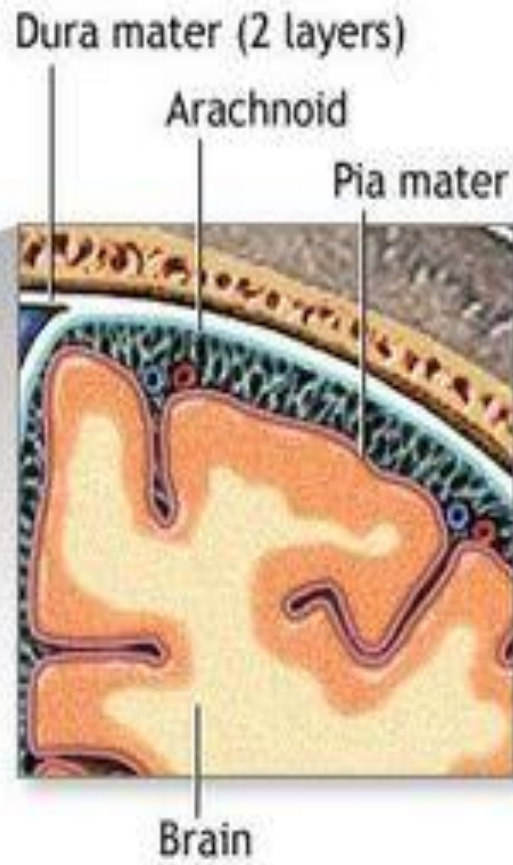


Central nervous system infection

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CNS Infection

The meninges are the membranes covering the brain and spinal cord



Meningitis

- The skull and vertebrae protect the CNS from blunt or penetrating trauma.
- The brain is suspended in these structures by **cerebrospinal fluid (CSF)** and is surrounded by the **meninges**.
- The meninges are made up of three separate membranes: dura mater, arachnoid, and pia mater.
- **Dura mater**, lies directly beneath and is adherent to the skull.
- **Pia mater** lies directly over brain tissue.
- **Arachnoid**, the middle layer, lies between the dura mater and the pia mater.
- The subarachnoid space, located between the arachnoid and the pia mater, is the conduit for **CSF**.

Cont. . . .

- By definition, **meningitis** refers to inflammation of the subarachnoid space or spinal fluid, whereas **encephalitis** is an inflammation of the brain itself
- **Cerebrospinal Fluid**
 - Clear, protein content 50 mg/dL, a glucose concentration of 50% to 66% of the simultaneous peripheral serum glucose concentration, and a PH of approximately 7.4;
 - Contains fewer than five WBCs/mm³, all lymphocytes.

Acute bacterial meningitis

- Is an inflammation of the membranes of the brain or spinal cord, i.e. of the dura matter or the pia-arachnoid matter in response to bacterial infection
- The meninges, the subarachnoid space, and the brain parenchyma are all frequently involved in the inflammatory reaction (meningoenkephalitis)
- Commonly caused by *N. meningitidis*, *S. pneumoniae*, *H. influenza* , GBS
- The disease is characterized by an intense headache, fever, intolerance to light and sound and rigidity of muscles, especially those of the neck

Cont. . . .

- **Causes: common**
- *Streptococcus pneumoniae*
- *Neisseria meningitidis*
- *Haemophilus influenza*
- **Causes in specific population**
- *Listeria monocytogenes*
- Gram negative bacilli
- post trauma or neurosurgery
- *T. pallidum*

Cont. . . .

Viral

- Enteroviruses
- Arboviruses
- Herpesviruses
- HIV

Fungal

- Cryptococcal

Cont. . . .

- Cause of chronic meningitis
- Bacterial
- Mycobacterium tuberculosis
- Syphilis , Brucella , Leptospirosis , Nocardia
- Fungus
- Cryptococcus , Aspergillus, Candida sp.

