table>
<thead>
<tr>
<th>Indication</th>
<th>Antibiotic</th>
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<tbody>
<tr>
<td>Preterm infants to infants &lt;1 month</td>
<td>Ampicillin + cefotaxime</td>
</tr>
<tr>
<td>Infants 1–3 mos</td>
<td>Ampicillin + cefotaxime or ceftriaxone</td>
</tr>
<tr>
<td>Immunocompetent children &gt;3 mos and adults &lt;55</td>
<td>Cefotaxime or ceftriaxone + vancomycin</td>
</tr>
<tr>
<td>Adults &gt;55 and adults of any age with alcoholism or other debilitating illnesses</td>
<td>Ampicillin + cefotaxime or ceftriaxone + vancomycin</td>
</tr>
<tr>
<td>Hospital-acquired meningitis, posttraumatic or postneurosurgery meningitis, neutropenic patients, or patients with impaired cell-mediated immunity</td>
<td>Ampicillin + ceftazidime + vancomycin</td>
</tr>
</tbody>
</table>
ACUTE VIRAL MENINGITIS

• Patients with viral meningitis usually present with headache, fever, and signs of meningeal irritation coupled with an inflammatory CSF profile.

• The headache of viral meningitis is usually frontal or retroorbital and is often associated with photophobia and pain on moving the eyes.

• Nuchal rigidity is present in most cases but may be mild and present only near the limit of neck anteflexion. Constitutional signs can include malaise, myalgia, anorexia, nausea and vomiting, abdominal pain, and/or diarrhea.

• Patients often have mild lethargy or drowsiness; however, profound alterations in consciousness, such as stupor, coma, or marked confusion, are unusual in viral meningitis and suggest the presence of encephalitis or other alternative diagnoses.
Seizures or focal neurologic signs or symptoms or neuroimaging abnormalities indicative of brain parenchymal involvement are not typical of viral meningitis and suggest the presence of encephalitis or another CNS infectious or inflammatory process.
## Viral Etiology

### Acute Meningitis

**Common**
- Enteroviruses (coxsackieviruses, echoviruses, and human enteroviruses 68–71)
- Herpes simplex virus 2
- Arthropod-borne viruses
- HIV

**Less Common**
- Varicella-zoster virus
- Epstein-Barr virus
- Lymphocytic choriomeningitis virus

### Acute Encephalitis

**Common**
- Herpesviruses
  - Herpes simplex virus 1
  - Varicella-zoster virus
  - Epstein-Barr virus
- Arthropod-borne viruses
  - La Crosse virus
  - West Nile virus
  - St. Louis encephalitis virus

**Less Common**
- Rabies
- Eastern equine encephalitis virus
- Western equine encephalitis virus
- Powassan virus
- Cytomegalovirus\(^a\)
- Enteroviruses\(^a\)
- Colorado tick fever
- Mumps

\(^a\)Immunocompromised host.
SUBACUTE MENINGITIS

M. tuberculosis,
C. neoformans
H. capsulatum
C. İmmitis
T. pallidum
The classic CSF abnormalities in tuberculous meningitis are as follows:

(1) elevated opening pressure
(2) Lymphocytic pleocytosis (10–500 cells/µL)
(3) Elevated protein concentration in the range of 1–5 g/L (10–500 mg/dL)
(4) Decreased glucose concentration in the range of 1.1–2.2 mmol/L (20–40 mg/dL).

The combination of unrelenting headache, stiff neck, fatigue, night sweats, and fever with a CSF lymphocytic pleocytosis and a mildly decreased glucose concentration is highly suspicious for tuberculous meningitis.
Progressive multifocal leukoencephalopathy (PML)

Progressive disorder characterized pathologically by multifocal areas of demyelination of varying size distributed throughout the brain but sparing the spinal cord and optic nerves.

In addition to demyelination, there are characteristic cytologic alterations in both astrocytes and oligodendrocytes.

Astrocytes are enlarged and contain hyperchromatic, deformed, and bizarre nuclei and frequent mitotic figures. Oligodendrocytes have enlarged, densely staining nuclei that contain viral inclusions formed by crystalline arrays of JC virus (JCV) particles.

Patients often present with visual deficits (45%), typically a homonymous hemianopia; mental impairment (38%) (dementia, confusion, personality change); weakness, including hemi- or monoparesis; and ataxia.

Seizures occur in ~20% of patients, predominantly in those with lesions abutting the cortex.
Almost all patients have an underlying immunosuppressive disorder. In recent series, the most common associated conditions were AIDS (80%), hematologic malignancies (13%), transplant recipients (5%), and chronic inflammatory diseases (2%).
SSPE is a rare chronic, progressive demyelinating disease of the CNS associated with a chronic nonpermissive infection of brain tissue with measles virus.

