

(7)

Infectious Diseases  
PY-3 Fall 2011  
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## Meningitis

### Educational Outcomes

1. Explain how the drug characteristics, the anatomy of the CNS and the organism impact the most appropriate route of administration for antibiotic therapy when treating CNS infections
2. Explain how pathogens invade the CNS to cause infection.
3. Explain why patients experience neurologic sequelae following CNS infections.
4. List the clinical manifestations associated with meningitis
5. Given the results of the LP, determine if the patient has a bacterial or viral infection.
6. Discuss the role of steroids in the treatment of CNS infections.
7. Given a patient case recommend an appropriate empiric and/or definitive treatment regimen including drugs, dose, route and duration of therapy.
8. Develop a monitoring plan for a patient being treated for bacterial meningitis
9. Identify strategies for preventing bacterial meningitis

What has had the greatest impact on the incidence of meningitis in the U.S.?

Vaccines/immunizations

HIB - can vaccinate children → 95% decrease since came out in 1986

- not high mortality as others, but high neurologic sequelae (particularly deafness)

Pneumococcal for children (highest neurologic sequelae risk)

Meningococcal - peak incidence in 18-24 y/o

Flu vaccine - Flu increases risk of getting meningitis

Which viral infection do you treat with anti-viral drugs? What antiviral drugs are used?

Viral encephalitis

Acyclovir (DOC)

Foscarnet

Which antifungals do you use for the treatment of cryptococcal infections?

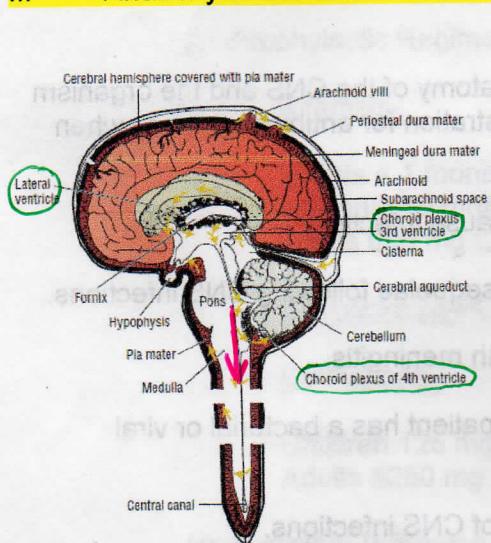
- Amp B (DOC)
- Fluconazole
- itraconazole
- Flucytosine

## I. Epidemiology – Why the treatment of meningitis is considered an emergency.

- A. Mortality Rates: 2-30% Still up to 20% mortality rate w/ ABOs depending on age & the pathogen

B. Neurologic Sequelae: 30-50% Get ABOs on quick to reduce risk of m/m  
→ STAT order

## II. Anatomy of the CNS – treatment implications



meninges go around  
the brain & down  
into spinal column

- subarachnoid space is between the arachnoid & pia mater
  - CSF flows through the subarachnoid space
  - inflammation in the subarachnoid space = meningitis
  - meningitis can be caused by bacteria, viruses, TB, fungal infections
  - encephalitis is usu. due to viruses

referred to as leptomeninges

- CSF Fluid produced in **3 places** (by choroid plexus)
  - CSF is unidirectional
    - Ventriculitis (infection in ventricle) or shunt infection  
not effectively treated by intrathecal ABGs
    - Intrathecal looking at reducing colony count in Meningitis
    - CNS infections not directly treated intraventricularly  
More often due to risk of another infection, contamination

ABOs given: IV, intrathecal (into spine), intraventricular

## II. Pathophysiology of CNS Infections

### A. Sequence of events

- most meningitis infections originate from the nasopharynx (from the GIT rarely)
  - many bacteria that cause meningitis produce IgA protease & use pili to get to epithelia
  - a lot of the bacteria also have a polysaccharide capsule resistant to phagocytosis & opsonization (via complement sys.)
- stimulates alternate complement system; helps keep numbers down

