Pathophysiology And Therapeutics Of Meningitis

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Pharmacotherapy, Assessment & Policy
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Objectives

- Identify the most common organisms for both viral and bacterial meningitis
- Understand the difference between viral and bacterial meningitis
- Know the composition of normal and abnormal CSF
Objectives

• List the risk factors for CNS infections
• Describe the clinical presentation and laboratory results of characteristic meningitis
• Know both empiric and pathogen-specific antibiotic regimens in meningitis
• Understand the recommended prophylactic regimens and their indications for use
Definitions

1. Meningitis
   Inflammation of the meninges; abnormal WBC in CSF
2. Septic versus Aseptic meningitis
3. Encephalitis
   Inflammation of the brain
4. Meningoencephalitis
   Inflammation of the brain accompanied by meningitis
Meninges

Dura Mater (pachymeninges)
   Directly beneath and is adherent to the skull

Pia Mater
   Lies directly over the brain tissue

Arachnoid
   The middle layer between the dura mater and the pia mater

Subarachnoid Space
   Between the pia mater and the arachnoid
Anatomy/Physiology of the CNS

Cerebrospinal Fluid

Origin

Infants: 40-60ml
Children: 60-100ml
Adults: 110-160ml
Viral Meningitis

1. Incidence
2. Clinical presentation
Viral Meningitis

Pathogens

A) Enteroviruses - 85%
B) Mumps Virus - 5-10%
C) Lymphocytic choriomeningitis virus
D) Herpes Simplex Virus
   HSV-2
Viral Meningitis

Other Pathogens

10%: adenoviruses, poliovirus, rhinoviruses, influenza A&B, rotavirus, CMV, coronavirus, Varicella-Zoster virus, Epstein-Barr virus
Enteroviruses

- **Group A coxsackie**
  - 23 serotypes
  - 14% of the cases

- **Group B coxsackie**
  - 6 serotypes
  - 12% of the cases

- **Echoviruses**
  - 31 serotypes
  - 75% of the cases
Enteroviruses

Respiratory
- Common cold
- Pharyngitis
- Pneumonia

Gastrointestinal
- Vomiting
- Diarrhea
- Abdominal pain

Eye
- Acute hemorrhagic conjunctivitis

Heart
- Myopericarditis

Skin
- Exanthem

Neurologic
- Meningitis
Enteroviruses

Most common - 85-95% of the cases
Seasonal
   Late summer to fall
Fecal to oral route
Effects all age groups
   Typically < 1 year old
Mumps Virus

Parotitis
Meningitis occurs in 10-30% of the cases
Encephalitis is rare
Second most common viral meningitis
10 to 20%
Peak late winter to early spring
Humans only natural hosts
Lymphocytic Choriomeningitis Virus

Nonspecific prodrome
Meningitis
Chronic infection of the house mouse
Infected rodent
Common in the winter
Herpes Simplex Virus

HSV-2

Neonates during birth
Sexually active adults
Treatment Viral Meningitis

SUPPORTIVE CARE
Antibiotics until bacterial meningitis is ruled out
Seizure control
Symptom control
Acyclovir
Bacterial Meningitis

Incidence:
0.2-2.9 cases/100,000/year (1986)
0.2-1.1 cases/100,000/year (1995)

Very Young and Very Old

Dramatic decrease in *H. flu*

Mortality

Sequelae
## Incidence and Mortality Rate

<table>
<thead>
<tr>
<th>Organism</th>
<th>% of Total Cases</th>
<th>Annual Incidence</th>
<th>Fatality Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. flu</td>
<td>45</td>
<td>7</td>
<td>2.9</td>
</tr>
<tr>
<td>S. pneumo</td>
<td>18</td>
<td>47</td>
<td>1.1</td>
</tr>
<tr>
<td>N. menin.</td>
<td>14</td>
<td>25</td>
<td>0.9</td>
</tr>
<tr>
<td>GBS</td>
<td>5.7</td>
<td>12</td>
<td>0.4</td>
</tr>
<tr>
<td>L. mono</td>
<td>3.2</td>
<td>8</td>
<td>0.2</td>
</tr>
<tr>
<td>other</td>
<td>15</td>
<td>1.0</td>
<td>18</td>
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</table>

