

CNS Infections

Bacterial meningitis - Pathophysiology - general

Specific organisms - Age
Hosts

Treatment/Prevention

Distinguish from viral disease

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

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 ?**

Meningitis - Neonate

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

Salmonella - fecal contamination

Antibiotics - Cover gram negatives/*Listeria*/ GBS

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

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

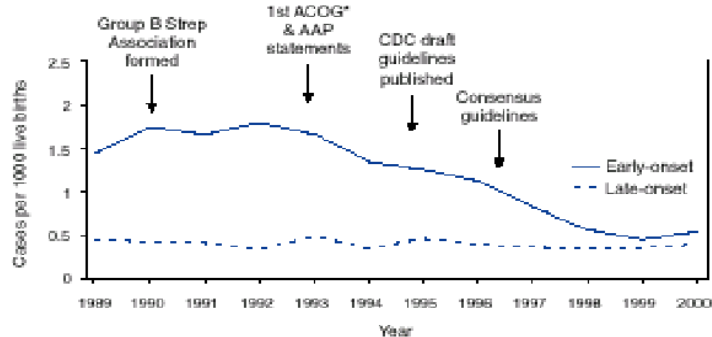
Clinical relevance – need for prolonged therapy ?

Prevention of Group B Streptococcal Disease

Treatment of those at high risk !

Colonized moms
Pre-term
Multiple births

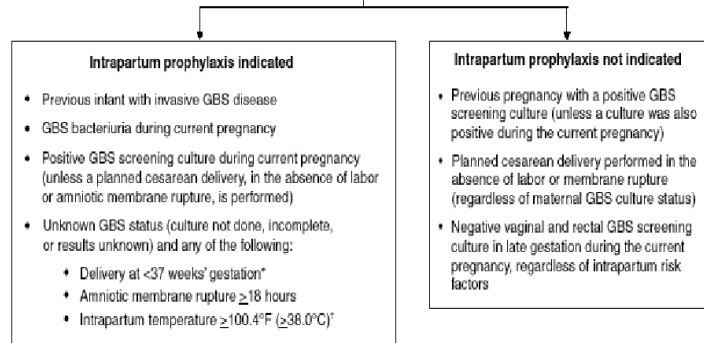
FIGURE 1. Incidence of early- and late-onset invasive group B streptococcal disease—selected Active Bacterial Core surveillance areas, 1989–2000, and activities for prevention of group B streptococcal disease



* 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)



* 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

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

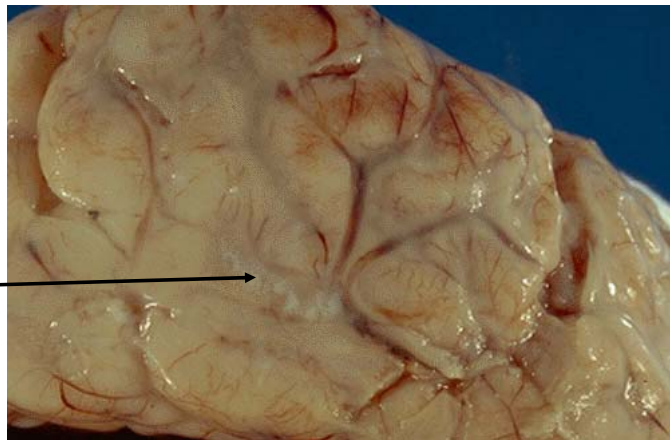
Clinical clues – high or low WBC
irritability – non specific sx’s

Meningitis in infants and toddlers:

