

# Bacterial Meningitis

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# Bacterial Meningitis

- Bacterial meningitis is an acute to subacute purulent infection of the subarachnoid space and spinal fluid pathways, incited by bacterial seeding and growth.
- Inflammation of the leptomeninges produces the clinical syndrome of headache, fever, and nuchal irritation.

# World Health Organization – Meningitis in Africa

<http://www.who.int/mediacentre/factsheets/fs141/en/index.html>

- The meningitis belt of sub-Saharan Africa, stretching from Senegal in the west to Ethiopia in the east, has the highest rates of the disease.
- In the 2009 epidemic season, 14 African countries implementing enhanced surveillance reported a total of 78 416 suspected cases, including 4053 deaths, the largest number since the 1996 epidemic.
- A new meningococcal conjugate A vaccine developed specifically for Africa should be available by the end of 2010.

# Case

58 y.o. previously healthy man presents with 3 days of headache, 12 hours of fever and obtundation.

Temp 39°C; neurologic exam is nonfocal; prominent nuchal rigidity is present and response is only to painful stimulation. There is a Brudzinski's sign present.

# Brudzinski's sign

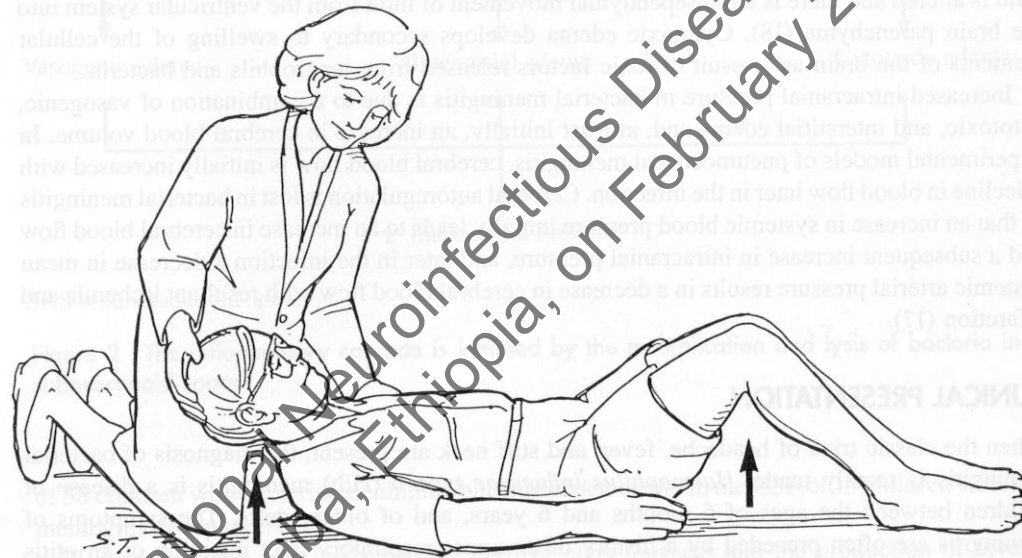


Figure 3 Brudzinski's sign of meningeal inflammation is elicited with the patient in the supine position, and is positive when passive flexion of the neck results in flexion of the hips and knees. (From Ref. 90.)

Roos, KL. Central Nervous System Infectious Diseases and Therapy, 1997, p 104

# Bacterial Meningitis

- Fever
- Stiff neck
- Altered mental status
  - Only 44% will have all three (van de Beek, NEJM 2004; 351:1849. N= 696)
  - Subacute onset, can be acute
  - Recognition and early treatment determine outcome

# Bacterial Meningitis -Clinical

- Bacterial meningitis incidence approximates 5-10/100,000 population per year in the United States.
- Untreated it is usually fatal.
- Headache is the usual heralding symptom.
- Seizures and altered consciousness are common.
- Malaise, fever, and chills as a prodrome are followed in 12-24 hours by Brudzinski's and Kernig's signs of neck stiffness.
- Meningeal signs can be absent in elderly, comatose, and immunosuppressed patients.

