

# Bacterial Meningitis

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# Changing Epidemiology Of Bacterial Meningitis, US, 1986-2003

	1986	1995	1998-2003*
<b>H. influenzae</b>	45%	7%	7%
<b>S. pneumoniae</b>	18%	47%	61%
<b>N. meningitidis</b>	14%	25%	16%
<b>S. agalactiae</b>	5.7%	12%	14%
<b>L. monocytogenes</b>	3.2%	8%	2%
<b>Median age</b>	15m	25y	39y
<b>≈ no. cases/year</b>	12,920	5755	4450

\*43rd IDSA meeting, 2005, abstract 65

# Community-acquired *L. monocytogenes* Meningitis In Adults (1998-2002)

696 episodes Dutch meningitis cohort  
30 (4%) *Listeria*; mean 65 years, all 10 immunocompetent > 50 years

27% > 4 days until presentation

GS(-) in 60%; 46% (+) BC

17% mortality (30% inadequate Abx)

Brouwer MC ,et al. *Clin Infect Dis* 2006; 43:1233-8.

Lorber B. *Clin Infect Dis* 2007; Mar 1.

# Human *S. suis* Outbreak, Sichuan, China 2005

**n=215, all slaughtered pigs**

**STSS (28%), 62% died**

**Sepsis (24%), meningitis (48%)**

**Clonal strain**

**Yu H, et al. Emerg Infect Dis 2006; 12:914-20.**

# Community-acquired bacterial meningitis in the “elderly” ( $\geq 60$ years)

37% in elderly (classic symptoms the same)

