

## Empiric Therapy of CNS Infections

### Acute Bacterial Meningitis (ABM)

Subset	Usual Pathogens	Preferred IV Therapy	Alternate IV Therapy	IV-to-PO Switch
Normal host	N. meningitidis H. influenzae S. pneumoniae	Ceftriaxone 2 gm (IV) q12h x 2 weeks	Cefotaxime 3 gm (IV) q6h x 2 weeks  or Ceftizoxime 3 gm (IV) q6h x 2 weeks	Chloramphenicol 500 mg (PO) q6h x 2 weeks
Elderly or malignancy	Listeria monocytogenes plus usual meningial pathogens in normal hosts	<u>Before culture results</u> Ceftriaxone 2 gm (IV) q12h x 2 weeks  <b>plus</b> Ampicillin 2 gm (IV) q4h x 2 weeks  <u>After culture results</u> <u>Listeria present</u> Ampicillin 2 gm (IV) q4h x 2 weeks  <u>Listeria not present</u> Treat as normal host	<u>After culture results</u> <u>Listeria present</u> TMP-SMX 5 mg/kg (IV) q6h x 2 weeks  <b>or</b> Chloramphenicol 500 mg (IV) q6h x 2 weeks  <u>Listeria not present</u> Treat as for normal host, above	<u>For Listeria meningitis only</u> TMP-SMX 5 mg/kg (PO) q6h x 2 weeks  <b>or</b> Chloramphenicol 500 mg (PO) q6h x 2 weeks  <u>For usual meningial pathogens</u> Chloramphenicol 500 mg (PO) q6h x 2 weeks
CNS shunt infections (VA shunts)  (Treat initially for MSSA; if later identified as MSRA, MSSE, or MSRE, treat accordingly)	S. aureus S. epidermidis (coagulase-negative staphylococci)	<u>MSSA/MSSE</u> Cefotaxime 3 gm (IV) q6h x 1 week after shunt removal  <b>or</b> Ceftizoxime 3 gm (IV) q6h x 1 week after shunt removal  <u>MRSA/MRSE</u> Linezolid 600 mg (IV) q12h x 1 week after shunt removal	<u>MSSA/MSSE</u> Cefepime 2 gm (IV) q8h x 1 week after shunt removal  <b>or</b> Meropenem 2 gm (IV) q8h x 1 week after shunt removal  <u>MRSA/MRSE</u> Vancomycin 1 gm (IV) q12h x 1 week after shunt removal plus 20 mg (IT) q24h until shunt removal	<u>MSSE/MRSE</u> Linezolid 600 mg (PO) q12h x 1 week after shunt removal  <u>MSSA/MRSA</u> Minocycline 100 mg (PO) q12h x 1 week after shunt removal  <b>or</b> Linezolid 600 mg (PO) q12h x 1 week after shunt removal

**Acute Bacterial Meningitis (ABM) (cont'd)**

Subset	Usual Pathogens	Preferred IV Therapy	Alternate IV Therapy	IV-to-PO Switch
CNS shunt infections (VP shunts)	E. coli K. pneumoniae Enterobacter S. marcescens	Cefotaxime 3 gm (IV) q6h x 2 weeks after shunt removal  or Ceftizoxime 3 gm (IV) q6h x 2 weeks after shunt removal	Ceftriaxone 2 gm (IV) q12h x 2 weeks after shunt removal  or TMP-SMX 5 mg/kg (IV) q6h x 2 weeks after shunt removal	TMP-SMX 5 mg/kg (PO) q6h x 2 weeks after shunt removal

MSSA/MRSA = methicillin-sensitive/resistant *S. aureus*; MSSE/MRSE = methicillin-sensitive/resistant *S. epidermidis*.  
Duration of therapy represents total time IV or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement

**Clinical Presentation:** Abrupt onset of fever, headache, stiff neck

**Diagnosis:** CSF gram stain/culture

**Acute Bacterial Meningitis (Normal Hosts)**

**Diagnostic Considerations:** Gram stain of centrifugated CSF is still the best diagnostic test. CSF antigen/CIE are unhelpful in establishing the diagnosis (many false-negatives). Blood cultures are positive for ABM pathogen in 80-90%. Typical CSF findings include a WBC count of 100-5000 cells/mm<sup>3</sup>, elevated opening pressure, elevated protein and lactic acid levels (> 4-6 mmol/L), and a positive CSF gram stain. If the WBC is extremely high (> 20,000 cells/mm<sup>3</sup>), suspect brain abscess with rupture into the ventricular system, and obtain a CT/MRI to confirm. *S. pneumoniae* meningitis is associated with cranial nerves abnormalities, mental status changes, and neurologic sequelae. With *H. influenzae* or *S. pneumoniae* meningitis, obtain a head CT/MRI to rule out other CNS pathology