# Case

- What test or treatment to provide first?
  - Do a lumbar puncture
  - Get a CT head scan
  - Start antibiotics
  - Draw blood cultures

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# Bacterial Meningitis

- First:
  - 1) Draw blood cultures (80% sensitive)
  - 2) Start antibiotics
  - 3) Do a lumbar puncture
  - 4) Get a CT head scan (optional) preferably before LP

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# Bacterial Meningitis

- When to get a CT scan before lumbar puncture (approximately a two hour window between start of antibiotics and significantly affecting CSF cultures)
  - Focal or lateralizing signs on neurologic exam
  - Signs potentially associated with herniation (coma)
  - Papilledema
  - Immune compromised state\*
  - New onset seizures\*

# Bacterial Meningitis -Clinical

- Focal signs are secondary to cerebritis, venous or arterial infarction, subdural empyema, or subdural effusion.
- Meningitis can cause cranial neuropathies, the syndrome of inappropriate ADH or hydrocephalus, as part of the primary inflammatory process.
- The most serious effect is cerebral edema.

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**Table 2.—Complications of Bacterial Meningitis  
in 43 of 86 Adult Patients**

Complications	Patients, No. (%)
Central nervous system	35 (40.7)
Cerebrovascular	13 (15.1)
Arterial	9 (10.5)
Venous	4 (4.7)
Brain swelling	12 (14.0)
Hydrocephalus	10 (11.6)
Intracerebral hemorrhage	2* (2.3)
Focal neurological signst	12 (14.0)
Brain abscess	1† (1.2)
Side effects of therapy	3§ (3.5)
Systemic	19 (22.1)
Septic shock	10 (11.6)
Adult respiratory distress syndrome	3 (3.5)
Disseminated intravascular coagulation	7   (8.1)
Arthritis	2¶ (2.3)
Pancreatitis	1 (1.2)
Septic panophthalmitis	1 (1.2)
Pulmonary embolism	2 (2.3)
Pneumonia	7 (8.1)
Alcoholic delirium tremens	2 (2.3)
Side effects of therapy	1# (1.2)

15.1%

14.0%

From Pfister, Feiden and Einhaypl. Spectrum of Complications During Bacterial Meningitis in Adults. Arch Neurol (1993) 50: 575-581.

# Case

- 58 y.o. previously healthy man presents with 3 days of headache, 12 hours of fever and obtundation. Temp 39°C; neurologic exam is nonfocal; prominent nuchal rigidity and response only to tactile stimulation
- CSF exam shows protein 432mg/dL, 635 WBC/ $\mu$ L (68% polys), glucose 18mg/dL
- What is the likely cause of meningitis?

# Meningitis

Lumbar puncture is required for confirmation and treatment of bacterial meningitis

## Spinal Fluid Patterns of Reaction

	<u>Protein</u>	<u>Glucose</u>	<u>WBC Count</u>	<u>Cell Type</u>
Normal	15-45 mg/dL	>40% s.glucose	<5 WBC/mm <sup>3</sup>	Lymphocytes
<b>Bacterial</b>	<b>&gt;100</b>	<b>&lt;40% s.glucose</b>	<b>&gt;500</b>	<b>PMN's</b>
Viral	<120	>40% s.glucose	10-500	Lymphocytes
Granulomatous	>50	<40% s.glucose	10-1000	Lymphocytes

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# Adult Bacterial Meningitis - Causes

What is available to establish the causative bacterium from spinal fluid?

- Gram's stain
- Bacterial culture
- Bacterial antigen assay
- Polymerase chain reaction (PCR)

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# Bacterial Antigen Assay in CSF

The latex agglutination reagents consist of polystyrene latex particles coated with antibodies to the bacterial antigens of interest. These particles agglutinate in the presence of sufficient homologous antigen.

Available for:

- Pneumococcus ( *Strep. pneumoniae* )
- *H. influenzae*
- *N. meningitis* groups A, C, Y, and W135
- group B *Streptococcus*

IDSA guidelines do not recommend the use of bacterial antigen assay

- Studies question whether it influences treatment decisions
- IDSA guidelines:

