CNS Infections

Bacterial meningitis - Pathophysiology - general
Specific organisms - Age
Hosts
Treatment/Prevention
Distinguish from viral disease

Meningitis - Neonate

Organisms - GBS – Group B Streptococci
E.coli K1 (Enteric bacteria)
Listeria monocytogenes
Enterococci
Salmonella - fecal contamination

Antibiotics - Cover gram negatives/Listeria/GBS

What is special about meningitis?

Privileged space –
Little room for inflammation
No complement
Minimal immunoglobulin
No PMN's

Well defended
Blood brain barrier
Specialized endothelial- capillary junctions

Only certain organisms – high grade bacteremia –
?recognition of specific receptors

GBS – *Streptococcus agalactiae*

Common commensal flora – childbearing women
Lack of preformed Ab – sepsis – meningitis in neonate

Early onset disease – Sepsis – pneumonia
Late onset disease – Sepsis – MENINGITIS

Vertical transmission – most important - Preventable

Approach:

What organisms are important in different age groups ?

Historically – Pediatric disease –
Changing epidemiology due to widespread vaccination

Epidemiology – Who is at risk ?
How can this be prevented ?

GBS pathogenesis:

Aspiration from the birth canal

High grade bacteremia – poor neonatal host defenses
(PMN function, complement function, lack of Ab for phagocytosis)

Meningeal receptors – endocytosis ?

Intracellular ? Replication – persistence

Clinical relevance – need for prolonged therapy ?
Prevention of Group B Streptococcal Disease

Treatment of those at high risk!

- Colonized moms
- Pre-term
- Multiple births

*E. coli* – K1 –
(not all *E. coli* - specific capsular type)

Maternal fecal flora – ascending infection

CHO – capsule – lack of antibody

High grade bacteremia – meningitis – specific receptors on meninges –

Problem with antibiotic resistance

Meningitis - Neonate

*Listeria monocytogenes*,
Gram positive bacillus - motile

Found in animal feces - very common!

Contamination of unpasteurized animal products
- organic produce - Mexican cheese

Epidemiology -
2000 cases/year

Associated with a “flu-like” illness in the mother

Immunocompromised patients - T cell function

Meningitis - Neonate/Young Infant

Greater incidence of sepsis - immature immune function

Greater incidence of meningitis - “Sepsis” work-up - includes LP - difficult to distinguish viral from bacterial disease

Clinical clues – high or low WBC
- irritability – non specific sx’s
Meningitis in infants and toddlers:

Case - 4 month old - T- 104 - seen by M.D. - rx’d with tylenol -
Still febrile the next day - seen again, said to have otitis media - prescribed amoxicillin -
Increasingly irritable -

Seen in CPMC E.R. (by clinical clerk)
chief complaint - "lump on head" -
which was a bulging fontanel -

*S. pneumoniae* in CSF -

Pathology is due to the host response

Not the bacteria invading the brain tissue!

Major pneumococcal virulence factors:

Cell wall fragments - *Inflammation*

Pneumolysin → Apoptosis

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**Pathophysiology:**

- *Inflammation*
- *Edema*
- Increased intracranial pressure → Loss of perfusion
- Breakdown of blood-brain barrier → Low glucose
- Loss of autoregulation - BP control → *SIADH*
**Pathophysiology**

Pneumolysin – stimulates neuronal apoptosis

Release of NO – tissue damage

**Activation of clotting cascade – PAF**
- *S. pneumo* binds and activates platelet activating factor

Local clotting
Lack of perfusion
Acidosis – lactate formation

**Endothelial cell activation – upregulation of ICAM**
PMN recruitment and activation
- Reactive oxygen species
- elastase – not good in the CNS

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**Goals for therapy:**

Reduce inflammation – steroids

Stop bacterial replication –

Effects of immunostimulatory bacterial components

cell wall fragments
peptidoglycan
LPS

Toll like receptors
MAPK’s
IL-8, IL-6, TNF
Pneumococcal meningitis

Sporadic cases - NP colonization - bacteremia - meningeal seeding - Inflammation -

Worst prognosis

Treatment - Achieve 20x MIC of the organism in the CSF

Penicillin MIC = 1.0 - need level of 20 micrograms/ml
only get 10% of the blood level –
Effects of steroids –
What to do ???

Crude invasive pneumococcal disease (IPD) mortality rates per 100,000 population by age group for children younger than 2 years in the United States, 1995 to 2001

Prevention of S. pneumoniae infections

Infants/children – Prevnar – Pneumococcal Vaccine
8 – capsular types + protein conjugate vaccine

Immunogenic
Effective

Adults – 23-valent polysaccharide vaccine

MMWR data

S. pneumoniae - invasive (blood and CSF isolates)

US (total to date – 2003) – 1,688 drug resistant
337 – kids < 5 yrs
> 50% - southern US
“Eradication” of a common disease:

*H. influenzae* – non typeable – otitis
acquire type B capsule – Poly ribose phosphate
Bacteremia – Meningitis

Paradigms for the management of meningitis –

Universal vaccination of infants –
HiB – PRP-protein conjugate vaccine
Disease gone in vaccinated children

Use of anti-inflammatory agents in meningitis

*H. influenzae experience* -

Give corticosteroids BEFORE antibiotics

Decreases the secondary increase in TNF due
to the release of bacterial cell wall fragments