Typical CSF findings in Meningitis



Bacterial meningitis

1. Presence of **neutrophils** in the CSF is associated with infection by *N. meningitidis*, *S. pneumoniae* etc.

2. CSF protein level reflects the degree of meningeal inflammation:-

10 X in bacterial infections

3. CSF glucose levels :-

very low in bacterial infections

Viral meningitis

1. Presence of **lymphocytes** is associated with infection by viruses or mycobacteria.

2. CSF protein level reflects the degree of meningeal inflammation:-

2-3 X in viral CNS infection

3. CSF glucose levels :-

normal with viral infections

Etiology


- Currently, the organisms most commonly responsible for community-acquired bacterial meningitis are:
 - *Streptococcus pneumoniae* (~50%)
 - *N. meningitidis* (~25%)
 - Group B streptococci (~15%)
 - *Listeria monocytogenes* (~10%)
 - *H. influenzae* (<10%)

Causes based on the age and immune status of the patient


<i>Predisposing Factor</i>	<i>Bacterial Pathogen</i>
Age <1 month	<i>S. agalacticae</i> , <i>E. coli</i> , <i>L. monocytogenes</i> , <i>K. pneumoniae</i>
1-23 month	<i>S. agalacticae</i> , <i>E. coli</i> , <i>H. influenzae</i> , <i>S. pneumoniae</i> , <i>N. meningitidis</i>
2-50 years	<i>S. pneumoniae</i> , <i>N. meningitidis</i>
>50 year	<i>S. pneumoniae</i> , <i>N. meningitidis</i> , <i>L. monocytogenes</i> , Gram negative bacilli
Immunodeficiency	<i>S. pneumoniae</i> , <i>N. meningitidis</i> , <i>L. monocytogenes</i> , Gram negative bacilli, <i>P. aeruginosa</i> , <i>M. tuberculosis</i> , <i>Cryptococcosis</i>
Skull fracture	<i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>Group A streptococci</i>
Post neurosurgery	<i>S. aureus</i> , coagulase negative staphylococci, Gram negative bacilli, <i>P. aeruginosa</i>

Pathophysiology

Source of Infection

- **Contiguous spread: Sinusitis, OM, birth defect**
 - **Hematogenous: bacteremia seeding meninges**
 - **Direct inoculation: Trauma, neurosurgical complications**
 - **Reactivation of latent disease: HSV, TB**
- 

CNS Response to Infection

- **Contact with bacterial cell wall components triggers cytokine releases (TNF, PAF, IL-1)**
 - **Platelet activating factor (PAF) triggers clotting cascade, forming microthrombi**
 - **Cytokine cascade stimulates vasodilation and vascular permeability**
 - **Compromised BBB allows entry of neutrophils and other blood components**
- 

Increased ICP



Decreased Cerebral Blood Flow



**Ischemia and Direct Tissue
Damage**

Signs/Sx of Meningitis

- **Headache**
- **Fever**
- **Neck stiffness**
- **Altered mental status**
- **Seizures**
- **Abnormal CSF findings**

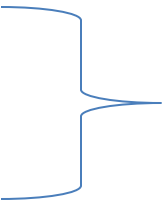
- N:B CNS bacterial pathogens produce an extensive polysaccharide capsule resistant to neutrophil Phagocytosis
- Host defense mechanisms within the subarachnoid space are inadequate to combat bacterial pathogens
- The neurologic sequelae occur as a result of the activation of the host's inflammatory pathways.
- Bacterial cell lysis and subsequent death can result in the release of cell-wall components

- Cell wall components cause capillary endothelial cells and CNS macrophages to release cytokines and TNF and other inflammatory mediators (IL-6, IL-8, platelet-activating factor [PAF], nitric oxide, arachidonic acid metabolites [eg, prostaglandin and prostacycline])
- Proteolytic products and toxic oxygen radicals are released from the capillary endothelium, causing an alteration in the permeability of the BBB.

