Central Nervous System Infections

Resource very limited vs Resource less limited settings

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Goals and Objectives

- Know most causes of meningitis
- Know standard of care (USA) for diagnosis and treatment
- Appreciate limitations of this approach in resource limited settings
- Design a study in the resource limited setting which may improve local outcomes
**Meningitis** (meningeal inflammation)
- Community-acquired meningitis
  - Acute meningitis - symptoms progress over hours to days
    - Bacterial or Viral
  - Chronic meningitis - symptoms present for weeks
    - TB or Cryptococcus

**Encephalitis** (diffuse brain inflammation)
- Viral (HSV, WNV)
- Listeria, Syphilis
- Malaria

**Brain abscess** (focal brain inflammation)
- Bacterial
- Toxoplasma
Meningitis

• Bacterial meningitis 10x as common in developing countries than in the rest of world
• Almost always fatal without treatment
• Symptoms:
  - Fever 75-95%
  - Headache 80-95%
  - Photophobia
  - Vomiting (children)
• Signs:
  - Neck stiffness 50-90%
  - Confusion 75-85%
• Only 44% of meningitis cases had all 3:
  - Neck stiffness, fever, confusion
Major Pathogens
community acquired meningitis

- *Streptococcus pneumoniae*
- *Neisseria meningitidis*
- *Haemophilus influenzae B*
- *Listeria monocytogenes*
- *Streptococcus suis (SE Asia)*
- *Tuberculosis*
- *Cryptococcus*
# Bacterial Etiologies and Age

<table>
<thead>
<tr>
<th>Predisposing Factor</th>
<th>Common Bacteria Isolated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 mo</td>
<td>GBStrep, <em>E. coli</em>, <em>Listeria</em></td>
</tr>
<tr>
<td>2-50 years</td>
<td><em>N. meningitidis</em>, <em>Strep pneumo</em></td>
</tr>
<tr>
<td>&gt;50 years</td>
<td><em>Strep pneumo</em>, <em>N. meningitidis</em>, <em>Listeria</em></td>
</tr>
</tbody>
</table>
### Other risk factors for meningo-encephalitis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF leak</td>
<td><em>Strep pneumoniae</em></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td><em>Listeria</em>, <em>Tuberculosis</em></td>
</tr>
<tr>
<td>AIDS</td>
<td><em>Toxoplasma</em>, <em>Tuberculosis</em>,</td>
</tr>
<tr>
<td></td>
<td><em>Cryptococcus</em></td>
</tr>
<tr>
<td>Animal bite</td>
<td>Rabies</td>
</tr>
<tr>
<td>Pig farming</td>
<td><em>Strep suis</em></td>
</tr>
</tbody>
</table>
# The Usual Suspects of acute bacterial meningitis

<table>
<thead>
<tr>
<th>Organism</th>
<th>% USA, Europe</th>
<th>Resource poor</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Strep pneumoniae</em></td>
<td>50</td>
<td>HIV rate dependent</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>0</td>
<td>Vaccination coverage dependent</td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td>30</td>
<td>Outbreaks in Africa</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>5</td>
<td>?</td>
</tr>
<tr>
<td>Group B <em>Streptococcus</em></td>
<td>5</td>
<td>?</td>
</tr>
<tr>
<td><em>Strep suis</em></td>
<td>0</td>
<td>Outbreaks in SE-Asia</td>
</tr>
</tbody>
</table>
Cryptococcus neoformans
India Ink stain
Toxoplasma Encephalitis

In AIDS patients
reactivation of latent *Toxoplasma* cysts
treat with oral sulfadiazine/pyrimethamine
prevent with oral TMP/SMX if IgG positive

multiple, ring-enhancing lesions
# Tests of CSF in Patients with Suspected CNS Infection

## Resource rich countries

### Routine tests
- RBC and WBC with differential
- Glucose and Protein concentration
- Gram stain (50-90% sensitive)
- Bacterial culture (97% sensitive)
- Opening pressure

### Selected specific tests based on clinical suspicion
- Smears/culture for AFB
- VDRL
- India ink stain and Cryptococcal antigen
- Fungal culture
- PCR (EBV, CMV, HSV, VZV, Enterovirus)
- Cytology
### Tests of CSF in Patients with Suspected CNS Infection