S. p. elderly 68%; N. m  $< 59$  years 50%

complications 72% vs. 57%

mortality 34% vs. 13%

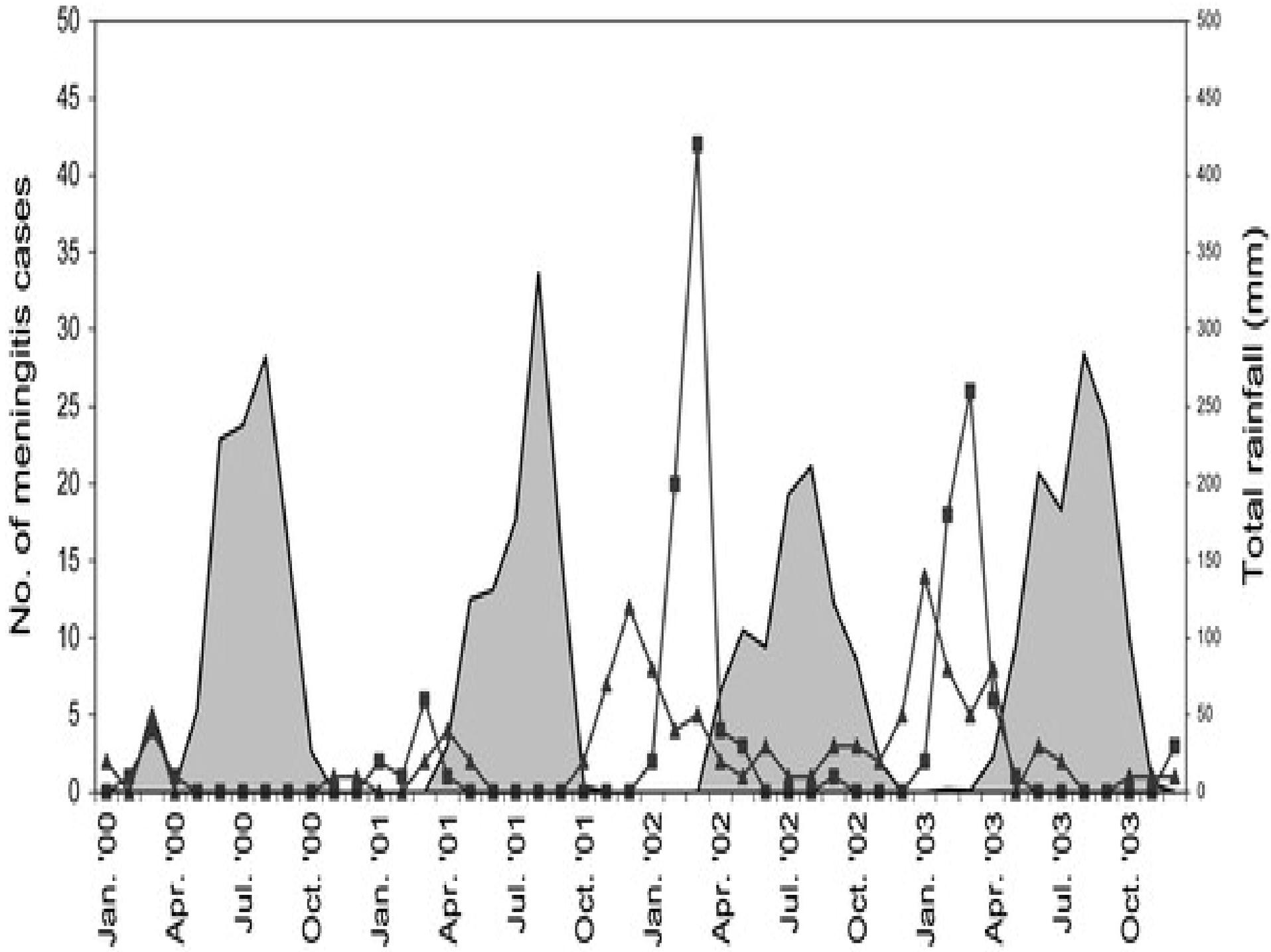
died CR failure 25% vs. 13%

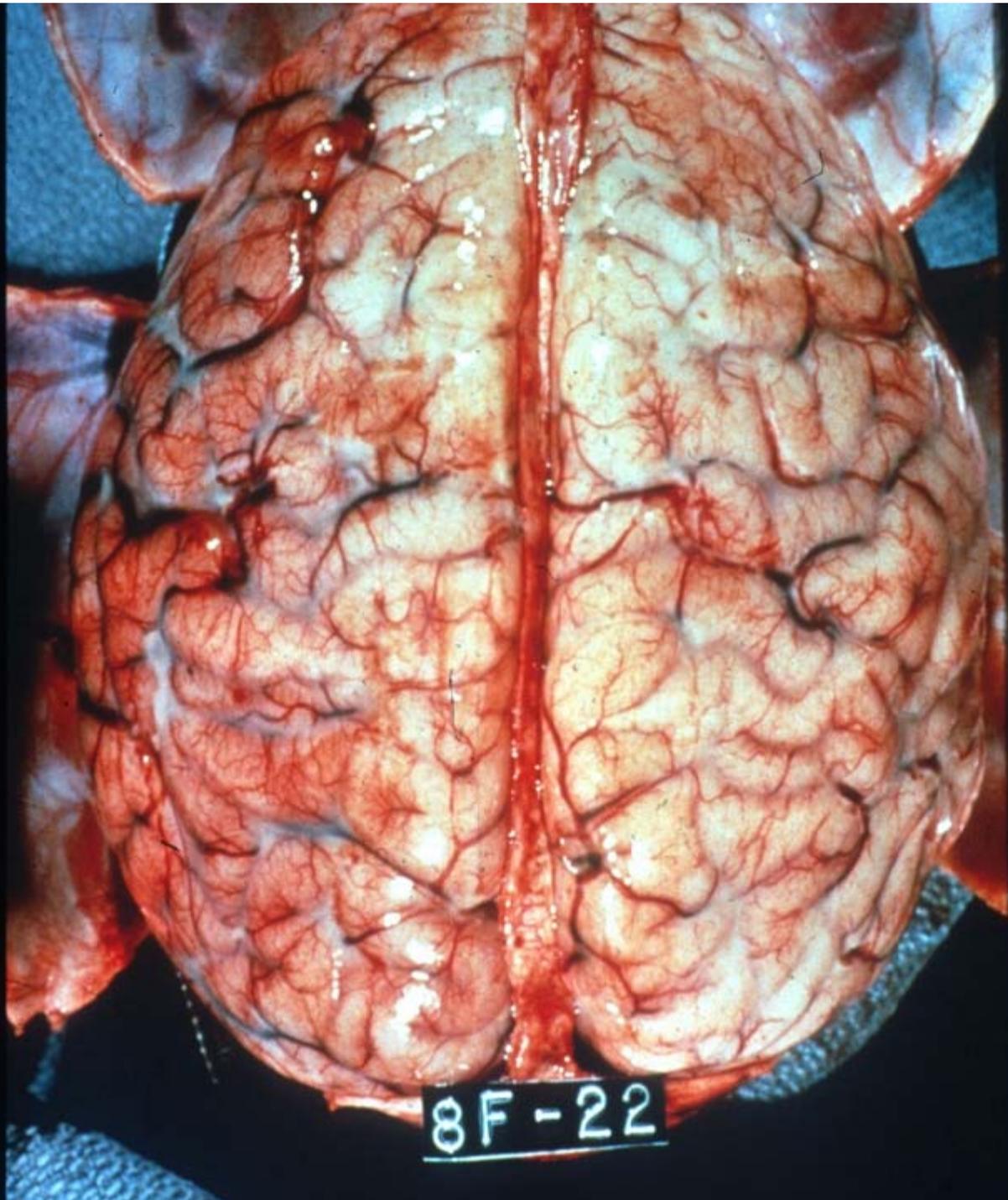
died brain herniation 2% vs. 23%

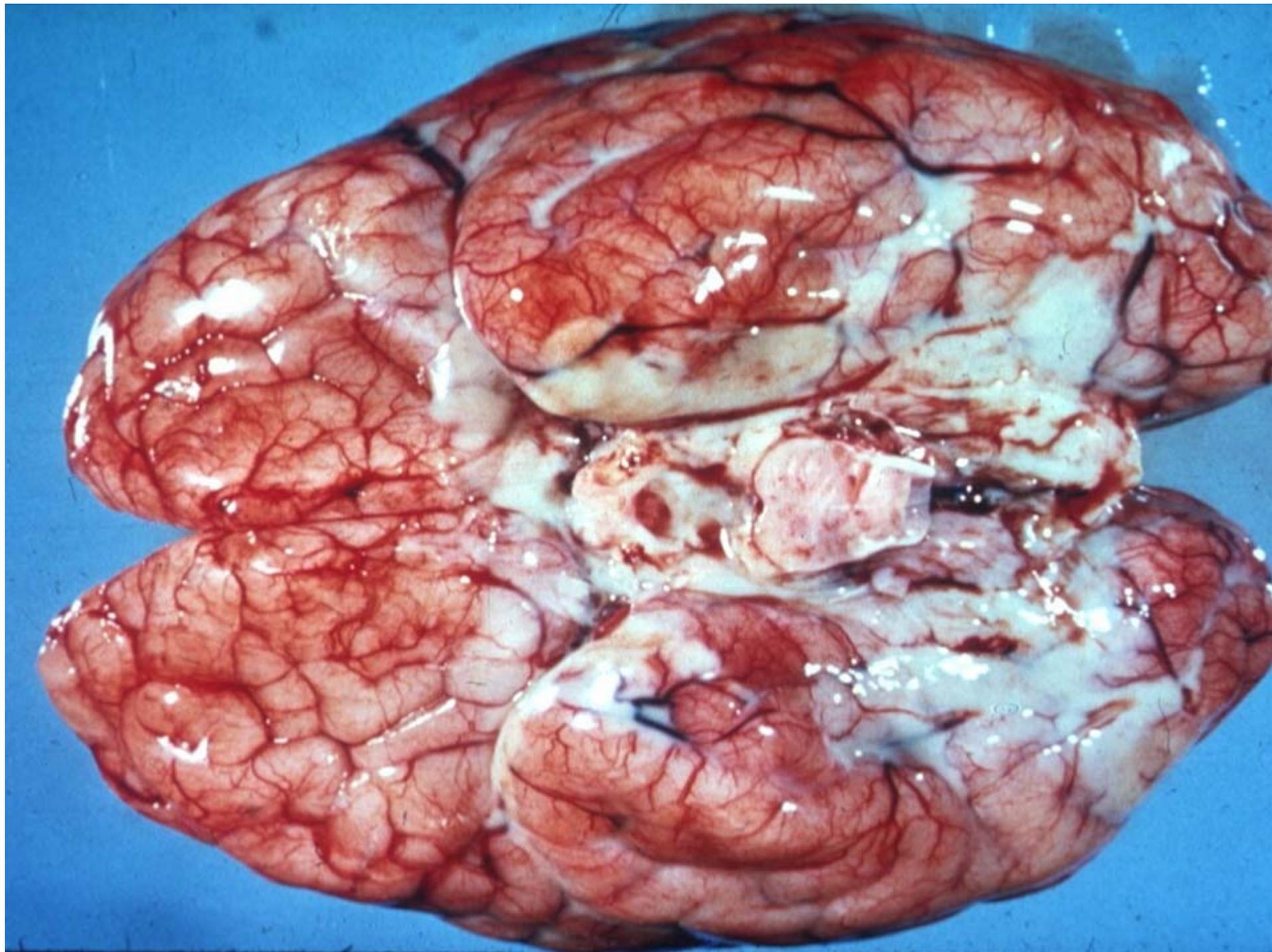
Weisfelt M, et al. J Am Geriatric Soc 2006; 54:1500-7.