# Bacterial Meningitis

## Most common organisms by population:

<table>
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<tr>
<th>Age Group</th>
<th>Common Organisms</th>
</tr>
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<tbody>
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<td>0-4 weeks</td>
<td>GBS, E. coli, L. monocytogenes, other gram negatives</td>
</tr>
<tr>
<td>4-12 weeks</td>
<td>GBS, E. coli, L. monocytogenes, H. influenzae, S. pneumoniae</td>
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<tr>
<td>3mo-4 yrs</td>
<td>N. meningitidis, S. pneumoniae, H. influenzae</td>
</tr>
<tr>
<td>5-9 yrs</td>
<td>N. meningitidis, S. pneumoniae/H. influenzae</td>
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Bacterial Meningitis

9-18 years:  N. meningitidis, S. pneumonieae, H. influenzae
18-60 years: S. pneumonieae, N. meningitidis
> 60 years:  S. pneumonieae, N. meningitidis, L. monocytogenes, other gram negatives
Neurosurg:  S. aureus, S. epidermidis, gram negatives
Closed Head: S. pneumonieae, H. influenzae
Open Head:  S. aureus, gram negatives
Pathogenesis

Bacterial Invasion

Parameningeal focus/colonization
  Adhesions, binding receptors, pili
  Hematogenous spread
  Parameningeal seeding
  Colonization of hardware
  Direct inoculation
Pathogenesis

Bacterial elements - inflammatory response
- Endotoxin/Lipopolysaccharide
- Peptidoglycan
- Lipoteichoic acid

Release of inflammatory mediators by astrocytes, microglial/endothelial cells
- TNF alpha
- IL-1
Pathophysiology

- Reduced cerebral perfusion secondary to edema
- Cerebral ischemia secondary to thrombosis
- Vasculitis
- Alteration of cerebral blood flow
- Direct neuronal cell damage secondary to bacterial elements, activated leukocytes, cytokines, and other inflammatory mediators
Pathophysiology

Increased intracranial pressure

- Vasogenic edema -- cytokines act on endothelial cells to damage the BBB
- Cytotoxic edema -- direct damage to cells allowing buildup of intracellular water
- Interstitial edema -- obstruction of CSF flow and removal

Brain herniation
Risk Factors

1. Respiratory tract infection
2. Otitis media
3. Mastoiditis
4. Head trauma
5. Splenectomy
6. Sickle cell disease
7. Immunosuppressive therapy
8. Immunocompromised host
9. Alcoholic patients
10. Patients with hardware (shunts, etc.)
Clinical Presentation

Physical signs/symptoms:
- Fever
- Headache
- Photophobia
- Nausea/vomiting
- Mental status changes
- Stiff neck/back
- Positive Brudzinski's sign
- Positive Kernig's sign
- Deafness
- Seizures
- Focal neurologic deficit
- Hydrocephalus
Laboratory Studies

Lumbar Puncture
- CSF cell count
- CSF chemistries
- CSF gram stain
- CSF culture

Blood Culture

Sputum Culture/Urine Culture

Peripheral CBC and Electrolytes
### Abnormal CSF-findings by type of meningitis

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Clinical Presentation and Diagnosis

Bacterial antigen detection tests

- 69% accurate when positive cultures
- Useful when antibiotics were given before the CSF culture was taken
- May react to other organisms

Other tests

- Counterimmunoelectrophoresis (CIE) and latex fixation (encapsulated organisms)
- Limulus lysate assay (gram-negative endotoxin)
Common Bacterial Organisms

**Haemophilus influenzae**
- Peak incidence: 6-12 months of age; declines after 24 months of age
- Deafness = 6%
- Coma/seizures common
- Close contacts are 200-1000 x risk
- Resistance pattern is growing throughout the U.S.
- Dramatic decrease in cases since 1990
Neisseria meningitidis