**Resource limited countries**

**Routine tests**
- RBC and WBC with differential, Glc and Prot concentration
  - Cloudy or bloody
  - Glc, Prot, Leucocyte esterase per (Urine dipstick)
- Opening pressure; How fast is CSF coming out?
- Gram stain
  - Centrifuge 3000G for 20 minutes
  - Microscopy for 10 mins (50-90% sensitive)
- Bacterial culture (97% sensitive)

**Selected specific tests based on clinical suspicion**
- Smears AFB (20 minutes)
  - Centrifuge 3000G for 20 minutes
  - Microscopy for 20 minutes
- VDRL
- India ink stain
Gram stain of Spinal fluid

Neisseria meningitidis
### Cell Count in CSF

<table>
<thead>
<tr>
<th>Cause of Meningitis</th>
<th>WBC count</th>
<th>Primary Cell Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral</td>
<td>50-1000</td>
<td>Mononuclear</td>
</tr>
<tr>
<td>Bacterial</td>
<td>1000-5000</td>
<td>Neutrophilic</td>
</tr>
<tr>
<td>Tuberculous</td>
<td>50-300</td>
<td>Mononuclear</td>
</tr>
<tr>
<td>Cryptococcal</td>
<td>20-500</td>
<td>Mononuclear</td>
</tr>
</tbody>
</table>

True WBC in CSF = actual CSF WBC - \( \frac{\text{WBC in blood} \times \text{RBC in CSF}}{\text{RBC in blood}} \)
Diagnostic Confounders

- Partially treated meningitis is very common (60% of all cases in Vietnam)
- Cerebral malaria difficult to distinguish
  - Malawi: 42% of children with bacterial meningitis received malaria treatment (0.5% had malaria)
  - Kenya: 14% of comatose children with malaria on smear had bacterial meningitis
USA vs world
Therapy for bacterial meningitis

- Adults Empiric therapy
  - Ceftriaxone 2gm Q12 hours
    plus
  - Vancomycin 15mg/kg Q8 hours (trough of >20)
- >50 years
  - Add ampicillin 2gm Q4 or continuous infusion

- \textit{S. pneumoniae}
  - 10-14 days (USA) vs 7 days (rest world-unless HIV+)
- \textit{N. meningitidis} or \textit{H. influenzae}
  - 7 days (USA) vs 5 days (rest world-unless HIV+)
Cryptococcal Meningitis

- Amphotericin B (0.7-1 mg/kg) + flucytosine (100 mg/kg/day) x 2 weeks
- Then fluconazole (400mg/day) x minimum of 10 weeks, then fluconazole (200mg/day) suppression (in immunocompromized/HIV+ patients)
Available antibiotics: Beta-lactams

- **Penicillins**: Streptococcus, Enterococcus, anaerobes
  - PCN
  - *Amoxicillin, Ampicillin:* Some GNR
  - *Amox/clav, Amp/sulb:* GNR, anaerobes, MSSA
  - Piperacillin/tazo, ticarcillin/clav: resistant GNR, Pseudomonas
  - Nafcillin, *Cloxacillin:* MSSA, NOT Enterococcus

- **Cephalosporins**: Streptococcus, NOT Enterococcus, NOT Listeria
  - 1\textsuperscript{st} Generation: *Cefazolin* Strep, MSSA, some GNR
  - 2\textsuperscript{nd} Generation: GNR
  - 3\textsuperscript{rd} Generation: Less MSSA, more (resistant) GNR
    - *Ceftriaxone*: NOT Pseudomonas
    - Cefipime, ceftazidime: Pseudomonas

- **Carbapenemems**: Streptococcus, Resistant GNR, Enterococcus
  - Imipenem, Meropenem, Doripenem: Pseudomonas
  - Ertapenem: NOT pseudomonas
**Available antibiotics: common non B-lactams**

- **Quinolones:**
  - **Ciprofloxacin:** GNR, atypicals, Strep NOT Staphylococcus Pseudomonas
  - **Levofloxacin, moxifloxacin:** More G+ coverage

- **Aminoglycosides:**
  - **Gentamicin**, tobramycin Aerobe GNR

- **Vancomycin:** Gram positives
- **Metronidazole:** Anaerobes
- **TMP/SMX (bactrim):** GNR, CA-MRSA
- Aztreonam Aerobe GNR
- Clindamycin Streptococci, anaerobes

- **Tetracyclines, Macrolides**
  - **TCN:** Minocycline, doxycycline G+ cocci, atypicals
  - **ML:** Azithromycin, **Erythromycin**
# Chloramphenicol