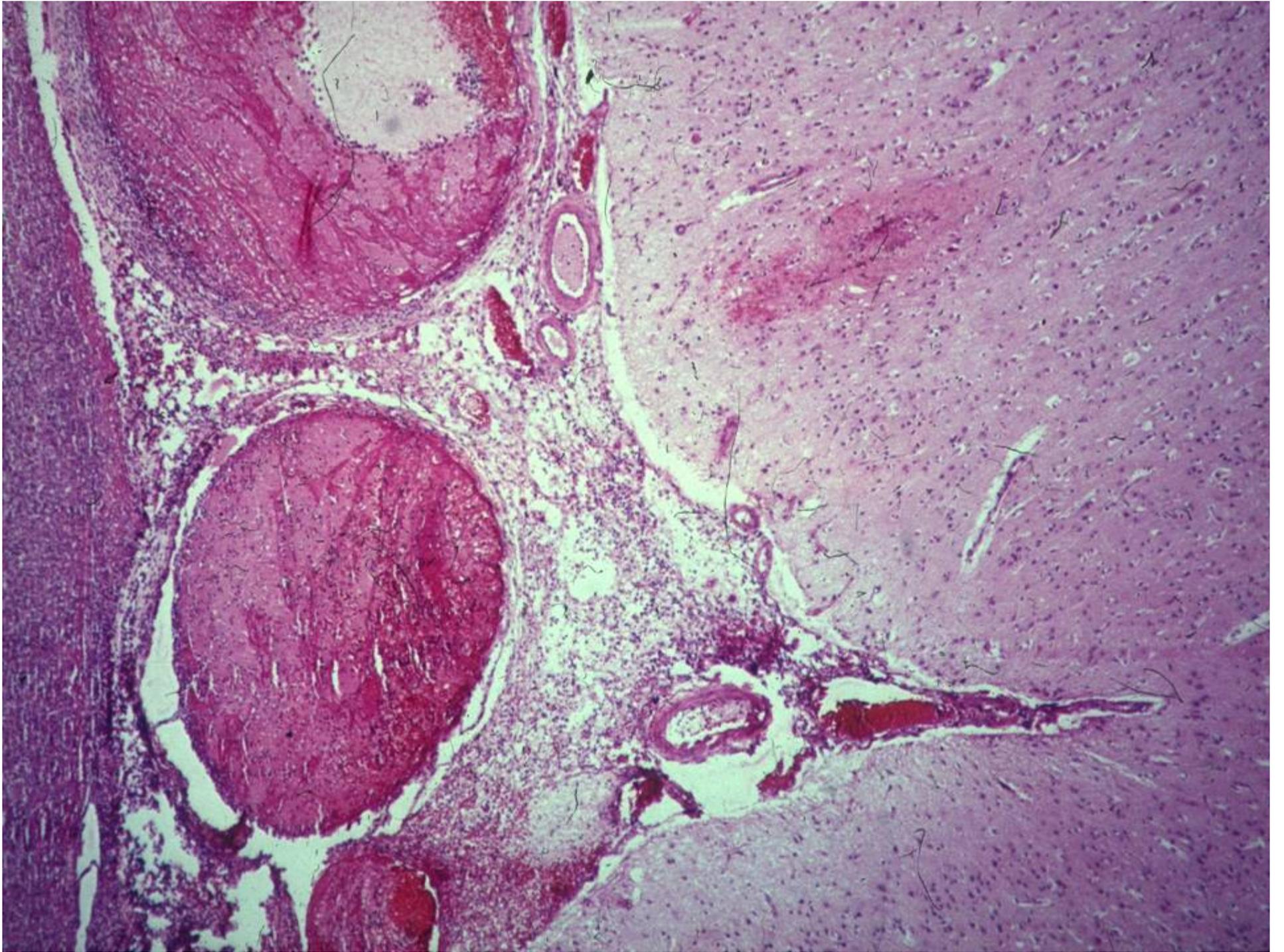
# Sub-Saharan African meningitis belt

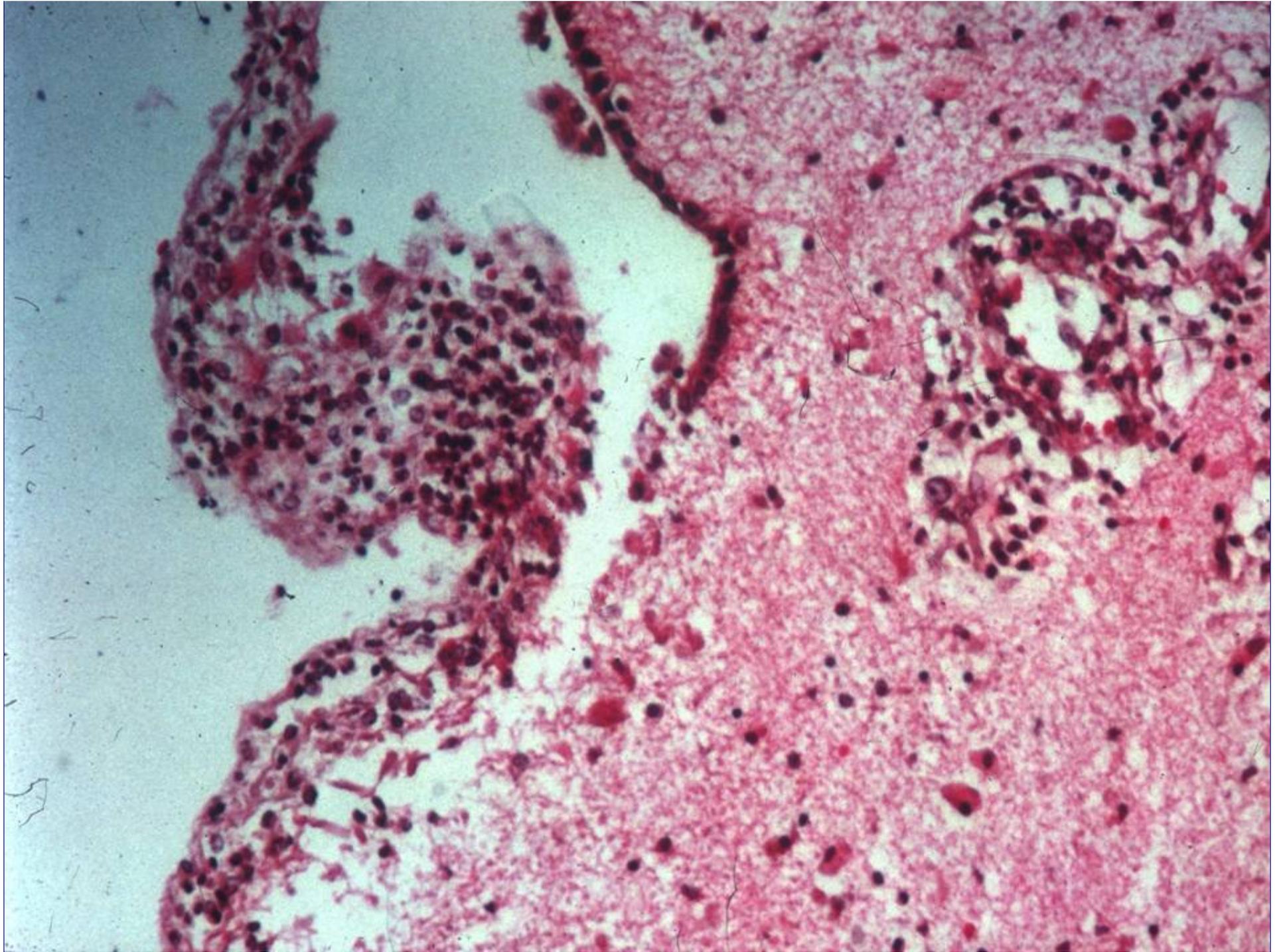


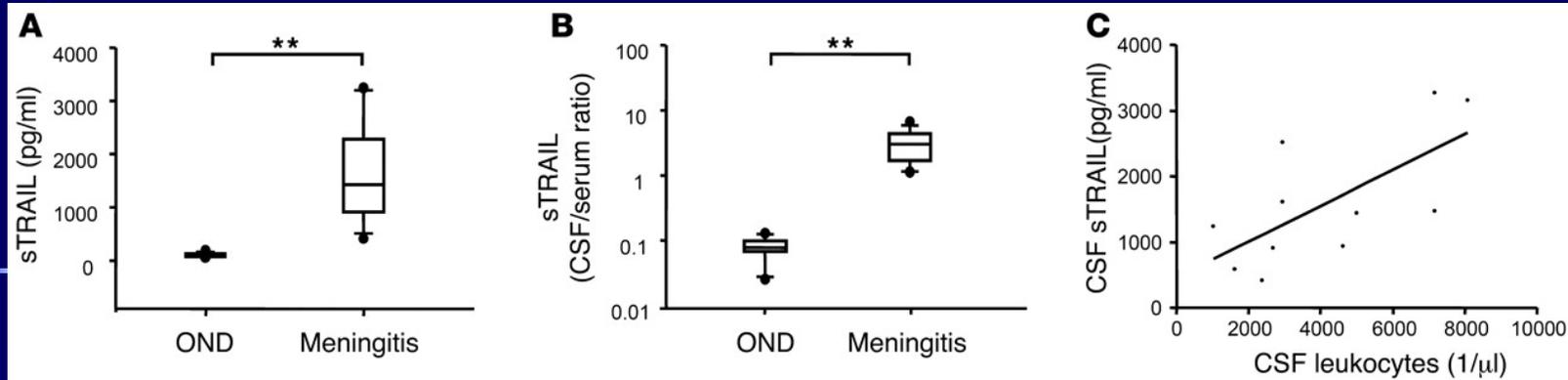






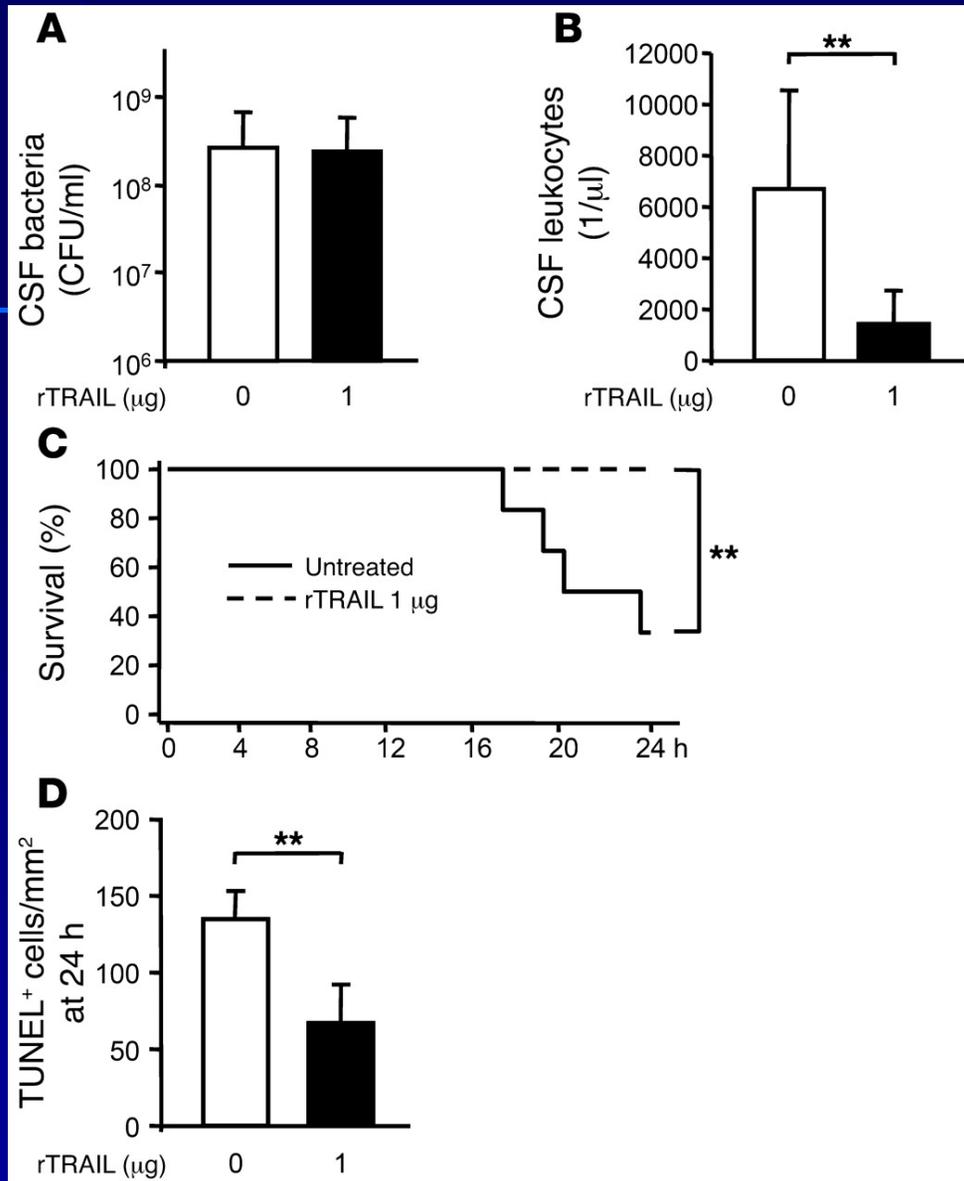




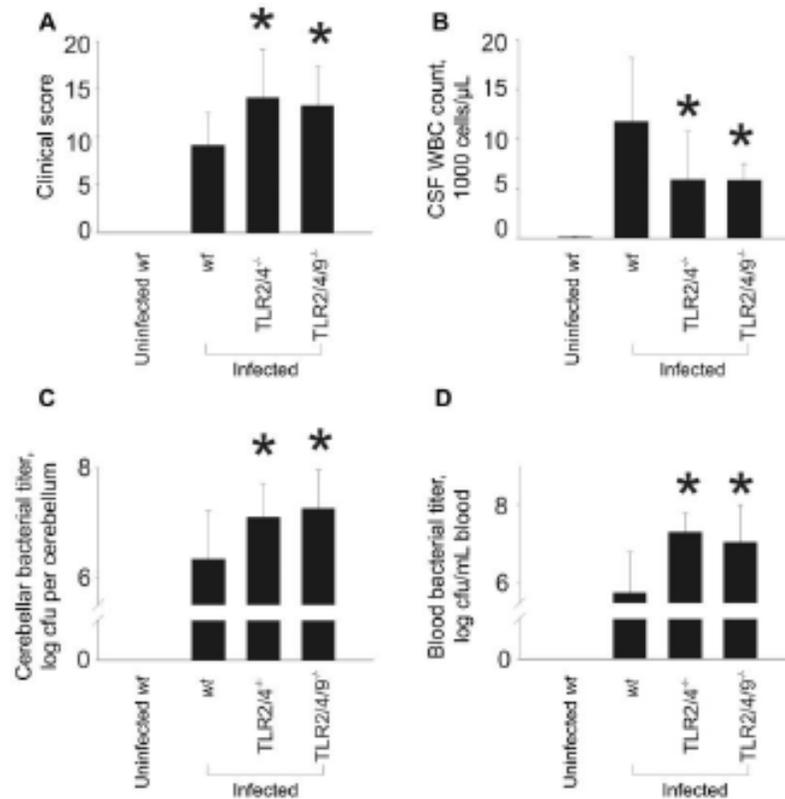


## Figure 1

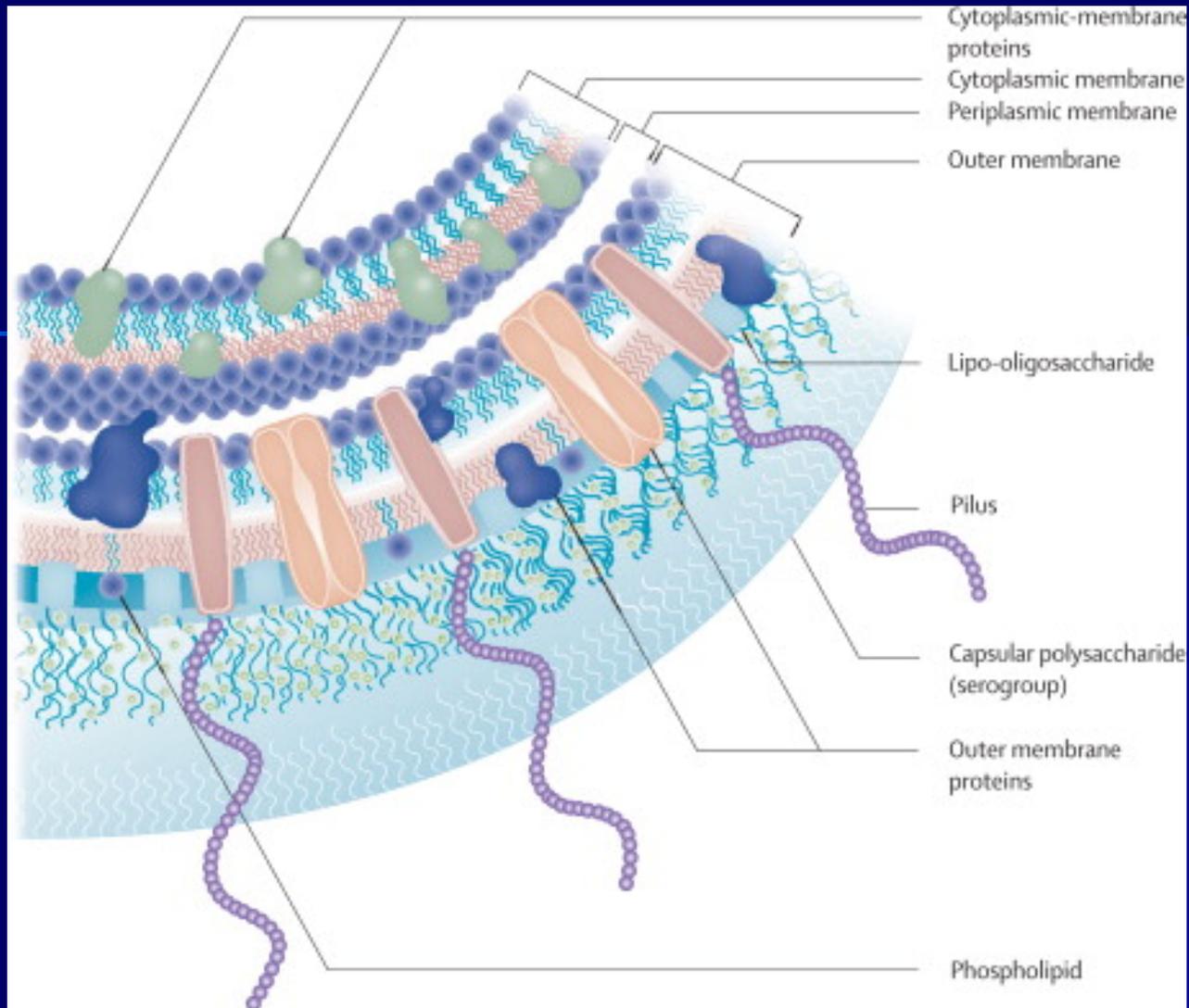
TRAIL is released into the CSF of patients with acute meningitis. (A) In CSF samples from patients with acute bacterial meningitis, the concentration of sTRAIL is significantly higher than in patients with other noninflammatory diseases (OND). \*\*P < 0.01, Student's t test. (B) The increased CSF/serum ratio supports an intrathecal source of sTRAIL during meningitis. \*\*P < 0.01, Student's t test. (C) The concentration of TRAIL in CSF correlated significantly with the cell count. Spearman's  $r = 0.717$ ;  $P = 0.016$ .



**Figure 6**  
**Effects of treatment with rTRAIL in meningitis induced by live pneumococci. (A)** At 24 hours after infection, bacterial load in the CSF in untreated and rTRAIL-treated wild-type mice did not differ. **(B)** CSF leukocyte concentration was significantly lower in rTRAIL-treated mice than in controls at 24 hours after infection with live pneumococci. **\*\*P < 0.01, Student's t test.** **(C)** During the experimental period of 24 hours, mortality was higher in untreated versus rTRAIL-treated mice with meningitis. **\*\*P < 0.01, log rank test.** **(D)** Apoptosis in the dentate gyrus at 24 hours after meningitis induction was reduced by treatment with 1  $\mu\text{g}$  rTRAIL. **\*\*P < 0.01, Student's t test.**



**Figure 1.