Steroids: What’s the Rage???

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Objectives

- Identify and review the basic structure and function of steroids
- Define the indications of use of steroids for fetal lung maturity
- Describe what steroid to use when for pressor-refractory hypotension or in cases of adrenal insufficiency
- Discuss the use of dexamethasone for extubation
Regulation of Hormone Secretion

- CRH – corticotropin-releasing hormone
- ACTH – adrenocorticotropic hormone
- Corticotropin – synthetic human ACTH
Structure of the Adrenal Glands

- 4 weeks gestation – cortical cells can be identified
- 8 weeks gestation – adrenal gland becomes encapsulated
- Fetal adrenal gland is steroidogenically active and large during gestation
Structure/Function of the Adrenal Glands

Medulla
- Secretes catecholamines

Cortex
- Secretes the 3 main types of steroid hormones
  - Glucocorticoids
  - Mineralocorticoids
  - Androgens
Structure of Steroids

Cholesterol backbone
ACETATE

CHOLESTEROL

C₂₀₂₂-lyase

PREGNENOLONE

17α-hydroxylase

PROGESTERONE

17α-hydroxylase

21-hydroxylase

DEOXYCORTICOSTERONE

11β-hydroxylase

CORTICOSTERONE

18-hydroxylase

18-HYDROXYCORTICOSTERONE

18-HSD

ALDOSTERONE

DEHYDROEPIANDROSTERONE SULFATE (DHEAS)

DEHYDROEPIANDROSTERONE (DHEA)

3β-HSD/isomerase

5-ANDROSTENEDIOL

ANDROSTENEDIONE

17β-HSD

TESTOSTERONE

SEX STEROIDS

DEOXYCORTISOL

11β-hydroxylase

CORTISOL

GLUCOCORTICOIDs

MINERALOCORTICOIDs

* 3β-HSD/isomerase = 3β-hydroxysteroid dehydrogenase-Δ⁵₄-isomerase

◊ 17β-HSD = 17β-hydroxysteroid dehydrogenase

x 18-HSD = 18-hydroxysteroid dehydrogenase
Steroids of Interest

Cortisol
- Glucocorticoid
- Synthetic: hydrocortisone

Aldosterone
- Mineralocorticoid
- Synthetic: fludrocortisone
Glucocorticoids

Function:
- Intermediary metabolism
- Cardiovascular function
- Growth
- Immunity
Mechanism of Action

Mechanism of Action
Take Home Points

机制 of作用的类固醇

- 非基因表位活化
- DNA-依赖性调节
- 蛋白质干扰机制

您将不会在测验中被问到这个 😊
Mineralocorticoids

Mechanism of Action
- MC binds to MC receptors in the cytoplasm of target cells → drug-receptor complex activates a series of events similar to the GC-receptor complex

Function
- Promotes reabsorption of sodium from the distal convoluted and proximal collecting renal tubules, loosely coupled to the excretion of $\text{K}^+$ and $\text{H}^+$ ions

MC: mineralocorticoid, GC-receptor: glucocorticoid-receptor

# Steroid Comparison

<table>
<thead>
<tr>
<th>Glucocorticoid: Anti-inflammatory</th>
<th>Mineralocorticoid: Salt-Retaining</th>
<th>Equivalent Oral Dose</th>
<th>Forms Available</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short- to Medium-acting glucocorticoids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone (HC)</td>
<td>1</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Prednisone</td>
<td>4</td>
<td>0.3</td>
<td>5</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
<td>0.3</td>
<td>5</td>
</tr>
<tr>
<td><strong>Methylprednisolone</strong></td>
<td>5</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td><strong>Intermediate-acting glucocorticoids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>5</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td><strong>Long-acting glucocorticoids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betamethasone</td>
<td>25-40</td>
<td>0</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Dexamethasone (Dex)</strong></td>
<td>30</td>
<td>0</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>Mineralocorticoids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>10</td>
<td>250</td>
<td>2</td>
</tr>
</tbody>
</table>

1Potency relative to hydrocortisone  
2Inj: injectable, Top: topical

Identify and review the basic structure and function of steroids

Define the indications of use of steroids for fetal lung maturity

Describe what steroid to use when for pressor-refractory hypotension or in cases of adrenal insufficiency

Discuss the use of dexamethasone for extubation
Antenatal Corticosteroid Therapy for Fetal Maturation

Dosing Strategies
- Betamethasone 12 mg IM q24hrs x 2 doses
- Dexamethasone 6 mg IM q12hr x 4 doses

- Cross placenta in active form
- Lack mineralocorticoid activity
- Relatively weak immunosuppressive activity with short-term use