- Usually occurs winter/spring
- Five main serogroups: A, B, C, Y, and W-135 (A and C—epidemics; B—individual cases; Y—pneumonia)
- May present with a characteristic immune reaction 10-14 days after infection (fever, arthritis, pericarditis). Rx with NSAID's
Neisseria meningitidis
- 50% die within the first 24 hours
- Coma and seizures are uncommon
- Deafness = 10.5%
- Close contacts are 500-1000x risk
- No problem with penicillin resistance yet
Common Bacterial Organisms

Streptococcus pneumoniae
Gram positive diplococci
"Pneumococcus"
Deafness = 31%
Coma and seizures are more common
Resistance is becoming a problem
Listeria monocytogenes

Peak incidence in summer/early fall

Gram positive rod (coccobacilli)

Most common ages:

Very young (< 3 months)

Older (> 60 years)

Susceptible to ampicillin
Antibiotic Therapy

Factors Enhancing Antimicrobial Penetration
- Small MW
- Unionized at physiologic pH
- Lipid soluble
- Large Free Fraction

Factors Reduce Antibiotic Activity
- Low pH of fluid
- High concentration of protein in fluid
- High temperature of fluid
Antibiotic Therapy

Without inflamed meninges
- Chloramphenicol
- Rifampin
- INH
- Sulfonamides
- Trimethoprim
- Triazole antifungals- fluconazole, itraconazole
Needs Inflammation

- Penicillin
- Ampicillin
- Carbenicillin
- Ciprofloxacin
- Ticarcillin (clavulanate)
- Cefuroxime
- Ceftizoxime
- Ceftazidime
- Mezlocillin
- Imipenem
- Aztreonam
- Piperacillin (tazobactam)
- Vancomycin
Questionable concentrations

Aminoglycosides
  Gentamicin
  Streptomycin
  Amikacin
  Kanamycin
  Tobramycin
  Polymyxin
Empiric choice of antibiotic:

- 0-4 weeks: ampicillin/cefotaxime or ampicillin/gentamicin
- 4-12 weeks: ampicillin/cefotaxime
- 3mo-4 years: vancomycin/ceftriaxone or cefotaxime
Treatment

5-9 years: vancomycin/ceftriaxone or cefotaxime
9-18 years: vancomycin/ceftriaxone or cefotaxime
18-60 years: vancomycin/ceftriaxone or cefotaxime
> 60 years: ampicillin/ceftriaxone or ampicillin/cefotaxime
Treatment

Definitive Choice of Antibiotic

H. influenzae:
- β-lactamase (-) ampicillin
- β-lactamase (+) cefotaxime or ceftriaxone

N. meningitidis: penicillin G or ampicillin

L. monocytogenes: ampicillin
Treatment

Enterobacteriaceae: cefotaxime
P. aeruginosa: ceftazidime/tobramycin
S. aureus:
  MSSA: nafcillin
  MRSA: vancomycin
S. epidermidis: vancomycin/rifampin
Treatment

*Streptococcus pneumoniae*

**Sensitive: Penicillin**

Penicillin MIC < 0.06 µg/mL

**Intermediate Resistance: Third Generation**

Penicillin MIC 0.12 - 1 µg/mL
Ceftriaxone MIC < 0.5 µg/mL

**Resistant: Vancomycin + Third Generation**

Penicillin MIC > 2 µg/mL
Ceftriaxone MIC > 2 µg/mL
Dexamethasone

- Blocks TNF alpha and IL-1 release
- Decreases ICP, CNS edema, fever duration, and CSF lactate and protein levels
- Increased CSF glucose level
- Decreases neurologic complications (e.g. ataxia, seizures, focal deficit) and hearing loss by approximately 50%

Children with *H. influenzae* type B
Dexamethasone

Indication: > 6 weeks of age, and clinical CSF findings of H. flu meningitis
0.15 mg/kg/dose IV Q6H x 4 days
First dose given with/before antibiotics
Dexamethasone/Antibiotic Interaction

Significant reduction of vancomycin/BBB penetration
Somewhat lower CSF concentrations of ceftriaxone
Dexamethasone/Antibiotic Interaction

Paris et.al.