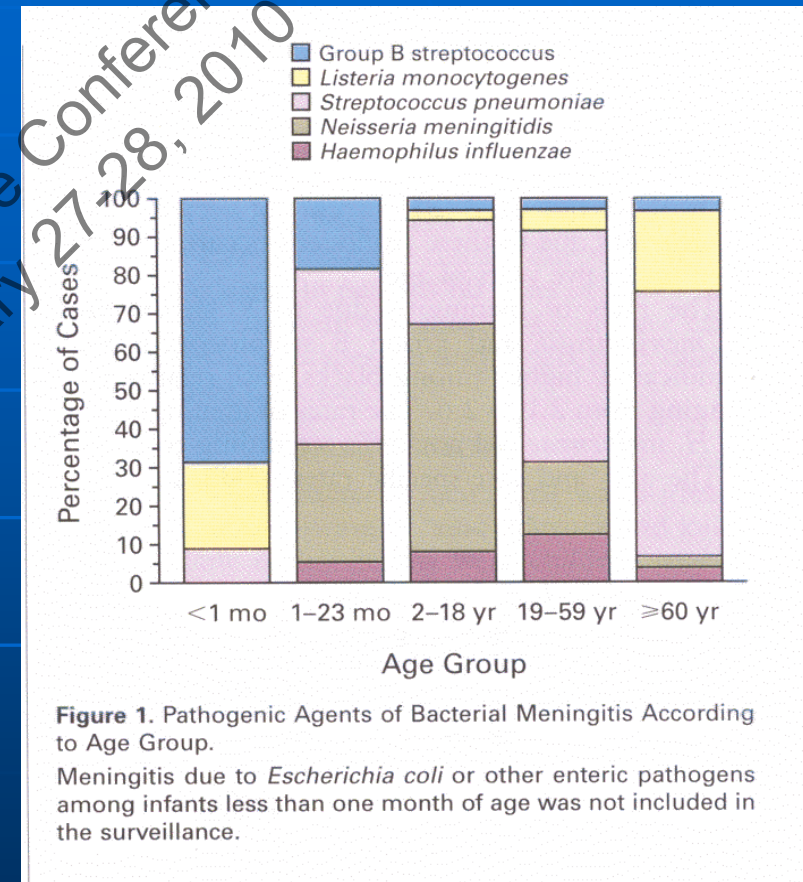
<http://www.idsociety.org/content.aspx?id=4430#bm>



# Bacterial Meningitis - Agents In Adults

## ■ **Pneumococcus** (*Streptococcus pneumoniae*) is the most common cause in adults.

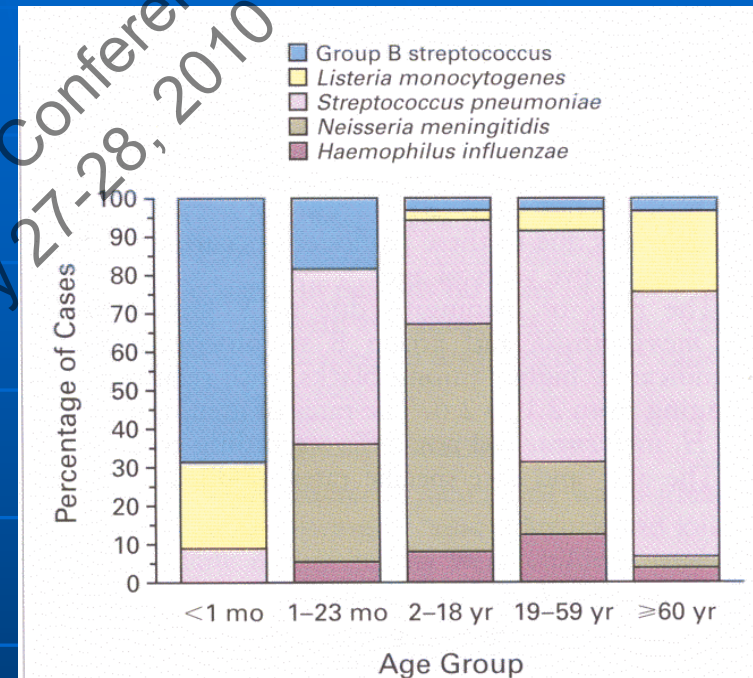
- Splenectomy and humoral defects are predisposing factors.
- Antibiotic resistant strains are more common, which influences empiric treatment choices.



Schuchat, et al; N Engl J Med  
1997;337:970-6

# Bacterial Meningitis - Agents In Adults

- **Meningococcus** (*Neisseria meningitidis*) peak age of incidence is teenage years and young adulthood.
  - It causes **skin petechiae** or purpura in 50-75% of affected patients, though rarely this can be seen with pneumococcus as well.
  - This agent is responsible for 20-30% of all cases of meningitis.
  - It is acquired by respiratory transmission so contacts are treated with prophylaxis with Rifampin 10 mg/kg every 12 hours for four doses.
  - *Meningococcus* groups A, B, C, Y, and W135



**Figure 1.** Pathogenic Agents of Bacterial Meningitis According to Age Group.

Meningitis due to *Escherichia coli* or other enteric pathogens among infants less than one month of age was not included in the surveillance.