Improved clinical outcome

Other organisms - Other ages

**Meningitis - Haemophilus influenzae type B**

Antibody - polyribose phosphate capsule
Allows efficient phagocytosis

Development of conjugate vaccines:

- PRP - Diphtheria toxin
- Meningococcal OMP

Sporadic cases - adults who lack Ab

**Case** - 20 year old college sophomore - goes to nurse with headache, T= 102. Diagnosed as having “flu”. Still feels unwell, nurse gives tylenol with codeine… spends night at dorm - collapses and is un-arousable. Sent to local hospital, T=103, WBC=2500
CSF - WBC=120 - 100% PMN’s; Glucose 20/96, Protein-275. PE - Diffuse petecchiae, cold, clammy extremities, Poor air entry……

**MMWR data – 2003 (cumulative)**

*Hemophilus influenzae - invasive*

Serotype b – US – 16 cases !

Non serotype b – 73 – changing epidemiology

Prevent the disease with vaccination

Gram stain of CSF - note PMN’s and intracellular bacteria
**N. meningitidis**

- Epidemic strains/endemic strains - "meningitis" belt in sub-Saharan Africa (type A)
- W135

Sporadic cases – types B, A, W135, C

Gram negative (LPS) - Rapid uptake by the epithelial cells - Receptor mediated endocytosis

Encapsulated - requires IgG + complement to phagocytose

Carriers in the population - increased carriage - disease in those lacking antibody

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Meningococcemia – Fulminant sepsis

? LPS of *N. meningitidis*

Rapid progression

As well as Meningitis –

Complex pathophysiology –

Need for careful monitoring –

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MMWR data – 2003 (cumulative)

Meningococcal Disease

1278 cases – US (1460 – last year)

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*N. meningitidis* – OUTBREAKS!

Who is at risk?

How is the organisms spread - carriers (18% US study)

How can disease be prevented
**N. meningitidis**

Development of protective immunity - cross reactive CHO’s commensal flora (*Neisseria lactamica*)

Vaccines - (epidemic types) - A and C, Y, W 135
Not B - associated with sporadic cases
Sialic acid epitopes - look like self

Who to vaccinate? College students? Military, travellers to endemic areas

Prophylaxis - Rifampin, ciprofloxacin, ceftriaxone achieve levels in naso-pharyngeal secretions

**Diagnosis of meningitis:**

When to do a lumbar puncture – low index of suspicion

What do you look for in the spinal fluid?

- **Gram stain**
- Cell count – 1 angry poly
- **Chemistries** -

**Polysaccharide vaccine** – standard of care
A, C, Y, W-135 – not B - ages 2 yrs and up

**New conjugate vaccine** – “Menactra” A, C, Y, W135-conjugated to diphtheria toxoid
Indicated for children and adolescents ages 11-18
Adults – to age 55

Travel
Complement deficiencies, asplenia
HIV
Adolescents at “preadolescent assessment”
Adolescents at high school entry
College freshman

Guillian-Barre syndrome ??

**Gram stain – Gram positive / Gram negative organisms**

- ? Too large – Fungi
- No organisms – partially treated?
- **Viral disease**

**Chemistries** –

- Protein – elevated – loss of tight junctions – loss of Blood Brain Barrier
- Glucose - LOW – deranged Blood Brain Barrier
  
  NOT bacterial consumption !

**Other CSF tests:**

- Not obviously bacterial infection:
  - Mycobacterial infection
  - Viral culture
  - PCR

- Antibody – Western blot

- India Ink stain - cryptococcus

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**Table 1: Schedule for administering chemoprophylaxis for meningococcal disease**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age group</th>
<th>Dosage</th>
<th>Duration and route of administration</th>
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</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>Children aged &lt;1 month</td>
<td>5 mg/kg, every 12 hrs</td>
<td>2 days, orally</td>
</tr>
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<td></td>
<td>Children aged 1 month</td>
<td>5 mg/kg, every 12 hrs</td>
<td>2 days, orally</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>500 mg, every 12 hrs</td>
<td>2 days, orally</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Adults</td>
<td>500 mg</td>
<td>Single dose, orally</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Children aged &lt;10 yrs</td>
<td>125 mg</td>
<td>Single dose, IM^2</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>250 mg</td>
<td>Single dose, IM</td>
</tr>
</tbody>
</table>

*^Rifampin is not recommended for pregnant women because the drug is teratogenic in animal studies.

For the reliability of using co-trimoxazole may be affected by infant feeding. Anti-epileptic and psychotropic medication may be considered as a treatment. Rx trimethoprim is contraindicated.

*^Ceftriaxone is contraindicated in patients with a history of allergy to cephalosporins.

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Imaging techniques:

CT – computed tomography - ? Increased intracranial pressure – ventricular size – infarcts

MRI – later in management – not necessary for Acute bacterial meningitis – more often for diagnostic purposes

Treatment of meningitis:

Decrease inflammation – S. pneumo

Antimicrobial agents that get into the CSF
  Cover age specific pathogens

Fluid – CNS pressure management

Septic shock management

Public health considerations

Sequellae of meningitis

Hearing loss
Seizure disorder
Major neurological dysfunction -
  Hydrocephalus - obstructed ventricular drainage

Soft neurological dysfunction
  Attention deficit disorder
  Behavioral abnormalities