

Therapy of Meningitis

Yacoub Irshaid, MD, PhD, ABCP

Department of Pharmacology

Therapy of Meningitis

Goals of treatment:

1. Eradication of infection.
2. Amelioration of signs and symptoms.
3. Prevention of the development of neurologic sequelae, such as **seizures**, **deafness**, **coma**, and **death**.

Therapy of Meningitis

It is important to:

- 1) Prevent the disease through timely introduction of vaccination and chemoprophylaxis.**
 - 2) Understand antibiotic selection and the issues surrounding antibiotic penetration into the central nervous system.**
- Until a pathogen is identified, immediate empirical antibiotic coverage is needed.**

Therapy of Meningitis

- The first dose of antibiotics should **NOT** be withheld, even when lumbar puncture is delayed or neuro-imaging is being performed.
- This is because changes in the CSF after antibiotic administration usually take upto 12 - 24 hours to occur.

Therapy of Meningitis

- Continued therapy should be based on the assessment of clinical improvement, culture, and susceptibility testing results.
- Once a pathogen is identified, antibiotic therapy should be tailored to the specific pathogen.

Etiologies and Empirical Therapy by Age Group

Age	Most Likely Organisms	Empirical Therapy
<1 month	<i>Streptococcus agalactiae</i> Gram-negative enterics (<i>E. coli</i> , <i>Klebsiella spp</i> , <i>Enterobacter spp</i>) <i>Listeria monocytogenes</i>	Ampicillin + cefotaxime <u>or</u> Ampicillin + aminoglycoside
1-23 months	<i>Streptococcus pneumoniae</i> <i>Neisseria meningitidis</i> <i>Haemophilus influenzae</i> <i>Streptococcus agalactiae</i>	Vancomycin + 3rd generation cephalosporin (cefotaxime or ceftriaxone) Vancomycin to cover penicillin-resistant <i>S. pneumoniae</i>
2-50 years	<i>Neisseria meningitidis</i> <i>Streptococcus pneumoniae</i>	Vancomycin + 3rd generation cephalosporin (cefotaxime or ceftriaxone) Vancomycin to cover penicillin-resistant <i>S. pneumoniae</i>
>50 years	<i>Streptococcus pneumoniae</i> <i>Neisseria meningitidis</i> Gram-negative enterics (<i>E. coli</i> , <i>Klebsiella spp</i> , <i>Enterobacter spp</i>) <i>Listeria monocytogenes</i>	Vancomycin + ampicillin + 3rd generation cephalosporin (cefotaxime or ceftriaxone) Vancomycin to cover penicillin-resistant <i>S. pneumoniae</i>

Penetration of Antimicrobial Agents into the CSF

Therapeutic Levels in CSF

With/Without Inflammation:

Acyclovir, Levofloxacin, Linezolid,
Ciprofloxacin, Metronidazole,
Fluconazole, Moxifloxacin,
Flucytosine, Pyrazinamide,
Foscarnet, Rifampin,
Fosfomycin, Sulfonamides,
Ganciclovir, Trimethoprim,
Isoniazid, Voriconazole

Therapeutic Levels in CSF With

Inflammation of Meninges:

Ampicillin ± sulbactam,
Imipenem, Aztreonam,
Meropenem, Cefepime, Nafcillin,
Cefotaxime, Ofloxacin, Ceftazidime,
Penicillin G, Ceftriaxone,
Piperacillin/tazobactam,
Cefuroxime, Pyrimethamine,
Colistin, Quinupristin/dalfopristin,
Daptomycin, Ticarcillin ± clavulanic acid,
Ethambutol, Vancomycin

Penetration of Antimicrobial Agents into the CSF

Non-therapeutic Levels in CSF With or without Inflammation:

- Aminoglycosides
- Amphotericin B
- β -lactamase inhibitors
- First-generation cephalosporins
- Second-generation cephalosporins
- Doxycycline
- Itraconazole

Antimicrobial Agents by Organism

Gram-Positive Organisms:

Streptococcus pneumoniae: duration 10-14 days.

