# CNS Infections

Bacterial meningitis - Pathophysiology - general

Specific organisms - Age
Hosts

Treatment/Prevention

Distinguish from viral disease

# Meningitis - Neonate

Aspiration - colonization - lack of preformed Ab

Organisms - GBS
*E.coli* K1 (Enteric bacteria)
*Listeria monocytogenes*
*Enterococci*

*Salmonella* - fecal contamination

Antibiotics - Cover gram negatives/Listeria/ GBS

**GBS pathogenesis:**

**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 ?**

## GBS – *Streptococcus agalactiae*

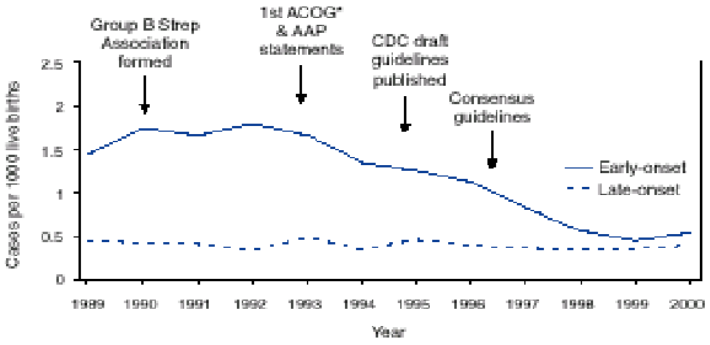
Common commensal flora – childbearing women
Lack of preformed Ab – sepsis – meningitis in neonate

Early onset disease – Sepsis – pneumonia

Late onset disease – Sepsis – MENINGITIS

Vertical transmission – most important - Preventable

**FIGURE 1. Incidence of early- and late-onset invasive group B streptococcal disease—selected Active Bacterial Core surveillance areas, 1989–2000, and activities for prevention of group B streptococcal disease**




* ACOG, American College of Obstetricians and Gynecologists; AAP, American Academy of Pediatrics. **Source:** Adapted from CDC. Early-onset group B streptococcal disease, United States, 1998–1999. MMWR 2000;49:793–6; and Schrag SJ, Zywicki S, Farley MM, et al. Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. N Engl J Med 2000;342:15–20.

**FIGURE 2. Indications for intrapartum antibiotic prophylaxis to prevent perinatal GBS disease under a universal prenatal screening strategy based on combined vaginal and rectal cultures collected at 35–37 weeks' gestation from all pregnant women**

Vaginal and rectal GBS screening cultures at 35–37 weeks' gestation for **ALL** pregnant women (unless patient had GBS bacteriuria during the current pregnancy or a previous infant with invasive GBS disease)

**Intrapartum prophylaxis indicated**

- Previous infant with invasive GBS disease
- GBS bacteriuria during current pregnancy
- Positive GBS screening culture during current pregnancy (unless a planned cesarean delivery, in the absence of labor or amniotic membrane rupture, is performed)
- Unknown GBS status (culture not done, incomplete, or results unknown) and any of the following:
  - Delivery at <37 weeks' gestation*
  - Amniotic membrane rupture ≥18 hours
  - Intrapartum temperature ≥100.4°F (≥38.0°C)†

**Intrapartum prophylaxis not indicated**

- Previous pregnancy with a positive GBS screening culture (unless a culture was also positive during the current pregnancy)
- Planned cesarean delivery performed in the absence of labor or membrane rupture (regardless of maternal GBS culture status)
- Negative vaginal and rectal GBS screening culture in late gestation during the current pregnancy, regardless of intrapartum risk factors

* If onset of labor or rupture of amniotic membranes occurs at <37 weeks' gestation and there is a significant risk for preterm delivery (as assessed by the clinician), a suggested algorithm for GBS prophylaxis management is provided (Figure 3).
† If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis.

***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

## *Listeria* - pathogenesis

Maternal infection

↓

Preterm delivery (not always)
Pneumonia - sepsis - meningitis

Intracellular pathogen - ? Lack of T cell function in the neonate

Cell to cell spread - like Shigella - breaks out of phagosome - avoids Ab - Need T cell function- macrophage activation