ways they avoid natural defense mechanisms

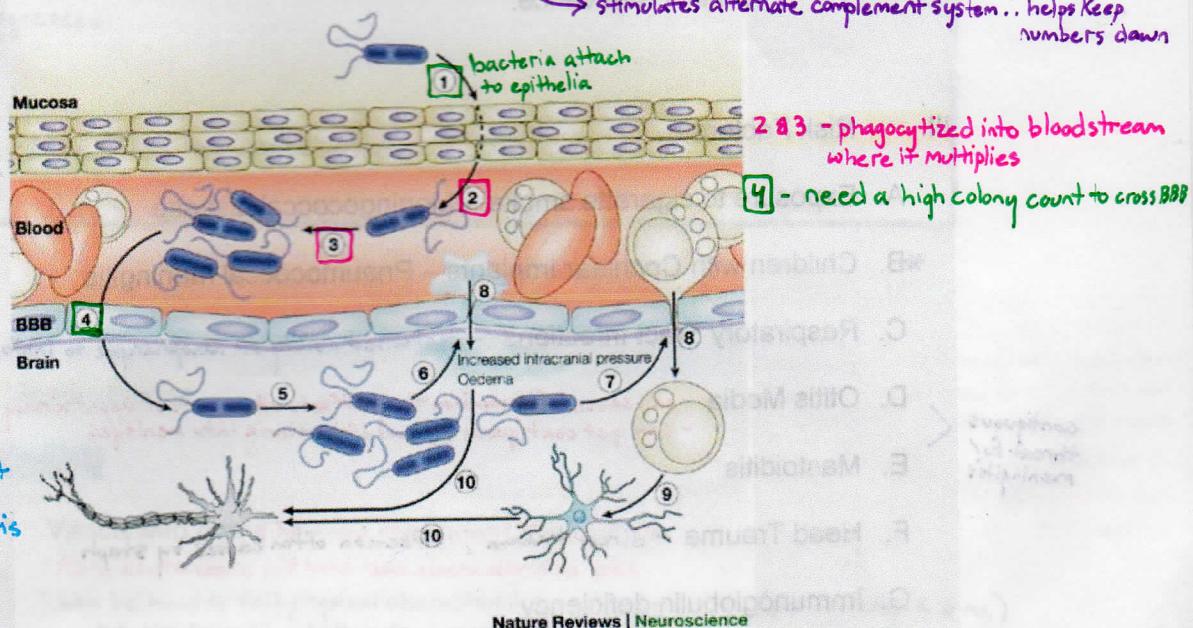
- still have alternate complement system

asplenic patients (those w/o a spleen, either physically or functionally, like w/ sickle cell) cannot activate the alternate complement system

→ at higher risk of getting infection from organisms w/ polysac capsule & higher risk of bacterial meningitis b/c they don't have a defense

### Organisms w/ polysac. capsule

- Neisseria meningitidis
  - S. pneumoniae
  - H. influenzae B (HIB)
  - E. coli
- Big 3 that cause meningitis



The different steps include mucosal colonization (1), invasion of bloodstream (2), survival and multiplication (3) causing high levels of bacteremia, crossing of the blood-brain barrier (4), and invasion of the meninges and the central nervous system (5). Subsequently, bacteria can induce an increased permeability of the blood-brain barrier (BBB; 6) and pleocytosis (7), leading to edema and increased intracranial pressure (8), and to the release of proinflammatory compounds from infiltrated white blood cells and other host cells (9). Ultimately, these process lead to neuronal injury (10)

IL-1  
PG<sub>E</sub>2  
TNF

Kwang Sik Kim Nature Reviews Neuroscience 4, 376-385 (May 2003)

- neuronal injury = the major morbidity associated w/ meningitis
  - due to cytokines released during inflammatory process
  - may also be due to cell wall toxins from the bacteria itself (important when using anti-inflammatory)

## B. Neurologic Sequelae See Figure 115-3 in Dipiro

Key Concept: Neurologic sequelae are not due to the presence of the bacteria, but due to inflammation resulting from the activation of the patient's inflammatory pathways by the pathogen or their products

### Clinical Relevance:

## III. Risk Factors

- A. Exposure to cigarette smoke – Meningococcal disease
- \*B. Children with Cochlear Implants – Pneumococcal meningitis
- C. Respiratory Tract Infections - decreased ability of nasopharynx to inhibit bacterial growth
- D. Otitis Media - can cause inflammation that affects other parts of upper airway  
- can get contiguous spread of bacteria into meninges
- E. Mastoiditis
- F. Head Trauma - direct trauma ; infection often caused by staph
- G. Immunoglobulin deficiency
- H. Immunosuppression (Disease and/or drug induced)
- I. Patients who are unable to activate the alternate complement pathway

?? Who?

