Meningitis & CNS Infections

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IDSA Meningitis Guidelines CID 2004

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
Arachnoid → Subdural Space
Pia Mater → Subarachnoid Space
CSF Channel → Brain

Capillary of Choroid Plexus (BCSFB)

Blood Brain Barrier (BBB)

Normal Tissue Capillary

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

- 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 problems for direct antibiotic placement
    - Intraventricular- drug injected into one of the lateral ventricles
    - Intracisternal- drug injected into the cisternal space at base of the skull
    - Intrathecal- drug injected into the subarachnoid space at L4-L5

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
  - 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

Meningitis Bacterial Pathogens

- 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

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
What's New From ICAAC 1999

Antimicrobial Agents of First Choice and Alternative Choice in Treatment of Enterobacteriaceae, Haemophilus influenzae, and Escherichia coli (meningococcal)

Bacterial Meningitis: Most Likely and Empiric Therapy by Age Group

Antimicrobial Agents of First Choice and Alternative Choice in Treatment of Meningitis Caused by Gram-positive Microorganisms

Morbidity & Mortality
- Seizure Disorder
- Blindness
- Deafness
- Learning Disabilities
- Death

Intraventricular and Intrathecal Antibiotic Dosage Recommendation

Antibiotic | Dose (mg) | Expected CSF conc (mg/L)
--- | --- | ---
Amphotericin B | 0.05-0.25 mg/d to 0.05-1 mg 1-3 times weekly | --
Nalidixic acid | 500 | --
Telithromycin | 500 | --
Vancomycin | 500 | --
Penicillin G | 200,000 | --
**Dexamethasone**
Tunkel AR et al IDSA Guidelines CID 39(November) 2004

- 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

**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

**Management algorithm infants and children with bacterial meningitis**

<table>
<thead>
<tr>
<th>Suspension for bacterial meningitis</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppression, history of selected CNS diseases, papilledema, altered consciousness, or focal neurologic deficit</td>
<td>Blood cultures STAT</td>
<td>Dexamethasone + empirical Antimicrobial therapy</td>
</tr>
<tr>
<td>Blood cultures and lumbar puncture STAT</td>
<td>Yes</td>
<td>Dexamethasone + empirical Antimicrobial therapy</td>
</tr>
<tr>
<td>CSF findings c/w bacterial meningitis</td>
<td>Negative CT scan of the head</td>
<td>Yes</td>
</tr>
<tr>
<td>Continue therapy</td>
<td>Perform lumbar puncture</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Recommendations for antimicrobial therapy in adult patients with presumptive pathogen identification by positive gram stain**

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Recommended Therapy</th>
<th>Alternative Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>Ceftriaxone or cefotaxime</td>
<td>Meropenem (C-III), fluoroquinolone (B-II)</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>Ceftriaxone or cefotaxime</td>
<td>Ciprofloxacin, rifampin</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Ceftriaxone or cefotaxime</td>
<td>Meropenem (C-III), fluoroquinolone (B-II)</td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
<td>Ceftriaxone or cefotaxime</td>
<td>Ciprofloxacin, rifampin</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>Ceftriaxone or cefotaxime</td>
<td>Ciprofloxacin, rifampin</td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td>Ciprofloxacin</td>
<td>Rifampin, meropenem</td>
</tr>
</tbody>
</table>

**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

**What's New From ICAAC 1999**
**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
- Quadrivalent 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)
- CIE, coagglutination, or latex agglutination
- 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)
- C-reactive proteins (CRP) (Elevated in bacterial meningitis)
- 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

**Eye Ground Exam in Meningitis**

- Normal
- Papilledema

**Brudzinski’s Sign**

[Diagram of Brudzinski’s Sign]
Kernig’s Sign

Typical Patient with Bacterial Meningitis
- CSF cloudy
- Opening CSF pressure 200-500 mm (water)
- WBC 1,000-5,000/mm3 (>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)

Clinical Presentation and Diagnosis
Abnormal CSF-findings by type of meningitis

<table>
<thead>
<tr>
<th>Type</th>
<th>WBC (mm³)</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*

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