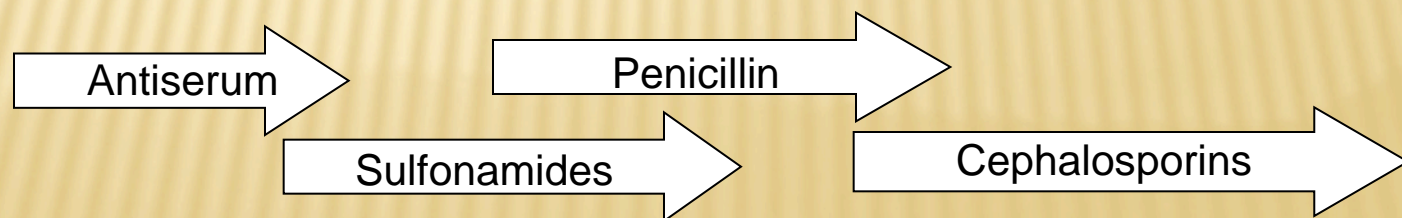
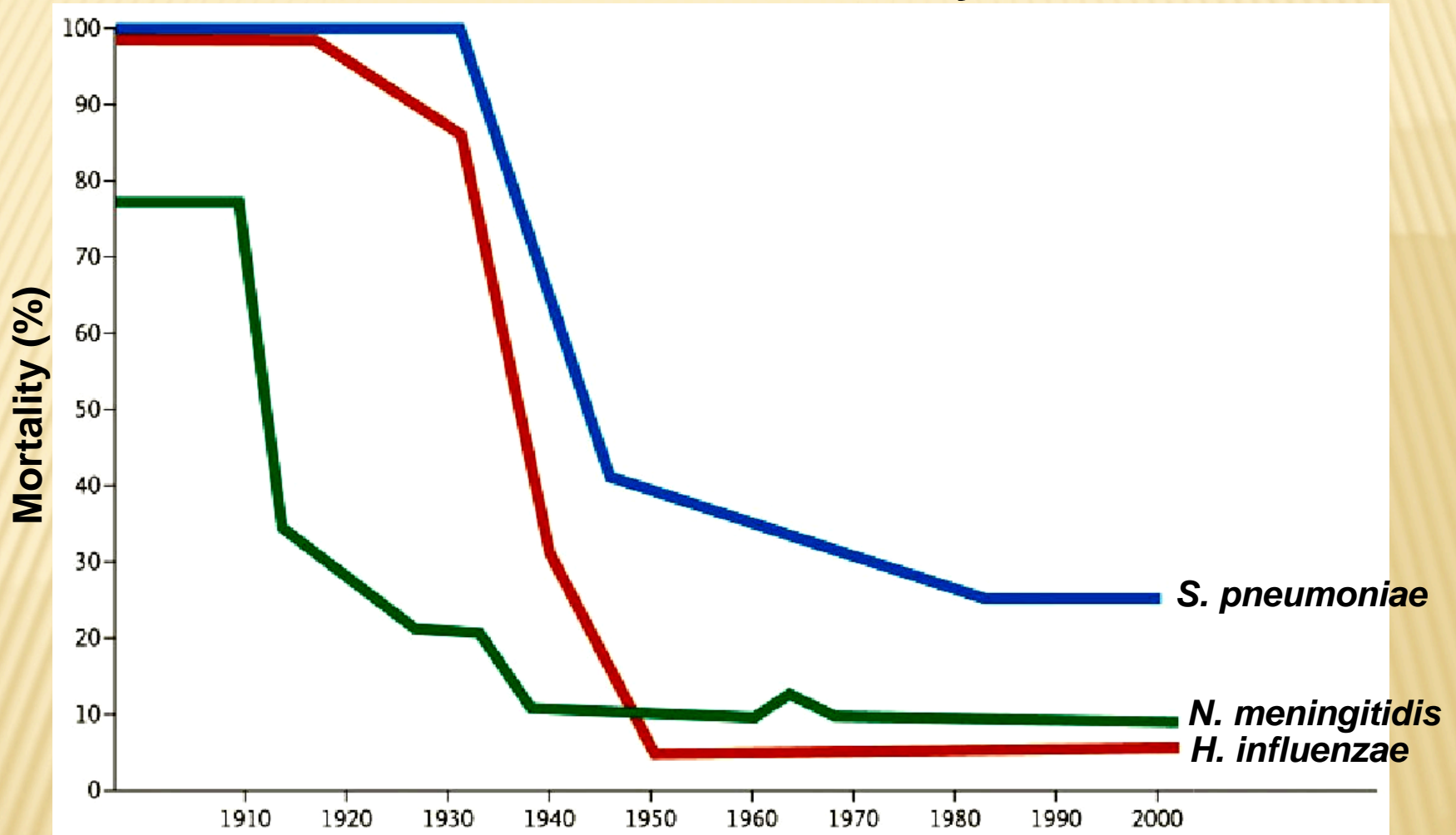