The incidence has declined dramatically since the introduction of a measles vaccine.

Most patients give a history of primary measles infection at an early age (2 years), which is followed after a latent interval of 6–8 years by the development of progressive neurologic disorder.

Some 85% of patients are between 5 and 15 years old at diagnosis.

Initial manifestations include poor school performance and mood and personality changes.
A brain abscess is a focal, suppurative infection within the brain parenchyma, typically surrounded by a vascularized capsule.

The term cerebritis is often employed to describe a nonencapsulated brain abscess.
**FIGURE 29-4**
Pneumococcal brain abscess. Note that the abscess wall has hyperintense signal on the axial T1-weighted MRI (A, black arrow), hypointense signal on the axial proton density images (B, black arrow), and enhances prominently after gadolinium administration on the coronal T1-weighted image (C). The abscess is surrounded by a large amount of vasogenic edema and has a small “daughter” abscess (C, white arrow). (Courtesy of Joseph Lurito, MD; with permission.)
Predisposing conditions

Otitis media
Mastoiditis
Paranasal sinusitis
Pyogenic infections in the chest or other body sites
Penetrating head trauma
Neurosurgical procedures, Dental infections.
Etiologic agents

In immunocompetent host
- **Streptococcus spp.** [anaerobic, aerobic, and viridans (40%)], **Enterobacteriaceae** [Proteus spp., E. coli sp., Klebsiella spp. (25%)], **Anaerobes** [e.g., Bacteroides spp., Fusobacterium spp. (30%)], and **Staphylococci** (10%).

In immunocompromised hosts
- Nocardia spp., **Toxoplasma gondii**, Aspergillus spp., Candida spp., and **C. neoformans**.

In Latin America, the most common cause of brain abscess is Taenia solium (neurocysticercosis).

In India and the Far East, mycobacterial infection (tuberculoma) remains a major cause of focal CNS mass lesions.
SUBDURAL EMPYEMA

FIGURE 29-5
Subdural empyema.
**FIGURE 29-6**

Subdural empyema. There is marked enhancement of the dura and leptomeninges (A, B, straight arrows) along the left medial hemisphere. The pus is hypointense on T1-weighted images (A, B) but markedly hyperintense on the proton density-weighted (C, curved arrow) image. (Courtesy of Joseph Lurito, MD; with permission.)
FIGURE 29-7
Cranial epidural abscess is a collection of pus between the dura and the inner table of the skull.
Suppurative intracranial thrombophlebitis is **septic venous thrombosis of cortical veins and sinuses**.

This may occur as a **complication of bacterial meningitis; SDE; epidural abscess; or infection in the skin of the face, paranasal sinuses, middle ear, or mastoid.**
Chronic inflammation of the meninges (pia, arachnoid, and dura) can produce profound neurologic disability and may be fatal if not successfully treated.

The condition is most commonly diagnosed when a characteristic neurologic syndrome exists for >4 weeks and is associated with a persistent inflammatory response in the cerebrospinal fluid (CSF) (white blood cell count >5/µL).

Five categories of disease account for most cases of chronic meningitis:
(1) meningeal infections,
(2) malignancy,
(3) noninfectious inflammatory disorders,
(4) chemical meningitis,
(5) parameningeal infections.
# Infectious Causes of Chronic Meningitis

