

# Therapy of Meningitis

# 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 to 24 hours to occur.
- 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>L. Monocytogenes</i>	Ampicillin + cefotaxime <u>or</u> Ampicillin + aminoglycoside
1-23 months	<i>S. pneumoniae</i> <i>N. meningitidis</i> <i>H. influenzae</i> <i>S. agalactiae</i>	Vancomycin + 3rd generation cephalosporin (cefotaxime or ceftriaxone) Vancomycin to cover penicillin-resistant <i>S. pneumoniae</i>
2-50 years	<i>N. meningitidis</i> <i>S. pneumoniae</i>	Vancomycin + 3rd generation cephalosporin (cefotaxime or ceftriaxone) Vancomycin to cover penicillin-resistant <i>S. pneumoniae</i>
>50 years	<i>S. pneumoniae</i> <i>N. meningitidis</i> Gram-negative enterics ( <i>E. coli</i> , <i>Klebsiella spp</i> , <i>Enterobacter spp</i> ) <i>L. 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,  
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

# 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. $\beta$ -lactamase negative:

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

## 2. $\beta$ -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, Piperacillin + Tobramycin, Colistin sulfomethate, 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.
- 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

- Corticosteroid use in bacterial meningitis was associated with lower rates of **severe hearing loss**, and neurological sequelae, but did not reduce overall mortality (some other studies).
- **Current recommendations are with the use of adjunctive dexamethasone in infants and children (6 weeks of age and older) with H. influenza meningitis.**
- **The recommended intravenous dose is 0.15 mg/kg every 6 hours for 2 to 4 days, initiated 10 to 20 minutes prior to or concomitant with, but not after, the first dose of antibiotics.**



# Dexamethasone as an Adjunctive Treatment for Bacterial Meningitis

- 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 organisms:**
  - a) Vancomycin + a third- or fourth-generation cephalosporin + metronidazole, depending on risk factors.**

# Bacterial Brain Abscess

- b) A carbapenem (meropenem) could replace the cephalosporin and metronidazole.**
- 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 and should include consideration of the causative pathogen, size of abscess, use of surgical treatment, and response to therapy.**
- **It is prolonged, usually 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 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. 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.**
- **The benefit of dexamethasone in the treatment of brain abscess is unclear and not routinely recommended, unless signs of cerebral edema are identified.**

# *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 alone for 4 weeks, or in combination with **fluconazole** (400 mg twice daily) for 2 weeks in HIV-positive patients.
- **Voriconazole** in combination with **amphotericin B** can be used.

# *Cryptococcus neoformans*

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

# *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.
- Duration of treatment  $\geq 24$  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.
- Such therapy is recommended for close contacts of patients infected with:  
*H. influenzae* or *N. meningitidis*.

# Chemoprophylaxis of Meningitis

- **Close contacts are defined as 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*

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



# 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.**