## 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

**Very small premature infants**

**Complex congenital heart diseas**
**Premature infants – improved ventilatory support**

**Coagulase negative staphylococci – sepsis/meningitis**

**Enterococci – selection by antibiotics**

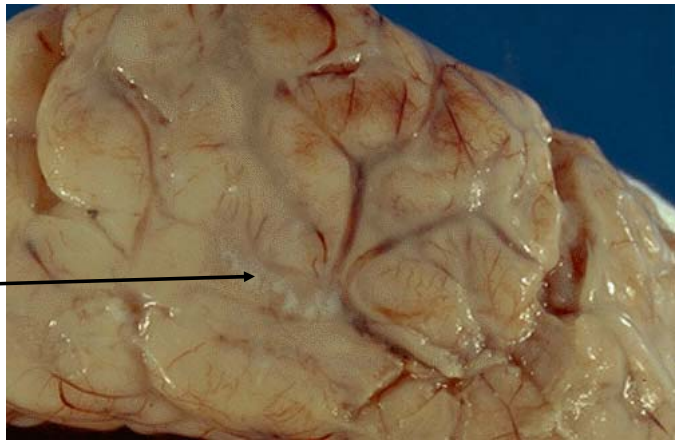
**Fungi**

**Meningitis in infants and toddlers:**

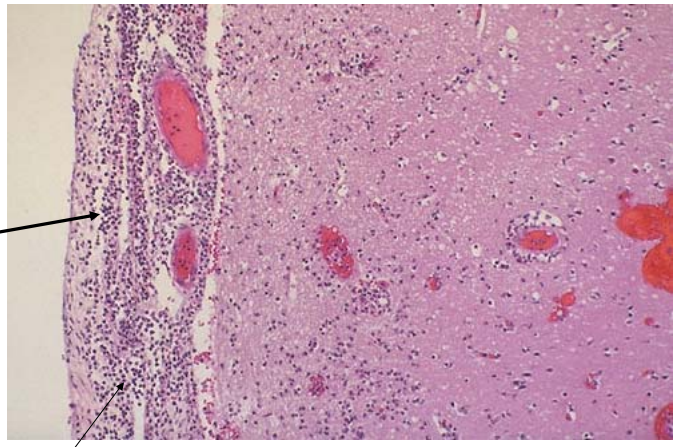
Case - 4 month old - T- 104 - seen by M.D. - rx'd with tylenol -
Still febrile the next day - seen again, said to have otitis media - prescribed amoxicillin -
Increasingly irritable -

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

*S. pneumoniae* in CSF -



Arrow - exudate - pus




Cortex - note edema

**Pathophysiology**:

Inflammation

Edema

Increased intra-cranial pressure → Loss of perfusion

PMN's

Elevated CSF protein

Breakdown of blood-brain barrier

Loss of autoregulation - BP control

Low glucose

SIADH

## Pneumococcal meningitis

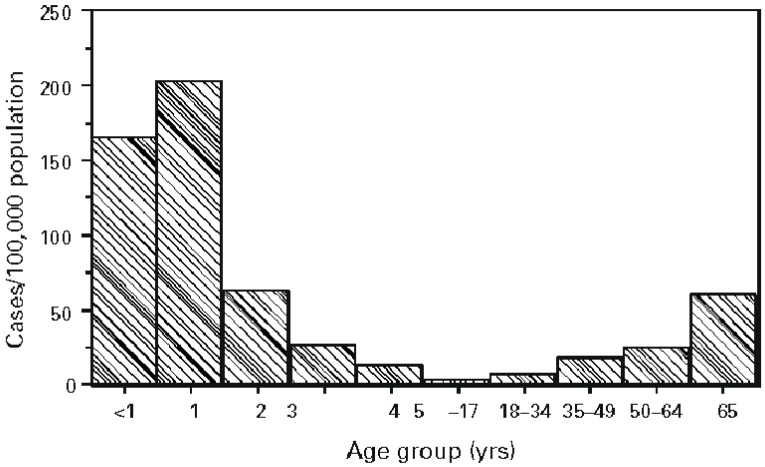
Sporadic cases - NP colonization - bacteremia - meningeal seeding - Inflammation -

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 -
What to do ???

**FIGURE 1. Rates of invasive pneumococcal disease by age group — United States, 1998**




**Source:** CDC, Active Bacterial Core Surveillance (ABCs)/Emerging Infectious Program (EIP) Network, 2000. Available at <http://www.cdc.gov/ncidod/dbmd/abcs/survreports/spneu98.pdf>. Accessed August 22, 2000.