<table>
<thead>
<tr>
<th>CAUSATIVE AGENT</th>
<th>CSF FORMULA</th>
<th>HELPFUL DIAGNOSTIC TESTS</th>
<th>RISK FACTORS AND SYSTEMIC MANIFESTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partially treated suppurative meningitis</td>
<td>Mononuclear or mixed mononuclear-</td>
<td>CSF culture and Gram’s stain</td>
<td>History consistent with acute bacterial meningitis and incomplete treatment</td>
</tr>
<tr>
<td>Parameningeal infection</td>
<td>polymorphonuclear cells</td>
<td>Contrast-enhanced CT or MRI to detect parenchymal, subdural, epidural, or sinus infection</td>
<td>Otitis media, pleuropulmonary infection, right-to-left cardiopulmonary shunt for brain abscess; focal neurologic signs; neck, back, ear, or sinus tenderness</td>
</tr>
<tr>
<td><strong>Mycobacterium tuberculosis</strong></td>
<td>Mononuclear cells except polymorphonuclear cells in early infection (commonly &lt;500 WBC/µL); low CSF glucose, high protein</td>
<td>Tuberculin skin test may be negative; AFB culture of CSF (sputum, urine, gastric contents if indicated); tuberculostearic acid detection in CSF; identify tubercle bacillus on acid-fast stain of CSF or protein pellicle; PCR</td>
<td>Exposure history; previous tuberculous illness; immuno-suppressed or AIDS; young children; fever, meningismus, night sweats, miliary TB on x-ray or liver biopsy; stroke due to arteritis</td>
</tr>
<tr>
<td>Lyme disease (Bannwarth’s syndrome)</td>
<td>Mononuclear cells; elevated protein</td>
<td>Serum Lyme antibody titer; Western blot confirmation; patients with syphilis may have false-positive Lyme titer</td>
<td>History of tick bite or appropriate exposure history; erythema chronicum migrans skin rash; arthritis, radiculopathy, Bell’s palsy, meningoencephalitis–multiple sclerosis–like syndrome</td>
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<tr>
<td><em>Borrelia burgdorferi</em></td>
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<tr>
<td>Syphilis (secondary, tertiary)</td>
<td>Mononuclear cells; elevated protein</td>
<td>CSF VDRL; serum VDRL (or RPR); FTA or MHA-TP; serum VDRL may be negative in tertiary syphilis</td>
<td>HIV seropositive individuals at increased risk of aggressive infection; “dementia”; cerebral infarction due to endarteritis</td>
</tr>
<tr>
<td><em>Treponema pallidum</em></td>
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</tbody>
</table>
### Uncommon Bacterial Causes

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Cellular Features</th>
<th>Diagnostic Approaches</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinomyces</td>
<td>Polymorphonuclear cells</td>
<td>Anaerobic culture</td>
<td>Parameningeal abscess or sinus tract (oral or dental focus); pneumonitis</td>
</tr>
<tr>
<td>Nocardia</td>
<td>Polymorphonuclear; occasionally mononuclear cells; often low glucose</td>
<td>Isolation may require weeks; weakly acid fast</td>
<td>Associated brain abscess may be present</td>
</tr>
<tr>
<td><strong>Brucella</strong></td>
<td>Mononuclear cells (rarely polymorphonuclear); elevated protein; often low glucose</td>
<td>CSF antibody detection; serum antibody detection</td>
<td>Intake of unpasteurized dairy products; exposure to goats, sheep, cows; fever, arthralgia, myalgia, vertebral osteomyelitis</td>
</tr>
<tr>
<td>Whipple’s disease</td>
<td>Mononuclear cells</td>
<td>Biopsy of small bowel or lymph node; CSF PCR for <em>T. whippellii</em>; brain and meningeal biopsy (with PAS stain and EM examination)</td>
<td>Diarrhea, weight loss, arthralgias, fever, dementia, ataxia, paresis, ophthalmoplegia, oculomasticatory myoclonus</td>
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</tbody>
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### Rare Bacterial Causes

Leptospirosis (occasionally if left untreated may last 3–4 weeks)
## Infectious Causes of Chronic Meningitis