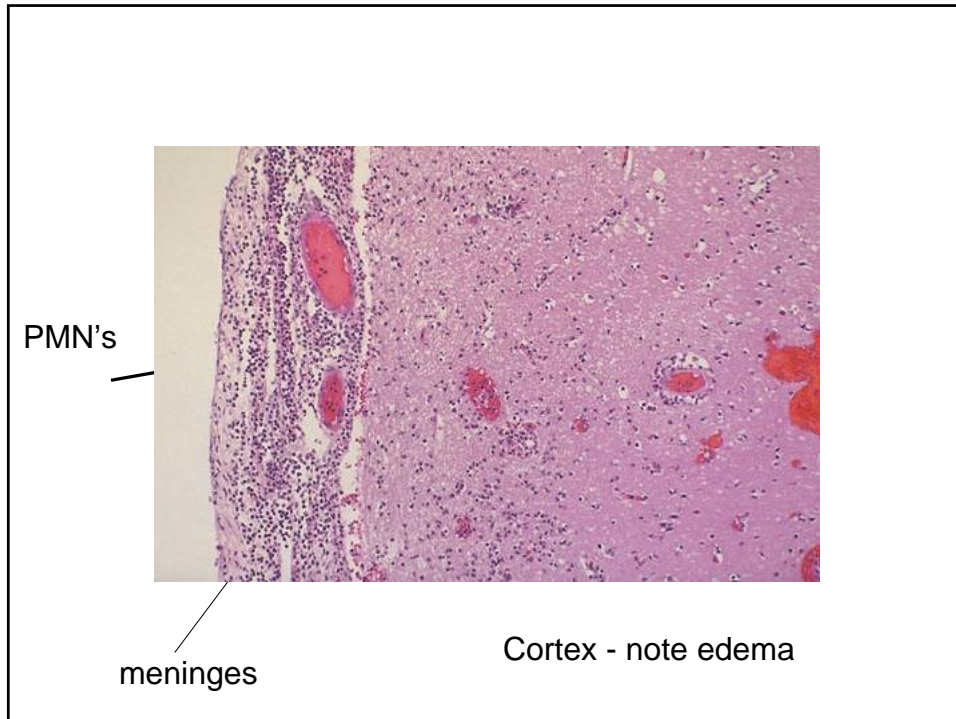
Case - 4 month old - T- 104 - seen by M.D. - rx'd with tylenol -
Still febrile the next day - seen again, said to have otitis
media - prescribed amoxicillin -
Increasingly irritable -