Antenatal Corticosteroid Therapy for Fetal Maturation

Single course:

- Pregnant women between 24-34 weeks gestation who are at risk of preterm delivery within 7 days
- Women with PROM before 32 weeks of gestation to reduce the risks of RDS, perinatal mortality and other morbidities

Unclear:

- Efficacy at 32-33 completed weeks of gestation for PROM

PROM: premature rupture of membranes, RDS: respiratory distress syndrome
Repeat doses
- Single rescue course may be considered if:
  - the previous course was given more than 2 weeks prior
  - gestation age is < 32 6/7
  - likely to give birth within the next week

Not recommended
- Use before fetal age of viability
- Regularly scheduled repeat course or multiple courses (more than two)
Objectives

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- Discuss the use of dexamethasone for extubation
Steroids for Hypotension

The Management of Hypotension in the Very-Low-Birth-Weight Infant

Evidence-based clinical guideline during the first 3 days of prenatal life

Management of Hypotension in the Very-Low-Birth-Weight Infant


Defining Hypotension

- 2 most common parameters used to define hypotension during immediate transition period
  - Blood pressure that falls below MAP < 30 mmHg
  - MAP with a number lower than GA

MAP: mean arterial pressure, GA: gestational age
Dopamine should be considered prior to dobutamine for treatment of hypotension alone in VLBW infants when the cause of hypotension is unknown.

Dobutamine may be drug of choice in cases of hypotension and LSBF during the first postnatal day.

- Immature myocardium’s ability to pump against sudden increased PR
- Vasoconstriction of the immature forebrain vasculature

VLBW: very low birth weight, LSBF: low systemic blood flow, PR: peripheral resistance

If hypotension is related to evidence of infection, dopamine is first-line agent

If not effective, treatment with epinephrine should be considered

Practice Recommendations

Practice Recommendations

The use of hydrocortisone is as effective as dopamine in improving hypotension in VLBW infants, but data on the long-term safety of corticosteroids for this use are insufficient.

- Thus should be reserved for refractory hypotension
- Hydrocortisone should NOT be used concurrently with indomethacin

A single dose of dexamethasone may increase blood pressure in hypotensive VLBW but cannot be recommended because of its documented negative effect on neurodevelopmental outcomes if given during the first postnatal days.

Timely hydrocortisone therapy in children with fluid-refractory, catecholamine-resistant shock and suspected or proven absolute (classic) adrenal insufficiency

No strict definitions exist, but absolute adrenal insufficiency in the case of catecholamine-resistant septic shock is assumed at a random total cortisol concentration < 18 mcg/dl

A post 30- or 60-min ACTH stimulation test increase in cortisol of ≤9 mcg/dl has been used to define relative adrenal insufficiency

Trial of HC if MAP remains $\leq 10^{th}$ percentile for GA and PNA norms despite volume administration and high-dose pressor/inotrope support

Steroid dosing

- No capillary leak or previous exposure: HC 1 mg/kg/DOSE BID for 1-3 days (n=16; 17 courses)
- Severe capillary leak and/or previous exposure: HC 3-6 mg/g/DAY of HC divided BID/QID for 2-3 days (n=5; 6 courses)

PNA: postnatal age

### Demographics

<table>
<thead>
<tr>
<th></th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational Age</strong></td>
<td>26.9 ± 3.9 weeks</td>
</tr>
<tr>
<td><strong>Birth weight</strong></td>
<td>952 ± 607 grams</td>
</tr>
<tr>
<td><strong>Postnatal age</strong></td>
<td>11.3 ± 13.1 days</td>
</tr>
</tbody>
</table>

**Dopamine alone**

- **Range**: 19.1 ±8 mcg/kg/MIN to 8-40 mcg/kg/MIN

**Combination with:**

- **Dobutamine**
  - **Range**: 8.4 ± 4.9 mcg/kg/MIN to 5-20 mcg/kg/MIN
- **Epinephrine**
  - **Range**: 0.38 ± 0.56 mcg/kg/MIN to 0.01-1.2 mcg/kg/MIN

Effect of hydrocortisone on mean blood pressure at 2 and 4 hours after the first dose of the drug

Mean Blood Pressure

$n = 23$

Pre-HC  HC [2 h]  HC [4 h]

mm Hg

20  30  40  50  60
Effect of hydrocortisone on mean blood pressure and the dose of dopamine during the first 24 hours of hydrocortisone treatment
Changes in individual and mean fluid intake and urine output during the study

A. Fluid Intake

B. Urine Output

* indicates significant difference from baseline.
Pathophysiology of pressor-resistant hypotension has not been fully clarified. Probable causes include:

- Downregulation of adrenergic receptors in cases of critical illness and exogenous catecholamine administration
- Relative or absolute adrenal insufficiency
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- Discuss the use of dexamethasone for extubation
Steroids for Extubation

Focus on the use of corticosteroids in neonates with VLBW for the prevention or treatment of CLD

CLD: chronic lung disease

2002 AAP Recommendations

- Systematic and meta-analyses (1983-2001) on the use of steroids for the prevention and/or treatment of CLD in preterm infants.

