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)

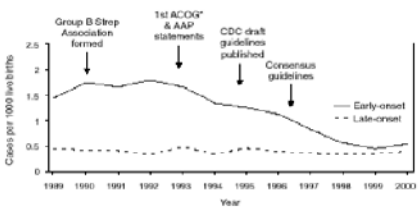
Maternal fecal flora – ascending infection

CHO – capsule – lack of antibody

- **High grade bacteremia – meningitis – specific receptors on meninges -**

Problem with antibiotic resistance

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.

Meningitis - neonate

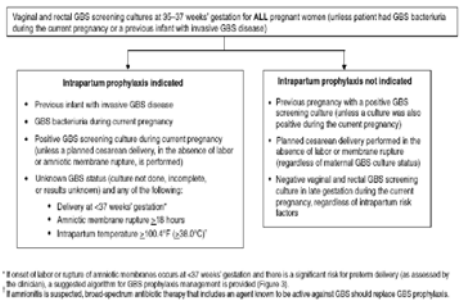
Listeria monocytogenes -
Gram positive bacillus - motile
Found in animal feces - very common !

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

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.

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 -

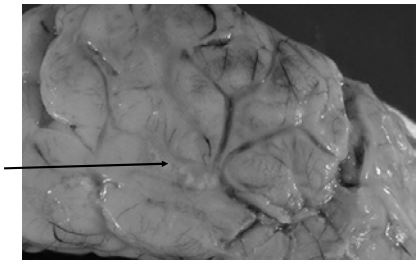
Pathology is due to the host response

Not the bacteria invading the brain tissue !

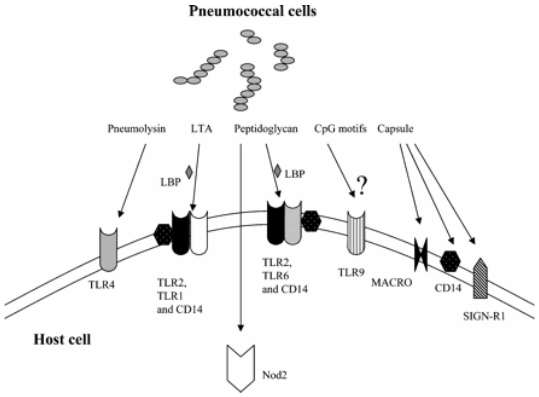
Major pneumococcal virulence factors:

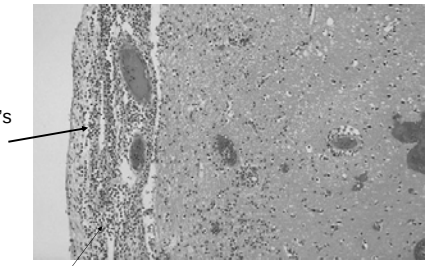
Cell wall fragments - *Inflammation*

Pneumolysin ---Apoptosis



Arrow - exudate - pus





Cortex - note edema

Pathophysiology:

PMN's

Inflammation

Edema

Elevated CSF protein

Increased intra-cranial 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

<u>Activation of clotting cascade</u> – PAF –
***S. pneumo* binds and activates platelet activating factor**

Local clotting
Lack of perfusion
Acidosis – lactate formation

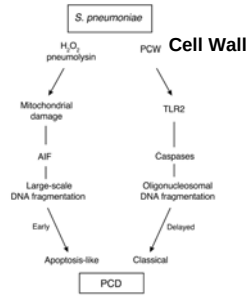
<u>Endothelial cell activation</u> – upregulation of ICAM
PMN recruitment and activation
- Reactive oxygen species
– elastase – not good in the CNS

Mechanisms of Brain Injury

Herniation

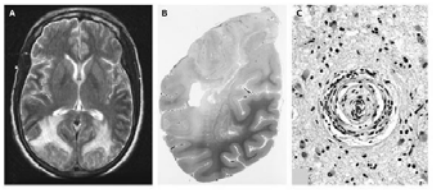
Infarct

Dual pathways of pneumococcal-induced Programmed Cell Death



Bermpohl, D. et al. J. Clin. Invest. 2005;115:1607-1615

Cerebrovascular Complications in Bacterial Meningitis



van de Beek D et al. N Engl J Med 2006;354:44-53

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

Complications during the Clinical Course and Outcomes in Adults with Bacterial Meningitis

Table 1. Complications during the Clinical Course and Outcomes in Adults with Bacterial Meningitis.*