Schuchat, et al; N Engl J Med  
1997;337:970-6

# Meningitis

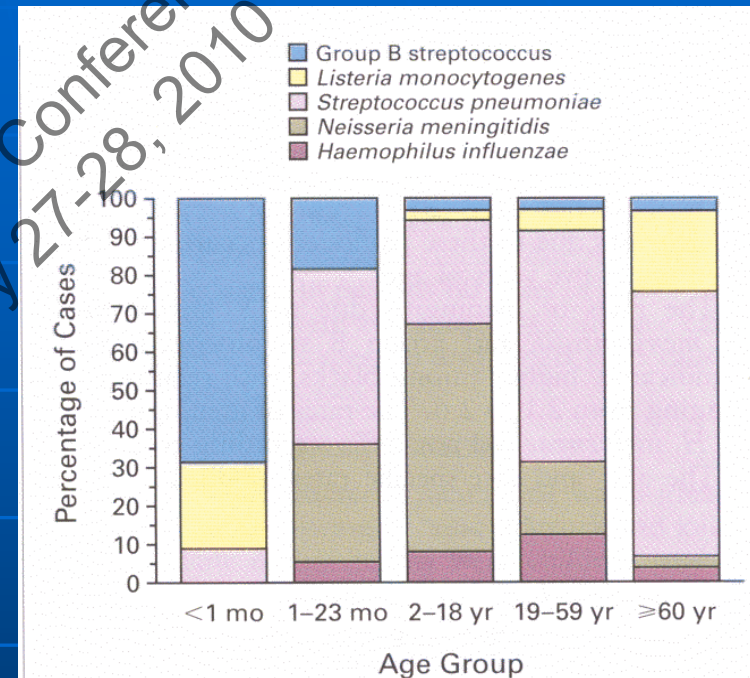


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Meningococcal meningitis associated purpura  
Schmutzhard and Pfaussler; Neurology Chronicle 1992; 2:1-8

# Bacterial Meningitis - Agents In Adults

- ***Haemophilus influenzae*** - This agent was the most frequent cause in children age **3 months to 6 years**.
  - However, since the advent of the **Hib** vaccine, it is rare.
  - It may still occur in non-vaccinated children.
  - It can also occur in adults, especially if debilitated or with upper respiratory infection, most who have never been vaccinated.
- ***Staphylococcus*** is most commonly **associated with surgery or trauma**.
  - Its presence without that history should suggest a break in the blood-brain barrier or bacteremia.

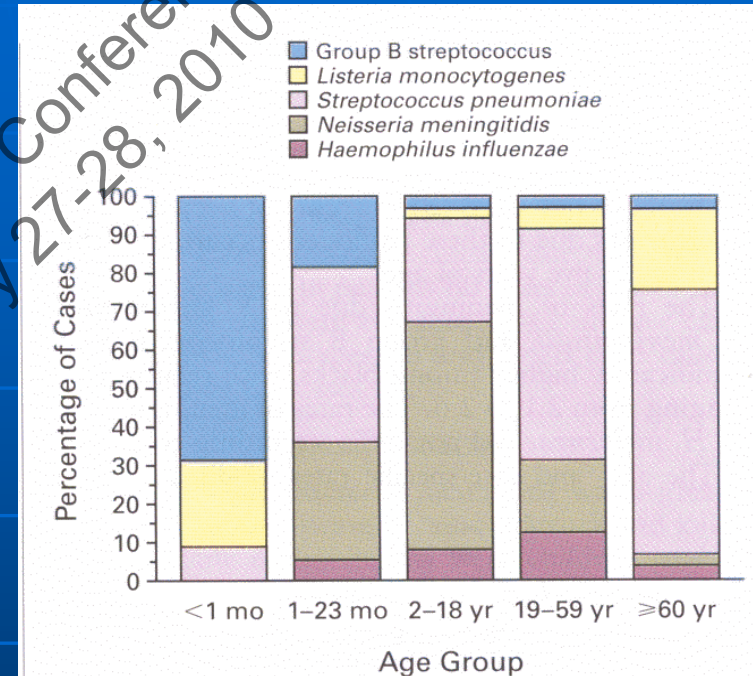


**Figure 1.** Pathogenic Agents of Bacterial Meningitis According to Age Group.

Meningitis due to *Escherichia coli* or other enteric pathogens among infants less than one month of age was not included in the surveillance.