- Results presented in 5 sections:
  - First 3 – effects of systemic steroids on the basis of age
  - Effects of inhaled
  - Neurodevelopmental outcomes

< 96 hours of age
- IV Dexamethasone most commonly used
- 0.5 mg/kg/DAY x 3 days, followed by a tapering course of 0.25, 0.125 and 0.05 mg/kg/DAY each x 3 days

- The combined outcome of death or CLD at 28 days’ PNA or at 36 wks PMA was significantly decreased
  - No effect on death alone, decreased CLD alone
- 10 infants would need to be treated with CS to prevent 1 from developing CLD at 28days’ PNA or at 36 wks PMA

PMA: postmenstrual age, CS: corticosteroids

7-14 days PNA
- All studies used IV dexamethasone
- Initial dosage was 0.5 mg/kg/DAY which was either:
  - Maintained for the duration of the study period
  - Decreased over 7-42 days
  - Followed by inhaled budesonide

- The combined outcome of death or CLD was decreased at 28 days PNA and at 36 wks PMA
- The NNT was 7 and 4 to prevent CLD at 28 days PNA and 36 wks PMA, respectively

NNT: number needed to treat

Systemic Delayed Therapy

> 3 weeks

- Dexamethasone (IV or enteral) at 0.5-1 mg/kg/DAY for a duration of 3 days – 3 weeks.
  - Dose tapered every 3 days in different ways, some patients transitioned over to hydrocortisone

Inhaled Therapy

Enrolled 2 weeks after birth
- No benefit was shown except borderline significant decrease of subsequent administration of systemic dexamethasone

Enrolled after 2 weeks of age – inhaled steroids for 1-4 weeks
- Appeared to improve extubation rate; however, no heterogeneity between studies for this finding

2 systematic reviews

#1: included 5 trials → 475 / 522 survivors were followed

- No difference in mortality between steroid & control groups

- Motor dysfunction was significantly greater with steroid treatment (11.9% favoring control)

- Rate of survival free of motor dysfunction was lower in the steroid group (7.8% favoring control)

Systemic administration of dexamethasone to preterm infants who are mechanically ventilated decreased the incidences of CLD and extubation failure but does not decrease overall mortality.

Treatment of infants with VLBW with dexamethasone is associated with an increased risk of short- and long-term complications, including impaired growth and neurodevelopmental delay.

No substantial short- or long-term benefits have been demonstrated from the use of inhaled corticosteroids in the prevention or treatment of CLD.
2002 Recommendations

- Routine use of dexamethasone for the prevention or treatment of CLD in infants with VLBW is NOT recommended.

- If used, should be limited to carefully designed randomized double-masked controlled trials.
  - Long-term neurodevelopmental assessment is strongly recommended.

- Clinical trials using alternative anti-inflammatory corticosteroids, systemic and inhaled, are required before additional recommendations can be made.

- Outside of trials, use should be limited to exceptional clinical circumstances. Parents to be informed and agree to therapy.
Multicenter randomized control trial (RCT)

Primary aim: assessment of the effects of low-dose dexamethasone on long-term rates of survival free of major neurologic disability

Secondary aim: examine the short-term effects, especially respiratory, of low-dose dexamethasone given after the first 1 week of life for vent-dependent, very preterm/VLBW infants
192 infants eligible (11 centers, 3 countries)

- 70 randomized
- 122 not included*

35 dexamethasone – all analyzed
35 placebo – all analyzed

- 43 not approached
- 51 parents declined
- 26 infants too sick, given steroids
- 2 not approached, no reason given
Protocol:

Dexamethasone

- 0.15 mg/kg/DAY x 3 days
- 0.1 mg/kg/DAY x 3 days
- 0.05 mg/kg/DAY x 2 days
- 0.02 mg/kg/DAY x 2 days

Placebo – equivalent volume of 0.9% saline

Course could be repeated (with the same blinded drug)

Use of open-label corticosteroids after randomization was discouraged but not prohibited
DART Demographics

