What's New From ICAAC 1999

Meningitis & CNS Infections

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IDSA Meningitis Guidelines

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

CNS-macrophage

Decreased Cerebral CSF lactate

Bacterial Components

Endothelial Cells

Inflammatiion-Venous

Increased BBB Permeability

Vasogenic Edema, Increased CSF protein

CSF overflow resistance

Interstitial Edema

Cytotoxic Edema

ICP

ICP

Oxygen Depletion

Decreased

Increased

ICP

CSF glucose

CSF lactate

Morbidity & Mortality

- Seizure Disorder
- Blindness
- Deafness
- Learning Disabilities
- Death
Meningitis

If a physician were attempting to do a “spinal tap” to obtain CSF for analysis, where would the needle likely be inserted and what would be the anatomical target?

Meninges

- Dura Mater
- Skull
- Subdural Space
- Arachnoid
- Subarachnoid Space
- Pia Mater
- CSF Channel
- Brain

Meningitis

What would be the typical profile of CSF if the meningitis were caused by bacteria in terms of WBC, glucose, & protein?

Typical Patient with Bacterial Meningitis

- CSF cloudy
- Opening CSF pressure 200-500 mm (water)
- WBC 1,000-5,000/mm$^3$ (>80% Neutrophils)
- Protein 100-500 mg/dL
- Glucose < 40 mg/dL
- CSF glucose/Blood glucose ratio ≤ 0.4
- Gram Stain positive 60-90%
- CSF culture positive 70-85%

Tunkel AR et al IDSA Guidelines CID 39(November 2004)

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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>50-66% serum</td>
</tr>
<tr>
<td>Bact</td>
<td>400-100,000</td>
<td>&gt;90% PMN's</td>
<td>80-500</td>
<td>&lt; 50% serum</td>
</tr>
<tr>
<td>Viral</td>
<td>5-500</td>
<td>&gt;50% lymphs+</td>
<td>30-150</td>
<td>NML/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

Meningitis

What is/are the likely pathogen/s?

- 4 day old child
- 8 mo old child
- 30 yr old adult
- 85 yr old adult
- 25 yr old adult MVA victim in ICU
**Meningitis Bacterial Pathogens**

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

**Mechanical Barriers Intact**

- *S. pneumoniae* (pneumococci)
- *N. meningitidis* (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

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

<table>
<thead>
<tr>
<th>Age Category</th>
<th>Most Likely Organism</th>
<th>Empiric Therapy</th>
<th>Risk Factors for All Age Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn (≤ 1 month)</td>
<td><em>E. coli</em>, <em>S. pneumoniae</em>, Group B streptococci</td>
<td><em>Ampicillin</em> + <em>Cefotaxime</em> or <em>Ceftriaxone</em> or <em>Aminoglycoside</em> and <em>Vancomycin</em></td>
<td>Respiratory tract infection, Rail Trauma, Alcoholism, High dose steroids, Splenectomy, Sickle cell disease, Immunodeficiency disorders</td>
</tr>
<tr>
<td>1 month – 4 years</td>
<td><em>E. coli</em>, <em>S. pneumoniae</em></td>
<td><em>Cefotaxime</em> or <em>Ceftriaxone</em> and <em>Vancomycin</em></td>
<td>Immune deficiencies, Splenectomy, Neurologic disorders, Alcoholism, Head trauma</td>
</tr>
<tr>
<td>5 – 19 years</td>
<td><em>S. pneumoniae</em>, <em>H. influenzae</em>, <em>N. meningitidis</em></td>
<td><em>Cefotaxime</em> or <em>Ceftriaxone</em> and <em>Vancomycin</em></td>
<td>Head trauma, Alcoholism, High dose steroids, Rail Trauma, Splenectomy, Immunodeficiency disorders, Neutropenia</td>
</tr>
<tr>
<td>&gt; 20 years</td>
<td><em>S. pneumoniae</em>, <em>N. meningitidis</em>, <em>H. influenzae</em></td>
<td><em>Cefotaxime</em> or <em>Ceftriaxone</em> and <em>Vancomycin</em></td>
<td>High dose steroids, Splenectomy, Alcoholism, Head trauma, Neurologic disorders, Immune deficiencies</td>
</tr>
</tbody>
</table>

**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 diplococci or diphtheroid
  - 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

**FDA Pneumonia Breakpoints for *S. pneumoniae* (2008)**

- **Sensitive**
  - PCN MIC ≤ 2 (Previously 0.06 mg/L)
- **Non-susceptible**
  - PCN MIC = 4 (Previously 0.12 to 1.0 mg/L)
- **Resistant**
  - PCN MIC ≥ 8 mg/L (Previously ≥ 2 mg/L)
  - Meningitis breakpoint for penicillin sensitive remains at ≤ 0.06 mg/L
    - Mechanism of resistance is alteration of penicillin binding proteins not beta-lactamase production

- **Respiratory tract infection**
- **Otitis media**
- **Mastoiditis**
- **Head Trauma**
- **Alcoholism**
- **High-dose steroids**
- **Splenectomy**
- **Sickle cell disease**
- **Immunoglobulin deficiency**
- **Immunosuppression**
A consensus regarding recommended agents for the treatment of CNS infections caused by anthrax, or other biological warfare agents, has not been reached. Optimal treatment must be tailored to the particular pathogen and/or genetic variants of the pathogen.