- **Abx spectrum:**
  - G+, G-, anaer, MRSA
- **Aplastic anemia:**
  - 1:20,000

<table>
<thead>
<tr>
<th>Brand</th>
<th>Country/Region</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alficetyn</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphicil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biomicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlornitromycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloromycetin</td>
<td>(U.S., IV)</td>
<td></td>
</tr>
<tr>
<td>Chlorsig</td>
<td>(U.S., Australia, eye drops)</td>
<td></td>
</tr>
<tr>
<td>Dispersadron C</td>
<td>(Greece, eye drops)</td>
<td></td>
</tr>
<tr>
<td>Edrumycetin 250 mg</td>
<td>(Bangladesh)</td>
<td></td>
</tr>
<tr>
<td>Fenicol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kemicetine</td>
<td>(UK, IV)</td>
<td></td>
</tr>
<tr>
<td>Laevomycetin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brochlor</td>
<td>(Aventis Pharma Ltd)</td>
<td></td>
</tr>
<tr>
<td>Golden Eye</td>
<td>(Typharm Ltd)</td>
<td></td>
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<tr>
<td>Optrex Infected Eyes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oftan Chlora</td>
<td>(eye ointment)</td>
<td></td>
</tr>
<tr>
<td>Phenicol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevimycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renicol</td>
<td>(India, eye drops)</td>
<td></td>
</tr>
<tr>
<td>Silmycetin</td>
<td>(Thailand, eye drops)</td>
<td></td>
</tr>
<tr>
<td>Synthomycine</td>
<td>(Israel, eye ointment)</td>
<td></td>
</tr>
<tr>
<td>Tifomycine</td>
<td>(France)</td>
<td></td>
</tr>
<tr>
<td>Vernacetin</td>
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</tr>
<tr>
<td>Veticol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orchadexoline</td>
<td>(Egypt, eye drops)</td>
<td></td>
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<tr>
<td>Isoptophenicol</td>
<td>(Egypt, eye drops)</td>
<td></td>
</tr>
<tr>
<td>Cedoctine</td>
<td>(Egypt, IV)</td>
<td></td>
</tr>
<tr>
<td>Chloramex</td>
<td>(So. Africa, eye ointment)</td>
<td></td>
</tr>
</tbody>
</table>
Rest of world Empiric Therapy for bacterial meningitis

- PCN IV (6 x a day) or AMP IM, IV 6 x a day
- Ceftriaxone IM, IV (once a day)-generic!
- Chloramphenicol IM, IV, PO (4 x a day)

- 7 days vs 10 days equal (India)
- 3 days vs 7 days equal (Chilean study) *N. meningitidis, H. influenza*

- Epidemic in meningococcal meningitis in Africa:
  - 4 gm ceftriaxone x 1 or
  - oil-susp chloramphenicol 3 gm IM x 1

- Add gentamicin for neonates
PCN/AMP vs chloramphenicol vs ceftriaxone

- Studies in 1980’s: no difference in outcome with PCN vs ceftriaxone vs chloramphenicol
- *H. influenza* 20% R to PCN/Chloramphenicol
- *S. pneumo* 20% R to PCN/Chloramphenicol
  - 5% I to ceftriaxone
- Vancomycin not available
- FQ-but not much data
- Rifampin-but problem with TB
Meningitis Prevention

- *Haemophilus influenzae*
  - HiB vaccine routinely recommended for children
  - HiB decreased rate by 90% (Kenya) and 99% (Uganda)
  - Worldwide 2006; 22% of birth cohort received HiB vs 8% in 1999

- *Streptococcus pneumoniae*
  - 23 valent vaccine

- *Neisseria meningitidis*
  - Vaccination for serogroups A and C (important in military, college students and travelers to Meningococcal belt in sub-Saharan Africa and Mecca)
African Meningitis Belt

Fig. 1. The African meningitis belt. Source: WHO.
**Weekly Updates on WHO website**

