CNS Infections

Bacterial meningitis - Pathophysiology - general

Specific organisms - Age
Hosts

Treatment/Prevention

Distinguish from viral disease

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

Meningitis - Neonate

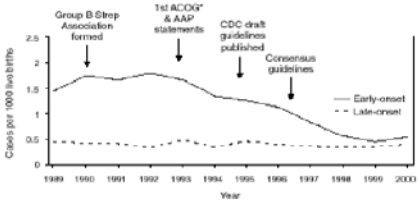
Aspiration - colonization - lack of preformed Ab

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

Salmonella - fecal contamination

Antibiotics - Cover gram negatives/Listeria/ GBS

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.

GBS pathogenesis:

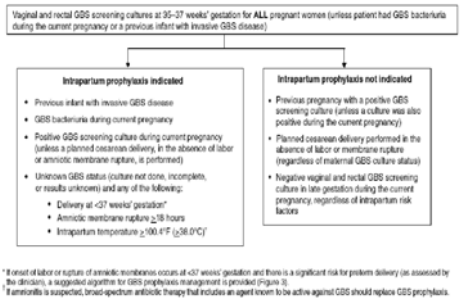
High grade bacteremia – poor neonatal host defenses (PMN function, complement function, lack of Ab for phagocytosis)

Meningeal receptors – endocytosis ?

Intracellular ? Replication – persistence

Clinical relevance – need for prolonged therapy ?

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



* 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/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 - 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

Very small premature infants

Complex congenital heart diseas
Premature infants – improved ventilatory support

Coagulase negative staphylococci – sepsis/meningitis

Enterococci – selection by antibiotics

Fungi

Listeria - pathogenesis

Maternal infection
↓
Preterm delivery (not always)
Pneumonia - sepsis - meningitis

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

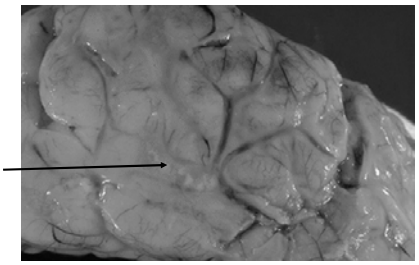
Cell to cell spread - like Shigella -
breaks out of phagosome - avoids Ab -
Need T cell function- macrophage activation

Meningitis 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

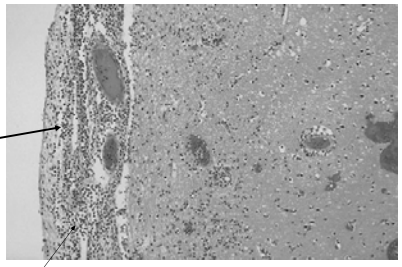
Pneumococcal meningitis

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

Worst prognosis

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

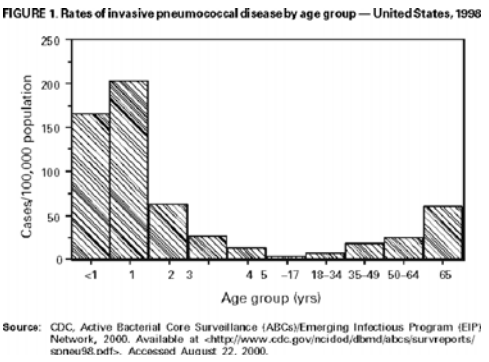
Penicillin MIC = 1.0 - need level of 20 micrograms/ml
only get 10% of the blood level -
What to do ???



PMN's

meninges

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

S. pneumoniae 1999

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

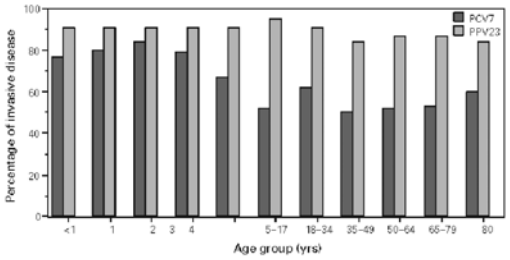
Syndrome	No.	(%)
Meningitis	195	(5.1)
Bacteremia without focus	1548	(40.1)
Bacteremic pneumonia	1976	(51.2)

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

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.

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

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 age 6 years

Prevention of *S. pneumoniae* infections

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

Immunogenic

Effective

Adults – 23-valent polysaccharide vaccine

"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

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 - Sepsis
Receptor mediated endocytosis

Encapsulated - requires IgG + complement to phagocytose

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

Use of anti-inflammatory agents in meningitis

H. influenzae experience -

Give corticosteroids **BEFORE** antibiotics

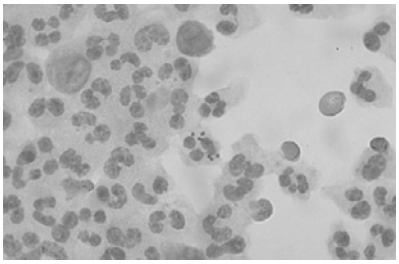
↓

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

↓

Improved clinical outcome

? Other organisms ? Other ages



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

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 - 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

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

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

Treatment of meningitis:

Decrease inflammation

Antimicrobial agents that get into the CSF

Fluid – CNS pressure management

Septic shock management

Public health considerations

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.

Sequellae of meningitis

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

Soft neurological dysfunction
Attention deficit disorder
Behavioral abnormalities