**Bacillus anthracis**
- Trimethoprim 10 mg/kg/day and sulfamethoxazole 50 mg/kg/day, q6h
- Ampicillin 220 – 400 mg/kg/day, q6h IV or Penicillin G max: 2 g q4h IV plus gentamicin*

**Listeria monocytogenes**
- Linezolid
- Vancomycin* Methicillin resistant
- Vancomycin*Nafcillin Penicillin resistant

**Staphylococcus epidermidis**
- Linezolid
- Vancomycin* Methicillin resistant
- Vancomycin*Nafcillin 200 mg/kg/day q4h IV max: 2g q4h IV Penicillin resistant

**Staphylococcus aureus**
- Ampicillin ± gentamicin*
- Cefotaxime
- Ceftriaxone
- Chloramphenicol*

**Group B streptococcus**
- Cefepime 50 mg/kg/dose q12h max: adult 2g q8h IV or Meropenem 40mg/kg q8h IV max: adults 1 g q8h IV with Vancomycin*
- Linezolid 600 mg q12h IV
- Cefotaxime or Ceftriaxone and Vancomycin* 30-40 mg/kg/day IV (60 mg/kg/day IV q6h)

**Penicillin resistant**
- Cefotaxime 200 mg/kg/day q4-6h IV max 2 g q4h
- Ceftriaxone 100 mg/kg/day q24 h IV max: adults 2 g q12h
- Chloramphenicol* 100 mg/kg/day q6h max 1.5 g q6h
- Penicillin G 200,000 –300,000 units/kg/day q4h IV max: 4 million units q4h IV

**Penicillin susceptible**

**Streptococcus pneumoniae**
- Alternative Antibiotics
- Antibiotic of First Choice
- Organism Antimicrobial Agents of First Choice and Alternative Choice in Treatment of Meningitis Caused by Gram-positive Microorganisms

**Dexamethasone**
- Tunkel AR et al IDSA Guidelines CID 39(November) 2004

- Concern is that steroids will reduce inflammation and ultimately antibiotic penetration
  - Vancomycin
  - Generally recommended for children & adults with proven or suspected *S. pneumoniae* or *H. influenzae* meningitis
  - Administer steroid 10-20 minutes prior to (or time of) starting antibiotics
  - Dexamethasone intravenously 0.15 mg/Kg Q6H for two or four days

**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

**Meningitis**
- You have a 35 yr old male patient with documented *S. pneumoniae* meningitis who was initially treated last evening with ceftriaxone and vancomycin. The attending asks whether he received dexamethasone?
  - What is the value if any of using dexamethasone?
  - If given how should dexamethasone be used?
  - Are there any potential drawbacks in using dexamethasone?

**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
**Meningitis**

- Your son or daughter is about to leave for college and their freshman year living in the dorm.
- Are there any meningitis issues that should be addressed apriori?

**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 with Prevnar
  - Prevnar 13 Phase 3 (2008)
  - Menactra®, Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine
  - Group B not included
  - Wyeth has a group B vaccine in phase II (2008)

**Meningitis**

- Your attending is concerned about antibiotic penetration into CSF in a patient with *S. pneumoniae* meningitis being treated with ceftriaxone. Should a direct route of administration be used in this situation?

**Intraventricular and Intrathecal Antibiotic Dosage Recommendation**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose (mg)</th>
<th>Expected CSF conc (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>10–50</td>
<td>60–300</td>
</tr>
<tr>
<td>Methicillin</td>
<td>25–100</td>
<td>160–400</td>
</tr>
<tr>
<td>Nafcillin</td>
<td>75</td>
<td>500</td>
</tr>
<tr>
<td>Cefalothin</td>
<td>25–100</td>
<td>160–400</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>25–100</td>
<td>160–400</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1–10</td>
<td>6–60</td>
</tr>
<tr>
<td>Quinupristin/</td>
<td>1–2</td>
<td>7–13</td>
</tr>
<tr>
<td>Dalfopristin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td>1–10</td>
<td>6–60</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>0.05–0.25 mg/d to 0.05–1 mg 1-3 times weekly</td>
<td></td>
</tr>
</tbody>
</table>

**CSF**

- 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 & venus 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-L5
**Patient Complaints**
- Headache
- Nausea
- Emesis
- Fever
- Photophobia
- Seizure
- Personality Changes
- Changes in mental status
  - Irritable, delirium, drowsy, lethargy, or coma

**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)
  - ELISA, Coagglutination, or latex agglutination
  - Limulus lysate for gram negative endotoxin
  - PCR (N.meningitidis, S. pneumoniae, H. influenzae, S. agalactiae, L. monocytogenes & enteroviruses)
  - Lactate (>4.2 mmol/L considered positive for bacterial meningitis)
  - Procalcitonin (> 5 micrograms/L suggestive of bacterial meningitis)
  - Creatinine (CRP) (Elevated in bacterial meningitis)
- Culture for pathogens (> 24hrs)
- Blood, Urine, & Sputum Cultures

**Eye Ground Exam in Meningitis**
- Normal
- Papilledema

**Brudzinski’s Sign**

**Kernig’s Sign**

**Antibiotic Therapy for Bacterial Meningitis**
- Start antibiotics ASAP
  - Get diagnostic studies prior to antibiotic therapy
- Start steroids prior to antibiotics
  - Pick cidal antibiotics with low molecular weight, low degree of protein binding, & are lipophilic
- Duration
  - N. meningitidis & H. influenzae 7 days
  - S. pneumoniae 10-14 days
  - S. agalactiae 14-21 days
  - Aerobic gram negatives 21 days
  - L. monocytogenes > 21 days

IDSA Guidelines November 2004
### Meningitis Viral Pathogens

- **Causes**
  - Coxackie, 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

### 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

### 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**