# Bacterial Meningitis - Agents

- **Gram-negative bacteria**, usually are associated with systemic bacteremia when causing a meningitis.
- **Group B *Streptococcus*** is the most common cause of meningitis in newborn infants.
- ***Listeria monocytogenes*** meningitis occurs in the elderly or alcoholic patient.
  - Brainstem encephalitis has also been described associated with or without the meningitis.

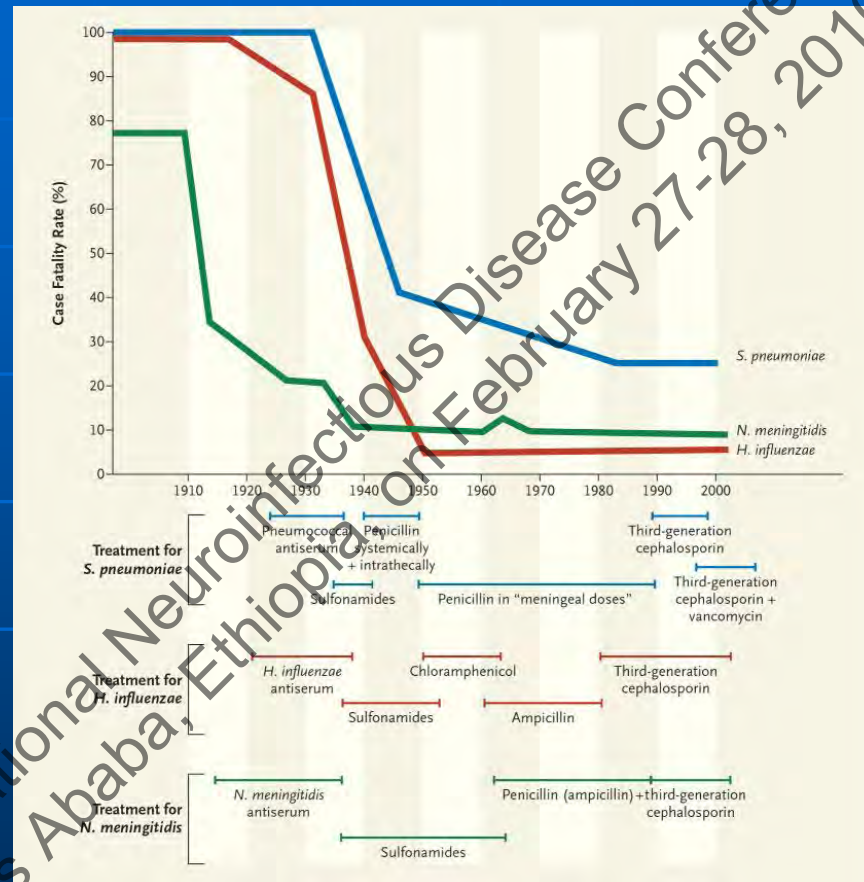


**Figure 1.** Pathogenic Agents of Bacterial Meningitis According to Age Group.

Meningitis due to *Escherichia coli* or other enteric pathogens among infants less than one month of age was not included in the surveillance.

Schuchat, et al; N Engl J Med  
1997;337:970-6

# Bacterial Meningitis



Swartz M. Bacterial Meningitis-A view of the past 90 years. NEJM 2004; 351(18):1826-1828

# Empiric Antibiotic Therapy of Suspected Bacterial Meningitis

## ■ Adults

- Community Acquired
  - Vancomycin, 1 g q 12 hrs. IV (until sensitivities of organism are known)
  - Ceftriaxone, 2 g q. 12 hrs. IV or Cefotaxime, 3 g q. 6 hrs. IV
  - **Dexamethasone** 10mg q 6 hrs. for 4 days (NEJM 2002; 347:1549-56) for pneumococcus, +/- others
- Alcoholism or Advanced Age
  - above plus Ampicillin, 2 g q. 4 hrs. IV (for Listeria)
- Neurosurgical procedure or trauma
  - Cefepime 2 g q 8 hrs.
  - plus Vancomycin, (above doses)
  - plus Metronidazole, 500 mg q. 6 hrs. IV (if contaminated wound is suspected)

## ■ Children

- Ceftriaxone, 50 mg/kg q. 12 hrs. IV
- or
- Cefotaxime, 75 mg/kg q. 6 hrs. IV
- plus
- Vancomycin, 15 mg/kg q. 6 hrs. IV
- Dexamethasone, 0.15 mg/kg q 6 hrs. for 4 days