S. pneumoniae susceptibility in area
If resistant is a probability then use ceftriaxone or cefotaxime and vancomycin with dexamethasone
Found vancomycin significant for killing bacteria (4 times MIC)
Treat for minimum of 10 days
Prevention

Vaccines

a. \textit{N. meningitidis}
   covers serotypes A, C, Y, W-135
   type B causes 50\% of cases
   compliment deficiency, asplenia

b. \textit{H. influenzae}
   all children at 2 months
Prevention

Vaccine (cont.)

c. **S. pneumoniae**

1) Capsular polysaccharide vaccine
Covers 23 serotypes (88% of cases)

   patients with chronic disease (e.g. CHF, COPD, diabetes, alcoholism, cirrhosis, > 65 yrs, asplenia, sickle cell disease, lymphoma, chronic renal failure, HIV, transplant patients)

2) Heptavalent Conjugate Vaccine
Covers 7 serotypes
Standard immunization
Prophylaxis

A. *Neisseria meningitidis*
   - Close contacts of index case
   - Index case
   - Rifampin

B. *Haemophilus influenzae* type B
   - Close contacts of index case
   - If a contact is 4 yo and not immunized

C. *Streptococcus Pneumoniae*
   - Not recommended
Case Presentation

EB was a 8 mo female
  – 2 days PTA pt became “ill” with “cold” Sx’s
  – 1 day PTA pt went into the clinic and was Dx with a ROM; Rx’d with Amoxicillin and APAP prn
  – Morning of admission dad was holding her and she started cough. EB started to shake and then went into a GTC Sz
Case Presentation

EB was brought into the ER with GTC Sz

- Sz was stopped with multiple doses of midazolam, diazepam, and phenobarbital
  • Lasted 30 minutes
- Sx’s: Cough, anorexia, rhinorrhea, fussy, temp (102 F)
- Labs: CBC, ABG, CSF, Lytes, UA/UC
Clinical Presentation

Physical signs/symptoms:

- Fever
- Headache
- Nausea/vomiting
- Mental status changes
- Stiff neck/back
- Positive Brudzinski's sign
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- Deafness
- Seizures
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- Anorexia
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<tr>
<td>WBC: 217</td>
<td>WBC: 14.5</td>
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<tr>
<td>RBC: 31</td>
<td>HGB: 8.2</td>
</tr>
<tr>
<td>Glu: 57</td>
<td>PLTs: 244</td>
</tr>
<tr>
<td>Protein: 118</td>
<td>Lytes: NL</td>
</tr>
<tr>
<td>Gram stain (+) for GPC</td>
<td>Glu: 244</td>
</tr>
<tr>
<td>AG + for S. pneuco</td>
<td></td>
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<tr>
<td>Cx pending</td>
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## Clinical Presentation and Diagnosis

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Case Study

EB was started on:
Vancomycin 15 mg/kg IV q 6 hrs
Ceftriaxone 100 mg/kg/day divided BID
Phenobarbital 5 mg/kg/day divided BID
Case Study

S. Pneumo sensitivities

Preliminary results:
Kirby Bauer- resistant to penicillin

Final:
Penicillin MIC = 0.094
Ceftriaxone MIC = 0.032
Vancomycin was stopped
EB continued to improve
Never had another seizure to date
CT did reveal a small bilateral subdural effusion
Follow up CT: present but decreasing in size
No neurological deficits were noted to date
Pt got a total of 14 days of antibiotics
Repeat LP was WNL
Decreased Cerebral CSF lactate

Increased BBB Permeability

Increased CSF protein

CSF outflow resistance

CSF pleocytosis

Cytotoxic Edema

Interstitial Edema

Decreased CSF glucose

Increased CSF lactate

Increased ICP

Interstitial Edema

Decreased Cerebral Blood Flow

Oxygen Depletion

Increased CSF glucose

Increased CSF lactate

Blood Flow

Thrombosis

PAF

TNF and IL-1

Endothelium-leukocyte

Increased

PGE₂

IL-1

Endothelial Cells

CNS-macrophage

Bacterial Components