** Lack of Toll-like receptor (TLR) 2 and TLR4 expression and the impairment of the host response to pneumococcal meningitis and bacterial clearance. Mice lacking TLR2 and TLR4 (*TLR2/4<sup>-/-</sup>* mice) or TLR2, TLR4, and TLR9 (*TLR2/4/9<sup>-/-</sup>* mice) were infected and were analyzed 24 h after infection to determine the clinical score (A), the white blood cell count in cerebrospinal fluid (the CSF WBC count) (B), and the bacterial titers in the brain (C) and the blood (D). *TLR2/4<sup>-/-</sup>*, *TLR2/TLR4* double deficiency; *TLR2/4/9<sup>-/-</sup>*, *TLR2/TLR4/TLR9* triple deficiency; wt wild type. \**P* < .05.



**Figure 3. Cross-sectional view of the meningococcus**  
**Modified from , with permission from the author and publisher.**

# **Meningococemia: Plasma LPS And Survival**

<b>endotoxin units/ml</b>	<b>survival (%)</b>
<b>10-50</b>	<b>75</b>
<b>50-250</b>	<b>15</b>
<b>&gt; 250</b>	<b>0</b>

**Brandtzaeg P in Handbook of Meningococcal Disease 2006**

# Symptoms and Signs of Bacterial Meningitis

Rapid Onset (25%) hospitalized < 24h  
Respiratory Symptoms days – weeks

Headache 90%

Fever >90%

△ consciousness 80%

Vomiting – 30%

Seizures – 30%

Petechiae/purpura 50% (meningo.)

Meningismus 85%

Focal neurosigns 25%

Ocular palsies – 10%

Hemiparesis

Myalgias 20%

Papilledema 1%

# Diagnostic accuracy of physical findings in adults with suspected meningitis\*

297 patients, 80 (27%) with “meningitis”

18/80 microbiologic dx; 3 bacterial

Kernig’s, Brudzinskis signs: sens = 5%,  
NPV = 72%

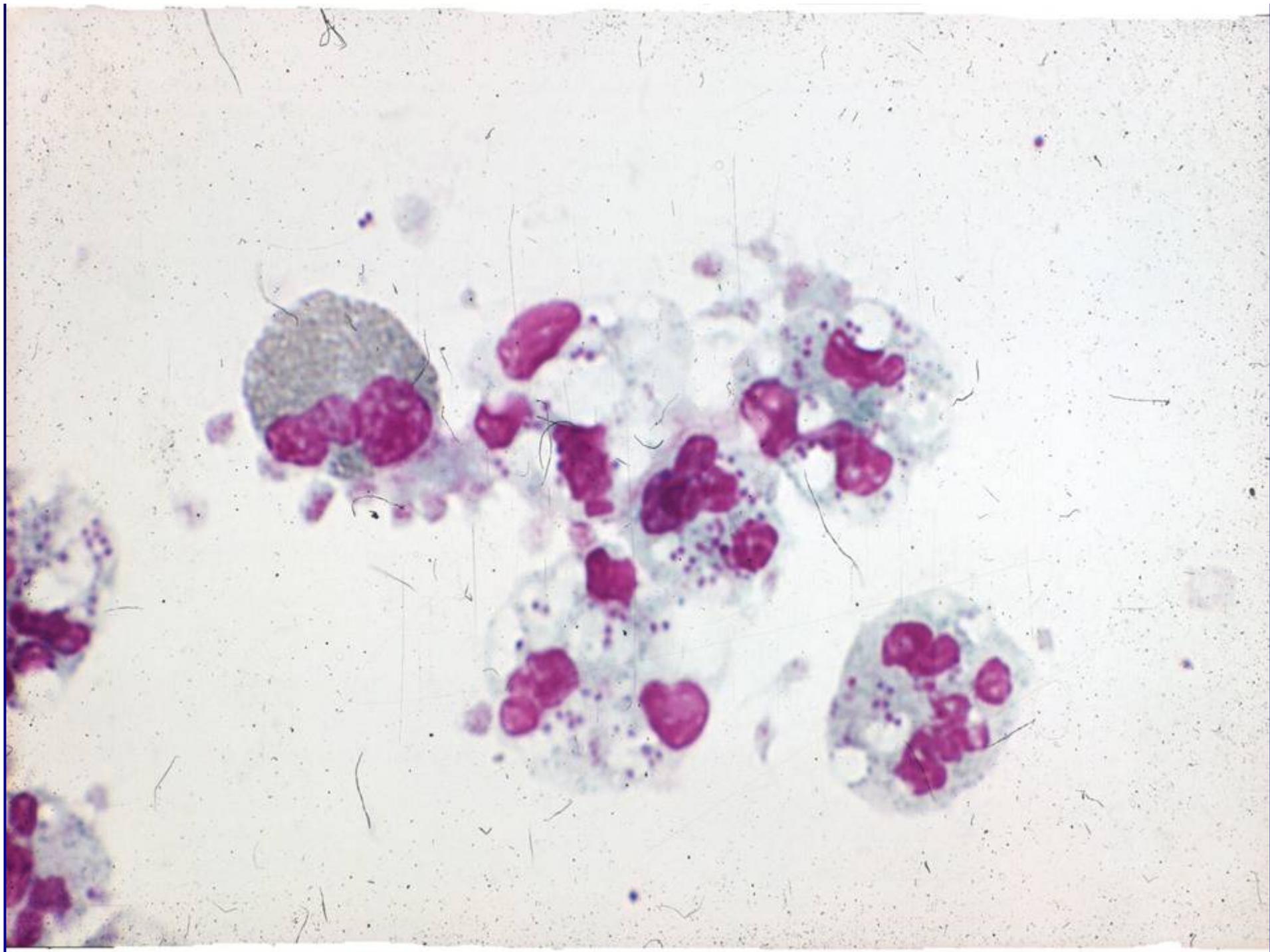
Nuchal rigidity sens = 30% NPV = 73%

CSF wbc >1000 sens = 100% NPV = 100%

\*Thomas KE, et al. Clin Infect Dis 2002; 35:46-52.