### Asplenic pts

- do not have a spleen
- have sickle cell, etc. and the spleen is non-functional

?? These patients are at increased risk of developing meningitis secondary to which pathogens

- H. influenzae B (HIB)
- Pneumococcal
- Meningococcal

Need to be vaccinated

#### IV. Clinical Manifestations

##### A. General

1. Varies with age & how long they've had the infection
  - More acute cases will have more characteristic s/sx
  - Can be hard to tell physical characteristics in small children (particularly < 6 mo.)
    - acting "weird" - lethargic, inconsolable (could be due to many things but want to rule out meningitis)
2. Viral vs bacterial indistinguishable based on symptoms

##### B. Signs and Symptoms

###### \* Fever

- Altered mental status
- Irritability
- Drowsiness, Lethargy
- Chills
- Vomiting (more common in children)

###### \* Photophobia

- \* Severe Headache
- Seizures (generalized; tonic-clonic)
  - Most common in children (rare to see in adults)

- Delirium
- Coma

### C. Physical Findings

Bulging Fontanel - in infants (when still open)

\*Nuchal Rigidity - stiff neck

Kernig's Sign - If pt leg straight up, they lift head

Brudzinski's Sign (more common in adults) → lift neck; pt lifts <sup>Knees</sup> up - trying to decrease pressure in spinal cord

not often present in children

Petechial/purpuric rash

? Associated with which type of infection

Meningococcal - pt may present w/ shock-like syndrome (very dangerous)  
- lowest risk of neurologic sequelae

### V. Diagnostic Studies

- will delay procedure if pt has high ICP → worried about brain herniating
- send for CT scan
- might have to give ABOs before culture

A. Lumbar Puncture (LP) Key diagnostic test - look at CSF

- ✓ Gram Stain - helps narrow therapy; done quickly
- ✓ Culture takes some time
- ✓ Antigen Detection Tests (Latex Agglutination, latex fixation, enzyme immunoassay (EIA))  
PCR is the ideal test but not as fast as Latex Agglutination

?? When and why?

- most useful if someone got a dose of ABOs before CSF was taken

- may get results faster than w/ culture

- ✓ Chemistry: Protein, Glucose
- ✓ Hematology: RBC, WBC with differential

CSF Analysis Normal and Abnormal CSF (Do not memorize values, but know the relative changes) - can distinguish betw. bacterial & viral before culture results

Mean Values of the Components of Normal and Abnormal Cerebrospinal Fluid

Type	Normal	Bacterial	Viral	Fungal	Tuberculosis
WBC (cells/mm <sup>3</sup> )	<5	1,000–5,000 ↑	100–1,000	40–400	100–500
Differential (%)	>90 <sup>a</sup>	≥ 80 PMNs	50 <sup>b,c</sup> mainly lymphocytes	>50 <sup>b</sup>	>80 <sup>b,c</sup>
Protein (mg/dL)	<50	100–500 ↑	30–150	40–150	40–150
Glucose (mg/dL)	50%–66% simultaneous serum value	<40 ↓ (<60% simultaneous serum value). ~50% ✗	<30–70	<30–70	<30–70

<sup>a</sup> Monocytes, <sup>b</sup> Lymphocytes, <sup>c</sup> Initial CSF-WBC differential may show a predominance of polymorphonuclear cells (PMNs)

From: Pharmacotherapy: A Pathophysiologic Approach, 8e Chapter 115. Central Nervous System Infections

\* if glucose in serum = 100 mg/dL then CSF glucose ≈ 50 mg/dL

- low glucose is more consistent w/ bacterial rather than viral

## B. Blood - often positive since high bacterial load needed to cross into CNS

1. Culture
2. WBC with differential

- May culture other fluids: Urine in the elderly, children

## VI. Treatment

- want to pick **BACTERICIDAL** agents against the pathogen

& want to achieve adequate levels in the CNS (not bacteriostatic levels)

### A. Antibiotic Penetration into the CNS

#### 1. Factors Affecting CNS Concentration in the CSF

##### Characteristics of the drug

- LMW
- Lipid soluble
- Non-ionized at physiologic pH
- Not highly protein bound (preferred; Ceftriaxone is highly protein-bound)

Increased permeability of the BBB due to inflammation

\* When a drug is to be used intrathecally or intraventricularly, the drug CANNOT contain a preservative & neither can the diluent  
↳ can be toxic to CNS