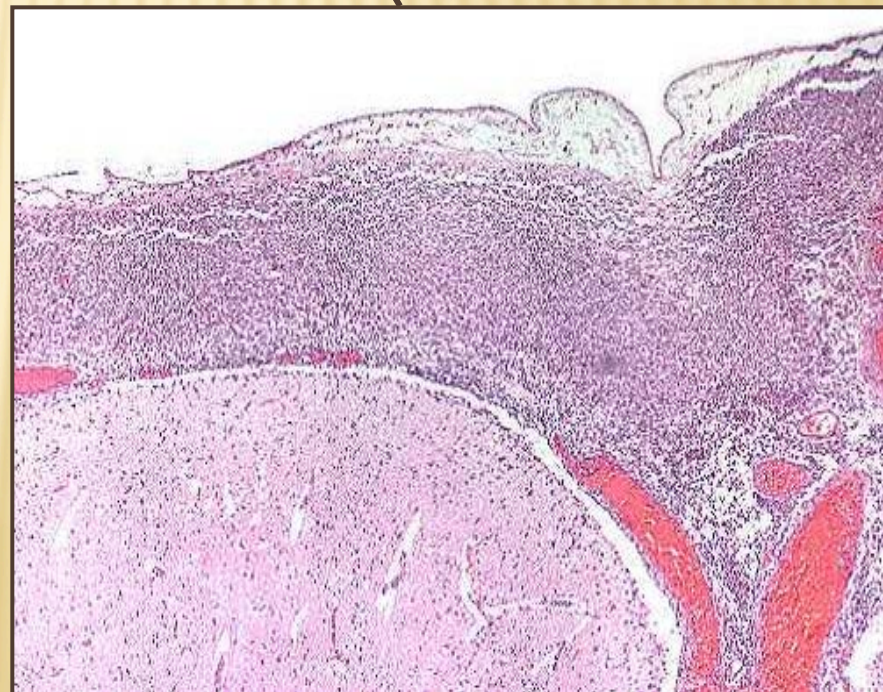
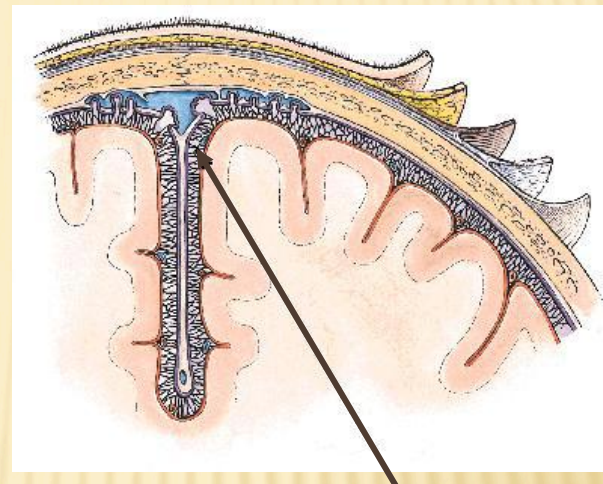
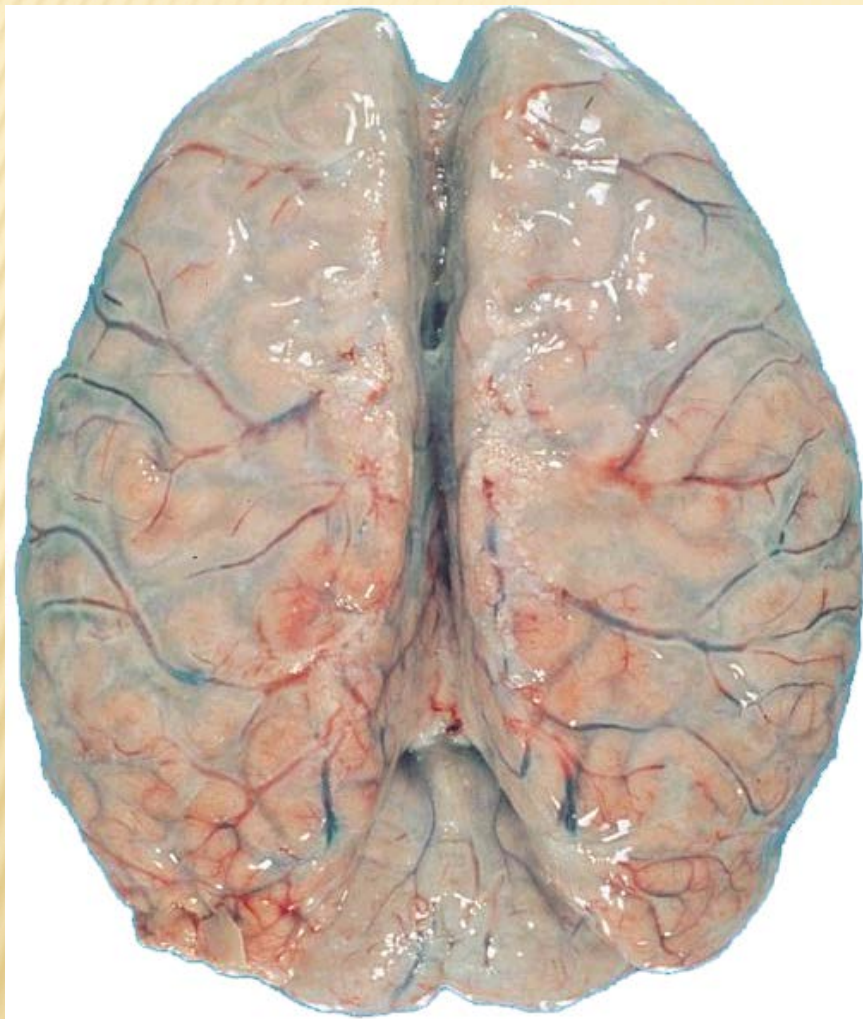
Rodrigo Hasbun,MD  
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# DOXYCYCLINE IN BACTERIAL MENINGITIS

