Corticosteroids in meningitis

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Conflicts of interest

- No conflicts of interest

- Financial support (Personal grants):
  - European Society for Clinical Microbiology and Infectious Diseases
  - European Federation of Neurological Societies
Corticosteroids in meningitis

- Dexamethasone in bacterial meningitis
- Dexamethasone in tuberculous meningitis
Bacterial meningitis

- 35,000 Europeans each year
- Most important causative microorganisms
  - *Streptococcus pneumoniae*
  - *Neisseria meningitidis*
- High mortality
- Frequently neurological sequelae

van de Beek et al, N Engl J Med, 2006
Brouwer et al, Clin Microbiol Rev, 2010
Meningitis mortality - history

Bacterial meningitis treatment

- Antibiotic treatment not enough to improve prognosis
- Long search for adjunctive treatment
  - Anti-inflammatory agents → corticosteroids, IgG, paracetamol
  - Neuroprotection → hypothermia
  - Osmotic agents → mannitol, glycerol
  - Anti-coagulants → heparin, activated protein C
Animal model and steroids

- Severity of disease
  - Bacterial load
  - Inflammatory response
- Inflammation continues after bacterial killing
- Severity inflammation ~ outcome
- Dexamethasone
  - Reduction inflammation
  - Reduction ICP

Scheld et al., J Clin Invest 1980
Giampoalo et al., Ann Neurol 1981
Tauber et al., Am J Pathol 1992
Initial clinical studies

- First studies published 1963 / 1969 - no effect
- Animal experiments early ‘80s
- Several small trials in children ‘80-’90s
  - Reduction in severe hearing loss
  - *Haemophilus influenzae* meningitis
  - Conflicting results

DXM reduces severe hearing loss

Only in *H. influenzae* meningitis

Vaccination *H. influenzae* type B 99% reduction cases

Trend towards lower mortality in pneumococcal meningitis

McIntyre et al, JAMA 1997
Randomized controlled trial 1993-2001

301 patients → 157 DXM, 144 placebo

DXM 10mg iv every 6 hours for 4 days, before or with antibiotics

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>Unfavorable outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DXM</td>
<td>Placebo</td>
</tr>
<tr>
<td>All patients</td>
<td>11/157 (7%)</td>
<td>21/144 (15%)</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>8/58 (14%)</td>
<td>17/50 (34%)</td>
</tr>
<tr>
<td></td>
<td>23/157 (15%)</td>
<td>36/144 (25%)</td>
</tr>
<tr>
<td></td>
<td>15/58 (26%)</td>
<td>26/50 (52%)</td>
</tr>
</tbody>
</table>

Following European DXM Trial

Treatment guidelines IDSA:

Standard treatment DXM in adults with bacterial meningitis

Proven effect only in pneumococcal meningitis

Stop DXM if meningococcus or other pathogen is identified

Tunkel et al, CID 2004
Negative trials 2002-2007

- Malawi, children, n=598, no effect
- Malawi, adults, n=465, no effect
- Vietnam, adults, n=217, no effect in suspected BM
  - However: reduced mortality confirmed BM
- South-America, children, n=654, reduction hearing loss *H. influenzae*
  - Methodological problems

Molyneux et al, Lancet 2002
Peltola et al, CID 2007
Interpretation

• False positive result European DXM trial?

• Differences in study population?
  – High rate of HIV positivity Malawi (90%)
  – Partially treated meningitis / tuberculous meningitis
  – Different genetic background?
Data of individual patients included in meta-analysis

- 5 Trials: Malawi (2), South-America, Europe, Vietnam
- Search for subgroups that benefit from DXM

No effect on mortality / hearing loss / neurological sequelae in prespecified subgroups

Reduction hearing loss in survivors (post-hoc)

Conclusion: effect DXM remains unproven

van de Beek et al, Lancet Neurology, 2010
Inclusion of all RCTs on DXM in bacterial meningitis

No effect on mortality overall

Trend towards lower mortality in adults

Lower rates of hearing loss and neurological sequelae

Subgroups: lower mortality in pneumococcal meningitis

Effect limited to high income countries
Value meta-analyses

• Individual patient data meta-analysis
  – Superior method
  – Ignores previous studies

• Cochrane meta-analysis
  – Includes trials of lower quality
  – More bias

• Back to own population
  – Fase IV (implementation) study in the Netherlands
Implementation study Netherlands

• Implementation of DXM in pneumococcal meningitis

• 2 nationwide prospective cohort studies in the Netherlands
  – 1998-2002, n=357, before DXM
  – 2006-2009, n=352, after DXM