Complications	Frequency (%)	Outcome	Frequency (%)
Systemic complications		Score on Glasgow Outcome Scale	
Cardiorespiratory failure	29	1 (death)	21
Hyponatremia	26	2 (vegetative state)	<1
Disseminated intravascular coagulation	8	3 (severe disability)	3
Arthritis	2–6	4 (moderate disability)	10
Endocarditis/myocarditis	<1	5 (mild or no disability)	66
Deterioration of consciousness		Focal neurologic abnormalities	
Clinical evidence of meningoencephalitis	15–20	Cranial-nerve palsies	
Seizures	15–23	Third nerve	1
Brain edema	6–10	Sixth nerve	3
Hydrocephalus	3–8	Seventh nerve	1
Focal neurologic abnormalities		Eighth nerve	14
Cerebrovascular complications	15–20	Aphasia	2
Arterial infarction or vasculitis	10–15	Hemiparesis	4
Venous infarction	3–5	Quadriparesis	1
Hemorrhage	<1	Late effects	
Hearing loss	14–20	Cognitive impairment	10
Subdural empyema	<1		
Brain abscess	<1		
Myelitis	<1		

* Frequencies are for patients who are not routinely treated with early dexamethasone therapy; if routine dexamethasone therapy is provided, complications and the sequelae are expected to decline.

van de Beek D et al. N Engl J Med 2006;354:44-53

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 ???

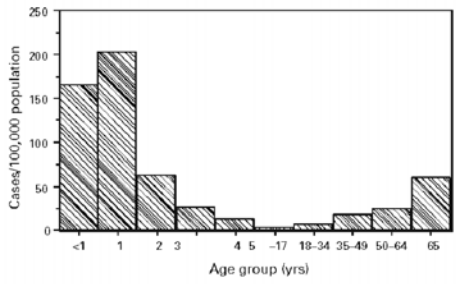
MMWR data

***S. pneumoniae* - invasive (blood and CSF isolates)**

US (total to date – 2003) – 1,688 drug resistant
337 – kids < 5 yrs

> 50% - southern US

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.

Prevention of *S. pneumoniae* infections

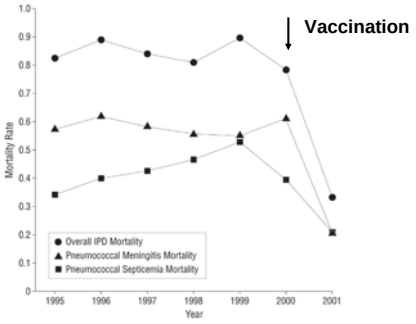
Infants/children – Prevnar – Pneumococcal Vaccine
8 – capsular types + protein conjugate vaccine

Immunogenic

Effective

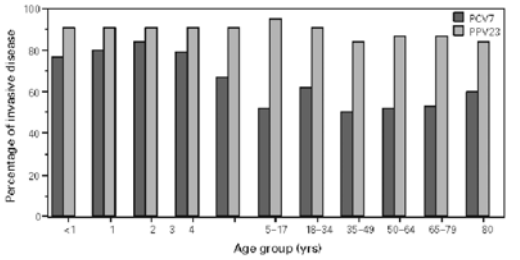
Adults – 23-valent polysaccharide vaccine

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



Redelings, M. D. et al. Arch Pediatr Adolesc Med 2005;159:195-b-196-b.

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.

"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 tyelenol 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…...

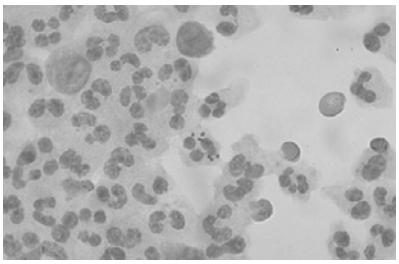
MMWR data – 2003 (cumulative)

Hemophilus influenzae - invasive

Serotype b – US – 16 cases !

Non serotype b – 73 – changing epidemiology

Prevent the disese with vaccination



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

N. meningitidis

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

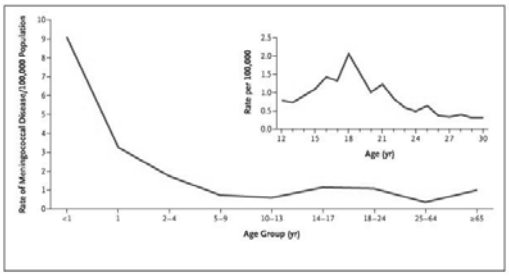
Sporadic cases – types B, A, W135, C

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

Rate of Meningococcal Disease in the United States, According to Age, 1991–2002



The NEW ENGLAND JOURNAL of MEDICINE

Gardner P. N Engl J Med 2006;355:1466-1473

Meningococcemia – Fulminant sepsis

? LPS of *N. meningitidis*

Rapid progression

As well as Meningitis –

Complex pathophysiology –

Need for careful monitoring –

MMWR data – 2003 (cumulative)

Meningococcal Disease

1278 cases – US (1460 – last year)

***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 !

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.

Other CSF tests:

Not obviously bacterial infection:

Mycobacterial infection
Viral culture
PCR

Antibody – Western blot

India Ink stain - cryptococcus

Imaging techniques:

CT – computed tomography - ? Increased intracranial pressure – venticular 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