# CSF Analysis For Bacterial Meningitis: Metaanalysis

	likelihood ratio
CSF: blood glucose $\leq 0.4$	18
wbc $\geq 500/\mu\text{l}$	15
Lactate $\geq 3.5$ mmol/L	21

Straus SE, et al. JAMA 2006; 296:2012-22.

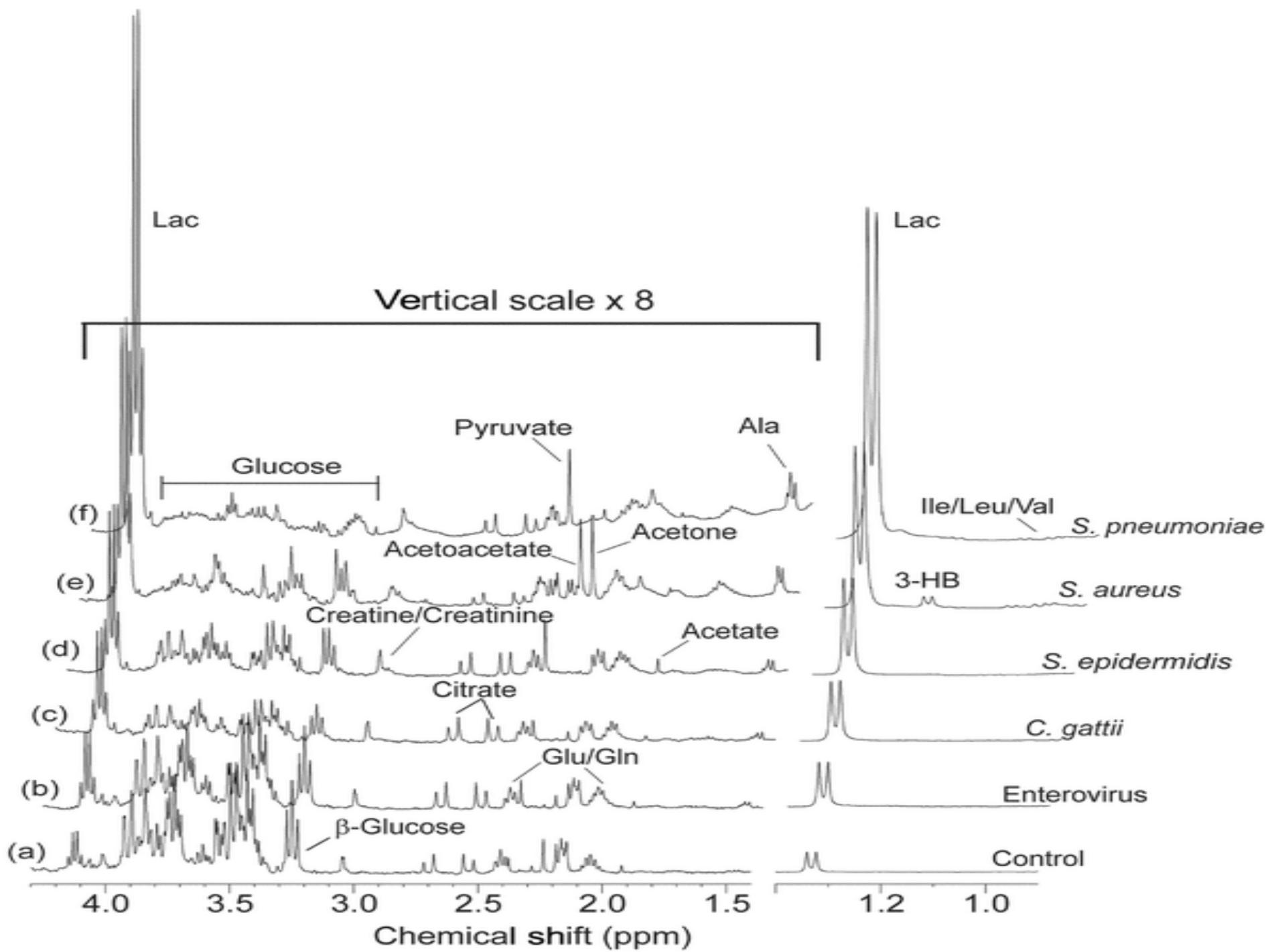
# Characteristics Of Laboratory Tests For Detection Of Gram-stain Negative Bacterial Meningitis

<b>CSF indices</b>	<b>Sensitivity (%)</b>	<b>Specificity (%)</b>	<b>NPV (%)</b>
<b>glucose</b> ( $<2.0$ mmol/L)	<b>31</b>	<b>100</b>	<b>79</b>
<b>protein</b> ( $>1.0$ g/L)	<b>64</b>	<b>96</b>	<b>88</b>
<b>wbc</b> ( $>2000 \times 10^6$ /L)	<b>64</b>	<b>99</b>	<b>90</b>

## Characteristics of laboratory tests for detection of Gram-stain-negative bacterial meningitis

<b>Blood indices</b>	<b>Sensitivity (%)</b>	<b>Specificity (%)</b>	<b>NPV (%)</b>
<b>wbc</b> ( $>20.0 \times 10^6/L$ )	<b>351</b>	<b>97</b>	<b>82</b>
<b>CRP</b> ( $>20 \text{ mg/l}$ )	<b>96</b>	<b>93</b>	<b>99</b>

\*Adapted from Sorminen P, et al. J Pediatr 1999; 134: 725-9



# **Clinical prediction of bacterial meningitis in children with CSF pleocytosis ( $\geq 10$ cells/mm<sup>3</sup>)**

**20 centers; ED 3295 patients, 3.7% BM**  
**Bacterial meningitis score, very low risk:**  
**negative CSF gram stain, CSF ANC <1000,**  
**blood ANC < 10,000, CSF protein < 80, no**  
**seizures (n=1714, 2 BM)**  
**negative predictive value 99.9%**  
**(80% with aseptic meningitis hospitalized)**

**Nigrovic LE, et al. JAMA 2007; 297:52-60.**

## **CT before LP in adults with suspected meningitis\***

**301 patients, CT performed in 235 (78%)**

**56/235 CT abnormal, 11(5%) mass effect**

**Predictive abnl CT: age >60,  
immunocompromise, sz, neurologic  
sx/signs**

**None present 96/235 (41%); CTnl 93/96**

**Mean time to Abx: 5.3h with CT vs 3.0 h**

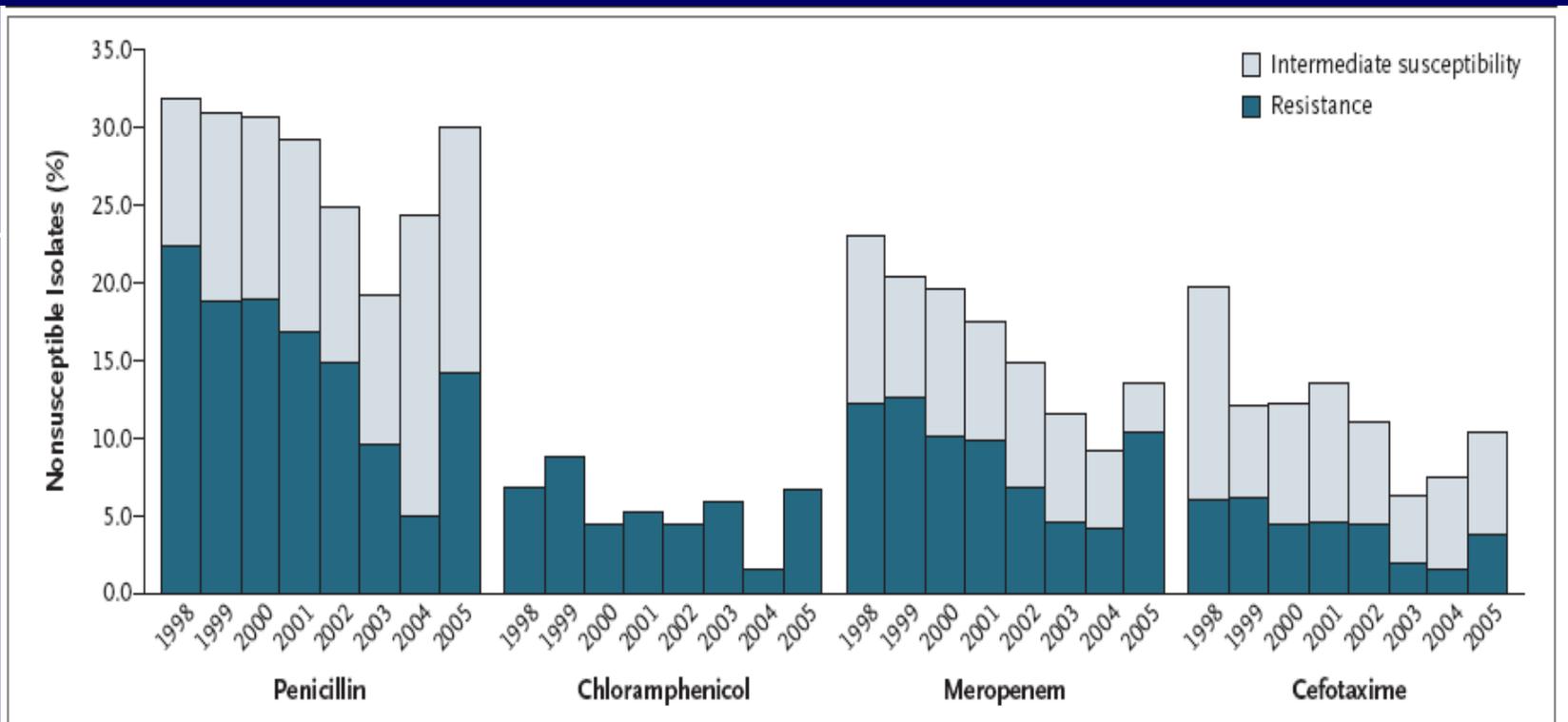
**Only 27% “meningitis” (6% bacterial)**

