Meningitis & CNS Infections

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Objectives

- Identify basic components of CNS anatomy
- Identify pathogens responsible causing CNS infection
- Be able to identify abnormalities in CSF chemistry & cytology associated with meningitis
- Be able to identify specific components of a physical exam that would suggest meningitis
- Identify appropriate empiric antibiotic regimens for bacterial meningitis

CNS Infections

- Meningitis
  - Infection of the subarachnoid space with meningeal involvement
  - Mechanical barriers intact vs. traumatic alteration
- Encephalitis
  - Inflammation of brain
- Meningoencephalitis
  - Inflammation of brain with meningeal involvement
- Shunt or Foreign Device Infections
  - Infected VP or VA shunt
  - CSF pressure monitoring devices
- Brain Abscess
- Pathogens may be bacterial, TB, viral, fungal, or parasitic
Meninges

Dura Mater

Skull

Subdural Space

Arachnoid

Subarachnoid Space

Pia Mater

CSF Channel

Brain

Somatosensory cortex

Motor cortex

Frontal lobe

Parietal lobe

Occipital lobe

Temporal lobe

Cerebellum

Brainstem

Spinal cord

Lobes of the cerebrum

Capillary of Choroid Plexus (BCSFB)

Tight junction

Specified epithelium of choroid plexus

Normal tissue capillary

Blood-brain barrier

Lipid-soluble substances

Specialized capillary

Glial cells

Mitochondria

Pinocytic vesicle

Lipid-soluble endothelial cell membrane

What's New From ICAAC 1999
About 85% of CSF produced by the choroid plexus which also controls the constituency of CSF.

- CSF volume varies by age with a normal adult having a steady state volume of ~150cc.

CSF travels in one direction through the ventricles and into the spinal column.
- Never communicates again with the point of origin.
- CSF cleared by arachnoid villi & venous plexus in spinal column.
- Creates problem for direct antibiotic placement.
  - Intraventricular - drug injected into one of the lateral ventricle.
  - Intracisternal - drug injected into the cisternal space at base of the skull.
  - Intrathecal - drug injected into the subarachnoid space at L4-5.

Hydrocephalus
- Cause
  - Rate of CSF production exceeds rate of clearance.
  - Blockage of CSF outflow.
- Therapeutic Dilemma
  - Lateral ventricles expand outward compressing brain against the skull.
  - Cannot communicate with the point of origin.
  - Shunt can become infected.

Children require shunt placement to control CSF volume and resulting pressure.
- VP or VA shunts.
- Shunts need to be modified as child grows.
- Shunt can become infected.

VP or VA shunts.
Meningitis Bacterial Pathogens

- Mechanical Barriers Intact
  - *S. pneumoniae* (pneumococci)
  - *N. meningiditis* (meningococci, Groups A,B,C,Y, & W135)
  - *H. influenzae* (type B or Hib)
  - Immunizations may also affect likely pathogen
  - Special situations *B. anthracis*
- Traumatic alteration or other risk factors
  - *S. aureus*
  - *E. coli* or *P. aeruginosa*
  - May depend on circumstances

Meningitis Bacterial Pathogens

- Neonatal
  - Children ≤ 1 month of age
  - Pathogens acquired from birth canal
    - *E. coli*
    - Group B Streptococci (*S. agalactiae*)

Listeria monocytogenes

- Uncommon CNS pathogen in adults
  - More commonly seen in the young, old, alcoholics, & immunocompromised
- Gram positive coccobacilli but can be confused as gram positive diplococcic or dipthroid
- At risk patients should have empiric coverage for this pathogen
- Probably best treated with Penicillin G or Ampicillin plus gentamicin
  - TMP/SMX maybe an alternative
Pathogenesis

- Most common cause is hematogenous spread
  - Nasal colonization (Hib & N. meningitidis)
  - Close contacts of patient need prophylactic antibiotic
  - Organisms introduced to systemic circulation
  - Bacteria seeded into meninges via bloodstream
- Contiguous spread
  - Parameningeal infection (ears, sinuses, etc) seed pathogens to meninges
- Traumatic
  - Direct mechanical seeding of meninges

Morbidity & Mortality

- Seizure Disorder
- Blindness
- Deafness
- Learning Disabilities
- Death
Antibiotic Therapy for Bacterial Meningitis

- Start antibiotics ASAP
- Empiric therapy must address likely pathogens & resistance issues
- Pick cidal antibiotics with low molecular weight, low degree of protein binding, & are lipophilic
- If steroids are to be used, they need to be administered prior to antibiotic therapy