1. Penicillin susceptible:

- Antibiotics of First Choice: Penicillin G or Ampicillin.
- Alternatives: Cefotaxime, Ceftriaxone, Cefepime or Meropenem.

2. Penicillin resistant:

- Antibiotics of First Choice: Vancomycin + Cefotaxime or Ceftriaxone.
- Alternatives: Moxifloxacin.

Antimicrobial Agents by Organism

3. Ceftriaxone resistant:

- **Antibiotics of First Choice: Vancomycin + Cefotaxime or Ceftriaxone.**
- **Alternative: Moxifloxacin.**

***Staphylococcus aureus*: duration 14-21 days.**

1. Methicillin susceptible:

- **Antibiotics of First Choice: Nafcillin or Oxacillin.**
- **Alternative: Vancomycin or Meropenem.**

Antimicrobial Agents by Organism

2. Methicillin resistant:

- Antibiotics of First Choice: Vancomycin.
- Alternative: TMP-SMX or Linezolid.

Group B *Streptococcus*: duration 14-21 days.

- Antibiotics of First Choice: Penicillin G or Ampicillin ± Gentamicin.
- Alternative: Ceftriaxone or Cefotaxime.

***Staph. epidermidis*:** duration 14-21 days.

- Antibiotics of First Choice: Vancomycin.
- Alternative: Linezolid.

Antimicrobial Agents by Organism

***Listeria monocytogenes*: duration \geq 21 days**

- **Antibiotics of First Choice: Penicillin G or Ampicillin \pm Gentamicin.**
- **Alternative: Trimethoprim-sulfamethoxazole, Meropenem.**

Antimicrobial Agents by Organism

Gram-Negative Organisms:

Neisseria meningitidis: duration 7-10 days.

1. Penicillin susceptible:

- Antibiotics of First Choice: Penicillin G or Ampicillin.
- Alternatives: Cefotaxime or Ceftriaxone.

2. Penicillin resistant:

- Antibiotics of First Choice: Cefotaxime or Ceftriaxone.
- Alternatives: Meropenem or Moxifloxacin.

Antimicrobial Agents by Organism

Haemophilus influenzae: duration 7-10 days.

1. β -lactamase negative:

- Antibiotics of First Choice: Ampicillin.
- Alternatives: Cefotaxime, Ceftriaxone, Cefepime or Moxifloxacin.

2. β -lactamase positive:

- Antibiotics of First Choice: Cefotaxime or Ceftriaxone.
- Alternatives: Cefepime or Moxifloxacin.

Antimicrobial Agents by Organism

***Enterobacteriaceae* (Including *E. coli* and *Klebsiella* spp.):**
duration 21 days.

- Antibiotics of First Choice: Cefotaxime or Ceftriaxone.
- Alternatives: Cefepime, Moxifloxacin, Meropenem or Aztreonam.

***Pseudomonas aeruginosa*:** duration 21 days.

- Antibiotics of First Choice: Cefepime or Ceftazidime ± Tobramycin.
- Alternatives: Ciprofloxacin, Meropenem, or Piperacillin-tazobactam + Tobramycin, Colistin, or Aztreonam.

Therapy of Meningitis

- **Supportive care** (administration of fluids, electrolytes, antipyretics, and analgesics) is critically important.
- **Venous thromboembolism prophylaxis** and **intracranial pressure (ICP) monitoring** may be needed in some patients.
- Mannitol 25% or hypertonic 3% saline may be needed to maintain an ICP of less than 15 mm Hg.
- **Appropriate antibiotic therapy (empirical or definitive) should be started as soon as possible.**

Dexamethasone as an Adjunctive Treatment for Bacterial Meningitis

- Dexamethasone is a commonly used adjunctive therapy in the treatment of meningitis.
- Corticosteroids inhibit the production of TNF, PAF and IL-1, potent proinflammatory cytokines.
- They also reduce cerebral edema, high ICP, neuronal injury, and vasculitis.
- Some clinical studies have shown that treatment with corticosteroids reduces both mortality and neurological sequelae in adults with community-acquired bacterial meningitis.

