**College of Pharmacy**

 **Fourth year. Clinical Pharmacy**

 **Infectious Diseases**

 **Central Nervous System Infections**

**Introduction**

**1-Central nervous system (CNS)** infections include a wide variety of clinical conditions and etiologies: **meningitis**, **meningoencephalitis**, **encephalitis**, **brain and meningeal abscesses**, and **shunt infections**. The focus of this lecture is **meningitis**.

2-CNS infections may be caused by a variety of **bacteria**, **fungi**, **viruses**, and **parasites**. **The most common causes of bacterial meningitis** are **Streptococcus pneumoniae**, group B **Streptococcus**, **Neisseria meningitidis**, **Haemophilus influenzae**, and **Listeria monocytogenes**

**Pathophysiology**

1-The critical **first step** in the acquisition of acute bacterial meningitis is **nasopharyngeal colonization** of the host by the bacterial pathogen.

2-Most cases of acute bacterial meningitis probably **occur following bacteremia**, but the high incidence of pneumococcal meningitis in patients with sinusitis and otitis media suggests that **direct spread to the CNS can also occur**.

3-The **neurologic sequelae of meningitis** occur due to the activation of host inflammatory pathways.

4-These events **lead to cerebral edema**, **elevated intracranial pressure**, **decreased cerebral blood flow**, **cerebral ischemia**, and **death**.

5-Passive and active exposure to **cigarette smoke** and the presence of a **cochlear implant** that includes a positioner both **increase the risk of bacterial meningitis**.

**Clinical presentation**

1-**Signs and symptoms of acute bacterial meningitis include** fever, nuchal rigidity, altered mental status, chills, vomiting, photophobia, and severe headache.

2-**Up to 95% of patients exhibit at least two of the following symptoms:** fever, nuchal rigidity, headache, and altered mental status.

3-**Kernig** and **Brudzinski** signs may be present but are poorly sensitive and **frequently** **absent in children**.

4-Clinical signs and symptoms in **young children** may include bulging fontanelle, apnea, purpuric rash, and convulsions.

5-**Purpuric and petechial skin** lesions typically indicate **meningococcal involvement,** although the lesions may be present with H. influenza meningitis. Rashes rarely occur with pneumococcal meningitis.

6-Meningitis causes **changes in CSF fluid**, and these changes can be used as diagnostic markers of infection (**Table1**).

7-**CSF culture is the gold standard for diagnosis** of bacterial meningitis .

8-**Gram stain is a rapid, inexpensive, and accurate method to assess the presence of bacteria in CSF**. However, prior antibiotic therapy may cause the Gram stain and CSF culture to be negative, but the antibiotic therapy rarely affects CSF protein or glucose.

9-Polymerase chain reaction (**PCR**) techniques can rapidly diagnose CNS infections and may be **particularly useful in patients who have received antimicrobial therapy** before lumbar puncture.

**Table 1: Mean Values of the Components of Normal and Abnormal Cerebrospinal Fluid**



**a**Initial cerebrospinal fluid (CSF), white blood cell (WBC) count may reveal a predominance of polymorphonuclear neutrophils (PMNs). In CNS infection due to tuberculosis, “therapeutic paradox” may occur in which a lymphocytic predominance becomes neutrophilic during antituberculous treatment.

**Treatment**

1-**Goals of Treatment**: Effective eradication of infection, amelioration of signs and symptoms, and reduction of morbidity and mortality.

2-Key elements include initiating **appropriate antimicrobials**, providing **supportive** **care**, and **preventing disease** through timely introduction of vaccination and chemoprophylaxis.

3-Administration of **fluids**, **electrolytes**, **antipyretics**, and **analgesics** may be indicated for patients presenting with a possible CNS infection.

4-Additionally, **venous thromboembolism prophylaxis**, **antiepileptic therapy**, and **ICP monitoring may be needed.**

**Pharmacologic Therapy**

1-**Empiric antimicrobial therapy** should be instituted as soon as possible to eradicate the causative organism (**Table-2**). Antimicrobial therapy should **last at least 48–72 hours** or **until the diagnosis of bacterial meningitis can be ruled out.**

2-**The time period from suspected diagnosis to initiation of antibiotic treatment should not exceed 1 hour**.

**Table 2: Bacterial Meningitis: Most Likely Etiologies and Empiric Therapy by Age Group**



3-**Once a pathogen is identified, antibiotic therapy should be tailored to the specific pathogen.**

4-With increased meningeal inflammation, there will be greater antibiotic penetration (**Table-3**). **Problems of CSF penetration** can be overcome by direct **instillation of antibiotics intrathecally or intraventricularly.**

5-Advantages of direct instillation, however, must be weighed against the **risks of invasive CNS procedures and adverse effects**. **Intraventricular delivery** may be necessary in patients who have **shunt infections that are difficult to eradicate** .

6-See (**Table-4**) for **antimicrobial agents of first choice and alternatives** for treatment of meningitis caused by gram-positive and gram-negative microorganisms.

