Pyogenic Meningitis
What is meningitis

- Inflammation of meninges identified by abnormal number of white cells in CSF.

- **Acute meningitis**
  'Onset of meningeal symptoms over the course of hours to a few days'
  Classic triad of headache/neckstiffness/photophobia.

- **Chronic meningitis**
  - lasts weeks or months ie symptoms, signs, CSF abnormal for at least 4 weeks)
Bacterial Meningitis Pathogenesis.

Nasopharyngeal Colonisation

Local Invasion

Bacteraemia

Meningeal Invasion
Pathogenesis (cont)

Replication in Subarachnoid space
release of components: cell wall/LPS

Cerebral microvascular endothelium
Macrophages

IL-1/TNF

BBB permeability
SA space inflammation

Cerebral vasculitis
hydrocephalus
cytotoxic oedema
interstitial oedema

Vasogenic oedema
raised IC pressure
cerebral infarction

decreased cerebral blood flow/loss of cerebrovascular auto regulation
Epidemiology of Bacterial meningitis

- 170,000 die every year.
- 1/3 deaths due to meningococcal disease.
- In developing countries incidence is 10 times than developed countries in children.
- Mortality 5-15% developed countries
- Mortality 15-50% developing countries
- Sequelae 12-20% in developed countries
- In developing unknown (?) >30%
Presentations

Headache > 90%
Meningismus > 85%
Altered sensation 80%
Kernigs > 50%
Brudzinski > 50%
Vomiting 35%
Seizures 30%
Focal (CN palsies) 10-20%
Papilloedema <1%
NEONATES

• not usually meningismus,

• instead temperature instability

• high pitch crying

• Lethargy

• failure to feed

• vomiting and diarrhoea.

• Bulging fontanelle 17% (late sign),

• opisthonus 33%, convulsions 12%
Bacterial meningitis

- Most important pathogens worldwide.

1. *Neisseria meningitidis*
2. *Strep.Pneumoniae*
3. *Haemophilus Influenzae.*
## Causes

<table>
<thead>
<tr>
<th>Neonatal</th>
<th>Purulent</th>
<th>Lymphocytic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B streptococcus</td>
<td>HSV</td>
<td>HSV</td>
</tr>
<tr>
<td>Salmonella spp</td>
<td>Enterovirus</td>
<td>Enterovirus</td>
</tr>
<tr>
<td>E.coli and other coliforms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Listeria spp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older</td>
<td>Purulent</td>
<td>Lymphocytic</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>S. pneumomiae</td>
<td>M.Tb</td>
<td></td>
</tr>
<tr>
<td>Salmonella spp</td>
<td>Leptospirosis</td>
<td></td>
</tr>
<tr>
<td>(H. Influenzae)</td>
<td>Treponoma</td>
<td></td>
</tr>
<tr>
<td>N. meningitidis</td>
<td>Borrellia</td>
<td></td>
</tr>
<tr>
<td>Listeria spp</td>
<td>Enterovirus</td>
<td>ARBO virus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adeno/Toga</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LCV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HIV</td>
</tr>
</tbody>
</table>
Viral meningitis

- A specific viral aetiology only found in 11%.
- Coxsackie B, adenovirus, CMV, HIV

HIV
Can infect meninges and persist after initial infection.
Can be the primary presentation.
5-10% of patients with acute sero-conversion illness present with a meningo-encephalitis.
Neisseria Meningitidis

• Gram-ve diplococcus
• First described in 1805, outbreak in Geneva.
• Causative organism identified in 1887.
• Most commonly children, young adults.
• Case mortality 10-15%
• 5 main serotypes: A/B/C/ W135 Y
• C5-C9 deficiencies have increased risk of infection.
• 3 main forms of disease. Meningeal/Septicaemic and Pneumonic.
• Inhabits mucosal membrane of throat/nose.
• 5-10% population are asymptomatic carriers.
Meningitis Belt

• Epidemics have been seen regularly over at least a century. Between West Africa and the Sudan
• The Meningitis Belt
• latitudes 4 and 16 north Pop^n 300x10^6
• Increasing in size now to Algeria and Zambia
• High level of endemicity
• Large epidemics usually serotype A (80%). Seeing increasing W135 recent Burkina Faso (probably originating from Saudi)
• Usually end Nov-end of June Decline in rainy season.
• Predisposing factors - overcrowding, poor hygiene. (risk in schools, slums, barracks, refugee camps, prisons)
What is an epidemic?

- In hyperendemic areas;
  - 15 cases /100,000 / week averaged over 2 weeks.

Once epidemic is detected lower level acceptable as definition in contiguous area 5/100,00.