Clinical presentation

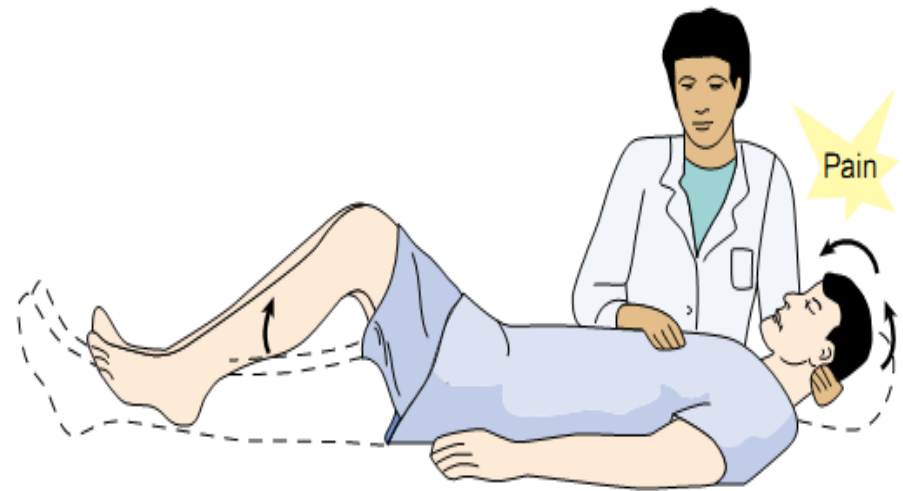
- Subjective complaint
 - the classic triad: **fever, nuchal rigidity, altered mental status**
 - Chills, vomiting, photophobia, and severe headache;
 - Altered mental status: >75% of patients can vary from lethargy to coma
 - seizure
 - ↑ICP: vomiting, lethargy, headache, 6th nerve palsy
- Clinical signs and symptoms in young children may include bulging fontanelle, apneas, purpuric rash, and convulsions in addition to those just mentioned

Cont. . . .

- **Physical signs:**
 - Nuchal rigidity
 - Kernig's sign, and
 - Brudzinski's sign
- 
- meningeal irritation
- Their absence does not exclude meningitis



Kernig's Signs



Brudzinski's signs

Differential Signs and Symptoms

- Purpuric and petechial skin lesions typically indicate *meningococcal involvement*, although the lesions may be present with *H. influenzae* meningitis.
- Rashes rarely occur with pneumococcal meningitis.
- A rapid eruption of multiple hemorrhagic lesions associated with a shock-like state, is associated with meningococcal meningitis

- H influenza meningitis and meningococcal meningitis both can cause involvement of the **joints** during the illness.
- A history of **head trauma** with or without skull fracture or presence of a chronically **draining ear** is associated with **pneumococcal** involvement.

CHILDREN/ADULTS



Stiff neck



Headache



Fever



Vomiting



Light Sensitivity



Drowsiness or
confusion



Joint pain



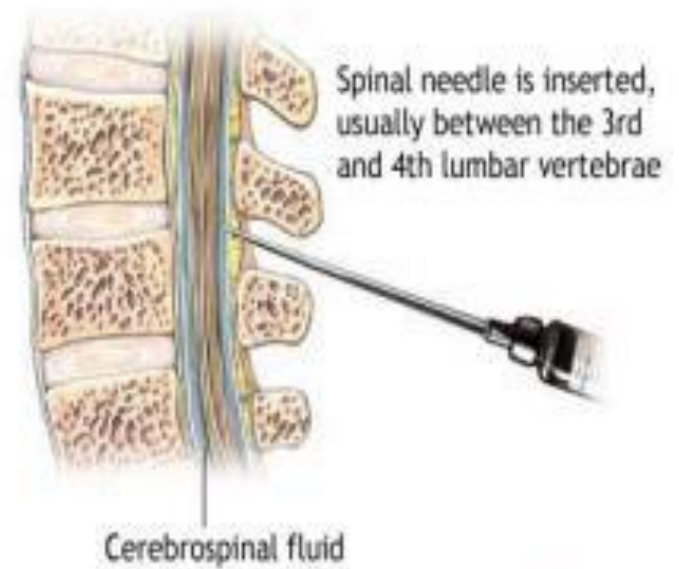
Fitting

Diagnosis

- CSF via lumbar puncture (LP) for chemistry, microbiology, and hematology tests.
 - An elevated CSF protein
 - CSF glucose concentration of $< 50\%$ of the simultaneously obtained peripheral
- Gram stain and culture of the CSF
- Magnetic resonance imaging (MRI) or cranial computed tomography (CT) (seizure, lesion, impaired consciousness)
- Culture of blood and other specimens

Lumbar puncture

Cerebrospinal fluid drawn
from between two vertebrae



CSF findings

Type	Normal	Bacterial	Viral	Fungal	TB
WBC (cells/mm ³)	<5	1,000–5,000	500- 1000	100– 400	50–500
Protein (mg/dL)	20-45	100–500	50–100	100– 200	40–150
Glucose (mg/dL)	45-80	5-40 (<60% serum value)	30–70	<30– 70	<30–70
Opening pressure	< 20 mm Hg	> 20 mm Hg	< 20 mm Hg	> 20 mm Hg	> 20 mm Hg

Cont. . . .