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

S. pneumoniae in CSF -



Arrow - exudate - pus



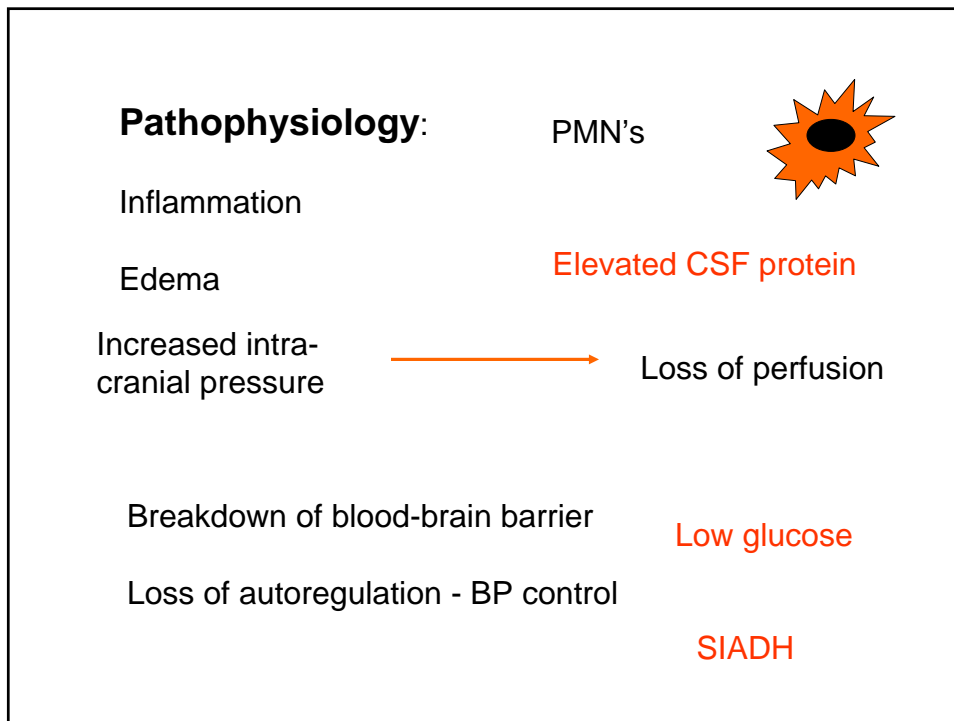
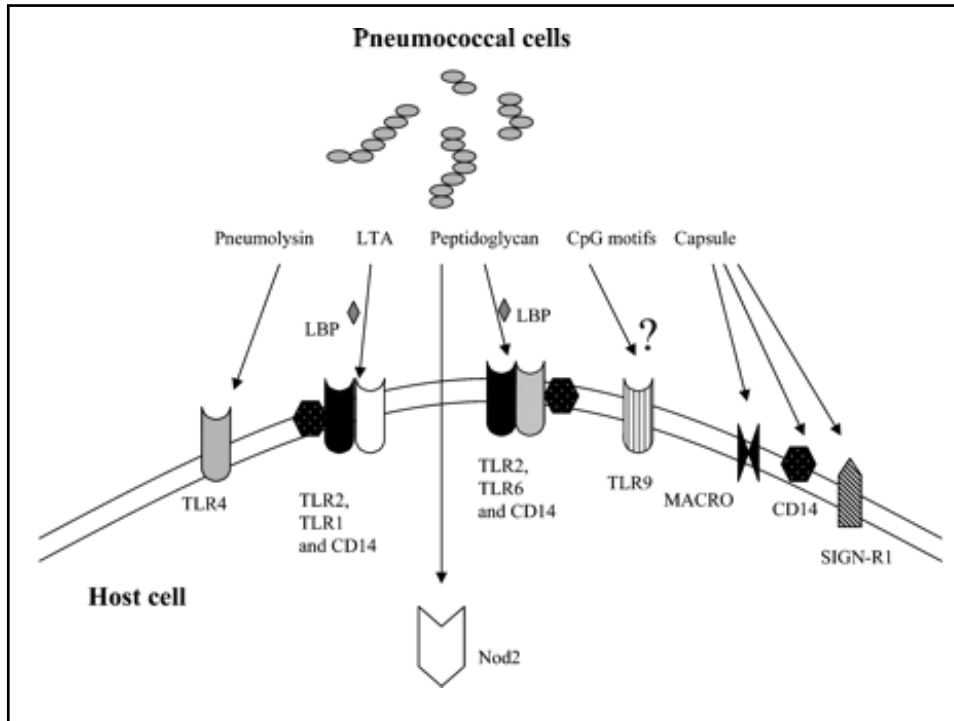
Pathology is due to the host response

Not the bacteria invading the brain tissue !

Major pneumococcal virulence factors:

Cell wall fragments - ***Inflammation***

Pneumolysin ---Apoptosis



Pathophysiology

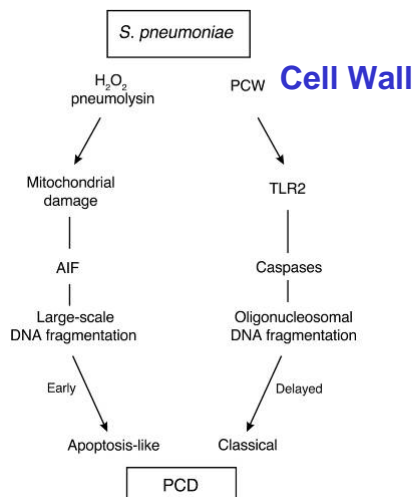
Pneumolysin – stimulates neuronal apoptosis
Release of NO – tissue damage

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

Dual pathways of pneumococcal-induced Programmed Cell Death



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



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Goals for therapy:

Reduce inflammation – steroids

Stop bacterial replication –

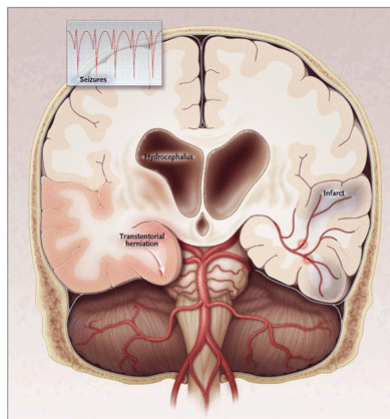
Effects of immunostimulatory bacterial components