- Other situations;
  - 3-4 fold increase compared to previous year,
  - or doubling of cases from one week to the next over a period of 3 weeks.
**Strep. Pneumoniae**

- Gram+ve diplococcus
- Most common cause of BM in Malawi
- 25% mortality
- Recurrence and poorer outcome associated with inherited or acquired immune insult.
- Splenectomy/asplenic states/sickle cell disease/hypogammaglobulinaemia/
- Particular association with CSF leak traumatic or non-traumatic.
**Haemophilus influenzae**

- Gram-ve coccobacillus
- Most often in children under 6 yrs.
- Most common was Haem. Inf b (capsular type) peak incidence was 6-12 months
- Profound reduction in children with introduction of Hib vaccine
Increasing Hib antibiotic resistance
1996-June 2002
Queen Elizabeth Hospital, Blantyre, Malawi
HIB VACCINE INTRODUCTION

January 2002
Trends in Hi & Sp paediatric (<5y) meningitis

Hi cases decrease
Causes of meningitis in the developing world

- *S. pneumoniae*: 6.7 - 48%
- *H. influenzae b*: 16.5 - 47%
- *Salmonella*: 0 - 12.4
- *N. Meningitidis*: 2.6 - 27
- No growth: 21 - 44.9

*Malawi, Rwanda, South Africa*
<table>
<thead>
<tr>
<th>Location</th>
<th>Year</th>
<th>No.</th>
<th>Group B %</th>
<th>E.coli %</th>
<th>Salm %</th>
<th>Kleb %</th>
<th>Other %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eng/Wal</td>
<td>96/7</td>
<td>144</td>
<td>48</td>
<td>18</td>
<td>0.7</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>Taiwan</td>
<td>84-9</td>
<td>85</td>
<td>32</td>
<td>20</td>
<td>0</td>
<td>3.5</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Ethiopia</td>
<td>87-9</td>
<td>30</td>
<td>0</td>
<td>23</td>
<td>7</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.Africa</td>
<td>81-9</td>
<td>87</td>
<td>32</td>
<td>23</td>
<td>0</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malawi</td>
<td>96-9</td>
<td>37</td>
<td>38</td>
<td>19</td>
<td>24</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td></td>
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</tr>
</tbody>
</table>

**Causes of bacterial meningitis in neonates**

*Others inc N.M, S.pneum, Hib*
Strep. Agalactiae

• Group B Strep commonest cause in neonates. 12-27% mortality.

• 15-40% pregnant woman, asymptomatic +ve rectal/vaginal swabs.

• Biggest risk is vertical transmission (risk related to size of inoculum), but horizontal is described.

• Most neonatal due to subtype 3 in first week of life. Early or late disease.
Listeria Monocytogenes

- 2-3% cases  20-30% mortality. Gram+ve bacillus
- Isolated in dust/soil/water/sewerage/decaying vegetable matter.
- Commonest in neonates (10% cases),
- Pregnant woman can harbour organism asymptomatically in rectum and genital tract thus risk to foetus and baby.
- Perinatal takes 2 forms
  1. Early: intrauterine infection producing granulomatosis infantisepticum.
  2. Late: Just after birth meningitis in 2\textsuperscript{nd}/3\textsuperscript{rd} week of life.

No increase found in HIV, although association with deficiencies in cell-mediated immunity.

Outbreaks associated with dairy products and vegetables

Gastric acidity provides protection.
## Case fatality rate and (sequelae) of Bacterial Meningitis in developing countries

<table>
<thead>
<tr>
<th>Organism</th>
<th>CFR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. pneumoniae</em></td>
<td>17-52</td>
</tr>
<tr>
<td><em>H. influenzae b</em></td>
<td>37-59.5</td>
</tr>
<tr>
<td><em>N. Meningitidis</em></td>
<td>±13</td>
</tr>
<tr>
<td><em>Salmonella spp</em></td>
<td>39 - 57.2</td>
</tr>
<tr>
<td><em>GNR</em></td>
<td>39.3</td>
</tr>
<tr>
<td>No Growth</td>
<td>30</td>
</tr>
</tbody>
</table>

Overall: 12-38 (10-44)  
Developing world: (5-10)  
Malawi, Brazil, Gambia, Pakistan, Mozambique, PNG  
Overall: <5
First line antibiotic treatment for bacterial meningitis

• Chloramphenicol; 25mg/kg 6 hourly.
  +
• Benzyl Penicillin; 100,000 iu/kg 6 hourly

Epidemic NM Tyfomycine (long acting CAP 3 g as stat dose.)