**\*Hasbun R, et al. N Engl J Med 2001; 345:1727-33  
(and Steigbigel NH. N Engl J Med 2001; 345:1768-70).**

# **S. Pneumoniae Resistance In The USA (2002-3)**

<b>penicillin</b>	<b>34.2 %</b>
<b>ceftriaxone</b>	<b>6.9</b>
<b>erythromycin</b>	<b>29.5</b>
<b>clindamycin</b>	<b>9.4</b>
<b>tetracycline</b>	<b>16.2</b>
<b>TMP-SMX</b>	<b>31.9</b>
<b>&lt;QRDRs&gt;</b>	<b>21.9</b>

**Doern GV, et al. Clin Infect Dis 2005; 41: 139-48.**

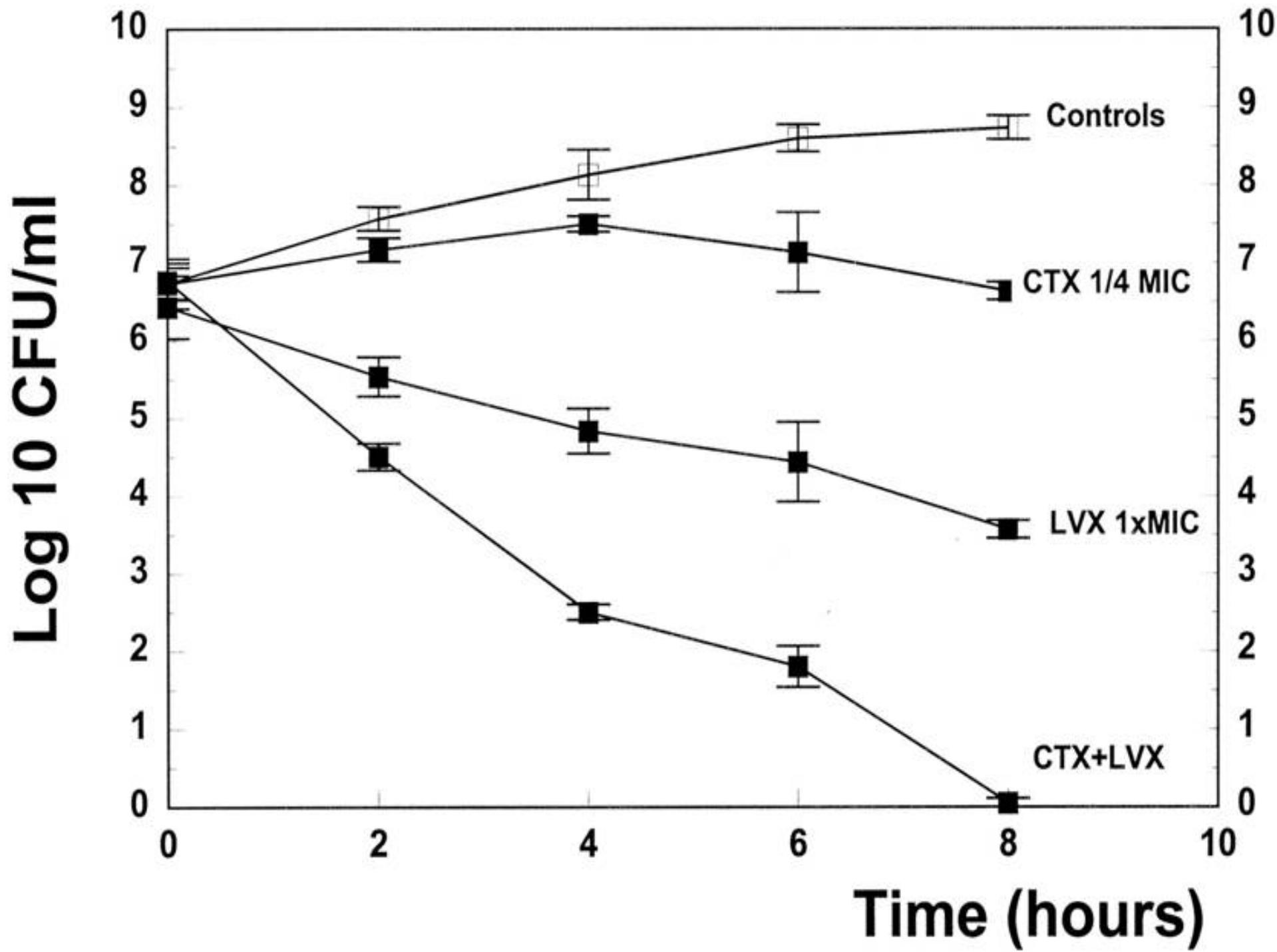


**Figure 2.** Percentage of Pneumococcal Isolates, from 1239 Cases, That Were Nonsusceptible to Various Antibiotics, According to Year and Degree of Nonsusceptibility.

For 1998–2005, 140 isolates lacking serotype or susceptibility data were excluded. The total number of isolates tested was 147 in 1998, 191 in 1999, 179 in 2000, 154 in 2001, 161 in 2002, 155 in 2003, 119 in 2004, and 133 in 2005. In 2002, only 160 of the 161 isolates were tested for susceptibility to chloramphenicol.

## Potential Regimens for Treatment of Presumed Penicillin-resistant Pneumococcal Meningitis

- Ceftriaxone or cefotaxime (TGC)
- Vancomycin
- Chloramphenicol
- Vancomycin plus rifampin
- Ampicillin plus TGC
- Q-D
- Meropenem
- Quinolones
- TGC plus vancomycin
- TGC plus quinolone
- Linezolid
- Daptomycin



# Meningitis In The ICU; GCS And Mortality

GCS	Mortality (%)
3-8	33
9-12	10
13-15	0

Intensive Care Med 2003; 29: 1967-73.

# **Drotrecogin Alfa For Meningitis And Sepsis? (Median Apache II=22)**

	<b>ICH (%)</b>
<b>bacterial meningitis</b>	<b>5.7</b>
<b>all others</b>	<b>1.0</b>

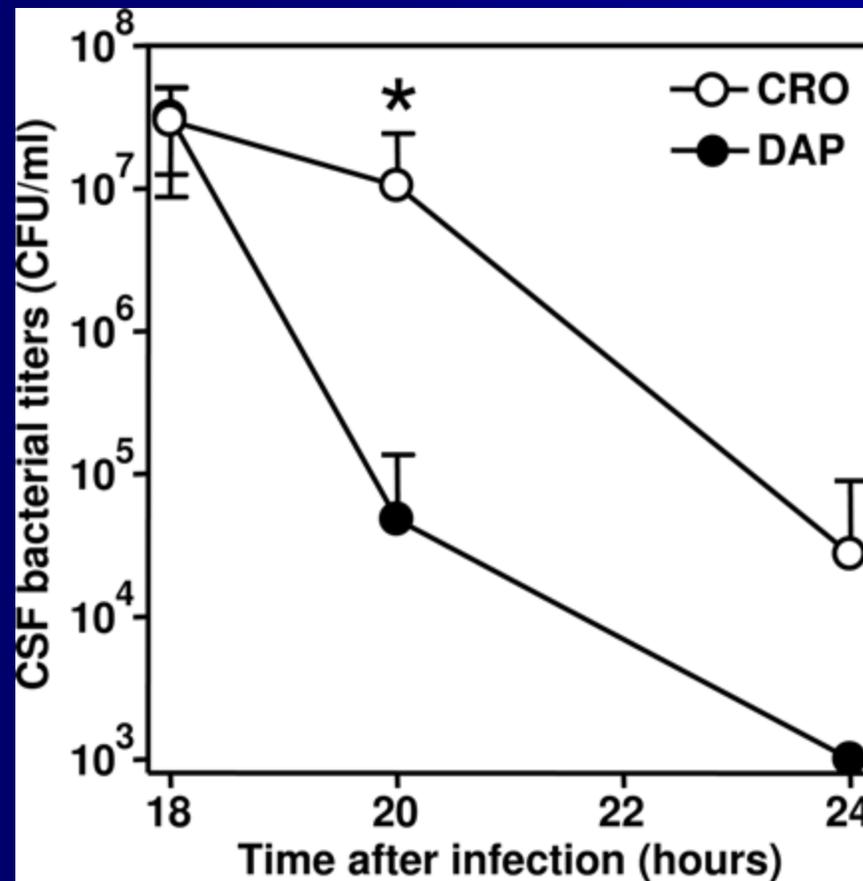
**Crit Care 2005; 9: R331-43.**

# Daptomycin Vs. Ceftriaxone For Experimental Pneumococcal Meningitis In Rats

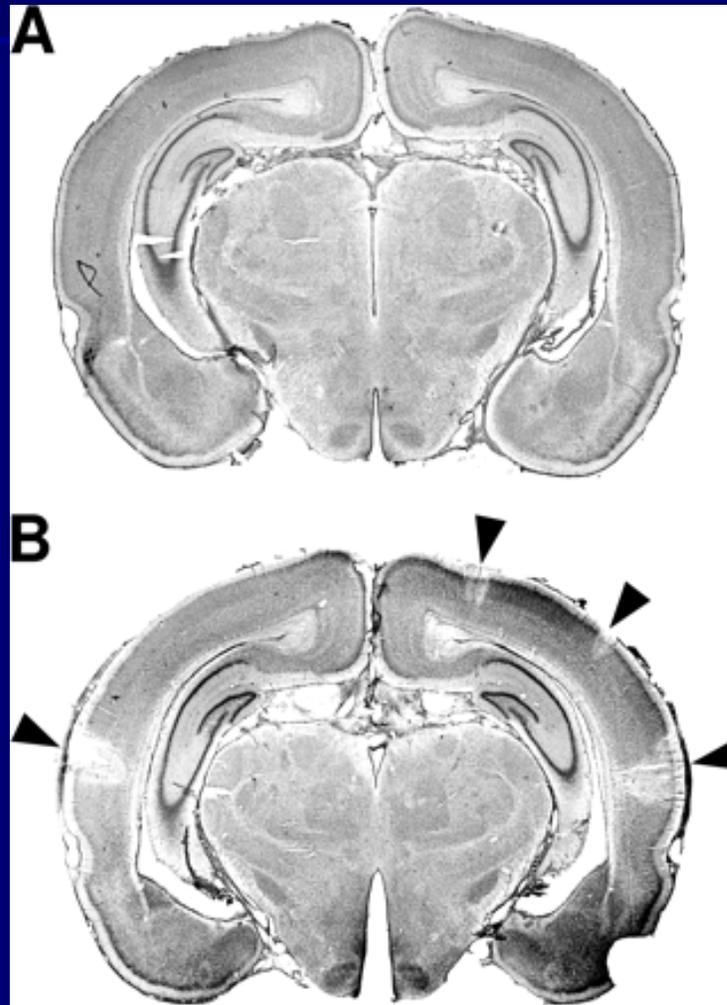
- faster bacterial clearance
- reduced inflammation (e.g. ↓ MMP 9)
- reduced cortical damage (0/30 vs. 7/28)

Grandgirard D, et al. Antimicrob Agents Chemother 2007; 51: 2173-8.