Dexamethasone as an Adjunctive Treatment for Bacterial Meningitis

- Other studies have shown that corticosteroid use in bacterial meningitis was associated with lower rates of **severe hearing loss**, and **neurological sequelae**, but **did not reduce overall mortality**.
- **Adjunctive steroids** are effective in reducing inflammation and improving clinical outcomes in some causes of meningitis such as *S. pneumoniae* (mortality), *H. influenzae* (hearing loss), *N. meningitidis* (arthritis), and *M. tuberculosis* (mortality).

Dexamethasone as an Adjunctive Treatment for Bacterial Meningitis

- The use of corticosteroid therapy can be **detrimental** in *L. monocytogenes*, and *Cryptococcus neoformans* meningitis because of immunosuppression.
- Intact immune system is needed to kill these organisms.

Dexamethasone as an Adjunctive Treatment for Bacterial Meningitis

- The recommended intravenous dose is 0.15 mg/kg every 6 hours for 2 to 4 days, initiated 10 - 20 minutes prior to /or concomitant with, but not after, the first dose of antibiotics.
- With adjunctive dexamethasone use, signs and symptoms of GI bleeding and hyperglycemia, should be monitored carefully.
- However, routine use of dexamethasone in meningitis is still controversial.

Bacterial Brain Abscess

Etiology:

- 1. Those arising from spread of infection from oropharynx, middle ear, and paranasal sinuses are commonly caused by streptococci and oral anaerobes (Actinomyces spp., Bacteroides spp., Fusobacterium spp., Peptostreptococcus).**
- 2. Staphylococci, aerobic and gram-negative bacilli are commonly involved in postoperative abscesses or those following head trauma.**

Bacterial Brain Abscess

- 3. *P. aeruginosa* and *Nocardia* spp. can cause brain abscesses but are more commonly seen in immunocompromised patients.**
- Brain abscesses are commonly polymicrobial, thus, empiric antimicrobial therapy should include antibiotics with activity against gram-positive, gram-negative, and anaerobic microorganisms:**

Bacterial Brain Abscess

Empiric Therapy:

1. **Vancomycin + a third- or fourth-generation cephalosporin + metronidazole, depending on risk factors.**
2. **A carbapenem (meropenem) could replace the cephalosporin and metronidazole.**

Bacterial Brain Abscess

- **De-escalation of therapy should be performed once a causative organism is identified.**
- **De-escalation means changing an empiric broad-spectrum antibiotic regimen to a narrower antibiotic regimen by changing the antimicrobial agent or changing from combination therapy to monotherapy.**

Bacterial Brain Abscess

- Duration of therapy should be determined for each individual patient.
- Duration is based on causative pathogen, size of abscess, use of surgical treatment, and response to therapy.
- Duration is usually prolonged to **4-8 weeks**.
- United Kingdom guidelines recommend 4-6 weeks if the abscess has been drained or excised and 6-8 weeks if the abscess is treated without drainage.

Bacterial Brain Abscess

The following categories require a longer duration of therapy (6-8 weeks or longer):

- 1. Patients with an abscess with organized capsule with evidence of tissue necrosis.**
- 2. Patients with a multiloculated abscess.**
- 3. Patients with lesions in vital locations such as the brain stem or the motor strip (particularly if not surgically drained).**
- 4. Immunocompromised patients.**
- 5. In case of needle aspiration rather than open surgical excision.**

Bacterial Brain Abscess

- Anticonvulsant therapy is recommended for at least 1 year, because seizures are common complication of brain abscesses (**phenytoin, carbamazepine, valproate, and levetiracetam**).
- The benefit of dexamethasone in the treatment of brain abscess is unclear and **not routinely recommended, unless there is signs of cerebral edema or imminent brain herniation.**