**Pitfalls:** If ABM is suspected, always perform lumbar puncture (LP) before obtaining a CT scan, since early antibiotic therapy is critical to prognosis. A CT/MRI should be obtained before LP *only* if a mass lesion/suppurative intracranial process is of primary concern, after blood cultures have been drawn. A stiff neck on physical examination has limited diagnostic value in the elderly, since nuchal rigidity may occur without meningitis (e.g., cervical arthritis) and meningitis may occur without nuchal rigidity. Recurrence of fever during the first week of *H. influenzae* meningitis is commonly due to subdural effusion, which usually resolves spontaneously over several days. Meningococcal meningitis may occur with or without meningococemia. On gram stain, *S. pneumoniae* may be mistaken for *H. influenzae*, and *Listeria* may be mistaken for *S. pneumoniae*

**Therapeutic Considerations:** Do not reduce meningeal antibiotic dosing as the patient improves. Repeat LP only if the patient is not responding to antibiotics after 48 hours; lack of response may be due to therapeutic failure, relapse, or a non-infectious CNS disorder. For *S. pneumoniae* meningitis, obtain penicillin MICs on all CSF isolates; nearly all penicillin-resistant strains have relatively low MICs (2-5 mcg/mL) and are susceptible to meningeal doses of beta-lactam antibiotics (e.g., ceftriaxone). All but the most highly penicillin-resistant pneumococci are still effectively treated with meningeal doses of beta-lactams. Highly resistant pneumococcal strains (rare in the CSF) may be treated for 2 weeks with meropenem 2 gm (IV) q8h, cefepime 2 gm (IV) q8h, linezolid 600 mg (IV) q12h, or vancomycin (IV/IT). Dexamethasone 0.15 mg/kg (IV) q6h x 4 days may be given to children with ABM to reduce the incidence/severity of neurologic sequelae, although the value of steroids in adult ABM is unclear; if used, give dexamethasone 30 minutes before the initial antibiotic dose

**Prognosis:** Uniformly fatal without treatment. Case-fatality rates in treated adults are 10-20%. Neurological deficits on presentation are associated with a poor prognosis. Permanent neurological

deficits are more frequent with *S. pneumoniae* than *H. influenzae*, even with prompt therapy. In meningococcal meningitis with meningococemia, prognosis is related to the number of petechiae, with few or no neurological deficits in survivors

**Acute Bacterial Meningitis (Elderly Patients/Malignancy)**

**Diagnostic Considerations:** Diagnosis by CSF gram stain/culture. ABM pathogens include usual pathogens in normal hosts plus *Listeria monocytogenes*, a gram-positive, aerobic, bacillus. *Listeria* is the most common ABM pathogen in patients with malignancies, and is a common pathogen in the elderly. With *Listeria* meningitis, CSF cultures are positive in 100%, but CSF gram stain is negative in 50%. Meningeal carcinomatosis is suggested by multiple cranial nerve abnormalities

**Pitfalls:** "Diphtheroids" isolated from CSF should be speciated to rule out *Listeria*. *Listeria* are motile and hemolytic on blood agar plate, diphtheroids are not

**Therapeutic Considerations:** Elderly patients and cancer patients with ABM require empiric coverage of *Listeria* plus other common pathogens in normal hosts (*N. meningitidis*, *H. influenzae*, *S. pneumoniae*). Specific monotherapy can be administered once the organism is known. Third-generation cephalosporins are not active against *Listeria*

**Prognosis:** Related to underlying health of host

**Acute Bacterial Meningitis (CNS Shunt Infections)**

**Diagnostic Considerations:** Diagnosis by CSF gram stain/culture. *S. epidermidis* meningitis usually occurs only with infected prosthetic implant material (e.g., CNS shunt/plate)

**Pitfalls:** Blood cultures are usually negative for shunt pathogens

**Therapeutic Considerations:** 15% of *S. epidermidis* strains are resistant to nafcillin/clindamycin. In addition to systemic antibiotics in meningeal doses, adjunctive intraventricular/intrathecal antibiotics are sometimes given to control shunt infections before shunt removal

**Prognosis:** Good if prosthetic material is removed

**Acute Non-Bacterial Meningitis/Chronic Meningitis**

Subset	Usual Pathogens	IV Therapy	IV-to-PO Switch
Viral (aseptic)	EBV VZV LCM Enteroviruses WNE	Not applicable	Not applicable
	HSV-1 HSV-2	Acyclovir 10 mg/kg (IV) q8h x 14-21 days	Acyclovir 400 mg (PO) 5x/day x 14-21 days <b>or</b> Valacyclovir 500 mg (PO) q8h x 14-21 days <b>or</b> Famciclovir 500 mg (PO) q8h x 14-21 days
Primary amebic meningo-encephalitis (PAM)	<i>Naegleria fowleri</i>	Amphotericin B 1 mg/kg (IV) q24h until cured <b>plus</b> Amphotericin B 1 mg into ventricles via Ommaya reservoir q24h until cured	Not applicable