- **Contraindication to Lumbar puncture**
- Raised intracranial pressure
- Thrombocytopenia or other bleeding diathesis (including ongoing anticoagulant therapy)
- Suspected spinal epidural abscess
- **Complication of LP**
- Post-LP headache
- Infection
- Bleeding
- Cerebral herniation
- Back pain

General principle of treatment

- The most important initial issues:
 - avoidance of delay
 - choice of drug regimen
- **Avoidance of delay:**
- Antibiotics should be started immediately
- **Components of delay**
- time from triage to contact with a physician
- time from LP until administration of antibiotics
- performance of CT to exclude mass lesion

Cont...

- **Supportive care**
- Administration of fluids, electrolytes, antipyretics, analgesics,
- Appropriate antibiotic therapy (empirical or definitive) should be started as soon as possible
- **Goals:**
- eradication of infection with amelioration of signs and symptoms
- prevention of neurologic sequelae, such as seizures, deafness, coma, and death

Cont. . .

CSF Penetration Characteristics of Various Antimicrobials

- **Very Good**
 - Chloramphenicol, metronidazole, TMP-SMX, linezolid
- **Good**
 - Penicillins: Penicillin G, ampicillin, nafcillin
 - Other β -lactams: Aztreonam, clavulanic acid, imipenem, meropenem,
 - Cephalosporins: Cefepime, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone
 - Other agents: Rifampin
- **Fair to Poor**
 - Aminoglycosides: Amikacin, gentamicin, tobramycin
 - Other agents: Azithromycin, clarithromycin, clindamycin, erythromycin,
 - vancomycin, daptomycin

Antibiotics Used in Empirical Therapy of Bacterial Meningitis

Indication

Preterm infants to infants <1 month

Antibiotic

Ampicillin +
cefotaxime/aminoglycoside

Infants 1–3 mos

Ampicillin + cefotaxime or
ceftriaxone

Immunocompetent children >3 mos and
adults <55

Cefotaxime or ceftriaxone +
vancomycin

Adults >55 and adults of any age with
alcoholism or other debilitating illnesses

Ampicillin + cefotaxime or
ceftriaxone + vancomycin

Hospital-acquired meningitis, posttraumatic
or postneurosurgery meningitis, neutropenic
patients, or patients with impaired cell-
mediated immunity

Ampicillin + ceftazidime +
vancomycin

Antimicrobial therapy based on pathogen

Organism	Antibiotic
Neisseria meningitis	
• Penicillin sensitive	Penicillin G or Ampicillin
• Penicillin resistant	Ceftriaxone or Cefotaxime
Streptococcus pneumoniae	
• Penicillin sensitive	Penicillin G
• Penicillin resistant	Ceftriaxone or Cefotaxime or Cefipime + vancomycin
Pseudomonas aeruginosa	Ceftazidime or Cefipime or meropenam
Staphylococci spp.	Naficilin/ vancomycin
Listeria monocytogenes	Ampicillin + gentamicin
Haemophilus influenzae	Ceftriaxone or Cefotaxime

Dosing of Antimicrobial Agents by Age Group

Ampicillin	Gentamycin
Children 75mg/kg Q 6h	Children 7.5mg/kg /d in divided doses Q 8hr
Adults 2g Q 4h	Adults 5mg/kg /d in divided doses Q 8hr
Ceftriaxone	Vancomycin
Children 100mg/kg/d	Children 15mg/kg Q 6 hr
Adult 2g Q 12-24hr	Adult 15mg/kg Q 8-12hr

Cont...

