Therapy of Meningitis

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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; because changes in the CSF after antibiotic administration usually take up to 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	*Streptococcus agalactiae* Gram-negative enterics *(E. coli, Klebsiella spp, Enterobacter spp)* *Listeria monocytogenes*	Ampicillin + cefotaxime or Ampicillin + aminoglycoside
1-23 months	*Streptococcus pneumoniae* *Neisseria meningitidis* *Haemophilus influenzae* *Streptococcus agalactiae*	Vancomycin + 3rd generation cephalosporin (cefotaxime or ceftriaxone) Vancomycin to cover penicillin-resistant S. pneumoniae
2-50 years	*Neisseria meningitidis* *Streptococcus pneumoniae*	Vancomycin + 3rd generation cephalosporin (cefotaxime or ceftriaxone) Vancomycin to cover penicillin-resistant S. pneumoniae
>50 years	*Streptococcus pneumoniae* *Neisseria meningitidis* Gram-negative enterics *(E. coli, Klebsiella spp, Enterobacter spp)* *Listeria monocytogenes*	Vancomycin + ampicillin + 3rd generation cephalosporin (cefotaxime or ceftriaxone) Vancomycin to cover penicillin-resistant S. pneumoniae

Penetration of Antimicrobial Agents into the CSF

Therapeutic Levels in CSF With/Without Inflammation:

Acyclovir, Levofloxacin, Chloramphenicol, 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/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 ≥ 21 days**

- **Antibiotics of First Choice: Penicillin G or Ampicillin ± 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.**

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.**