#### 2. Penetration of Antimicrobial Agents into the CSF

Therapeutic levels in CSF with or without inflammation	Therapeutic levels in CSF with inflammation of meninges	Non-therapeutic levels in CSF with or without inflammation
Choramphenicol Cycloserine Ethionamide Isoniazid Metronidazole Pyrazinamide Rifampin Sulfonamides Trimethoprim	Acyclovir Ampicillin ± sulbactam Aztreonam Carbenicillin Cefotaxime Ceftazidime Ceftizoxime Ceftriaxone Cefuroxime Ciprofloxacin Colistin Daptomycin Ethambutol Fluconazole Flucytosine Foscarnet	Ganciclovir Imipenem Levofloxacin Linezolid Meropenem Mezlocillin Moxifloxacin Nafcillin Ofloxacin Penicillin G Piperacillin Pyrimethamine Quinupristin/dalfopristin Ticarcillin ± clavulanic acid Vancomycin Vidarabine

<sup>1</sup> Cefuroxime is an exception

<sup>2</sup> Achieves therapeutic brain tissue concentrations.

<sup>3</sup> Achieves therapeutic

concentrations for Cryptococcus neoformans therapy

From: Pharmacotherapy: A Pathophysiologic Approach, 8e > Section 16. Infectious Diseases > Chapter 115. Central Nervous System Infections

Cefotaxime is the 3rd-gen Ceph used in children < 1 mo.  
→ do not use ceftriaxone (biliary sludging)

## B. Empiric Therapy

### MEMORIZE

Bacterial Meningitis: Most Likely Pathogens and Empirical Therapy by Age Group

Age Commonly Affected	Most Likely Organisms	Empirical Therapy
Newborn-1 mo	Group B <i>Streptococcus</i> - most common Gram-negative enterics E.coli - 2nd Klebsiella <i>Listeria monocytogenes</i> - 3rd	Ampicillin + <u>cefotaxime</u> or an aminoglycoside (Gent) AMP+GENT over 3rd-gen Ceph (resistance issues) in neonatal units
1 mo- 29 y	<i>S. pneumoniae</i> <i>N. meningitidis</i> <i>H. influenzae</i> <sup>1</sup> - series of vaccines usu. complete by 15 mo.	Vancomycin <sup>2</sup> and cefotaxime or ceftriaxone (3rd-gen Ceph)
30-60 y	<i>S. pneumoniae</i> <i>N. meningitidis</i>	Vancomycin <sup>2</sup> and cefotaxime or ceftriaxone
>60 y	<i>S. pneumoniae</i> Gram-negative enterics E.coli Klebsiella spp Enterobacter spp <i>L monocytogenes</i>	Vancomycin <sup>2</sup> and <u>ampicillin</u> and cefotaxime or ceftriaxone

<sup>1</sup>If not immunized with HIB vaccine. <sup>2</sup>Vancomycin use should be based on local incidence of penicillin-resistant *S. pneumoniae* and until cefotaxime or ceftriaxone minimum inhibitory concentration results are available.

Adapted from: Pharmacotherapy: A Pathophysiologic Approach, 8ed. Section 16. Chapter 115. Central Nervous System Infections

## C. Definitive Therapy

Antimicrobial Agents of First Choice and Alternative Choice in the Treatment of Meningitis Caused by Gram-Positive and Gram-Negative Microorganisms

Organism	Antibiotic of First Choice	Alternative Antibiotics	Recommended Duration of Therapy
<b>Gram-positive</b>			
<i>Streptococcus pneumoniae</i>			10-14 days
Penicillin susceptible <i>MIC: &lt; 0.06</i>	Penicillin G or Ampicillin (A-III)	Cefotaxime (A-III), Ceftriaxone (A-III), Chloramphenicol (A-III)	
Penicillin intermediate <i>MIC: 0.1 - 1.0</i>	Cefotaxime or Ceftriaxone (A-III)	Cefepime (B-II), Meropenem (B-II), Moxifloxacin (B-II), Linezolid (C-III)	Meropenem assoc. w/seizures
Penicillin resistant <i>MIC: &gt; 2.0</i>	Vancomycin <sup>a</sup> plus Cefotaxime or Ceftriaxone (A-III) <i>usu. use 2 drugs for highly resistant organisms</i>	Cefepime (B-II), Meropenem (B-II), Moxifloxacin (B-II), Linezolid (C-III) <i>FQ's get into CNS</i>	
Group B <i>Streptococcus</i>	Penicillin G or Ampicillin ± Gentamicin <sup>a</sup> (A-III)	Cefotaxime (B-III), Ceftriaxone (B-III), Chloramphenicol (B-III)	14-21 days

**Antimicrobial Agents of First Choice and Alternative Choice in the Treatment of Meningitis Caused by Gram-Positive and Gram-Negative Microorganisms (continued)**