**(Sample summary from March 2008)**

<table>
<thead>
<tr>
<th>Pays</th>
<th>Case</th>
<th>Death</th>
<th>Létalité (%)</th>
<th>District en Alert</th>
<th>District en Epidémie</th>
<th>Semaines notifies</th>
<th>En districts (%)</th>
<th>En semaines (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benin</strong></td>
<td>180</td>
<td>24</td>
<td>13.3</td>
<td>0</td>
<td>0</td>
<td>01-11</td>
<td>100.0</td>
<td>99.9</td>
</tr>
<tr>
<td><strong>Burkina Faso</strong></td>
<td>5046</td>
<td>519</td>
<td>10.3</td>
<td>20</td>
<td>11</td>
<td>01-11</td>
<td>114.5</td>
<td>100.0</td>
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<tr>
<td><strong>Cameroun</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Centrafrique</strong></td>
<td>202</td>
<td>57</td>
<td>28.3</td>
<td>0</td>
<td>1</td>
<td>01-10</td>
<td>47.1</td>
<td>99.6</td>
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<tr>
<td><strong>Côte d'Ivoire</strong></td>
<td>693</td>
<td>112</td>
<td>16.2</td>
<td>0</td>
<td>2</td>
<td>01-11</td>
<td>95.4</td>
<td>68.5</td>
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<tr>
<td><strong>Ethiopia</strong></td>
<td>89</td>
<td>5</td>
<td>5.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>01-09</td>
<td>-</td>
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<tr>
<td><strong>Ghana</strong></td>
<td>123</td>
<td>25</td>
<td>20.3</td>
<td>0</td>
<td>0</td>
<td>01-07</td>
<td>-</td>
<td>75.0</td>
</tr>
<tr>
<td><strong>Mali</strong></td>
<td>503</td>
<td>38</td>
<td>7.6</td>
<td>3</td>
<td>1</td>
<td>01-10</td>
<td>88.1</td>
<td>100.0</td>
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<tr>
<td><strong>Niger</strong></td>
<td>369</td>
<td>26</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>01-11</td>
<td>100.0</td>
<td>99.6</td>
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<tr>
<td><strong>Nigeria</strong></td>
<td>649</td>
<td>72</td>
<td>11.1</td>
<td>6</td>
<td>4</td>
<td>01-11</td>
<td>56.7</td>
<td>99.9</td>
</tr>
<tr>
<td><strong>RD Congo</strong></td>
<td>123</td>
<td>17</td>
<td>13.8</td>
<td>1</td>
<td>3</td>
<td>01-04</td>
<td>-</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Tchad</strong></td>
<td>321</td>
<td>39</td>
<td>12.1</td>
<td>3</td>
<td>0</td>
<td>01-10</td>
<td>56.0</td>
<td>91.2</td>
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<tr>
<td><strong>Togo</strong></td>
<td>208</td>
<td>41</td>
<td>19.7</td>
<td>1</td>
<td>0</td>
<td>01-10</td>
<td>100.0</td>
<td>98.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>8,506</td>
<td>975</td>
<td>11.5</td>
<td>34</td>
<td>22</td>
<td>01-11</td>
<td>67.7</td>
<td>97.0</td>
</tr>
</tbody>
</table>

**Définition des seuils d’alerte/épidémie non applicable à ce pays situé en dehors de la ceinture de la méningite**

*Definition of Alert/epidemic thresholds not applicable to this country outside the meningitis belt*
What is special about the belt?

- Climate
- Outbreaks occur during the dry season
- Crowding
- Migration
- Displaced and dispersed populations
- Clonal nature of the organism able to spread rapidly
The Meningitis Vaccine Project (MVP) is a partnership between the World Health Organization (WHO) and the Program for Appropriate Technology in Health (PATH). Created in 2001 with core funding from the Bill & Melinda Gates Foundation, its goal is to eliminate epidemic meningitis as a public health problem in Sub-Saharan Africa.
Infection Control

Droplet Precautions x 24 hours on adequate therapy

- Unknown cause of meningitis (bacterial)
- *Neisseria meningitidis*
- *Haemophilus influenzae* B
Other issues

- Counterfeit drugs
  - Penicillin
  - Tetracycline
  - Chloramphenicol

- Expired shelf life/storage (ceftriax (<25 C)

- Dexamethasone
  - Developed countries: yes
  - No benefits in resouce poor settings:
    - Largely HIV+late presentation, prior Abx
    - Vietnam study +/- but most Strep. suis and pretreated
    - No Harm if using it (except cost lower penetration Abx)

- How to perform efficacy trials?
- How to conduct them ethically?
Evidence Based Medicine

- How to perform efficacy trials?
- How to conduct them ethically?
Trial design

- How many days (in USA or Africa) to treat?
- **Meningococcal meningitis treatment:**
  - PO cipro vs IV ceftriaxone vs chloramphenicol
  - Who pays?
  - Consent, malaria testing, HIV testing?
  - Offer vaccination?