**cell wall fragments
peptidoglycan
LPS**



**Toll like receptors
MAPK's
IL-8, IL-6, TNF**

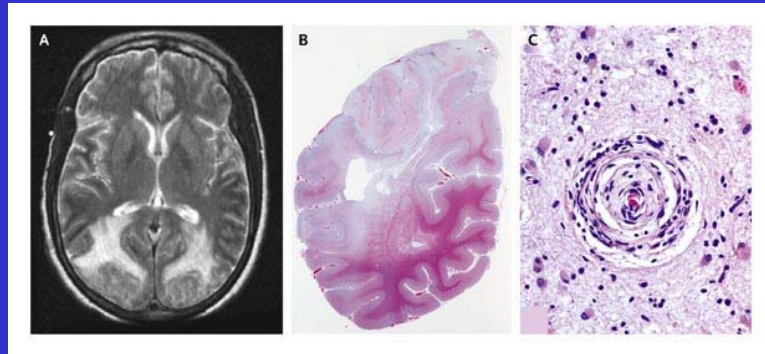
Mechanisms of Brain Injury



Herniation

Infarct

Cerebrovascular Complications in Bacterial Meningitis



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

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

Table 3. 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 | | | |
| Seizures | 15-23 | Cranial-nerve palsies | |
| Brain edema | 6-10 | Third nerve | 1 |
| Hydrocephalus | 3-8 | Sixth nerve | 3 |
| Focal neurologic abnormalities | | | |
| Cerebrovascular complications | 15-20 | Eighth nerve | 14 |
| Arterial infarction or vasculitis | 10-15 | Aphasia | 2 |
| Venous infarction | 3-5 | Hemiparesis | 4 |
| Hemorrhage | <1 | Quadruparesis | 1 |
| Hearing loss | 14-20 | Late effects | |
| Subdural empyema | <1 | Cognitive impairment | 10 |
| 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

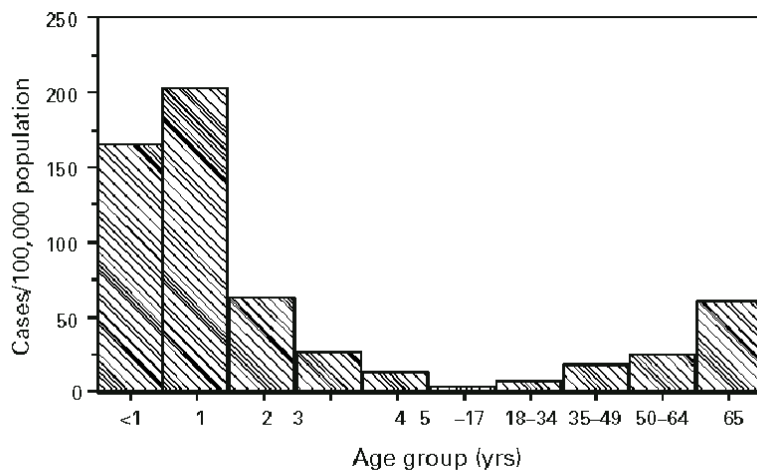
Treatment - Achieve 20x MIC of the organism in the CSF

Penicillin MIC = 1.0 - need level of 20 micrograms/ml
only get 10% of the blood level –

