Update on Neonatal Postnatal Steroids

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Irish and American Paediatric Society

Founded in Portugal in 1962 by 3 eminent paediatricians:
• Fred Burke from Washington
• Tom Cone from Boston
• Bill Kidney from Dublin

Bill Kidney

Bill Northway
Postnatal Steroids for CLD

**History**
- Baden et al 1972; Kramer and Hultzen 1978
- Mammel et al 1983; Avery et al 1985
- Many RCTs 1985-1998
- Yeh et al 1998; O’Shea et al 1999; Shinwell et al 2000
- EAPM (2001); AAP/CPS (2002) recommendations
- New consensus or more research?

Postnatal Steroids: first RCT

- Baden et al - Pediatrics 1972
- Hydrocortisone for RDS
- N=44 – “Although no immediate detrimental effects of the therapy were seen, the postnatal use of corticosteroids did not appear to carry any obvious benefit for the infant with RDS”

First RCT: Follow-up Studies

- Taeusch 1973 and Fitzhardinge 1974 – Pediatrics
- Increase in severe IVH at autopsy
- Increase in neurodevelopmental problems and EEG abnormalities
- “Risks seem to outweigh benefits”

First Report of Dexamethasone Use

- 11 infants of 27 to 36 weeks’ gestation
- Georgetown University Hospital
- Ventilator-dependent with BPD
- Course of dexamethasone (dose unknown)
- Prompt clinical improvement in lung disease
- Dexamethasone “Useful but not Benign”


Dexamethasone in 1980s

- Mammel et al 1983 and Avery et al 1985
- In total 22 infants with BPD – sequential designs
- Both terminated early for “benefit”
- Large doses – 0.5 better than 0.1 mg/kg/day on basis of responses in 2 infants
- “Dexamethasone cannot be recommended without further study” and “Dexamethasone is a dangerous drug with many side effects”
- Many RCTs in late 1980s

Tsu Yeh
Taiwan
**Postnatal Steroids - Timing**

<table>
<thead>
<tr>
<th>Trials</th>
<th>Babies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (&lt; 96 h)</td>
<td>21</td>
</tr>
<tr>
<td>Mod. Early (7-14 d)</td>
<td>7</td>
</tr>
<tr>
<td>Delayed (&gt; 3 wk)</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
</tr>
</tbody>
</table>

Halliday et al, Cochrane Library 2001

**Postnatal Steroids: Updated Meta-analyses**

Early (≤ 7 days): 28 studies and 3740 infants  
Late (> 7 days): 19 studies and 1345 infants  
TOTAL: 47 studies and 5085 infants  

Halliday, Ehrenkranz and Doyle, Cochrane Library 2009

**Steroids and CLD (36 wk)**

<table>
<thead>
<tr>
<th>Babies</th>
<th>RR</th>
<th>95% CI</th>
<th>NNT</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (≤ 7 days)</td>
<td>3286</td>
<td>0.79</td>
<td>0.71-0.88</td>
<td>14</td>
</tr>
<tr>
<td>Late (&gt; 7 days)</td>
<td>471</td>
<td>0.72</td>
<td>0.61-0.85</td>
<td>6</td>
</tr>
</tbody>
</table>

Halliday, Ehrenkranz and Doyle, Cochrane Library 2009

**Steroids and Neonatal Mortality**

<table>
<thead>
<tr>
<th>Babies</th>
<th>RR</th>
<th>95% CI</th>
<th>NNT</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (≤ 7 days)</td>
<td>2950</td>
<td>1.02</td>
<td>0.88-1.19</td>
<td>-</td>
</tr>
<tr>
<td>Late (&gt; 7 days)</td>
<td>656</td>
<td>0.49</td>
<td>0.28-0.85</td>
<td>17</td>
</tr>
</tbody>
</table>

Halliday, Ehrenkranz and Doyle, Cochrane Library 2009

**Steroids and Cerebral Palsy (1st 3 Years)**

<table>
<thead>
<tr>
<th>Babies</th>
<th>RR</th>
<th>95% CI</th>
<th>NNH</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (≤ 7 days)</td>
<td>1452</td>
<td>0.45</td>
<td>1.06-1.98</td>
<td>33</td>
</tr>
<tr>
<td>Late (&gt; 7 days)</td>
<td>777</td>
<td>0.14</td>
<td>0.79-1.64</td>
<td>-</td>
</tr>
</tbody>
</table>

Halliday, Ehrenkranz and Doyle, Cochrane Library 2009

**Recommendations**

**EAPM (2001)**

- Avoid if at all possible  
- No indication to give in first 3-4 days  
- Do not give if spontaneously breathing  
- May be indicated for very ill ventilator-dependent infants  
- Use should be discussed with parents  
- Lowest possible dose for shortest possible duration
### Recommendations

**AAP / CPS (2002)**
- Systemic steroids are not recommended
- Limit use to RCTs with long-term outcomes
- Long-term outcomes needed for all trials
- Trials of alternative drugs including inhaled needed
- Outside RCTs limit use to exceptional clinical circumstances (maximal ventilatory support). Parents should be informed.