• Inclusion criteria
  – Positive CSF culture, community acquired meningitis

• Multivariate analysis to correct for confounders

Brouwer et al, Neurology, 2010
Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2006-2009 357 Episodes</th>
<th>1998-2002 352 Episodes</th>
<th>Absolute difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – year (means ±SD)</td>
<td>59±15</td>
<td>58±17</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>167 (47%)</td>
<td>171 (49%)</td>
<td>-2%</td>
</tr>
<tr>
<td>Classic triad</td>
<td>206/352 (58%)</td>
<td>188/347 (54%)</td>
<td>-4%</td>
</tr>
<tr>
<td>Coma</td>
<td>65/257 (18%)</td>
<td>68/351 (19%)</td>
<td>-1%</td>
</tr>
<tr>
<td>Individual CSF predictors of bacterial meningitis</td>
<td>328/348 (94%)</td>
<td>301/320 (94%)</td>
<td>0%</td>
</tr>
</tbody>
</table>

Brouwer et al, Neurology, 2010
## Treatment characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2006-2009 357 Episodes</th>
<th>1998-2002 352 Episodes</th>
<th>Absolute difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay in therapy due to imaging</td>
<td>155 (43%)</td>
<td>149 (42%)</td>
<td>+1%</td>
</tr>
<tr>
<td>Antibiotic treatment according to guidelines</td>
<td>118 (33%)</td>
<td>117 (33%)</td>
<td>0%</td>
</tr>
<tr>
<td>Strains in PCV7 vaccine</td>
<td>125/327 (38%)</td>
<td>149 (42%)</td>
<td>-4%</td>
</tr>
<tr>
<td>Antibiotic resistance rate</td>
<td>2/327 (0.6%)</td>
<td>2 (0.6%)</td>
<td>0%</td>
</tr>
</tbody>
</table>

Brouwer et al, Neurology, 2010
### Dexamethasone Treatment

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone received</td>
<td>329 (92%)</td>
<td>59 (17%)</td>
<td>75%*</td>
</tr>
<tr>
<td>Started before or with first dose of antibiotics</td>
<td>301 (84%)</td>
<td>11 (3%)</td>
<td>81%*</td>
</tr>
<tr>
<td>10mg QID for 4 days started before or with first dose of antibiotics</td>
<td>276 (77%)</td>
<td>11 (3%)</td>
<td>74%*</td>
</tr>
</tbody>
</table>

*B p < 0.001

Brouwer et al, Neurology, 2010
<table>
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<tr>
<th>Characteristic</th>
<th>2006-2009 357 Episodes</th>
<th>1998-2002 352 Episodes</th>
<th>Absolute difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic complications</td>
<td>239 (60%)</td>
<td>263 (75%)</td>
<td>-15%</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiorespiratory failure</td>
<td>133 (37%)</td>
<td>134 (38%)</td>
<td>-1%</td>
<td>0.82</td>
</tr>
<tr>
<td>Death</td>
<td>71 (20%)</td>
<td>107 (30%)</td>
<td>-10%</td>
<td>0.001</td>
</tr>
<tr>
<td>Complete recovery</td>
<td>218 (61%)</td>
<td>175 (50%)</td>
<td>+11%</td>
<td>0.002</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>33/280 (12%)</td>
<td>55/243 (22%)</td>
<td>-10%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Brouwer et al, Neurology, 2010
Brouwer et al, Neurology, 2010

- 11%  
- 10%

Unfavorable outcome

Mortality

p=0.002, RR 0.77  p=0.001, RR 0.65
(95% CI 0.65-0.92) (95% CI 0.50-0.86)
Dexamethasone

Dexamethasone regimen

% Unfavorable outcome

- 0.7%
- 12.6%
- 3.6%

No: n=28
Standard: n=276
Other: n=53

Predicted
Observed

Brouwer et al, Neurology, 2010
Conclusion implementation study

- After successful implementation DXM similar reduction in mortality and unfavourable outcome of pneumococcal meningitis as found in European trial
- No other explanation for improved prognosis but dexamethasone
- Supports further use of DXM
Implementation study 2 - meningococci

- Similar design
- 1998-2002, n=258 vs. 2006-2011, n=100
- Clinical presentation similar, less rash
- Strong reduction Serogroup C following vaccination
- DXM before or with antibiotics in 89% in 2006-2011 cohort
- Full 4 day course 81%

Brouwer et al, presented at ICAAC Chicago, 2011
### Implementation study 2 - meningococci