*S. pneumoniae* 1999

* Cases or deaths per 100,000 population for ABCs areas

| Syndrome | No. | (%) |
|---|---|---|
| Meningitis | 195 | (5.1) |
| Bacteremia without focus | 1548 | (40.1) |
| Bacteremic pneumonia | 1976 | (51.2) |

*S. pneumo* - 1999 data

| Age (years) | Cases No. (Rate*) | Deaths No. (Rate*) |
|---|---|---|
| <1 | 371 (153.9) | 1 (0.41) |
| 1 | 450 (188.7) | 3 (1.26) |
| 2-4 | 215 (29.9) | 4 (0.56) |
| 5-17 | 122 (3.9) | 3 (0.10) |
| 18-34 | 307 (7.1) | 23 (0.54) |
| 35-49 | 785 (17.9) | 68 (1.55) |
| 50-64 | 546 (22.6) | 66 (2.74) |
| ≥65 | 1056 (53.5) | 211 (10.69) |
| Total | 3857 (22.2) | 380 (2.19) |

* Cases or deaths per 100,000 population for ABCs areas

| Antibiotic Susceptibility | S* % | I† % | R‡ % |
|---|---|---|---|
| Penicillin | 73.0 | 10.6 | 16.4 |
| Cefotaxime | 83.3 | 10.8 | 5.9 |
| Erythromycin | 79.7 | 0.0 | 20.3 |
| TMP/Sulfa | 67.7 | 5.6 | 26.7 |
| Levofloxacin | 99.7 | 0.0 | 0.3 |
| Vancomycin | 100.0 | 0.0 | 0.0 |

Based on reference lab testing of 2,719 isolates.
* Susceptible; † Intermediate; ‡ Resistant

## Prevention of *S. pneumoniae* infections

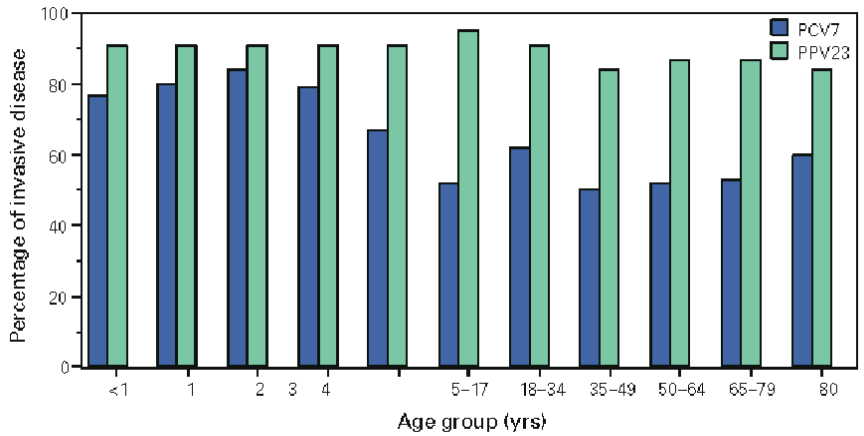
**Infants/children – Prevnar – Pneumococcal Vaccine**
**8 – capsular types + protein conjugate vaccine**

**Immunogenic**

**Effective**

**Adults – 23-valent polysaccharide vaccine**

**FIGURE 2. Serotype distribution of invasive pneumococcal disease by age group and vaccine coverage — United States, 1998**




Source: Active Bacterial Core Surveillance (ABCs)/Emerging Infections Program (EIP) Network, unpublished data, 2000. Additional information is available at <http://www.cdc.gov/ncidod/dbmd/abcs>. Accessed August 22, 2000.

**TABLE 8. Summary of recommendations for use of 7-valent pneumococcal conjugate vaccine (PCV7) among infants and children**

| Children for whom PCV7 is recommended |
|---|
| All children aged ≤23 mos |
| Children aged 24–59 mos with the following conditions: |
| • Sickle cell disease and other sickle cell hemoglobinopathies, congenital or acquired asplenia, or splenic dysfunction |
| • Infection with human immunodeficiency virus |
| • Immunocompromising conditions, including |
| — Congenital immunodeficiencies: B- (humoral) or T-lymphocyte deficiency; complement deficiencies, particularly c1, c2, c3, and c4 deficiency; and phagocytic disorders, excluding chronic granulomatous disease |
| — Renal failure and nephrotic syndrome |
| — Diseases associated with immunosuppressive therapy or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin's disease; or solid organ transplantation |
| • Chronic illness, including |
| — Chronic cardiac disease, particularly cyanotic congenital heart disease and cardiac failure |
| — Chronic pulmonary disease, excluding asthma unless on high dose corticosteroid therapy |
| — Cerebrospinal fluid leaks |
| — Diabetes mellitus |
| **Children for whom PCV7 should be considered** |
| All children aged 24–59 mos, with priority given to |
| • Children aged 24–35 mos |
| • Children of Alaska Native or American Indian descent |
| • Children of African-American descent |
| • Children who attend group day care centers* |

* Defined as a setting outside the home where a child regularly spends ≥4 hours per week with ≥2 unrelated children under adult supervision.

**"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**

## 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

## 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

Case - 20 year old college sophomore - goes to nurse with headache, T- 102. Diagnosed as having "flu". Still feels unwell,nurse gives tyelenol with codeine… spends night at dorm - collapses and is un-arowsable. 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…...