Effects of steroids –

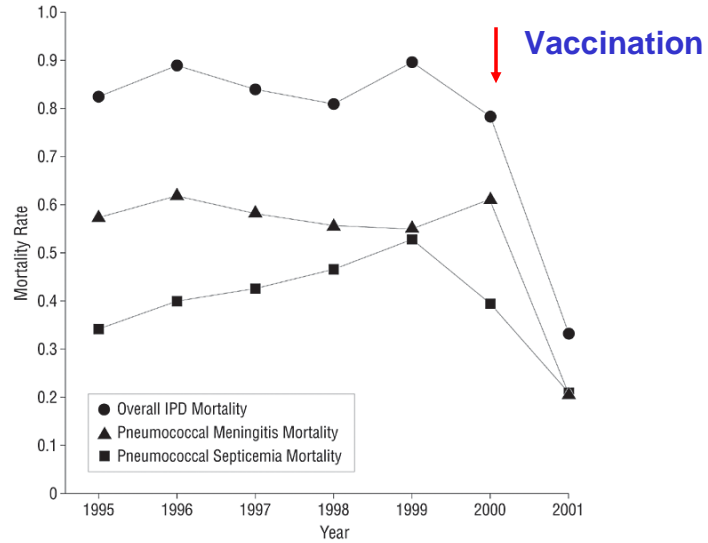
What to do ???

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/dlbd/abc/surveys/soneu98.pdf>>. Accessed August 22, 2000.

Crude invasive pneumococcal disease (IPD) mortality rates per 100 000 population by year for 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.

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

Prevention of *S. pneumoniae* infections

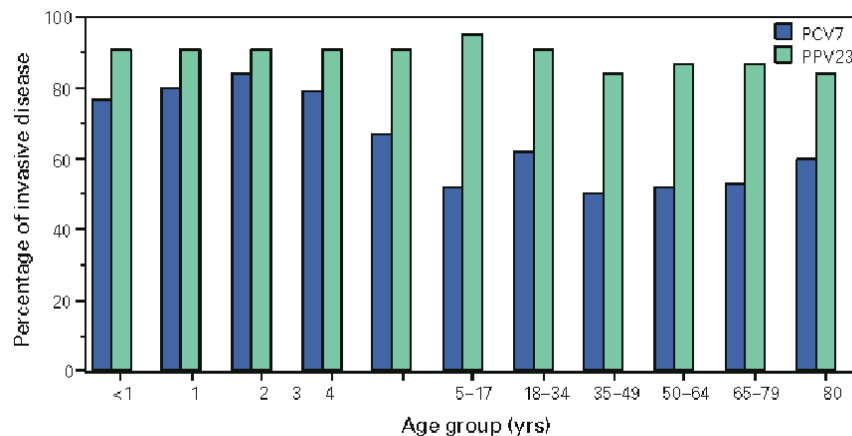
Infants/children – Prevnar – Pneumococcal Vaccine
8 – capsular types + **protein conjugate** vaccine

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/abc>>. 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

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

MMWR data – 2003 (cumulative)

Hemophilus influenzae - invasive

Serotype b – US – 16 cases !

Non serotype b – 73 – changing epidemiology

Prevent the disease with vaccination

Use of anti-inflammatory agents in meningitis

H. influenzae experience -

Give corticosteroids **BEFORE** antibiotics



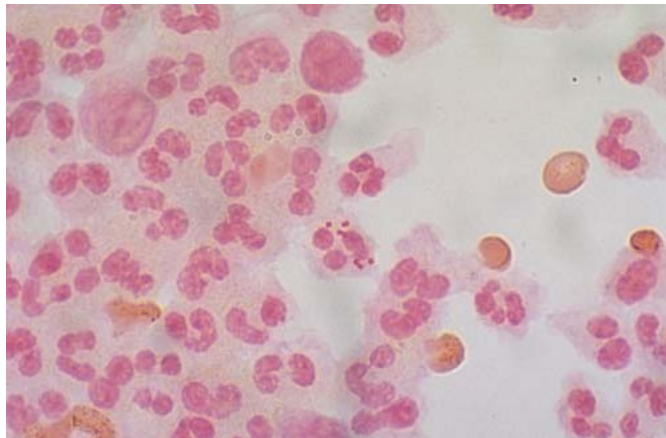
Decreases the secondary increase in TNF due to the release of bacterial cell wall fragments



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 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.....