<i>Staphylococcus aureus</i>			14–21 days <sup>e</sup>
Methicillin susceptible	Nafcillin or Oxacillin (A-III)	Vancomycin <sup>a</sup> (A-III), Meropenem (B-III)	
Methicillin resistant	Vancomycin <sup>a</sup> (A-III)	Trimethoprim-sulfamethoxazole (A-III), Linezolid (B-III)	
<i>Staphylococcus epidermidis</i>	Vancomycin <sup>a</sup> (A-III)	Linezolid (B-III)	14–21 days <sup>d</sup>
<i>Listeria monocytogenes</i>	Penicillin G or Ampicillin ± Gentamicin <sup>a</sup> (A-III)	Trimethoprim-sulfamethoxazole (A-III), Meropenem (B-III)	≥21 days
<b>Gram-negative</b>			
<i>Neisseria meningitidis</i>			7 days
Penicillin susceptible	Penicillin G or Ampicillin (A-III)	Cefotaxime (A-III), Ceftriaxone (A-III), Chloramphenicol (A-III)	
Penicillin resistant	Cefotaxime or Ceftriaxone (A-III)	Chloramphenicol (A-III), Meropenem (A-III), Fluoroquinolone (A-III)	
<i>Haemophilus influenzae</i>			7 days
β-Lactamase negative	Ampicillin (A-III)	Cefotaxime (A-III), Ceftriaxone (A-III), Chloramphenicol (A-III), Cefepime (A-III), Fluoroquinolone (A-III)	
β-Lactamase positive	Cefotaxime or Ceftriaxone (A-I)	Cefepime (A-I), Fluoroquinolone (A-III), Chloramphenicol (A-III)	
<i>Enterobacteriaceae</i> (E.coli, and <i>Klebsiella</i> spp)	Cefotaxime or Ceftriaxone (A-II)	Cefepime (A-III), Fluoroquinolone (A-III), Meropenem (A-III), Aztreonam (A-III)	21 days
<i>Pseudomonas aeruginosa</i>	Cefepime or Ceftazidime (A-II) ± Tobramycin <sup>a,b</sup> (A-III)	Ciprofloxacin (A-III), Meropenem (A-III), Piperacillin plus Tobramycin <sup>a,b</sup> (A-III), Colistin sulfomethate <sup>a,c</sup> (B-III), Aztreonam (A-III)	21 days

<sup>a</sup> Monitor drug levels in serum. <sup>b</sup> Direct central nervous system administration may be added; <sup>c</sup> Should be reserved for multidrug-resistant pseudomonal or *Actinetobacter* infections for which all other therapeutic options have been exhausted. <sup>e</sup> Based on clinical experience; no clear recommendations.

Antibiotic Doses		
Antimicrobial Agent	Infants and Children	Adults
Ampicillin	75 mg/kg every 6 h	2 g every 4 h
Aztreonam		2 g every 6–8 h
Cefepime	50 mg/kg every 8 h	2 g every 8 h
Cefotaxime	75 mg/kg every 6–8 h	2 g every 4–6 h
Ceftazidime	50 mg/kg every 8 h	2 g every 8 h
Ceftriaxone	100 mg/kg once daily	2 g every 12–24 h
Chloramphenicol	25 mg/kg every 6 h	1–1.5 g every 6 h
Ciprofloxacin	10 mg/kg every 8 h	400 mg every 8–12 h
Colistin <sup>a,c</sup>	5 mg/kg once daily	5 mg/kg once daily
Gentamicin <sup>a,b</sup>	2.5 mg/kg every 8 h	2 mg/kg every 8 h
Levofloxacin	10 mg/kg once daily	750 mg once daily
Linezolid	10 mg/kg every 8 h	600 mg every 12 h
Meropenem	40 mg/kg every 8 h	2 g every 8 h
Oxacillin/Nafcillin	50 mg/kg every 6 h	2 g every 4 h
PenicillinG	0.05 mUnits/kg every 4–6 h	4 mUnits every 4 h
Piperacillin	50 mg/kg every 4–6 h	3 g every 4–6 h
Tobramycin	2.5 mg/kg every 8 h	2 mg/kg every 8 h
TMP-SMZ <sup>d</sup>	5 mg/kg every 6–12 h	5 mg/kg every 6–12 h
Vancomycin	15 mg/kg every 6 h	15 mg/kg every 8–12 h

<sup>a</sup> Monitor drug levels in serum. <sup>b</sup> Direct central nervous system administration may be added <sup>c</sup> Should be reserved for multidrug-resistant pseudomonal or *Actinetobacter* infections for which all other therapeutic options have been exhausted. <sup>d</sup> Dosing based on trimethoprim component.