## *N. meningitidis*

***N. meningitidis*** - Epidemic strains/endemic strains - "meningitis" belt in sub-Saharan Africa (type A)

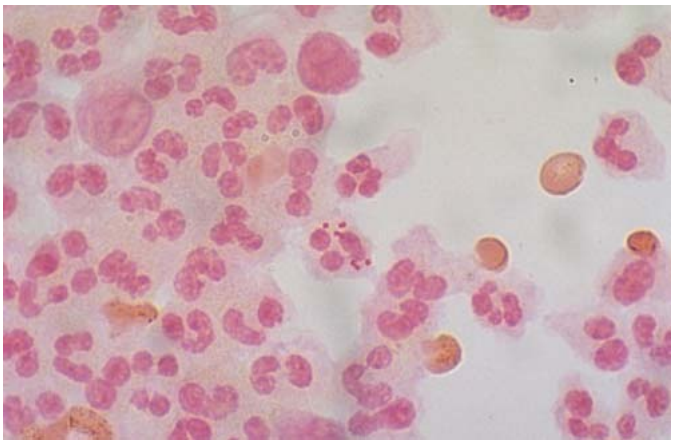
Sporadic cases – types B, A, W135,

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

Sepsis

Encapsulated - requires IgG + complement to phagocytose

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



Gram stain of CSF - note PMN's and intracellular bacteria

*N. meningitidis* - 1999 data

| Syndrome | Cases No. (%*) | | Deaths No. (Rate†) | |
|---|---|---|---|---|
| Meningitis | 147 | (47.4) | 18 | (12.3) |
| Bacteremia w/o focus | 122 | (39.4) | 16 | (13.6) |

*Percent of cases. †Deaths per 100 cases with known outcome

| Age (years) | Serogroups B No. (Rate*) | | C No. (Rate) | | Y No. (Rate) | | Other No. (Rate) | |
|---|---|---|---|---|---|---|---|---|
| <1 | 23 | (5.5) | 8 | (1.9) | 16 | (3.8) | 6 | (1.4) |
| 1 | 4 | (1.0) | 2 | (0.5) | 3 | (0.7) | 1 | (0.2) |
| 2-4 | 14 | (1.1) | 12 | (1.0) | 3 | (0.2) | 4 | (0.3) |
| 5-17 | 11 | (0.2) | 24 | (0.4) | 18 | (0.3) | 3 | (0.1) |
| 18-34 | 20 | (0.3) | 23 | (0.3) | 17 | (0.2) | 7 | (0.1) |
| 35-49 | 9 | (0.1) | 5 | (0.1) | 10 | (0.1) | 12 | (0.2) |
| 50-64 | 6 | (0.1) | 1 | (0.02) | 10 | (0.2) | 5 | (0.1) |
| ≥65 | 6 | (0.2) | 7 | (0.2) | 20 | (0.6) | 9 | (0.3) |
| Total | 93 | (0.3) | 82 | (0.3) | 97 | (0.3) | 47 | (0.2) |

* Cases per 100,000 population for ABCs areas

***N. meningitidis* – OUTBREAKS !**

**Who is at risk ?**

**How is the organisms spread - carriers?**

**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

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

| Drug | Age group | Dosage | Duration and route of administration |
|---|---|---|---|
| Rifampin* | Children aged <1 month | 5 mg/kg every 12 hrs | 2 days, orally |
| | Children aged≥1 month | 10 mg/kg every 12 hrs | 2 days, orally |
| | Adults | 600 mg every 12 hrs | 2 days, orally |
| Ciprofloxacin† | Adults | 500 mg | Single dose, orally |
| Ceftriaxone | Children aged <15 years | 125 mg | Single dose, IM§ |
| Ceftriaxone | Adults | 250 mg | Single dose, IM§ |

*Rifampin is not recommended for pregnant women because the drug is teratogenic in laboratory animals. Because the reliability of oral contraceptives may be affected by rifampin therapy, alternative contraceptive measures should be considered while rifampin is being administered.

† Ciprofloxacin is not generally recommended for persons <18 years of age or for pregnant and lactating women because the drug causes cartilage damage in immature laboratory animals. However, ciprofloxacin can be used for chemoprophylaxis of children when no acceptable alternative therapy is available.

§ Intramuscular.

Diagnosis of meningitis - When to do an L.P.

Interpretation of results –

ONE ANGRY POLY…..

CSF - gram stain

Culture

Antigen- detection - latex agglutination tests

Chemistries

LOW GLUCOSE – Deranged blood

Brain barrier – not bacteria eating lunch

HIGH PROTEIN

**Treatment of meningitis:**

**Decrease inflammation**

**Antimicrobial agents that get into the CSF**

**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