# Standardized treatment of bacterial meningitis in Africa

[http://www.who.int/csr/resources/publications/meningitis/WHO\\_CDS\\_EPR\\_2007\\_3.pdf](http://www.who.int/csr/resources/publications/meningitis/WHO_CDS_EPR_2007_3.pdf)

- Since 1996, WHO has recommended the use of oily chloramphenicol (OC) for the presumptive treatment of meningococcal epidemics in peripheral health centres. OC is:
  - effective as a single dose (100 mg/kg)
  - easy to use at district level (one intramuscular injection)
  - has a low risk of misuse due to its limited indication.
- However, it also has some drawbacks:
  - it cannot be used in pregnant or lactating women
  - it cannot be used in children less than two months of age
  - side effects, although rare, can be serious
  - there is only one manufacturer, thus there is a risk of production disruption.



# Standardized treatment of bacterial meningitis in Africa

[http://www.who.int/csr/resources/publications/meningitis/WHO\\_CDS\\_EPR\\_2007\\_3.pdf](http://www.who.int/csr/resources/publications/meningitis/WHO_CDS_EPR_2007_3.pdf)

- Ceftriaxone as an alternative to OC as presumptive treatment
  - Ceftriaxone, a third-generation cephalosporin, is the recommended treatment for bacterial meningitis in many developed countries because it has a wide spectrum of action and a long half-life (8 hours in blood, 14 hours in CSF).
  - It has been recommended by WHO as treatment for meningitis since 1997. However, until recently, ceftriaxone was considered in developing countries as second-line treatment for bacterial meningitis in all age groups due to the high cost. The patent has now expired and generic versions of good quality are available.

# Treatment of bacterial meningitis in the African meningitis belt in the absence of laboratory support

[http://www.who.int/csr/resources/publications/meningitis/WHO\\_CDS\\_EPR\\_2007\\_3.pdf](http://www.who.int/csr/resources/publications/meningitis/WHO_CDS_EPR_2007_3.pdf)

## In non-epidemic situations

Treatment should be adapted according to patients' age and most likely causative pathogen

## In meningococcal epidemic situations

### In children aged 0–23 months

Treatment should be adapted according to patients' age and most likely causative pathogen

### In children over 2 years and adults

*N. meningitidis* is the most likely pathogen. Presumptive treatment is justified

### Use of ceftriaxone

Single dose as presumptive treatment

OR

### Use of oily chloramphenicol

Single dose as presumptive treatment

# Treatment of bacterial meningitis in the African meningitis belt in the absence of laboratory support

[http://www.who.int/csr/resources/publications/meningitis/WHO\\_CDS\\_EPR\\_2007\\_3.pdf](http://www.who.int/csr/resources/publications/meningitis/WHO_CDS_EPR_2007_3.pdf)

Age group	Principal causes	Treatment	Monitoring
2–5 years	<i>S. pneumoniae</i> <i>H. influenzae</i> <i>N. meningitidis</i>	Ceftriaxone 100 mg/kg single dose IM	Clinical monitoring at 24 and 48 h If no improvement:2 - after 24 h, give second dose of ceftriaxone 100 mg/kg - after 48 h, treat for total of 5 days with ceftriaxone, or refer
> 5–14 years	<i>N. meningitidis</i> ( <i>S. pneumoniae</i> )	Ceftriaxone 100 mg/kg single dose IM	Clinical monitoring at 24 and 48 h If no improvement:2 - after 24 h, give second dose of ceftriaxone 100 mg/kg - after 48 h, treat for total of 5 days with ceftriaxone, or refer
> 14 years	<i>N. meningitidis</i> ( <i>S. pneumoniae</i> )	Ceftriaxone 100 mg/kg (max. 4 g) single dose IM	Clinical monitoring at 24 and 48 h If no improvement:2 - after 24 h, give second dose of ceftriaxone 100 mg/kg - after 48 h, treat for total of 5 days with ceftriaxone, or refer

# ANTIBIOTIC CONCENTRATIONS IN THE CSF

<u>Good Concentrations in CSF With &amp; Without Meningitis</u>	<u>Adequate Concentrations in CSF in Meningitis</u>	<u>Fair to Poor Concentrations in Meningitis</u>
<b>Chloramphenicol</b>	<b>Penicillin</b>	Early cephalosporins
Sulfonamides	<b>Ampicillin</b>	Cephalothin
<b>Cephalosporins</b> <b>Cefotaxime</b> <b>Ceftriaxone</b> Ceftazidime Moxalactam <b>Cefepime</b> <b>Metronidazole</b>	Methicillin Oxacillin Nafcillin Carbenicillin Ticarcillin Tetracycline Erythromycin	Cefoxitin Aminoglycosides Gentamycin Tobramycin Amikacin Clindamycin Benzathine penicillin
<b>Trimethoprim-sulfamethoxazole</b>	Ethambutol Rifampin	
Isoniazid	<b>Vancomycin</b> <b>Meropenem</b>	