# BACTERIAL MENINGITIS: Mortality & Antibiotics



# BACTERIAL MENINGITIS: Inflammation



# BACTERIAL MENINGITIS: Adjuvant Corticosteroids

**Corticosteroids for acute bacterial meningitis**  
**Cochrane Database Syst Rev. 2007 Jan 24;(1)**  
**van de Beek D, de Gans J, McIntyre P, Prasad K.**



**Studies:** Analysis of 18 randomised controlled trials of corticosteroids as an adjuvant therapy in acute bacterial meningitis involving 2750 patients.

**Participants:** Any age and in any clinical condition.

**Intervention:** Antibacterial agents and randomised to corticosteroid therapy (or placebo) of any type.

**Outcome:** At least case fatality rate or hearing loss

**Main results: All patients**

<b>Mortality:</b>	186/1387 (Ster.) vs 220/1363 (Cont.)	
<b>Severe hearing loss:</b>	50/884 (Ster.) vs 77/863 (Cont.)	p=0.01
Short-term sequelae (0-6 wks):	108/617 (Ster.) vs 116/558 (Cont.)	p= ns
Long-term sequelae (6-12 month):	36/596 (Ster.) vs 51/567 (Cont.)	p=0.05

# BACTERIAL MENINGITIS: Adjuvant Corticosteroids

Corticosteroids for acute bacterial meningitis, Cochrane Database Systematic Review 2007

## Mortality

All patients	186/1387 (Ster.) vs 220/1363 (Cont.)	p =0.03
<b>Adults (&gt; 16 y); Outcome</b>	<b>36/308 (Ster.) vs 69/315 (Cont.):</b>	<b>p =0.002</b>
Children	142/1051 (Ster.) vs 139/1023 (Cont.)	P = ns
<i>Causative species:</i>		
Haemophilus influenzae:	31/354 (Ster.) vs 39/355 (Cont.)	p = ns
Neisseria meningitidis:	9/258 (Ster.) vs 13/259 (Cont.)	p = ns
<b>Streptococcus pneumoniae:</b>	<b>65/335 (Ster.) vs 95/306 (Cont.)</b>	<b>p =0.0001</b>
All non-H. influenzae:	107/717 (Ster.) vs 128/699(Cont.)	p =0.02
Low-income countries; <i>All patients</i> :	148/639 (Ster.) vs 165/627 (Cont.)	p = ns
High-income countries; <i>All patients</i> :	38/748 (Ster.) vs 55/736 (Cont.)	p = ns
Low-income countries; <i>children</i>	132/529 (Ster.), 132/508(Cont.)	p = ns
High-income countries; <i>children</i>	10/522 (Ster), 7/515 (Cont.)	p = ns
<i>Timing of steroids:</i>		
<b>Before/with first dose antibiotic:</b>	<b>153/921 (Treatment), 173/876 (Control)</b>	<b>p= 0.08</b>
After first dose antibiotic	23/389(Treatment), 34/408(Control)	p= ns
<b>Adult patients with pneumococcal meningitis before/with first dose antibiotic</b>		

# Nationwide implementation of adjunctive dexamethasone therapy for pneumococcal meningitis

**Table 3 Clinical course, mortality, disability, and neurologic findings at discharge<sup>a</sup>**

Characteristics	2006-2009	1998-2002	Difference (%)	p Value
No. of episodes	357	352		
<b>Clinical course, n (%)</b>				
Neurologic complications <sup>b</sup>	239 (60)	263 (75)	-15	<0.001
Seizures	60/344 (17)	85/349 (24)	-7	0.025
Cardiorespiratory failure	133 (37)	134 (38)	-1	0.823
<b>Score on Glasgow Outcome Scale, n (%)</b>				
1 (death)	71 (20)	107 (30)	-10	0.001
2 (vegetative state)	0	3 (1)	-1	
3 (severe disability)	18 (5)	17 (5)	0	
4 (moderate disability)	50 (14)	50 (14)	0	
5 (no or minor disability)	218 (61)	175 (50)	+11	0.002
<b>Neurologic findings at discharge, n (%)</b>				
Cranial nerve palsy	47/280 (17)	67/243 (28)	-11	0.003
Hearing impairment	33/280 (12)	55/243 (22)	-10	0.001
Focal cerebral deficits	32/280 (11)	26/243 (11)	0	0.791

<sup>a</sup> Neurologic examination was performed in 243 of 245 surviving patients of cohort 1998-2002 and 280 of 285 surviving patients of cohort 2006-2009.