#### D. The role of Dexamethasone in the Management of Patients with Meningitis

##### 1. Theoretical Rationale

Might be able to decrease inflammation from the release of cytokines etc if given with or before the 1st dose of ABOs

Is it effective in preventing neurologic damage to other pathogens besides HIB?

- no use for meningococcus (doesn't usually cause neurologic damage)

## 2. Pros/Cons

- shows positive outcomes vs. HIB
- decreased inflammation could affect penetration of some ABOs

### 3. Conflicting data

Early studies showed a positive outcome, but it was with HIB in children

- some studies show positive outcomes, some don't
- newer study showing positive outcomes in sicker patients regardless of organism
- no definitive answer, but if giving it:  
Dex has to be given 10-20 minutes before or w/ the 1<sup>st</sup> dose of ABO
- Before is preferred

not as common now

## 4. Current Recommendations

### A. Pediatric Patients:

- American Academy of Pediatrics: Consider administration of dexamethasone 0.15 mg/kg Q 6 h for 4 days in infants and children older than 2 months suspected of having HIB or pneumococcal meningitis. The first dose must be administered before the first dose of antibiotics. Alternative dose 0.4 mg/kg Q 12 h for 2 days
- Repeat LP in 24-48 h - want to make sure CSF is being sterilized (possible reduced ABO penetration due to Dex)

neurologic AEs  
in younger than 2 mo

## B. Adults

- Benefits: In patients suspected of having pneumococcal meningitis administer dexamethasone 0.15 mg/kg Q 6 h for 2-4 days

### E. Monitoring Therapy

- Improvement of symptoms: ↓ Fever, ↓ WBC, ↓ irritability, less physical symptoms & seizures
  - if these happen, not necessary to repeat lumbar puncture (LP)
  - if symptoms don't improve or if given Dex, repeat LP
- Hearing Function - audiography testing
- Serum trough levels for Vanco & aminoglycosides
  - Vanco: 15-20
  - Gent: trough  $\leq 2 \text{ mcg}$ , peak  $> 8$  (to ensure high)

## VII. Prevention of Meningitis

### A. Vaccines

	Hemophilus Influenza B Hib (several vaccines marketed)	Pneumococcal conjugate vaccine	Meningococcal
Primary Series	2,4,6,12-15 months	PCV-13 - covers 13 serotypes 2,4,6,12-15 months	MCV4 11-12 yr repeat at 16 yr
Adults	Anatomic or functional asplenia <i>if not vaccinated as child</i>	PPSV polysaccharide vaccine 65 yr - covers 23 strains Smoker Chronic diseases Asplenia Cochlear Implant HIV or other immunosuppressive condition	MCV4  Asplenia, compliment component deficiency

children  $\leq 2$  do not respond  
to polysaccharide  
∴ need for conjugate

CV tends to be better than PS

## B. Antibiotic Prophylaxis - decided by Dept. of Health

### Meningococcal Meningitis

1. Indication: Close contacts of the index case- day care center contacts, household contacts, and individuals who had contact with respiratory or oral secretions. (such as giving CPR during a code)

### 2. Prophylactic Regimens

#### Rifampin

- KNOW [ Infants < 1 month 5 mg/kg Q 12 h for 2 days  
≥ 1 month 10 mg/kg/dose Q 12 h for 2 days  
Adults 600 mg Q 12 h for 2 days

Ciprofloxacin PO 500 mg one dose adults and children > 12 y

#### Ceftriaxone

- Children 125 mg IM one dose  
Adults 250 mg IM one dose

### Hemophilus influenza B

1. Indications: Household contacts, individuals sharing sleeping quarters, day care center contacts, nursing home residents, and crowded confined populations.
2. Prophylactic regimen

Rifampin Children 20 mg/kg/day for 4 days; Adults 600 mg daily for 4 days.

Meningococcal	Meningococcal	Hemophilus influenza B	Hib
MCAT 11-15 yr leisure & 18 yr	PCA-13 - severe 13 serotype 5-7, 9-15-16 wounding	5-8, 13-15 wounding	Lumbar spinal
MCAT Asthma compliment component deficiency	PCV pneumococcal vaccines Hib group B streptococcal disease Aspergillus Coccidioidomycosis HIV or other immunocompetence secondary condition	Anterior or lumbar spinal	Antibiotic to administration of alternative doses