# Bacterial Meningitis Treatment Duration

- *Strep. pneumoniae* 10-14d
- *Listeria monocytogenes* >21d
- *Nisseria meningitidis* 7d
- *Staphylococcus* variable
- Gram negative bacilli 21d
- Group B *Streptococcus* 14-21d

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Addis Ababa, Ethiopia, on February 27-28, 2010

# Bacterial Meningitis - Pathophysiology

- The presence of bacteria in the subarachnoid space causes several complications:
  - Surrounding neural tissue is damaged by endotoxins from bacterial walls as well as cytokines released from inflammatory cells.
  - The blood brain barrier and the blood CSF barrier are disrupted as cells are recruited from the blood stream to ingest the bacteria.
  - The inflammatory response may partially block CSF flow and resorption.
  - Cerebral edema occurs as a result of the cytokine response and further opening the blood brain barrier.

# Pneumococcal meningitis in adults

Spectrum of complications and prognostic factors in a series of 87 cases

Stefan Kastenbauer and Hans-Walter Pfister

Intracranial complications:	74.7%
Diffuse edema:	28.7%
Hydrocephalus:	16.1%
Arterial:	21.8%
Venous:	9.2%
Intracranial hemorrhage:	9.2%
Seizures:	27.6%
Acute myelitis:	2.3%
Hearing loss:	19.5%

From: Stefan Kastenbauer and Hans-Walter Pfister. Pneumococcal meningitis in adults Spectrum of complications and prognostic factors in a series of 87 cases. Brain: 2003, 126: 1015-1025.

# Dexamethasone

- Decrease transcription: proinflammatory cytokines and chemokines
- Decrease synthesis: many inflammatory mediators
- Decrease cell activation and recruitment
- Stabilize lysosomes
- Decrease adhesion molecule expression & matrix metalloproteinase activity
- Temporary repair leaky BBB
- Reduce intracranial pressure
- Reduce cerebral edema formation
- Reduce meningeal inflammation
- Improve disturbances in CSF hydrodynamics
- Prevent changes to CBF



# Bacterial Meningitis

Table 1.—Characteristics of Dexamethasone Trials

Study	Antibiotic Regimen	Dexamethasone Regimen	Timing of Dexamethasone*	Mean Age (Age Range)
Dallas 1 <sup>3</sup>	Cefuroxime, 240 mg/kg per day, 3 doses	0.6 mg/kg per day, 4 doses, 4 d	Not stated; $\leq 1$ dose of PAB	15 mo (2-71 mo)
Dallas 2 <sup>3</sup>	Ceftriaxone sodium, 80 mg/kg per day, single dose	0.6 mg/kg per day, 4 doses, 4 d	Not stated; $\leq 1$ dose of PAB	16 mo (2-187 mo)
Dallas 3 <sup>23</sup>	Cefuroxime, 300 mg/kg per day, 3 doses	0.6 mg/kg per day, 4 doses, 4 d	<12 h after PAB	15 mo (3-76 mo)
Costa Rica <sup>24</sup>	Cefotaxime sodium, 200 mg/kg per day, 4 doses	0.6 mg/kg per day, 4 doses, 4 d	First dose 15-20 min before PAB	17 mo (not stated)
Switzerland multicenter <sup>25</sup>	Ceftriaxone sodium, 100 mg/kg per day, single dose	0.8 mg/kg per day, 2 doses, 2 d	First dose 10 min before PAB	37 mo (4-192 mo)
Canada multicenter <sup>26</sup>	Variable	0.6 mg/kg per day, 4 doses, 4 d	$\leq 24$ h after PAB	Median, 12 mo (1-153 mo)
US multicenter <sup>27</sup>	Ceftriaxone sodium, 100 mg/kg per day, 2 doses	0.6 mg/kg per day, 4 doses, 4 d	$\leq 4$ h after PAB	16 mo (not stated)
Finland multicenter <sup>28</sup>	Ceftriaxone sodium, 100 mg/kg per day, single dose	1.5 mg/kg per day, 3 doses, 3 d	Not stated; $\leq 1$ dose of PAB	52 mo (not stated)
Egypt <sup>29</sup>	Ampicillin sodium, 160 mg/kg per day; chloramphenicol, 100 mg/kg per day	16 mg/d if <12 y; 24 mg/d if $\geq 12$ y	With 1st antibiotic dose	5-25 y (see text)
Turkey <sup>30</sup>	Ampicillin sodium, 200 mg/kg per day; sulbactam, 100 mg/kg per day	0.6 mg/kg per day, 4 doses, 4 d	$\leq 15$ min before 1st antibiotic dose	7 y (2-16)
Mozambique <sup>31</sup>	Ampicillin sodium, 400 mg/kg per day; chloramphenicol, 100 mg/kg per day	0.4 mg/kg per day, 4 doses, 3 d	Not specified	16.5 mo (2-84 mo)