**Table 3: Penetration of Anti-infective Agents into the CSF**







**a** Using recommended CNS dosing and compared to MIC of target pathogens. **b** May not achieve therapeutic levels against organisms with higher MIC, as in P. aeruginosa. Tazobactam does not penetrate the blood-brain barrier. **c** Includes clavulanic acid, sulbactam, and tazobactam. **d** Cefuroxime is an exception. **e** Documented effectiveness for B. burgdorferi. **f** Achieves therapeutic concentrations for Cryptococcus neoformans therapy.

7-Meningitis caused by **S. pneumoniae** has been treated successfully with **10–14 days** of antibiotic therapy, while cases caused by **N. meningitidis** or **H. influenzae** usually can be treated with a **7-day course**.

8-In contrast, a longer duration (**21 days or more**) has been recommended for patients with **L. monocytogenes**, **Gram-negative or pseudomonal meningitis**.

**Table 4: Antimicrobial Agents of First Choice and Alternative Choice for Treating Meningitis Caused by Gram-Positive and Gram-Negative Microorganisms**









**Dexamethasone as an Adjunctive Treatment for Meningitis**

1-In addition to antibiotics, **dexamethasone is a commonly used adjunctive therapy** in the treatment of acute bacterial meningitis to **immunomodulate the inflammatory response**.

2-Recommendations call for the use of adjunctive dexamethasone in **infants and children** (6 weeks of age and older) **with H. influenzae meningitis**. The recommended intravenous dose is 0.15 mg/kg every 6 hours for **2–4 days**, initiated **10–20 minutes prior to or concomitant with the first dose of antibiotics.**

3-In infants and children with **pneumococcal meningitis**, adjunctive dexamethasone may be considered **after weighing the potential benefits and possible risks**.

4-If **pneumococcal** **meningitis** is suspected or proven, **adults should receive dexamethasone** 0.15 mg/kg (up to 10 mg) every 6 hours for 2–4 days with the first dose administered **10–20 minutes prior to first dose of antibiotics**.

**Neisseria meningitidis (Meningococcus)**

1-**N. meningitidis is a leading cause of bacterial meningitis** among children and young adults around the world. It is spread by direct person-to-person close contact, including respiratory droplets and pharyngeal secretions.

2-The presence of **petechiae** may be the primary clue that the underlying pathogen is N. meningitidis. Patients may also have disseminated **intravascular coagulation** (DIC).

3-**Deafness** unilaterally, or more commonly bilaterally, may develop early or late in the disease course.

4-**Third-generation cephalosporins** (ie, cefotaxime and ceftriaxone) are the recommended empiric treatment for meningococcal meningitis.

5-**Penicillin** **G or ampicillin is recommended for penicillin-susceptible isolates**. The recommended duration of therapy is typically **7 days** if there is good clinical response.

6-Antimicrobial **chemoprophylaxis** of close contacts should be started as soon as possible (ideally <24 hours after identification of the patient). Ciprofloxacin and rifampin are the two most used chemoprophylactic agents.

**Streptococcus pneumoniae (Pneumococcus or Diplococcus)**

1-Streptococcus group B is **a leading cause of community acquired bacterial meningitis in patients 2 months of age or older.**

2-Coma, hearing impairment, and seizures are common neurologic complications.

3-The combination of **vancomycin** and **ceftriaxone** can be used as empirical treatment

until antimicrobial susceptibility data are available.

**Haemophilus influenzae**

1-Widespread vaccination of infants and children has effectively decreased the incidence of bacterial meningitis due to **Hib** in children between the ages of 1 month and 5 years, resulting in a significant decline in all cases of bacterial meningitis.

2-**Third-generation cephalosporins** (cefotaxime and ceftriaxone) are the drugs of choice for empirical therapy for H. influenzae type b meningitis as they are active against β-lactamase–producing and non-β-lactamase–producing strains. **Cefepime** and **fluoroquinolones** **are suitable alternatives** regardless of β-lactamase activity.

3-Recommended duration of treatment is **7 days (adults) or 7–10 days (children).**

4-**Dexamethasone** is beneficial for treatment of **infants and children with Hib meningitis** to diminish the risk of hearing loss, if given **before or concurrently** with the first dose of antimicrobial agent(s).

5-**Chemoprophylaxis with rifampin** is indicated to reduce the risk of secondary invasive Hib disease in close contacts.

6-Rifampin should be administered orally, **once a day for 4 days** (20 mg/kg/dose; maximum, 600 mg).

**Listeria monocytogenes**

1-L. monocytogenes is implicated in approximately 10% of meningitis cases in patients **older than 65 years of age** and carries a case-fatality rate of approximately 18% in the United States.

2-Treatment of L. monocytogenes meningitis should consist of **penicillin G or ampicillin**. **The addition of aminoglycoside is also recommended in proven infection in both children and adults.**

3-Patients should be treated **a minimum of 21 days**. **Trimethoprim–sulfamethoxazole and meropenem may be effective alternatives** because adequate CSF penetration is achieved with these agents.

**Reference**

**Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach,**

**12th Edition. 2023.**