## POTENTIAL LIMITATIONS OR PITFALLS OF ADJUNCTIVE DEXAMETHASONE IN BACTERIAL MENINGITIS

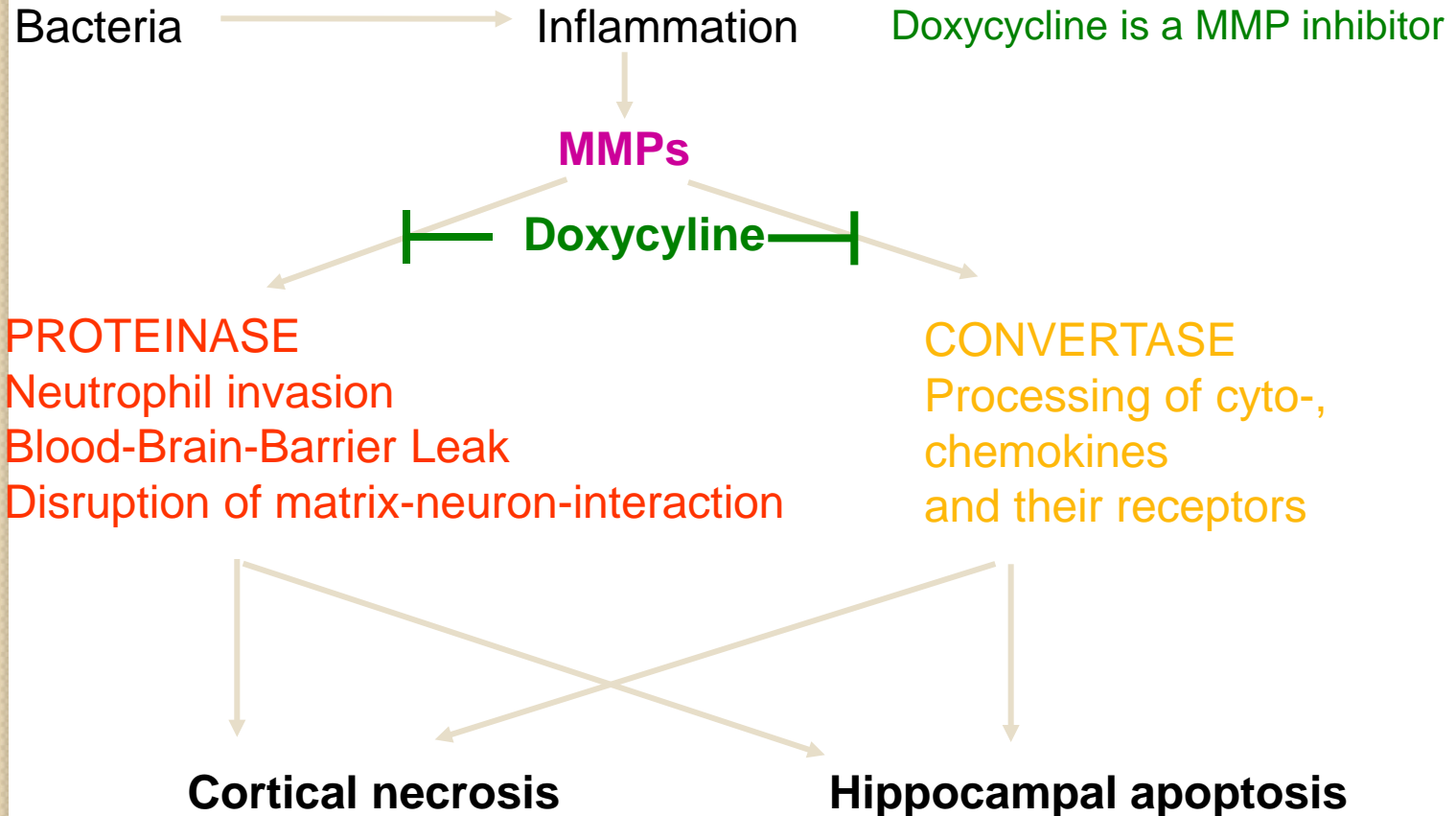
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- ✘ 1) Mortality is still 20% in pneumococcal meningitis
- ✘ 2) Can decrease CNS penetration of vancomycin and ceftriaxone
- ✘ 3) Increases apoptosis in the hippocampus in rats
- ✘ 4) Increases learning capabilities in the rat model