Neonates: Pen or Amp and Gent for 14-21 days
Causes of bacterial meningitis in Malawian children
n = 472

- *Strep. Pneumoniae* 245 (52%)
- *Haemophilus influenzae* 99 (21%)
- *Salmonella species* 57 (12%)
- *Neisseria meningitides* 6 (1.2%)
- No growth 61 (13%)
Outcomes among bacterial meningitis in Malawi

Died 31%

Outcome in survivors
Full recovery 54%
Neurological sequelae,
• cerebral palsy 24%
  - w/o seizures 4%
  - w/ seizures 20%
• global delay 24%
• motor delay 16%

Hearing loss, survivors 29%
Bilateral / profound HL

Predictors of Poor Prognosis
Todd Herson Score

- Severe coma 3
- Hypothermia 2
- Seizures 2
- Age <12 months 1
- Shock (BP<60mmHg systolic) 1
- CSF WBC <1000/cumm 1
- Hb <11gm/dl 1
- CSF glucose <20mg/dl (1mmol/L) 0.5
- Symptoms for longer than 3 days 0.5

- A score of ≥4.5 = high risk
Other Predictors of Poor Prognosis

- Salmonella meningitis
- HIV-1 infection
- Malnutrition
### At presentation

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>(n=598)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of fits</td>
<td>286 (40%)</td>
</tr>
<tr>
<td>Previous antibiotics</td>
<td>214 (36%)</td>
</tr>
<tr>
<td>Focus of infection</td>
<td>108 (18%)</td>
</tr>
<tr>
<td>BCS &lt;2</td>
<td>209 (35%)</td>
</tr>
</tbody>
</table>
Confounding factors in management and outcome of children with ABM

<table>
<thead>
<tr>
<th>Factor</th>
<th>Range</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (days)</td>
<td>1 - 5.7</td>
<td>(&gt;52% over 3)</td>
</tr>
<tr>
<td>Severe Coma</td>
<td>7 - 22%</td>
<td></td>
</tr>
<tr>
<td>Moderate Coma</td>
<td>50 - 56.8%</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>17 - 64%</td>
<td></td>
</tr>
<tr>
<td>Nutrition</td>
<td>4 - 38%</td>
<td>&lt;60% WFA</td>
</tr>
<tr>
<td></td>
<td>15 - 48%</td>
<td>&lt;80% WFA</td>
</tr>
<tr>
<td>Anaemia</td>
<td>14 - 21%</td>
<td>&lt;8gm/dl</td>
</tr>
<tr>
<td></td>
<td>45 - 49%</td>
<td>&lt;10 gms/dl</td>
</tr>
</tbody>
</table>

Bangladesh, Malawi, Mozambique, Brazil, PNG
HIV and Bacterial Meningitis

• Patients tend to present shocked with a focus of infection

• A high proportion is caused by *Streptococcus pneumoniae*

• Increased relative risk of recurrence.

• Outcome is significantly worse.
Diagnostics
Diagnostics

CSF

Colour
Gram stain
c/s, latex
Diagnostics

CSF

Colour
Gram stain
c/s, latex
Antigen
PCR
Diagnostics

**CSF**

- Colour
- Gram stain
- c/s, latex
- Antigen
- PCR

**Blood culture**

(USS, CT Scan)
Diagnostics

CSF

Colour
Gram stain
c/s, latex
Antigen
PCR

Blood culture
(USS, CT Scan)

*low threshold for LP*
## CSF findings

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Viral</th>
<th>Pyogenic</th>
<th>Tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Appearance</strong></td>
<td>Clear</td>
<td>Clear/Turbid</td>
<td>Turbid/</td>
<td>Turbid/</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>purulent</td>
<td>Viscous</td>
</tr>
<tr>
<td><strong>Mononuclear mm³</strong></td>
<td>&lt;5</td>
<td>10-100</td>
<td>&lt;50</td>
<td>100-300</td>
</tr>
<tr>
<td><strong>Polymorphs</strong></td>
<td>Nil</td>
<td>Nil</td>
<td>&gt;100/200</td>
<td>0-200 plus</td>
</tr>
<tr>
<td><strong>Protein g/l</strong></td>
<td>0.2-0.4</td>
<td>0.4-0.8</td>
<td>0.5-2.0</td>
<td>0.5-3.0</td>
</tr>
<tr>
<td><strong>Glucose cf blood glucose</strong></td>
<td>½-2/3</td>
<td>&gt;1/2</td>
<td>&lt;1/2</td>
<td>&lt;1/3</td>
</tr>
</tbody>
</table>
CSF Bacterial

- Opening pressure >18 cm/H$_2$O
- WCC 100-5000 mm$^3$ (>80% neutrophils)
- Protein raised.
- Glucose reduced
- Lactate raised
- Gram +ve 60-90%
- Culture +ve 70-85%
CSF neonates

- **WCC up to 30mm$^3$ (60% neutrophils)**
- **Protein 0.17 g/dl**
- **Raised glucose**
- **Gram stain 80% pick up.**
Gram Stain

- *N. meningitidis* 75%
- *S. pneumoniae* 90%
- *H. influenzae* 80%
- Gram −ve bacilli 50%
- *Listeria* spp <50%
Available supportive care