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

Meningococemia – Fulminant sepsis

? LPS of *N. meningitidis*

Rapid progression

As well as **Meningitis** –

Complex pathophysiology –

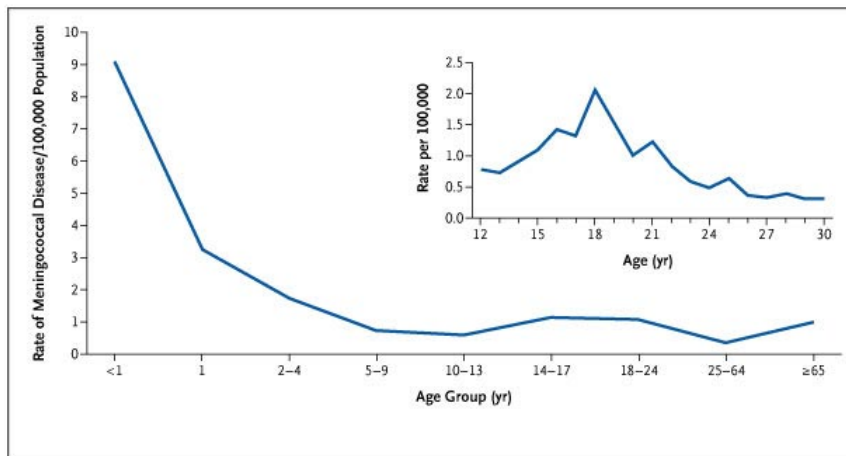
Need for careful monitoring –

MMWR data – 2003 (cumulative)

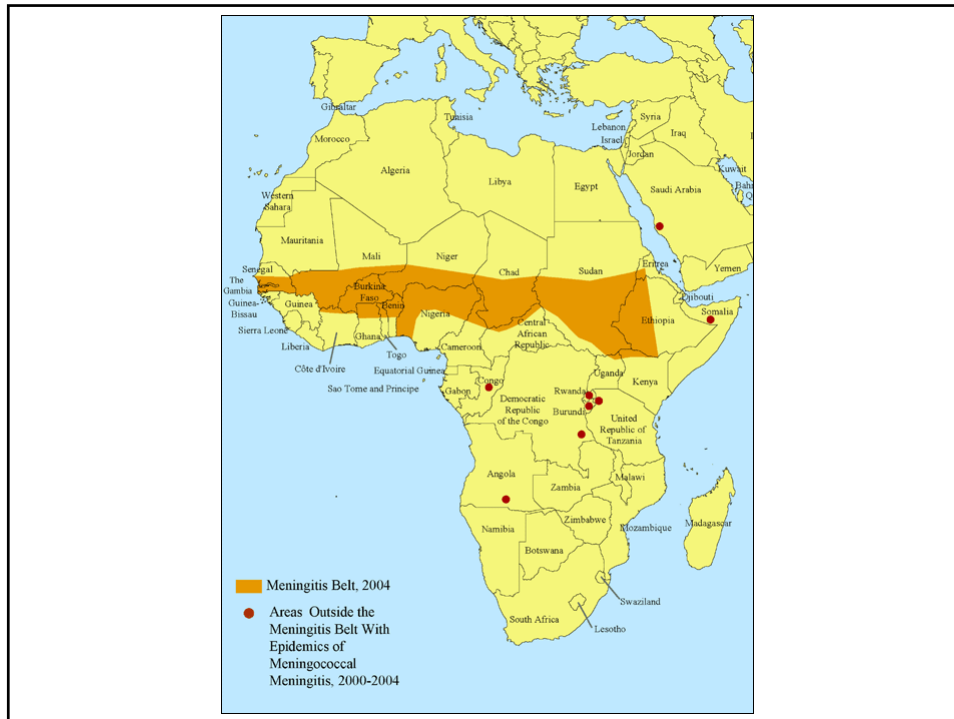
Meningococcal Disease

1278 cases – US (1460 – last year)

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



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



***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

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 ??

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 a lumbar puncture –
low index of suspicion

What do you look for in the spinal fluid?

Gram stain

Cell count – 1 angry poly

Chemistries -

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

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