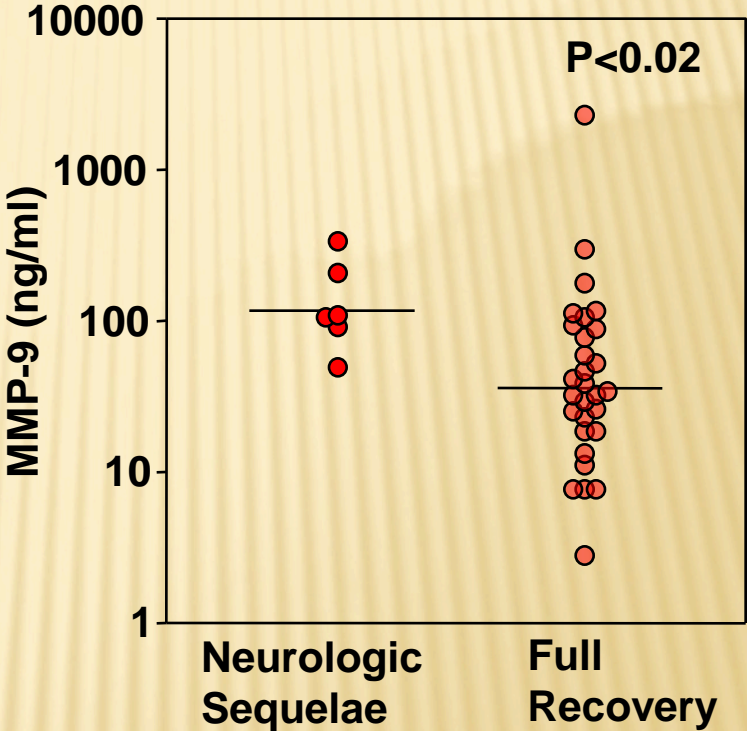
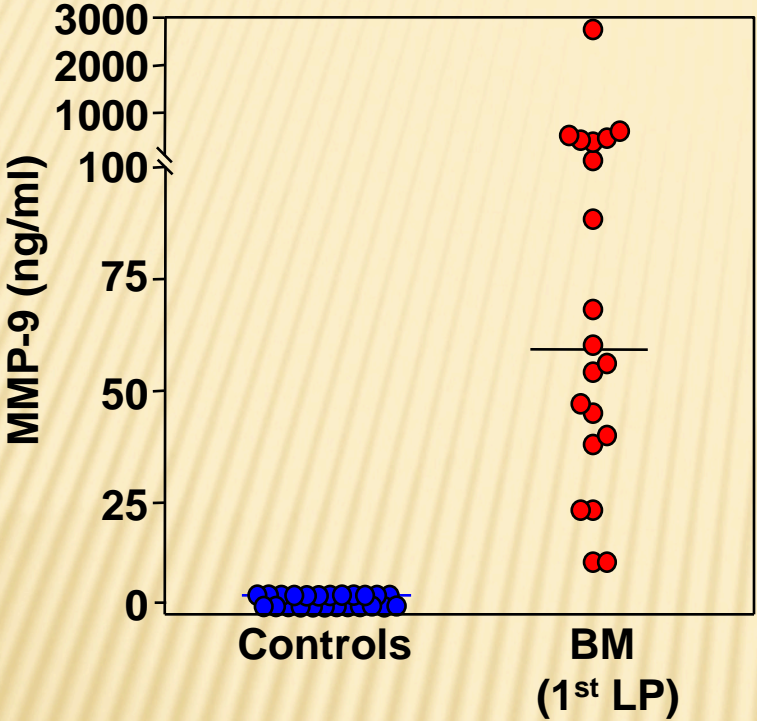
# EXPERIMENTAL BACTERIAL MENINGITIS: Effect of Matrixmetalloproteinase Inhibition by Doxycycline