**Acute Non-Bacterial Meningitis/Chronic Meningitis (cont'd)**

Subset	Usual Pathogens	Preferred IV Therapy	Alternate IV Therapy	PO Therapy or IV-to-PO Switch
Granulomatous amebic meningoencephalitis	Acanthamoeba	No proven treatment*		
TB	M. tuberculosis	IV Therapy Not applicable	PO Therapy INH 300 mg (PO) q24h x 6-9 months <b>plus</b> Rifampin 600 mg (PO) q24h x 6-9 months  If multiresistant TB strain likely, also add: EMB 15 mg/kg (PO) q24h x 6-9 months <b>plus</b> PZA 25 mg/kg (PO) q24h x 6-9 months	
Fungal Non-HIV	Cryptococcus neoformans	Amphotericin B 1 mg/kg (IV) q24h x 6 weeks <b>plus</b> 5-FC 1 mg/kg (PO) q6h x 6 weeks, <b>followed by</b> Fluconazole 800 mg (IV or PO) x 1 dose, then 400 mg (PO) q24h x 10 weeks	Amphotericin B lipid formulation 5 mg/kg (IV) q24h x 6 weeks, then 3x/week x 4 weeks <b>plus</b> Fluconazole 800 mg (IV or PO) x 1 dose, then 400 mg (PO) q24h x 10 weeks	PO therapy alone Not applicable
HIV	Cryptococcus neoformans	See p. 217		
Chronic meningitis	M. tuberculosis, Brucella, Leptospirosis, Listeria, T. pallidum, Cryptococcus, Coccidioidomycosis, Histoplasmosis, Toxoplasmosis, Toxocariasis, CMV, Neurocysticercosis, Neuroborreliosis, Enteroviruses	Treat specific pathogen after confirming diagnosis. Do not treat empirically		

*Duration of therapy represents total time PO (for TB), IV, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement*

\* Amphotericin B, fluconazole, ketoconazole, itraconazole, flucytosine, rifampin, isoniazid, aminoglycosides, sulfonamides, pentamidine mostly with little success. Success reported in transplant recipient with IV pentamidine followed by itraconazole, and in AIDS patient with ketoconazole plus flucytosine

**Viral (Aseptic) Meningitis**

**Clinical Presentation:** Headache, low-grade fever, mild meningismus, photophobia

**Diagnostic Considerations:** Diagnosis by specific serological tests/viral culture. HSV-2 genital infections are often accompanied by mild CNS symptoms, which usually do not require anti-viral therapy. HSV-1 causes a variety of CNS infections, including meningitis, meningoencephalitis, and

encephalitis (most common; see pp. 22-23). HSV meningitis is indistinguishable clinically from other causes of viral meningitis. EBV meningitis is usually associated with clinical/laboratory features of EBV infectious mononucleosis; suspect the diagnosis in a patient with a positive monospot and unexplained meningoencephalitis. VZV meningitis is typically associated with cutaneous vesicular lesions (H. zoster), and usually does not require additional therapy beyond that given for shingles. LCM meningitis begins as a "flu-like" illness usually in the fall after hamster contact, and may have low CSF glucose. Enterovirus meningitis is often associated with a maculopapular rash, non-exudative pharyngitis, diarrhea, and rarely low CSF glucose

**Pitfalls:** Consider NSAIDs and IV immunoglobulin as non-infectious causes of aseptic meningitis

**Therapeutic Considerations:** Treat specific pathogen

**Prognosis:** Without neurological deficits, full recovery is the rule

### **Primary Amebic Meningoencephalitis (PAM) (Naegleria fowleri)**

**Clinical Presentation:** Acquired by freshwater exposure containing the protozoa, often by jumping into a lake/pool. Affects healthy children/young adults. Organism penetrates cribriform plate and enters CSF. Symptoms occur within 7 days of exposure and are indistinguishable from fulminant bacterial meningitis, including headache, fever, anorexia, vomiting, signs of meningeal inflammation, altered mental status, coma. May complain of unusual smell/taste sensations early in infection. CSF has RBCs and very low glucose

**Diagnostic Considerations:** Diagnosis by demonstrating organism in CSF. Worldwide distribution. Free-living fresh water amoeba flourish in warmer climates. Key to diagnosis rests on clinical suspicion based on history of freshwater exposure in previous 1-2 weeks