Bacterial Meningitis: Most Likely and Empiric Therapy by Age Group

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>Most Likely Pathogens</th>
<th>Empiric Therapy</th>
<th>Drug Therapy for All Age Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns</td>
<td>H. influenzae, S. pneumoniae, S. aureus</td>
<td>Gentamicin or Cefotaxime or Ceftriaxone</td>
<td>Ceftriaxone (60 mg/kg/dose q12h) for neonates, 2 g IV q24h for adults</td>
</tr>
<tr>
<td>1 month - 4 years</td>
<td>H. influenzae, S. pneumoniae</td>
<td>Gentamicin or Cefotaxime</td>
<td>Ceftriaxone (60 mg/kg/dose q12h) for neonates, 2 g IV q24h for adults</td>
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<tr>
<td>5 - 12 years</td>
<td>S. pneumoniae, S. aureus</td>
<td>Gentamicin or Cefotaxime</td>
<td>Ceftriaxone (60 mg/kg/dose q12h) for neonates, 2 g IV q24h for adults</td>
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<td>13 - 49 years</td>
<td>S. pneumoniae</td>
<td>Gentamicin or Cefotaxime</td>
<td>Ceftriaxone (60 mg/kg/dose q12h) for neonates, 2 g IV q24h for adults</td>
</tr>
<tr>
<td>≥50 years</td>
<td>S. pneumoniae, Enterococci spp., S. enterica</td>
<td>Gentamicin or Cefotaxime</td>
<td>Ceftriaxone (60 mg/kg/dose q12h) for neonates, 2 g IV q24h for adults</td>
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Antimicrobial Agents of First Choice and Alternative Choice in Treatment of Meningitis Caused by Gram-positive Microorganisms

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<th>First Choice</th>
<th>Alternative Choice</th>
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<tr>
<td>Gram-positive</td>
<td>Ampicillin</td>
<td>Vancomycin*</td>
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<tr>
<td>Gram-negative</td>
<td>Ceftriaxone</td>
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<td>Ampicillin</td>
<td>Aztreonam</td>
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<td>Ceftriaxone</td>
<td>Meropenem</td>
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<td>Ceftazidime</td>
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<td>Imipenem</td>
<td>Piperacillin/tazobactam</td>
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<td>Vancomycin</td>
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**Enterobacteriaceae**

- **Pseudomonas aeruginosa**
  - Cefotaxime
  - Ceftriaxone
  - Ampicillin
  - 200–400 mg/kg/day q6h IV max: 2 g q4h IV
- **Escherichia coli**
  - Cefotaxime
  - Ceftriaxone
  - 200 mg/kg/day q4h IV max: 2 g q4h IV
  - *-lactamase negative
  - Ceftriaxone
  - Cefotaxime
  - *-lactamase positive
  - Haemophilus influenzae
  - Cefepime
  - 50–100 mg/kg/dose q12h IV
  - Max: adult 2 g q8h IV
  - Meropenem
  - 40–80 mg/kg q8h IV max: adult 1 g q8h IV
  - Chloramphenicol
  - 100–200 mg/kg/day q6h IV max: 1.5 g q6h IV
- **Neisseria meningitides (meningococcal)**
  - Alternative Antibiotics
  - **Antibiotic of First Choice**
  - Amikacin
  - 15–30 mg/kg/day q12h IV
- **Streptococcus pneumoniae**
  - Ceftriaxone
  - 100–200 mg/kg/day q24h IV max: 2 g q24h IV
- **Staphylococcus aureus**
  - Vancomycin
  - 15–30 mg/kg/day q12h IV

**Intraventricular and Intrathecal Antibiotic Dosage Recommendation**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose (mg)</th>
<th>Expected CSF concentration(^a) (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>10–50</td>
<td>40–300</td>
</tr>
<tr>
<td>Methicillin</td>
<td>25–100</td>
<td>100–600</td>
</tr>
<tr>
<td>Nafcillin</td>
<td>75</td>
<td>500</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1–10</td>
<td>6–60</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>1–2</td>
<td>7–15</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>0.05–0.25 mg id to 0.05–1 mg i3 times weekly</td>
<td>0.5–2 mg/L</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>5</td>
<td>30</td>
</tr>
</tbody>
</table>

**Dexamethasone**

American Academy of Pediatrics

- For children ≥ 2 months with *H. influenzae* or *S. pneumoniae*
- Administer steroid prior to starting antibiotics
  - Dexamethasone intravenously 0.15 mg/Kg Q6H for two or four days
  - Dexamethasone intravenously 0.4 mg/Kg Q12H for two days
Antibiotic Prophylaxis