Cryptococcus neoformans

- **Mainly affect persons with underlying impaired immunity.**
- **Acquired by inhalation of spores from the environment leading to CNS infection and less commonly pulmonary disease.**
- **Rapid sterilization of CNS through rapid fungicidal activity is the main approach of **induction therapy** (2 - 6 weeks), followed by **consolidation therapy** for 8 weeks.**

Cryptococcus neoformans

- Amphotericin B was the drug of choice for the treatment of acute cryptococcal meningitis due to its rapid fungicidal activity, despite poor penetration into the CSF.
- **Amphotericin B** (1 mg/kg/day) combined with **flucytosine** (100 mg/kg/day) for 2 weeks was more effective than amphotericin B alone for 4 weeks, or in combination with **fluconazole** (400 mg twice daily) for 2 weeks in HIV-positive patients.

Cryptococcus neoformans

- Amphotericin B and flucytosine are fungicidal, while fluconazole is fungistatic.
- **Flucytosine** is poorly tolerated, causing bone marrow suppression and GI distress.
- Careful monitoring of CBC, therapeutic drug monitoring (TDM) and dose adjustment for patients with renal insufficiency are recommended to avoid flucytosine-associated toxicities.

Cryptococcus neoformans

- Lipid formulations of amphotericin B at higher doses (3-5 mg/kg/day) can be used for **HIV-positive patients** with or predisposed to renal dysfunction and are recommended for **organ-transplant recipients**.
- **Voriconazole** in combination with **amphotericin B** can be used.

Mycobacterium tuberculosis

- Initial regimen of four drugs for empirical treatment of *M. tuberculosis* is recommended.
- This regimen consists of **isoniazid, rifampin, pyrazinamide, and ethambutol** for the first 2 months, followed by isoniazid plus rifampin for the remaining duration of therapy.
- Duration of treatment 9 - 12 months or longer with multiple-drug therapy.
- With rifampin-resistant strains duration may be 18 - 24 months.

Mycobacterium tuberculosis

- The recommended therapy for **HIV-positive individuals** is the same as for immunocompetent patients, but duration of treatment ≥ 24 months.
- Rifabutin may replace other rifamycins (rifampin) to minimize drug interactions with protease inhibitors and nonnucleoside reverse-transcriptase inhibitors.

Chemoprophylaxis of Meningitis

- The spread of some types of bacterial meningitis can be prevented by administering prophylactic antimicrobials to contacts of patients with bacterial meningitis.**
- This prevents transmission of the bacteria to susceptible hosts, and eradicates the organism from the nasopharynx of those who are already colonized.**

Chemoprophylaxis of Meningitis

- Such therapy is recommended for close contacts of patients infected with:
H. influenzae or *N. meningitidis*.
- Close contacts are house-hold or day-care members **who sleep or eat in the same dwelling** as the index patient.
- Therefore, health care workers do not require chemoprophylaxis unless close contact with the patient's secretions occurs, as in mouth-to-mouth resuscitation.

Chemoprophylaxis of Meningitis

Chemoprophylaxis for *Neisseria meningitidis*

Children < 5years	Ciprofloxacin single dose 30mg/kg po (max 125mg)
Children 5-12 years	Ciprofloxacin 250mg po single dose
Pregnant women	Ceftriaxone 250mg IM stat
Female adults on the oral contraceptive pill	Ciprofloxacin 500mg po single dose
Adults and children >12 years	Ciprofloxacin 500mg po single dose

Rifampin can be used, but the duration of therapy is 2 days.

Chemoprophylaxis of Meningitis

Chemoprophylaxis for *Haemophilus influenzae*

Infants under 1 year of age	Rifampin 10mg/kg once daily for 4 days
Adults and children	Rifampin 20mg/kg once daily for 4 days up to max of 600mg/day
Pregnant women	Not indicated

Vaccination

- **With *Haemophilus influenzae* type b, pneumococcal meningitis or *Neisseria meningitidis* Groups C, A, Y and W135, vaccination of contacts and index may be indicated.**