## MMP Effects in the Pathogenesis of Brain Injury



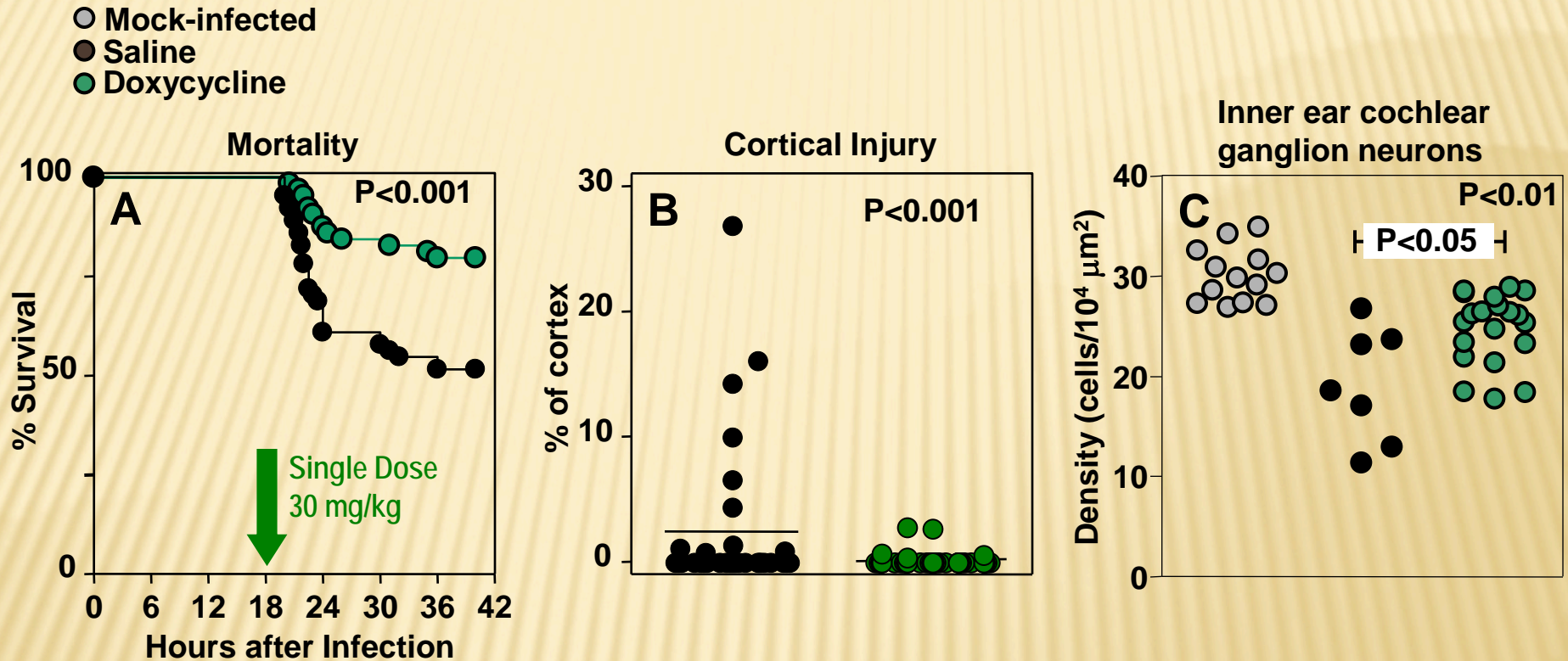


# BACTERIAL MENINGITIS: Matrix Metalloproteinase-9 (MMP-9) in Cerebrospinal Fluid



**In children with bacterial meningitis, high CSF concentrations of MMP-9 are a risk factor for the development of neurological sequelae.**


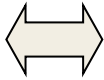













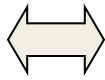








# EXPERIMENTAL BACTERIAL MENINGITIS: Effect of Adjuvant **Doxycycline**



**A, B:** A single dose of Doxycycline (30 mg/kg) reduced the mortality, and cortical brain injury.

**C:** Doxycycline (30 mg/kg given subcutaneously once daily for 4 days) attenuated hearing loss at 3 weeks after infection.

# Selected Experimental Therapeutic Strategies

Intervention	Cortical Injury	Hippocampal Injury	Learning Disabilities
iNOS Inhibition			
Endothelin antagonist			
Antioxidants			
MMP-inhibitors			
Dexamethasone			
Caspase-3 inhibitor			
BDNF			
Non-lytic antibiotica			

# RCT of doxy in suspected bacterial meningitis

- Doxycycline 100mg IV X 1 vrs placebo
- Sample sized needed is 162 (Power 80%, Alpha 0.05; difference between 40%-20%)

## Outcomes

- Glasgow outcome scale 1-4
- Audiogram
- Neurocognitive testing
- CSF MMP 9 and other cytokine levels.