Fluid types/rates

NGT feeds

Nursing care

Anticonvulsants

? Ventilation

? glycerol
Mortality from bacterial meningitis 1890s - 2000s

- 1890
- 1930s
- 1950s
- 1970s
- 2000s

- mortality
Antisera Intraventricular/IT

Drain CSF

Sulphonamides IT and S/c

1890 1930s 1950s 1970s 2000s
Sulphonamides IT and S/c

Penicillin IT IV

Chloramphenicol IV

Drain CSF
Antisera Intraventricular/IT

Drain CSF

Sulphonamides IT and S/c

Penicillin IT IV

Chloramphenicol IV

Penicillin IV/IM

1890 1930s 1950s 1970s 2000s
Antisera Intraventricular/IT

- Drain CSF
- Sulphonamides IT and S/c
- Penicillin IT IV
- Chloramphenicol IV
- Penicillin IV/IM
- ICU, seizure control
- Fluids
- Steroids

1890 1930s 1950s 1970s 2000s
<table>
<thead>
<tr>
<th>Cause</th>
<th>Treatment Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>NM</td>
<td>Penicillin, chloramphenicol, (Oily) penicillin</td>
</tr>
<tr>
<td></td>
<td>cefotaxime</td>
</tr>
<tr>
<td>SPn</td>
<td>ceftriaxone, chloramphenicol, penicillin, ampicillin</td>
</tr>
<tr>
<td>Hib</td>
<td>ceftriaxone, chloramphenicol, ampicillin</td>
</tr>
<tr>
<td>Salm spp</td>
<td>ceftriaxone, chloramphenicol, ciprofloxacin</td>
</tr>
</tbody>
</table>
Studies using dexamethasone as adjuvant treatment in ABM in developing countries

<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>Antibiotics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odio et al</td>
<td>101 infants/children</td>
<td>Cefotaxime</td>
<td>HL 5 v 16%</td>
</tr>
<tr>
<td>Costa Rica ‘91</td>
<td></td>
<td></td>
<td>Neuro 14 v 38%</td>
</tr>
<tr>
<td>Girgis et al</td>
<td>429 adults/children</td>
<td>Amp/chloramph</td>
<td>+ 13 v 40% (SPn)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>mainly in strep pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td>Cairo ‘89</td>
<td></td>
<td></td>
<td>HL 0 v 12%</td>
</tr>
<tr>
<td>Kanra et al</td>
<td>56 children &gt; 2 yrs</td>
<td>Amp/sulbactam</td>
<td>Neuro 7.4 v 23%</td>
</tr>
<tr>
<td>Turkey ‘95</td>
<td></td>
<td></td>
<td>HL 7.4 v 26.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>not statistically significant (P0.11/P.06)</em></td>
<td></td>
</tr>
<tr>
<td>Ciana et al</td>
<td>70, 2 mths to 72 mths</td>
<td>Amp/chloramph</td>
<td>23.5 v 36.3%</td>
</tr>
<tr>
<td>Maputo ‘88</td>
<td></td>
<td><em>no follow up, not statistically significant</em></td>
<td>early + &lt;1 yr 17 v 57%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>in coma 42 v 77%</td>
</tr>
<tr>
<td>Qazi et al</td>
<td>89, 2 mths to 12 yrs</td>
<td>Amp/chloramph</td>
<td>+ 25 v 12%</td>
</tr>
<tr>
<td>Pakistan ‘90-92</td>
<td></td>
<td><em>delay in presentation, prior antibiotics</em></td>
<td>HL 26 v 24%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>neuro 42 v 30%</td>
</tr>
<tr>
<td>Macaluso et al</td>
<td>179, 1 mth to 16 yrs</td>
<td>Xpen/chloramph</td>
<td>+ 14 v 24%</td>
</tr>
<tr>
<td>Recife ‘91-92</td>
<td></td>
<td><em>retrospective, not blinded/controlled, 50% no growth</em></td>
<td></td>
</tr>
</tbody>
</table>
Overall conclusion from study of 598 children in Malawi

Dexamethasone had no beneficial effect on outcome

Mortality Dex v Placebo  RR 1.0 (0.8-1.25)

Sequelea Dex v Placebo  RR 0.9 (0.78-1.27)
Background of patients

malnourished

anaemic

underlying illness
HIV/AIDS

Parasitic infections

delay in arrival
Mortality affected by:

- Age: OR 0.82, p = 0.053
- Malnutrition: OR 0.97, p = 0.0001
- Coma score <2: OR 5.47, p = 0.0001
- HIV positivity: OR 2.61, p = 0.0029
Way Forward

• Early diagnosis

• To treat acute bacterial meningitis with an effective course of antibiotics

• Good supportive care

• Manage underlying problems of malnutrition, anaemia, HIV etc