**FIG. 1. Bacterial titers in CSF of daptomycin (DAP)- and ceftriaxone (CRO)-treated animals. Titrers were determined before initiation of the therapy (18 h after infection;  $n = 18$  for each group), 2 h later (20 h after infection;  $n = 9$  per group), and 6 h later (24 h after infection;  $n = 9$ ). The origin of the y axis was set to the bacterial titer detection limit of  $10^3$  CFU/ml. \*, titers were significantly different at 20 h after infection ( $P < 0.015$ ). At 24 h after infection, the titers for the daptomycin-treated animals were under the detection limit.**



**FIG. 3. Representative histological sections of daptomycin-treated (A) or ceftriaxone-treated (B) animals stained with cresyl violet 40 h after infection. Regions of decreased neuronal density (arrowheads) were found only in the cortices of the ceftriaxone-treated animals.**



# **“Short” Course Therapy Of Meningococcal Disease ( $\leq 5$ Days)\***

- **Studies = 9**
- **Years 1974 – 1995**
- **No. patients = 278**
- **Deaths = 6.8%; treatment prolonged = 2.2%; relapses = 0%**
- **Rx: penicillin, chloramphenicol, ceftriaxone**
- **Deaths  $\leq 36$ h:  $\geq 67\%$**
- **Sterile CSF: 31/32  $\leq 24$ h; 83/83 @ 1-3 days**

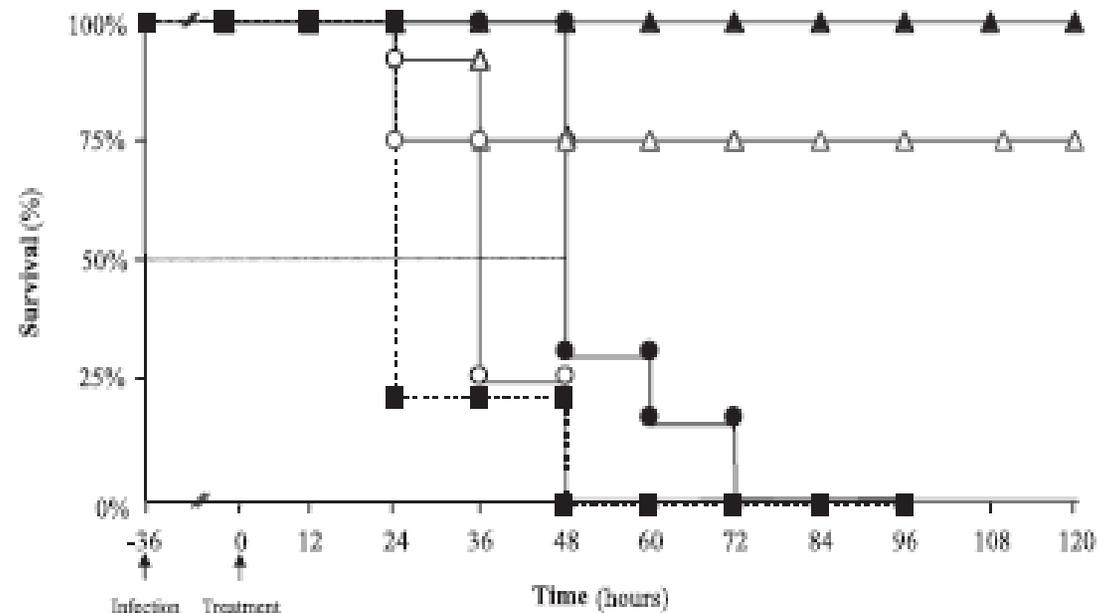


FIG. 1. Kaplan-Meier survival estimates for mice infected by *L. monocytogenes* according to various schemes of antibiotic administration. BALB/c mice were treated 36 h after intravenous infection by  $1 \times 10^5$  *L. monocytogenes* (EGD-e) organisms with a single dose of amoxicillin ( $50 \text{ mg} \cdot \text{kg}^{-1}$  i.p.;  $n = 12$ ) ○, a single dose of moxifloxacin ( $50 \text{ mg} \cdot \text{kg}^{-1}$  i.p.;  $n = 12$ ) ●, one dose of amoxicillin every 12 h for 5 days ( $50 \text{ mg} \cdot \text{kg}^{-1}$  i.p.;  $n = 20$ ) △, one dose of moxifloxacin every 12 h for 5 days ( $50 \text{ mg} \cdot \text{kg}^{-1}$  i.p.;  $n = 20$ ) ▲, or sterile isotonic saline (control;  $n = 5$ ) ■. The arrows indicate intravenous infection and the start of treatment.

# Complications During The Clinical Course In Adults With Meningitis

	%
cardiorespiratory failure	29
hyponatremia	26
DIC	8
seizures	15-23
brain edema	6-10
vascular	15-20
hearing loss	14-20

e.g. van de Beek D, et al. N Engl J Med 2004; 351: 1849-59.

# ICP Monitoring In Children With Meningitis In The USA

1997 and 2000; age <17 on MV  
ICP monitors used in 7%; associated with age (5-17 vs. < 1 year), patient volume, hospitals in the West; mortality 19.6%; no change with ICP monitor (↑ LOS, charges).

Odetola FO, et al. Pediatrics 2006; 117:2279-80.

# Corticosteroids And Adult Meningitis

301 patients, 5 countries, 9 years  
Dexamethasone 10 mg i.v. q6h x 4d  
~2/3 *S. pneumoniae*, *N. meningitidis*  
77/108 *S. pneumoniae* isolates tested,  
all MIC <0.1 µg/ml

\*de Gans J, et.al. N Engl J Med 2002; 347:1549-56.

# Corticosteroids And Adult Meningitis

## Overall:

Unfavorable outcome; RR 0.59; p=0.03

Mortality; RR 0.48; p=0.04

## Pneumococcal:

Unfavorable outcome; 26% vs 52%; RR 0.50; p=0.006

Mortality; 14% vs 34%

\*de Gans J, et al. N Engl J Med 2002; 347: 1549-56.

# Dexamethasone In Meningitis, Vietnam

1996-2005; n=435, age  $\geq$  14 years

61% prior Abx;  $\approx$  27% *S. suis* (vs 12-13% *S. pneumoniae*)

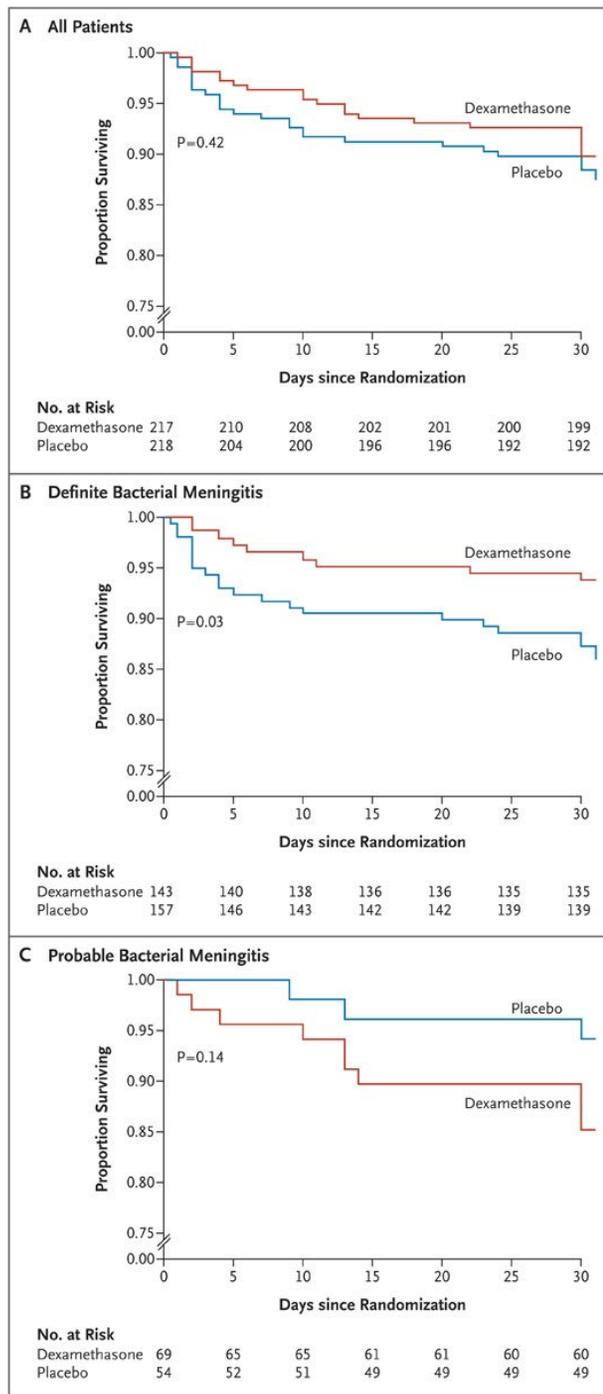
definite 69.0%, probable 18.3% other 2.8%  
(HIV < 0.9%)