- **H. influenzae**
  - Rifampin
    - Child 20 mg/Kg up to 600mg Qday X 4 days
    - Adult 600mg Qday X 4 days
    - Vaccinate if appropriate
- **N. meningitidis**
  - Ciprofloxacin
  - Rifampin
    - Child (<1 month) 10 mg/Kg up to 600mg Q12H X 2 days
    - Adult 600mg Q12H X 2 days

Bacterial Meningitis & Vaccination

- Prior to pediatric conjugate vaccines, *H. influenzae* type B (Hib) & *S. pneumoniae* were common cause of meningitis
- Today *H. influenzae* in children < 4 yrs rare in USA
  - Prior to immunization, most common pathogen for that age group
  - *Invasive S. pneumoniae* disease virtually eliminated among children vaccinated
  - Quadravalent vaccine (Groups A, C, Y, & W135) available for *N. meningitidis* (Group B not included)

Meningitis Viral Pathogens

- Causes
  - Coxsackie, Echo, & Enteroviruses cause ~85% cases
  - Mumps & Epstein Barr
  - Influenza A & B,
  - Lymphocytic Choriomeningitis Virus & CMV
  - HSV & varicella zoster
  - Arboviruses (St Louis, La Crosse, & West Nile)
- No definitive therapy for most viral disease
  - Support patient
  - Acyclovir for HSV I & Mosquito bite prophylaxis
Work up for Meningitis

- Physical Exam
  - Brudzinski’s & Kernig’s sign
  - Nuchal rigidity
  - Papilledema
- Lumbar puncture to obtain CSF
  - Chemistry (glucose & protein)
  - Cytology (WBC# & %PMN’s)
  - Gram stain or rapid identification test (< 24hrs)
  - Culture for pathogens (> 24hrs)
- Blood, Urine, & Sputum Cultures

Patient Complaints

- Headache
- Nausea
- Emesis
- Fever
- Photophobia
- Seizure
- Personality Changes
- Changes in mental status
  - Irritable, delirium, drowsy, lethargy, or coma

Brudzinski’s Sign

Diagram of Brudzinski’s Sign
Kernig’s Sign

Clinical Presentation and Diagnosis

Abnormal CSF-findings by type of meningitis

<table>
<thead>
<tr>
<th>Type</th>
<th>WBC (mm$^3$)</th>
<th>Differential</th>
<th>Protein (mg/dL)</th>
<th>Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 5</td>
<td>&gt;90% mono’s</td>
<td>&lt; 50</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Bact.</td>
<td>400-100,000</td>
<td>&gt;90% PMN’s</td>
<td>80-500</td>
<td>&lt;50%</td>
</tr>
<tr>
<td>Viral</td>
<td>5-500</td>
<td>&gt;50% lymphs+</td>
<td>30-150</td>
<td>Normal/low</td>
</tr>
<tr>
<td>Fungal</td>
<td>40-400</td>
<td>&gt;50% lymphs</td>
<td>40-150</td>
<td>NML/low</td>
</tr>
<tr>
<td>T.B.</td>
<td>100-1,000</td>
<td>&gt;80% lymphs+</td>
<td>40-150</td>
<td>NML/low</td>
</tr>
</tbody>
</table>

+ Initially CSF WBC may be PMN’s but will convert to Lymph’s over time.

Brain Abscess

• Spread
  • Contiguous focus
  • Sinuses, middle ear, dental infection
  • Hematogeneous spread from primary site

• Location
  • Frontal or temporal most common
  • Parietal vs cerebellar vs occipital
  • Epidural
  • Subdural
**Brain Abscess**

- **Microbiology**
  - Anaerobes
  - Streptococci (S. milleri)
  - Staphylococci
  - Gram negatives uncommon
  - Fungi & parasitic infections
- **Risk Factors**
  - Trauma, neurosurgery, HIV, immunocompromised, sinusitis, or mastoiditis

**Brain Abscess**

- Patients present similar to meningitis
- Focal neurological defects occur later in the course of the disease
- Headache, fever, papilledema (avoid LP), or evidence of space lesion in CNS
- Therapy includes high dose antibiotics (6-8 wks), neurosurgery, & +steroids

**Encephalitis**

- **Viruses USA**
  - Eastern & Western Equine
  - St Louis
  - West Nile
  - California group
- **Other world viruses**
  - Venezuelan equine
  - Japanese Encephalitis
- **Other viral concerns**
  - HSV, mumps, measles, VZ, EB, CMV, & Rabies
Conclusions

- Great progress made with immunizations for possible meningeal pathogens
- CNS infections still have mortality of ~30%
- Rapid diagnosis and treatment imperative to optimal outcome
- Role of steroids better defined
- Much work needs to be done in diagnosing and treating viral, fungal, and parasitic disease

What's New From ICAAC 1999