<table>
<thead>
<tr>
<th>Causative Agent</th>
<th>CSF Formula</th>
<th>Helpful Diagnostic Tests</th>
<th>Risk Factors and Systemic Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fungal Causes</strong></td>
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<tr>
<td>Cryptococcus neoformans</td>
<td>Mononuclear cells; count not elevated in some patients with AIDS</td>
<td>India ink or fungal wet mount of CSF (budding yeast); blood and urine cultures; antigen detection in CSF</td>
<td>AIDS and immune suppression; pigeon exposure; skin and other organ involvement due to disseminated infection</td>
</tr>
<tr>
<td>Coccidioides immitis</td>
<td>Mononuclear cells (sometimes 10–20% eosinophils); often low glucose</td>
<td>Antibody detection in CSF and serum</td>
<td>Exposure history—southwestern United States; increased virulence in dark-skinned races</td>
</tr>
<tr>
<td>Candida sp.</td>
<td>Polymorphonuclear or mononuclear</td>
<td>Fungal stain and culture of CSF</td>
<td>IV drug abuse; post surgery; prolonged intravenous therapy; disseminated candidiasis</td>
</tr>
<tr>
<td>Histoplasma capsulatum</td>
<td>Mononuclear cells; low glucose</td>
<td>Fungal stain and culture of large volumes of CSF; antigen detection in CSF, serum, and urine; antibody detection in serum, CSF</td>
<td>Exposure history—Ohio and central Mississippi River Valley; AIDS; mucosal lesions</td>
</tr>
<tr>
<td>Blastomyces dermatitidis</td>
<td>Mononuclear cells</td>
<td>Fungal stain and culture of CSF; biopsy and culture of skin, lung lesions; antibody detection in serum</td>
<td>Midwestern and southeastern United States; usually systemic infection; abscesses, draining sinuses, ulcers</td>
</tr>
<tr>
<td>Aspergillus sp.</td>
<td>Mononuclear or polymorphonuclear</td>
<td>CSF culture</td>
<td>Sinusitis; granulocytopenia or immunosuppression</td>
</tr>
<tr>
<td>Sporothrix schenckii</td>
<td>Mononuclear cells</td>
<td>Antibody detection in CSF and serum; CSF culture</td>
<td>Traumatic inoculation; IV drug use; ulcerated skin lesion</td>
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<tr>
<td><strong>Rare Fungal Causes</strong></td>
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<td>Xylohypha (formerly Cladosporium) trichoides and other dark-walled (dematiaceous) fungi such as Curvularia, Drechslera; Mucor, Pseudoallescheria boydii</td>
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<td><strong>Protozoal Causes</strong></td>
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<td>Toxoplasma gondii</td>
<td>Mononuclear cells</td>
<td>Biopsy or response to empirical therapy in clinically appropriate context (including presence of antibody in serum)</td>
<td>Usually with intracerebral abscesses; common in HIV seropositive patients</td>
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<tr>
<td>Trypanosomiasis Trypanosoma gambiense, T. rhodesiense</td>
<td>Mononuclear cells, elevated protein</td>
<td>Elevated CSF IgM; identification of trypanosomes in CSF and blood smear</td>
<td>Endemic in Africa; chancre, lymphadenopathy; prominent sleep disorder</td>
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<tr>
<td><strong>Rare Protozoal Causes</strong></td>
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<td>Acanthamoeba sp. causing granulomatous amebic encephalitis and meningoencephalitis in immunocompromised and debilitated individuals</td>
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<tr>
<td><strong>Helminthic Causes</strong></td>
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<td>Cysticercosis (infection with cysts of Taenia solium)</td>
<td>Mononuclear cells; may have eosinophils; glucose level may be low</td>
<td>Indirect hemagglutination assay in CSF; ELISA immunoblotting in serum</td>
<td>Usually with multiple cysts in basal meninges and hydrocephalus; cerebral cysts, muscle calcification</td>
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### Infectious Causes of Chronic Meningitis

#### Causative Agent | CSF Formula | Helpful Diagnostic Tests | Risk Factors and Systemic Manifestations
--- | --- | --- | ---
**Helminthic Causes (Continued)**
- *Gnathostoma spinigerum*  
  Eosinophils, mononuclear cells  
  Peripheral eosinophilia  
  History of eating raw fish; common in Thailand and Japan; subarachnoid hemorrhage; painful radiculopathy
- *Angiostrongylus cantonensis*  
  Eosinophils, mononuclear cells  
  Recovery of worms from CSF  
  History of eating raw shellfish; common in tropical Pacific regions; often benign
- *Baylisascaris procyonis*  
  (raccoon ascarid)  
  Eosinophils, mononuclear cells  
  Infection follows accidental ingestion of *B. procyonis* eggs from raccoon feces; fatal meningoencephalitis

#### Rare Helminthic Causes

*Trichinella spiralis* (trichinosis); *Echinococcus* cysts; *Schistosoma* sp. The former may produce a lymphocytic pleocytosis whereas the latter two may produce an eosinophilic response in CSF associated with cerebral cysts (*Echinococcus*) or granulomatous lesions of brain or spinal cord.

#### Viral Causes

- **Mumps**  
  Mononuclear cells  
  Antibody in serum  
  No prior mumps or immunization; may produce meningoencephalitis; may persist for 3–4 weeks
- **Lymphocytic choriomeningitis**  
  Mononuclear cells  
  Antibody in serum  
  Contact with rodents or their excreta; may persist for 3–4 weeks
- **Echovirus**  
  Mononuclear cells; may have low glucose  
  Virus isolation from CSF  
  Congenital hypogammaglobulinemia; history of recurrent meningitis
- **HIV (acute retroviral syndrome)**  
  Mononuclear cells  
  p24 antigen in serum and CSF; high level of HIV viremia  
  HIV risk factors; rash, fever, lymphadenopathy; lymphopenia in peripheral blood; syndrome may persist long enough to be considered as “chronic meningitis”; or chronic meningitis may develop in later stages (AIDS) due to HIV
- **Herpes simplex (HSV)**  
  Mononuclear cells  
  PCR for HSV, CMV DNA; CSF antibody for HSV, EBV  
  Recurrent meningitis due to HSV-2 (rarely HSV-1) often associated with genital recurrences; EBV associated with myeloradiculopathy, CMV with polyradiculopathy