### Postnatal Steroids – Which Dose?
- Courses differ in timing, dose and duration
- Most frequent regimen:
  - Dexamethasone
  - 0.5 mg/kg/day for 3 days
  - Halving every three days
  - Total course – 12 days

3 randomized trials compared doses of dexamethasone:
- 1994 Ramanathan et al - 0.2 vs 0.4 mg/kg/day: no difference
- 1996 McEvoy et al - 0.2 vs 0.5 mg/kg/day: higher dose better at reducing ventilation requirements but survival was not different
- 2001 Durand et al - 0.2 vs 0.5 mg/kg/day: no difference in lung function improvement

### DART Study
- RCT < 28 wk or < 1000 g and > 1 wk PNA
- Dexamethasone: starting at 0.15 mg/kg and reducing over 10 days (0.89 mg/kg)
- Primary outcome at 18 months
- Poor recruitment and stopped early

**Doyle et al, Pediatrics 2006**

### DART Study Results
- n = 70 from 11 centres in Australia
- GA 24.9 wk, BW 701 g and PNA 23 days
- **Extubated by 10 days** (60% vs 12%)
  - OR 11.2; 95% CI 3.2-39.0
- **Mortality** - OR 0.52; 95% CI 0.14-1.95
- **Oxygen at 36 wk** - OR 0.58; 0.13-2.66

**Doyle et al, Pediatrics 2006**

### Higher vs Lower Dexamethasone Doses
- 6 studies and 209 infants – meta-analysis
- 2 studies higher cumulative doses (> 2.7 mg/kg) and 4 studies lower (≤ 2.7 mg/kg)
- Similar rates of death and neurodevelopmental sequelae in higher and lower groups
- Higher dose more effective at reducing CLD
- Several drawbacks: small, heterogeneity, late rescue, missing neurodevelopmental data

**Onland et al, Pediatrics 2008; 122: 82-101**
Finding a Dosage Regimen
- 16 RCTs of dexamethasone > 7 days
- Meta-analysis and meta-regression
- Higher doses better at reducing death/BPD
- Largest effect with cumulative dose > 4 mg/kg
- Dose not related to neurodevelopmental outcome in > 3 week subgroup
- In 7-14 day subgroup death/CP decreased by 6% for each mg/kg increase in cumulative dose

Onland et al, Pediatrics 2009; 123: 367-377

Which Steroid?
- Retrospective observational study of 833 preterm infants born to mothers in Paris
- Assessed rates of cystic periventricular leukomalacia (PVL) in 3 non-randomized groups:
  - Prenatal betamethasone rate was 4.4%
  - Prenatal dexamethasone rate was 11.0%
  - Untreated control group rate was 8.4%

Baud et al NEJM 1999; 341: 1190

Antenatal Dexamethasone vs Betamethasone (NICHD)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dexa (n=1227)</th>
<th>Beta (n=1738)</th>
<th>None (n=635)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVL (%)</td>
<td>2.9</td>
<td>3.5</td>
<td>4.4</td>
</tr>
<tr>
<td>Severe IVH (%)</td>
<td>9.4</td>
<td>10.3</td>
<td>12.8</td>
</tr>
<tr>
<td>Neonatal* (Death %)</td>
<td>7.9</td>
<td>7.4</td>
<td>11.0</td>
</tr>
</tbody>
</table>

* Adjusted OR (95%CI) = 1.68 (1.07-2.57)  
Lee et al, Pediatrics 2006

Postnatal Steroids: Other Systemic Steroids
- Methylprednisolone: shorter half life, fewer adverse effects and apparently as effective as dexamethasone in weaning from ventilation BUT no randomized trials (RCTs) yet
- Betamethasone: fewer adverse effects (poor weight gain and hyperglycaemia) and similar short term outcomes as dexamethasone but not a RCT
- Low dose hydrocortisone (1 mg/kg/day) reduced risk of CLD in one small study BUT two larger RCTs showed increases in gastrointestinal perforations and were stopped early

Low dose hydrocortisone (RCTs)
- Watterberg et al, 1999 – 12 days; n=40
- Watterberg et al. 2004 – 15 days; n=360
- Peltonieni et al, 2005 – 10 days; n=51
- Latter 2 studies stopped early

Vandermeer, 2006 – unpublished data

Low dose hydrocortisone vs placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number</th>
<th>RR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI perforation*</td>
<td>451</td>
<td>2.08</td>
<td>1.08-4.00</td>
</tr>
<tr>
<td>Survival without BPD at 36 wk (all)</td>
<td>448</td>
<td>1.14</td>
<td>0.90-1.43</td>
</tr>
<tr>
<td>Survival without BPD at 36 wk (chorioamnionitis)</td>
<td>171</td>
<td>1.82</td>
<td>0.95-3.50</td>
</tr>
</tbody>
</table>