NEJM 2007; 357:2431-40

# Relative Risk Of Death (RRD) Dexamethasone In Meningitis, Vietnam

	<u>RRD (95% CI)</u>	<u>p value</u>
definite meningitis	0.43 (0.20-0.94)	0.03
probable meningitis	2.65 (0.73-9.63)	0.14
gram-positive	0.06 (0.01-0.45)	0.006
gram-negative	1.65 (0.52-5.21)	0.39

NEJM 2007; 357:2431-40



**Figure 2. Kaplan–Meier Survival Estimates According to Study Group. Panel A shows survival estimates for all patients who underwent randomization (intention-to-treat analysis). Panel B shows survival estimates for patients with definite bacterial meningitis, and Panel C estimates for patients with probable bacterial meningitis. P values are based on the log-rank test.**

# Deafness Following Meningitis, Vietnam

	deaf at least one ear (%)		
	dexa	placebo	p value
definite	9.6	21.8	0.008
definite + probable	11.7	21.3	0.02
<i>S. suis</i>	12.3	37.7	0.003

NEJM 2007; 357:2431-40

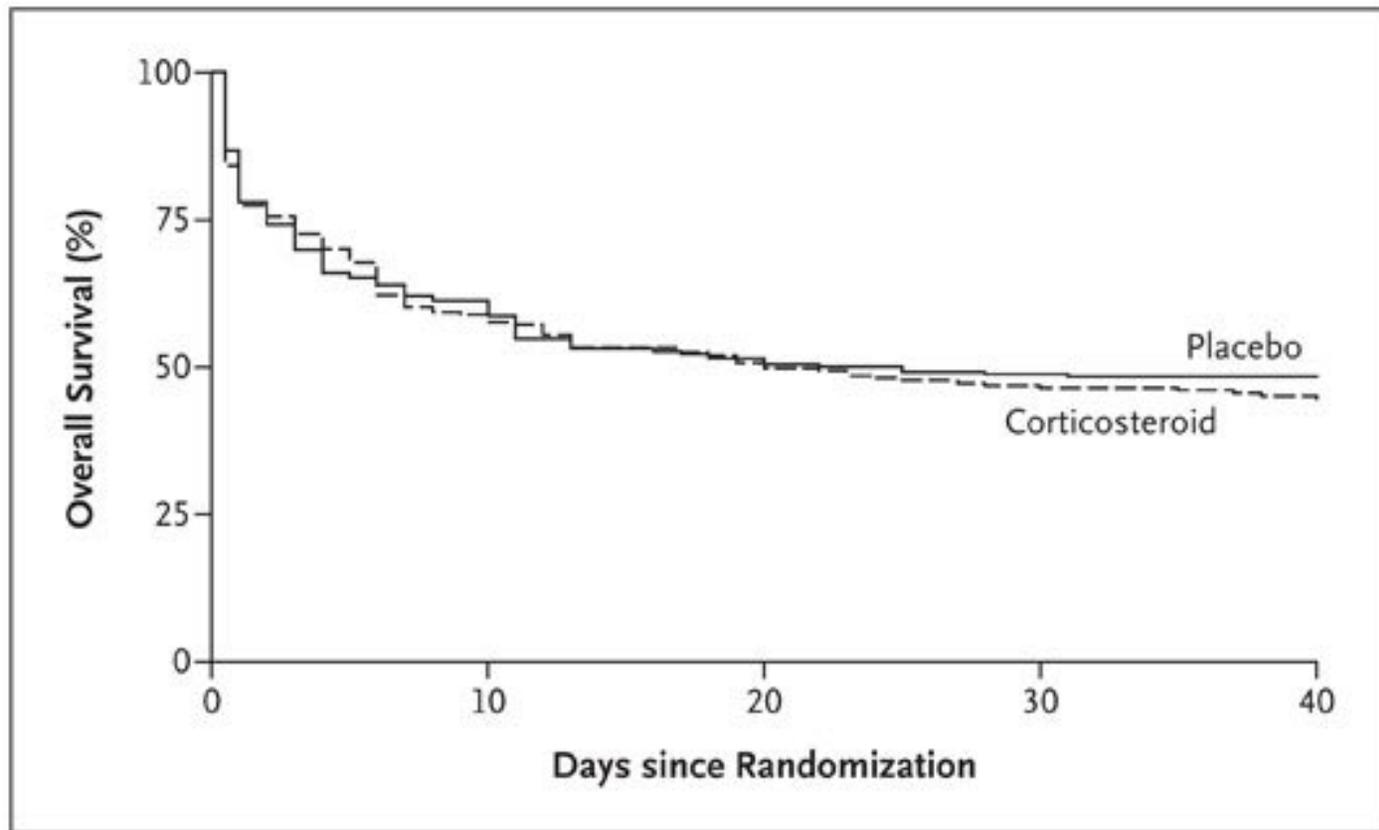
# Dexamethasone In Meningitis, Malawi

2002-2005; n=465, age  $\geq$  16 years

36-38% prior Abx; 59% *S. pneumoniae*

Definite 70%, probable 22%, other 8%  
(90% HIV)

NEJM 2007; 357:2441-50



**Figure 2. Kaplan–Meier Estimates of Survival for 459 Patients through Day 40.**

# **Glycerol And/Or Dexamethasone, Latin America**

**1996-2003; 6 countries; n=654; ages 2 mos-  
16 years (median 10-13 mos)**

**37% prior Abx; Hib >Spn> Nm  
(26% unknown) 13% died**

**Clin Infect Dis 2007; 45: 1277-86**

# Primary Outcomes, Bacterial Meningitis, Latin America

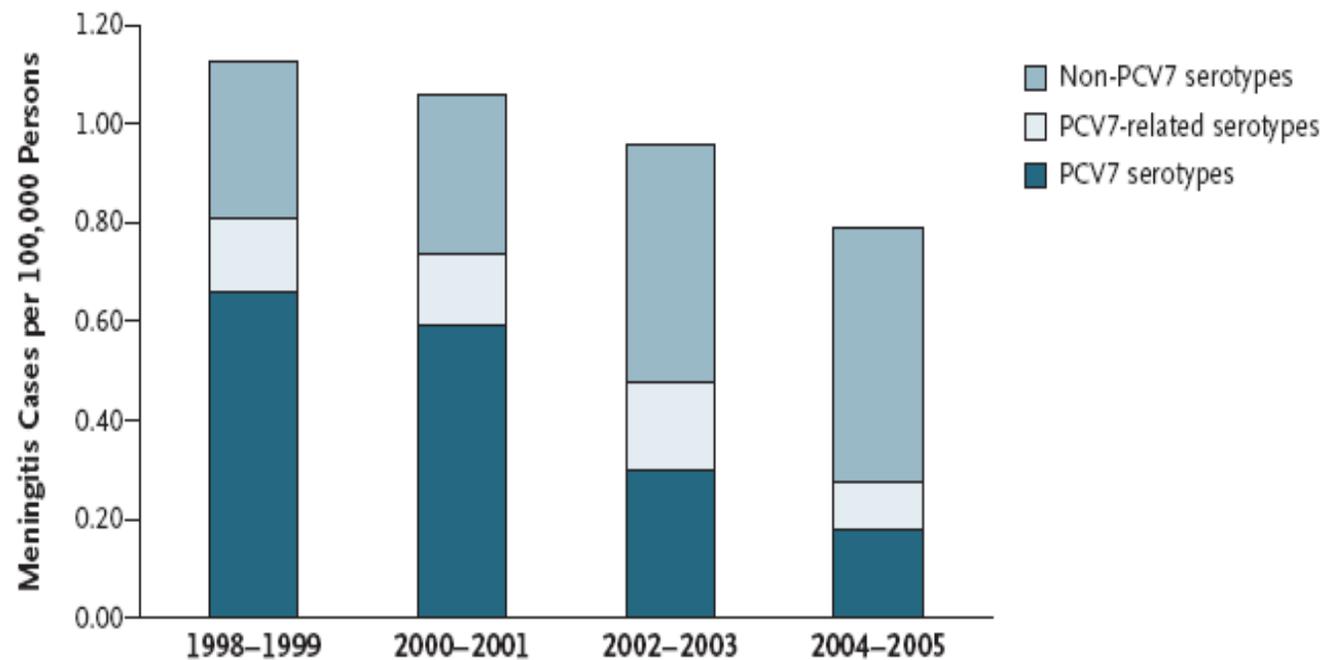
	odds ratio		
	dxm +placebo	dxm + glycerol	glycerol +placebo
death	0.82	0.69	0.58
severe sequelae	0.48	<u>0.39</u>	<u>0.31</u>
combined	0.65	<u>0.55</u>	<u>0.44</u>
hearing loss	0.79	0.73	0.96

Clin Infect Dis 2007; 45: 1277-86.

## Impact of PCV7 on Pneumococcal Meningitis (US, 8 sites)

	Rate / 10 <sup>5</sup> population	
	1998-9	2004-5
Overall	1.13	0.79
PCV7 serotypes	0.66	0.18
Non-PCV serotypes	0.32	0.51

NEJM 2009; 360:244-56



**Figure 1. Mean Annual Incidence of Pneumococcal Meningitis, According to Serotype Group and Time Period.**

Serotypes of the heptavalent pneumococcal conjugate vaccine (PCV7) were 4, 6B, 9V, 14, 18C, 19F, and 23F. PCV7-related serotypes were 6A, 9A, 9L, 9N, 18A, 18B, 18F, 19B, 19C, 23A, and 23B. Non-PCV7 serotypes were 3, 7F, 10A, 11A, 12F, 15A, 15B/C, 16F, 19A, 22F, 33F, 35B, 35F, and 38.