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 Episodes</td>
<td>258 Episodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>5/96 (5%)</td>
<td>32/258 (12%)</td>
<td>-7%</td>
<td>0.049</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>4 (4%)</td>
<td>19 (7%)</td>
<td>-3%</td>
<td>0.24</td>
</tr>
<tr>
<td>Unfavorable outcome</td>
<td>12 (12%)</td>
<td>30 (12%)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>No or minor disability</td>
<td>88 (88%)</td>
<td>228 (88%)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Neurologic findings at discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>3/96 (3%)</td>
<td>19/237 (8%)</td>
<td>-5%</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Brouwer et al, presented at ICAAC Chicago, 2011
Implementation study 2 - conclusion

- DXM safe in meningococcal meningitis
- Reduces auto-immune arthritis
- Trend towards lower hearing loss

Brouwer et al, presented at ICAAC Chicago, 2011
Implementation study 2 - conclusion

• DXM safe in meningococcal meningitis
• Reduces auto-immune arthritis
• Trend towards lower hearing loss

Why hesitate to give DXM?

Brouwer et al, presented at ICAAC Chicago, 2011
Is DXM harmful?

Are there complications of DXM therapy?

• Cohort studies / RCTs show no increase in
  – gastrointestinal bleedings
  – hyperglycemia requiring insulin
  – herpes zoster infections

• New complication?
  – Delayed intracerebral thrombosis
Delayed cerebral thrombosis

- 6 patients with pneumococcal meningitis
- DXM and antibiotics
- Excellent recovery
- Day 7-19 post admission fever, headache, coma
- Cerebral infarctions posterior circulation
- Inflammatory response CSF
- Negative CSF culture

Schut et al, Neurology 2009
Delayed cerebral thrombosis

• 4 dead, 2 severely disabled
• Autopsy (n=2): diffuse intravascular thrombosis w/o vasculitis
• 2 surviving patients received high dose steroids

Schut et al, Neurology 2009
Delayed cerebral thrombosis

- Reactivation of inflammation after effect DXM wears off?
- Immunologic reaction targeting cerebral vessels
- Not described in pre-dexamethasone era
- Incidence 1-2%
- Treatment high dose steroids, followed by tapering

NB the patients were included in the implementation study

Schut et al, Neurology 2009
Conclusion DXM in bacterial meningitis

- DXM reduces mortality and sequelae in adult pneumococcal meningitis in high income countries
Conclusion DXM in bacterial meningitis

• DXM reduces mortality and sequelae in adult pneumococcal meningitis in high income countries

• DXM is safe to give in adult meningococcal meningitis and reduces arthritis and probably hearing loss
Conclusion DXM in bacterial meningitis

- DXM reduces mortality and sequelae in adult pneumococcal meningitis in high income countries.
- DXM is safe to give in adult meningococcal meningitis and reduces arthritis and probably hearing loss.
- There is no effect of DXM in resource poor settings (Africa).
Conclusion DXM in bacterial meningitis

- DXM reduces mortality and sequelae in adult pneumococcal meningitis in high income countries
- DXM is safe to give in adult meningococcal meningitis and reduces arthritis and probably hearing loss
- There is no effect of DXM in resource poor settings (Africa)
- DXM reduces hearing loss in children
- DXM may be associated with delayed cerebral thrombosis
Future studies

• No new DXM trials are currently performed

• New anti-inflammatory drugs may be superior

• Complement component 5 antibodies in mouse model superior to DXM.

Whoerl B, Brouwer et al, J Clin Invest 2011
Future studies - genetics

- SNP glucocorticoid-induced transcript 1 gene
- SNP determines response to steroids in asthma
Genetic differences DXM treatment

- SNP GLCC1 Rs37972
- Minor allele frequency
  - European ancestry 44%
  - Sub-saharan Africa 15%
- Potential cause of differences between populations in response to dexamethasone in bacterial meningitis
- Genetic association study in progress (NL)

Dexamethasone in tuberculous meningitis
Small studies since 1953 showed
- Reduced CSF inflammation
- Reduced incidence of neurological complications
- Shorter time to recovery
- No effect on mortality
Tuberculous meningitis and DXM

• Egypt, children, n=280, 1991
  – Reduced mortality
  – Only in severely affected patients

• South Africa, children, n=141, 1997
  – Reduced mortality

• Vietnam, adults, n=545, 2004
  – Reduced mortality

Girgis IN, Pediatrics 1991; Schoeman Pediatrics 1997; Thwaites NEJM 2004
DXM in TBM for all?

Untreated HIV

• No effect in HIV infected patients
• Vietnamese study showed no harm

Only severely affected patients?

• Vietnamese study showed effect in all categories of disease severity
• All patients with TBM should receive DXM
• Dose 0.3-0.4 mg/kg/day depending on grade
• Tapering over 6-10 weeks
Thank you for your attention

Questions?