* Many also had indomethacin

Vandermeer, 2006 – unpublished data
### Dexamethasone vs Hydrocortisone

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>Babies</th>
<th>RR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLD (36 wk)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>2840</td>
<td>0.70</td>
<td>0.61 to 0.81</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>802</td>
<td>0.96</td>
<td>0.82 to 1.12</td>
</tr>
<tr>
<td>Death/CLD (36 wk)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>2484</td>
<td>0.87</td>
<td>0.80 to 0.94</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>836</td>
<td>0.95</td>
<td>0.86 to 1.06</td>
</tr>
<tr>
<td>Death in Hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>2840</td>
<td>1.03</td>
<td>0.90 to 1.18</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>880</td>
<td>0.88</td>
<td>0.67 to 1.17</td>
</tr>
</tbody>
</table>

Halliday, Ehrenkranz and Doyle, Cochrane Library 2009

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### Early Steroids (≤ 7 days) : Cerebral Palsy

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Babies</th>
<th>RR</th>
<th>95%CI</th>
<th>NNH</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>921</td>
<td>1.75</td>
<td>1.20 to 2.55</td>
<td>20</td>
<td>11 to 100</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>531</td>
<td>0.97</td>
<td>0.55 to 1.69</td>
<td>--</td>
<td>---------</td>
</tr>
</tbody>
</table>

Halliday, Ehrenkranz and Doyle, Cochrane Library 2009

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### Postnatal Steroids – Inhaled or Systemic

- Cochrane review (Shah et al, 2004) : 7 trials
  - No outcome differences between inhaled steroids and placebo except less use of late dexamethasone

- OSECT trial (Halliday et al, Pediatrics 2001): n=570
  - Inhaled budesonide (800 µg/kg/day) vs systemic dexamethasone (starting at 0.5 mg/kg/day): both early and late:
    - Inhaled as effective though fewer adverse effects

### Inhaled vs Systemic Steroids

- 5 trials but 2 excluded
- No difference in CLD at 36 weeks
- No difference in death by 36 weeks
- No differences in adverse events
- No evidence that inhaled steroids better than systemic for ventilator-dependent preterm infants

Shah et al, Cochrane Library, 2007

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### Postnatal Steroids – Inhaled vs Systemic

**Dexamethasone Treatment Showed**

- Earlier extubation
- Reduced oxygen needs
- Improved lung mechanics
- Hypertension
- Hyperglycaemia

Shah et al, Cochrane Library 2004
**OSECT Follow-up: UK and Ireland**

**Dexamethasone vs Budesonide**

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>95% Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP &gt; 95th percentile</td>
<td>3.23</td>
</tr>
<tr>
<td>Diagnosis of Asthma</td>
<td>2.60</td>
</tr>
</tbody>
</table>

*adjusted for gestation, birth weight, gender, antenatal steroids, method of delivery, Apgar score at 5 minutes and CRIB score

Wilson et al, Pediatrics 2006; 117: 2196-205

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**Instilled Budesonide with Surfactant**

- Pilot RCT of 116 infants < 1500 g with severe RDS
- 60 treated with 0.25 mg/kg Budesonide and 100 mg/kg Beractant every 8 hours
- 56 treated with 100 mg/kg Beractant every 8 hours
- Primary endpoint was death/CLD at 36 wk PMA

Yeh et al, Pediatrics 2008; 121: e1310-e1318

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**Instilled Budesonide and Beractant**

<table>
<thead>
<tr>
<th>Budesonide (n=60)</th>
<th>Control (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g) mean (SD)</td>
<td>881 (245)</td>
</tr>
<tr>
<td>Gestation (wk) mean (SD)</td>
<td>26.4 (2.2)</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>31 (52)</td>
</tr>
<tr>
<td>Prenatal steroids n (%)</td>
<td>46 (77)</td>
</tr>
<tr>
<td>Postnatal age (h) mean (SD)</td>
<td>2.1 (2.2)</td>
</tr>
<tr>
<td>FiO2 mean (SD)</td>
<td>0.74 (0.18)</td>
</tr>
</tbody>
</table>

Yeh et al, Pediatrics 2008; 121: e1310-e1318

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**Instilled Budesonide and Beractant**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Budesonide (n=60)</th>
<th>Control (n=56)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death - n (%)</td>
<td>10 (17)</td>
<td>18 (32)</td>
<td>0.08</td>
</tr>
<tr>
<td>CLD - n (%)</td>
<td>9 (15)</td>
<td>16 (29)</td>
<td>0.12</td>
</tr>
<tr>
<td>Death/CLD - n (%)</td>
<td>19 (32)</td>
<td>34 (61)</td>
<td>0.003</td>
</tr>
<tr>
<td>SBP on d 3 (mmHg) mean (SD)</td>
<td>50 (7)</td>
<td>46 (9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Yeh et al, Pediatrics 2008; 121: e1310-e1318

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**Effect on death or CP (RD, %)**

Doyle et al, Pediatrics 2005
**Suggested “New” Recommendations**

- Don’t give in the first week of life
- Consider if ventilator-dependent after the first 7-10 days of life
- Discuss risks and benefits with parents
- Use lowest dose for shortest duration
- No role yet for inhaled steroids
- Further studies needed

BAPM Working Group, 2005