\*PAB indicates parenteral antibiotics.

Dexamethasone trials in adults- meta-analysis  
McIntyre, et al; JAMA 1997;278:925-931

# Dexamethasone Treatment of Meningitis

**TABLE 2. OUTCOMES EIGHT WEEKS AFTER ADMISSION, ACCORDING TO CULTURE RESULTS.\***

OUTCOME AND CULTURE RESULTS	DEXAMETHASONE GROUP	PLACEBO GROUP	RELATIVE RISK (95% CI)†	P VALUE
	no./total no. (%)			
Unfavorable outcome				
All patients	23/157 (15)	36/144 (25)	0.59 (0.37–0.94)	0.03
<i>Streptococcus pneumoniae</i>	15/58 (26)	26/50 (52)	0.50 (0.30–0.83)	0.006
<i>Neisseria meningitidis</i>	4/50 (8)	5/37 (11)	0.75 (0.21–2.63)	0.74
Other bacteria	2/12 (17)	1/17 (6)	2.83 (0.29–27.8)	0.55
Negative bacterial culture‡	2/37 (5)	4/30 (13)	0.41 (0.08–2.06)	0.40
Death				
All patients	11/151 (7)	21/144 (15)	0.48 (0.24–0.96)	0.04
<i>S. pneumoniae</i>	8/58 (14)	17/50 (34)	0.41 (0.19–0.86)	0.02
<i>N. meningitidis</i>	2/50 (4)	1/47 (2)	1.88 (0.76–20.1)	1.00
Other bacteria	0/12 (0)	1/17 (6)	1.42 (0.10–20.5)	1.00
Negative bacterial culture	0/37 (0)	2/30 (7)	—	0.20
Focal neurologic abnormalities				
All patients	18/143 (13)	24/119 (20)	0.62 (0.36–1.09)	0.13
<i>S. pneumoniae</i>	14/49 (29)	11/33 (33)	0.67 (0.33–1.37)	0.32
<i>N. meningitidis</i>	3/46 (7)	5/44 (11)	0.57 (0.15–2.26)	0.48
Other bacteria	3/11 (27)	3/16 (19)	1.45 (0.36–5.92)	0.66
Negative bacterial culture	1/37 (3)	5/26 (19)	0.14 (0.02–1.13)	0.07
Hearing loss				
All patients	13/143 (9)	14/119 (12)	0.77 (0.38–1.58)	0.54
<i>S. pneumoniae</i>	7/49 (14)	7/33 (21)	0.67 (0.25–1.69)	0.55
<i>N. meningitidis</i>	3/46 (7)	5/44 (11)	0.57 (0.15–2.26)	0.48
Other bacteria	2/11 (18)	1/16 (6)	2.91 (0.30–28.3)	0.55
Negative bacterial culture	1/37 (3)	1/26 (4)	0.70 (0.05–10.7)	1.00

# Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa

- N Engl J Med. 2007;357(24):2441-50.
- CONCLUSIONS: Adjuvant therapy with dexamethasone for bacterial meningitis in adults from an area with a high prevalence of HIV did not reduce mortality or morbidity.
- In this setting, intramuscular administration was not inferior to intravenous administration of ceftriaxone for bacterial meningitis.

International Multidisciplinary Infectious Disease Conference  
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# Bacterial Meningitis - Summary

- The triad of fever, stiff neck and altered mental status is reliably present in only half of meningitis cases
- Lumbar puncture is required for confirmation and treatment of bacterial meningitis
- CT scan before lumbar puncture is recommended in some cases
- Early treatment with antibiotics determines outcome
- Dexamethasone is recommended for initial treatment