- **Duration of treatment**
- *S. pneumoniae*: 10-14 days
- *H. influenzae*: 7 days
- *N. meningitidis*: 7 days
- *L. monocytogenes*: 14-21 days
- *S. agalactiae*: 14-21 days
- Enterobacteriaceae: 21 days
- *P. aeruginosa*: 21+ days

Adjunctive Therapy

- **Dexamethasone** inhibits the synthesis of **IL-1** and **TNF** at the level of mRNA, decreasing CSF outflow resistance, and stabilizing the blood-brain barrier.
- Dexamethasone should be given 20 min before antibiotic therapy so that dexamethasone inhibits the production of TNF by macrophages before the cells are activated by endotoxin.
- Dexamethasone does not alter TNF production once it has been induced.
- Dose: 0.15 mg/kg IV every 6 hours for 2 to 4 days

Prevention - Chemoprophylaxis

- **H. influenzae type b children**
- Rifampin 20mg/kg/d (max 600mg) for 4 days
- **N. meningitidis children**
- Rifampin 10mg/kg PO (max 600mg) Q 12hr for 2 days or
- ceftriaxone 125 mg IM for one dose
- **Adult**
- Ciprofloxacin 500mg PO x 1 dose or Ceftriaxone 250mg IM x 1 dose or Rifampin 600mg PO Q12hrs x 2 days
- –Close contacts (droplets): > 4 hrs or exposure to nasopharyngeal secretions

Complication of acute bacterial meningitis

1. Hydrocephalus
2. Stroke with focal neurologic deficits (hemiparesis, deafness, visual ..)
3. Hyponatremia (SIADH)
4. Herniation

Predictors of mortality

- Decreased level of consciousness on admission
- Onset of seizures within 24 h of admission
- Signs of increased ICP
- Young age (infancy) and age >50
- Presence of comorbid conditions including shock
- Delay in the initiation of treatment
- Decreased CSF glucose concentration and markedly increased CSF protein concentration [>3 g/L (>300 mg/dL)]

Evaluation of Therapeutic Outcomes

- Improvement in signs and symptoms of fever, headache, meningismus (e.g., nuchal rigidity, Brudzinski's or Kernig's sign),
- Vital signs, and signs of cerebral dysfunction should be evaluated every 4 hours for the initial 3 days and then daily thereafter
- Microbiologic Findings
- CSF Examination

Other CNS infection

- **HSV encephalitis:** Acyclovir 10mg/kg IV Q8h
- **Tuberculosis:** INH, RIF, ETB, PZA total of 9month
- **Cryptococcal:**
- **Induction phase:** Amphotericin B 0.7–1 mg/kg/day **PLUS** flucytosine 100 mg/kg/day for 2 weeks of therapy,
- **followed by :**
- **Consolidation phase:** fluconazole 400 mg/day for 8 weeks,
Maintenance phase fluconazole 200 mg/ day until immune reconstitution occurs.
- **Brain Abscess:** Streptococci & Bacteroides
–Metronidazole Plus (Ceftriaxone or high dose Penicillin G)

Case study 1

- M.Y is a 3-month-old, female infant who presents to the ED in the arms of her mother. The mother reports that she developed a fever 1 day prior to presentation with some mild rhinorrhea and decreased appetite. She indicates that she become irritable and this morning, the mother had difficulty arousing her.
- **PMH**
- she has been treated for an ear infection 2 weeks ago with amoxicillin

- **Physical examination**
 - **G.A** Lethargic, ill-appearing infant
 - **VS**
 - BP 85/50, HR 148, RR 52, T 39.7°C; Wt 8.4 kg
 - **HEENT**: bulging fontanel
 - **CSF analysis**: color cloudy, glucose 40 mg/dL, protein 281 mg/dL, WBC 300/mm³
 - **Assessment** meningitis+ hypotension

Questions

1. What risk factors does this patient have for bacterial meningitis?
2. What clinical and laboratory findings indicate the presence of meningitis and its severity?
3. What could be the most common microorganism involved?
4. What are the goals of drug therapy in this situation
5. Describe the empiric antimicrobial regimen for this patient
6. Discuss role of adjuvant drug therapy for this patient
7. How do you manage the patients hypotension

THANK YOU