BACTERIAL MENINGITIS: Mortality & Antibiotics

BACTERIAL MENINGITIS: Inflammation
Corticosteroids for acute bacterial meningitis
Cochrane Database Syst Rev. 2007 Jan 24;(1)
vande 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
Mortality: 186/1387 (Ster.) vs 220/1363 (Cont.) p=0.03
Severe hearing loss: 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.)  \( p = 0.03 \)

Adults (> 16 y); Outcome

36/308 (Ster.) vs 69/315 (Cont.):  \( p = 0.002 \)

Children

142/1051 (Ster.) vs 139/1023 (Cont.)  \( P = \text{ns} \)

**Causative species:**

Haemophilus influenzae:  

31/354 (Ster.) vs 39/355 (Cont.)  \( p = \text{ns} \)

Neisseria meningitidis:

9/258 (Ster.) vs 13/259 (Cont.)  \( p = \text{ns} \)

Streptococcus pneumoniae:

65/335 (Ster.) vs 95/306 (Cont.)  \( p = 0.0001 \)

All non-H. influenzae:

107/717 (Ster.) vs 128/699(Cont.)  \( p = 0.02 \)

**Low-income countries; All patients :**

148/639 (Ster.) vs 165/627 (Cont.)  \( p = \text{ns} \)

**High-income countries; All patients :**

38/748 (Ster.) vs 55/736 (Cont.)  \( p = \text{ns} \)

**Low-income countries; children**

132/529 (Ster.), 132/508(Cont.)  \( p = \text{ns} \)

**High-income countries; children**

10/522 (Ster), 7/515 (Cont.)  \( p = \text{ns} \)

**Timing of steroids:**

Before/with first dose antibiotic:

153/921 (Treatment), 173/876 (Control)  \( p = 0.08 \)

After first dose antibiotic

23/389(Treatment), 34/408(Control)  \( p = \text{ns} \)

**Adult patients with pneumococcal menigitis before/with first dose antibiotic**
Nationwide implementation of adjunctive dexamethasone therapy for pneumococcal meningitis

Table 3  Clinical course, mortality, disability, and neurologic findings at discharge^a

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

^a Neurologic examination was performed in 243 of 245 surviving patients of cohort 1998-2002 and 228 of 225 surviving patients of cohort 2006-2009.
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

Bacteria → Inflammation → MMPs → Doxycycline

PROTEINASE
Neutrophil invasion
Blood-Brain-Barrier Leak
Disruption of matrix-neuron-interaction

CONVERTASE
Processing of cyto-, chemokines and their receptors

Doxycycline is a MMP inhibitor

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

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Cortical Injury</th>
<th>Hippocampal Injury</th>
<th>Learning Disabilities</th>
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<tbody>
<tr>
<td>iNOS Inhibition</td>
<td>↑</td>
<td>⇔</td>
<td>?</td>
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<tr>
<td>Endothelin antagonist</td>
<td>⇓</td>
<td>⇔</td>
<td>?</td>
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<tr>
<td>Antioxidants</td>
<td>⇓</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>MMP-inhibitors</td>
<td>⇓</td>
<td>⇓</td>
<td>↓</td>
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<tr>
<td>Dexamethasone</td>
<td>⇓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Caspase-3 inhibitor</td>
<td>⇔</td>
<td>⇓</td>
<td>?</td>
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<tr>
<td>BDNF</td>
<td>⇓</td>
<td>⇓</td>
<td>?</td>
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<tr>
<td>Non-lytic antibiotica</td>
<td>⇓</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
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.