**Pitfalls:** CSF findings resemble bacterial meningitis, but RBCs present

**Therapeutic Considerations:** Often fatal despite early treatment

**Prognosis:** Almost always fatal

### **Granulomatous Amebic Meningoencephalitis (Acanthamoeba)**

**Clinical Presentation:** Insidious onset with focal neurologic deficits ± mental status changes, seizures, fever, headache, hemiparesis, meningismus, ataxia, visual disturbances. May be associated with Acanthamoeba keratoconjunctivitis, skin ulcers, or disseminated disease. Usually seen only in immunocompromised/debilitated patients

**Diagnostic Considerations:** Diagnosis by demonstrating organism in brain biopsy specimen. CT/MRI shows mass lesions. "Stellate cysts" characteristic of Acanthamoeba vs. "round cysts" of Naegleria. Worldwide distribution. Strong association with extended wear of contact lenses

**Pitfalls:** Not associated with freshwater exposure, unlike primary amebic meningoencephalitis (Naegleria fowleri). Resembles subacute/chronic meningitis. No trophozoites in CSF. Skin lesions may be present for months before onset of CNS symptoms

**Therapeutic Considerations:** No proven treatment. Often fatal despite early treatment

**Prognosis:** Usually fatal

### **TB Meningitis (Mycobacterium tuberculosis)**

**Clinical Presentation:** Subacute onset of non-specific symptoms. Fever usually present ± headache, nausea, vomiting. Acute presentation and cranial nerve palsies uncommon

**Diagnostic Considerations:** Diagnosis by CSF AFB smear/culture; PCR of CSF is sensitive/specific. CSF may be normal, but often shows low glucose, increased protein, RBCs, and increased lactic acid. May find characteristic "pellicle" in CSF after 12 hours. Look for TB elsewhere

**Pitfalls:** CSF may have PMN predominance early, before developing typical lymphocytic predominance. Eosinophils in CSF is not a feature of TB, and should suggest another diagnosis

**Therapeutic Considerations:** Dexamethasone 4 mg (IV or PO) q6h x 2-4 weeks is useful to reduce CSF inflammation if given early

**Prognosis:** Poor prognostic factors include delay in treatment, neurologic deficits, or hydrocephalus. Proteinaceous TB exudates may obstruct ventricles and cause hydrocephalus, which

is diagnosed by CT/MRI and may require shunt

### **Fungal (Cryptococcal) Meningitis (Cryptococcus neoformans)**

**Clinical Presentation:** Insidious onset of non-specific symptoms. Headache most common. Chronic cases may have CNS symptoms for weeks to months with intervening asymptomatic periods. Acute manifestations are more common in AIDS, chronic steroid therapy, lymphoreticular malignancies. 50-80% of patients are abnormal hosts

**Diagnostic Considerations:** C. neoformans is the most common cause of fungal meningitis, and the only encapsulated yeast in the CSF to cause meningitis. Diagnosis by CSF India ink cryptococcal latex antigen/culture. Rule out HIV and other underlying immunosuppressive diseases

**Pitfalls:** CSF latex antigen titer may not return to zero in HIV/AIDS patients. Continue treatment until titers decline/do not decrease further, and until CSF culture is negative for cryptococci. India ink smears of CSF are useful for initial infection, but should not be relied on to diagnose recurrent episodes, since smears may be positive despite negative CSF cultures (dead cryptococci may remain in CSF for years). Diagnosis of recurrences rests on CSF culture

**Therapeutic Considerations:** Treat until CSF is sterile or initial CSF latex antigen titer is zero or remains near zero on serial lumbar punctures. After patient defervesces on amphotericin B/5FC, switch to oral fluconazole x 10 weeks. Amphotericin B lipid formulations may be used if amphotericin B cannot be tolerated. HIV patients require life-long suppressive therapy with fluconazole 200 mg (PO) q24h

**Prognosis:** Good. Poor prognostic factors include no CSF pleocytosis, many organisms in CSF, and altered consciousness on admission

### **Chronic Meningitis**

**Clinical Presentation:** Same as acute meningitis, but signs/symptoms less prominent and clinical presentation is subacute (> 1 month)

**Diagnostic Considerations:** Differential diagnosis is too broad for empiric treatment. Subacute/chronic clinical presentation allows time for complete diagnostic work-up. Culture CSF and obtain CSF/serum tests to identify a specific pathogen, then treat

**Pitfalls:** If infectious etiology is not found, consider NSAIDs, SLE, meningeal carcinomatosis, sarcoidosis, etc. Chronic CMV or enterococcal meningitis should prompt search for underlying host defense defects/immunosuppression

**Therapeutic Considerations:** If suspicion of TB meningitis is high, empiric anti-TB treatment is warranted. Otherwise, treat only after diagnosing specific infection

**Prognosis:** Related to underlying health of host