<table>
<thead>
<tr>
<th></th>
<th>Dexamethasone (n = 35)</th>
<th>Placebo (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA, median (IQR), wks</td>
<td>24 (24-25)</td>
<td>25 (24-26)</td>
</tr>
<tr>
<td>Birth weight, median (IQR), grams</td>
<td>652 (590-730)</td>
<td>700 (612-790)</td>
</tr>
<tr>
<td>Male, no (%)</td>
<td>16 (45.7)</td>
<td>21 (60)</td>
</tr>
<tr>
<td>Apgar score 1 min, median (IQR)</td>
<td>5 (4-6)</td>
<td>5 (3-6)</td>
</tr>
<tr>
<td>Apgar score 5 min, median (IQR)</td>
<td>7 (7-8)</td>
<td>7 (6-9)</td>
</tr>
<tr>
<td>Intubated in DR, no (%)</td>
<td>33 (94.3)</td>
<td>32 (91.4)</td>
</tr>
<tr>
<td>Surfactant, no. (%)</td>
<td>33 (94.3)</td>
<td>34 (97.1)</td>
</tr>
<tr>
<td>Before randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids, no (%)</td>
<td>6 (17.1)</td>
<td>5 (14.3)</td>
</tr>
</tbody>
</table>

IQR: interquartile range, DR: delivery room

*Pediatrics.* 2006;117:75-83.
## At Time of Randomization

<table>
<thead>
<tr>
<th></th>
<th>Dexamethasone (n = 35)</th>
<th>Placebo (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), d*</td>
<td>23 (20-34)</td>
<td>22 (13-28)</td>
</tr>
<tr>
<td>Type of ventilation**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFV, no (%)</td>
<td>5 (14.3)</td>
<td>8 (22.9)</td>
</tr>
<tr>
<td>IPPV, no (%)</td>
<td>30 (85.7)</td>
<td>26 (74.3)</td>
</tr>
<tr>
<td>Duration of IPPV, median (IQR), d</td>
<td>19 (10-24)</td>
<td>14 (6-24)</td>
</tr>
<tr>
<td>Duration of HFV, median (IQR), d</td>
<td>1 (0-11)</td>
<td>2 (0-11)</td>
</tr>
<tr>
<td>Mean airway pressure, median (IQR), cm H₂O</td>
<td>10 (8.4-11.5)</td>
<td>10 (9-11.4)</td>
</tr>
<tr>
<td>FIO₂, median (IQR), %</td>
<td>47 (40-55)</td>
<td>45 (33-60)</td>
</tr>
</tbody>
</table>

HFV: high-frequency ventilation, IPPV: invasive positive pressure ventilation, FIO₂: fraction of inspired oxygen

*Two children were 6 days of age when entered into study (1 per group) which was a protocol violation.

**One child in the placebo group was receiving NIPPV at time of randomization, which was a protocol violation.
# Major Infant Outcomes

<table>
<thead>
<tr>
<th></th>
<th>No. (%)</th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dexamethasone (n=35)</td>
<td>Placebo (n = 35)</td>
<td></td>
</tr>
<tr>
<td>Failure to extubate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>By day 3*</td>
<td>23 (65.7)</td>
<td>33/34 (97.1)</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>By day 7**</td>
<td>17 (48.6)</td>
<td>30/34 (88.2)</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>By day 10***</td>
<td>14 (40)</td>
<td>30/34 (88.2)</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>To discharge</td>
<td>3 (8.6)</td>
<td>5 (14.3)</td>
<td>NS</td>
</tr>
<tr>
<td>After discharge</td>
<td>1 (2.9)</td>
<td>2 (5.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Any time before follow-up evaluation</td>
<td>4 (11.4)</td>
<td>7 (20)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Includes 1 death in the placebo group, 1 death in the dex group and 1 withdrawal from the placebo group.
**Includes 1 additional death in the placebo group and 5 additional withdrawals in the placebo group.
***Includes 1 additional withdrawal in the placebo group.
# Major Infant Outcomes

<table>
<thead>
<tr>
<th></th>
<th>No. (%)</th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dexamethasone (n=35)</td>
<td>Placebo (n = 35)</td>
<td></td>
</tr>
<tr>
<td>BPD at 36 weeks****</td>
<td>28/33 (84.9)</td>
<td>29/32 (90.6)</td>
<td>0.48</td>
</tr>
<tr>
<td>Severe BPD (&gt;30% O(_2)) at 36 wk</td>
<td>10/33 (30.3)</td>
<td>13/32 (40.6)</td>
<td>0.38</td>
</tr>
<tr>
<td>Home with O(_2)</td>
<td>15 (42.9)</td>
<td>16 (45.7)</td>
<td>0.81</td>
</tr>
<tr>
<td>Death or BPD at 36 wk</td>
<td>30 (85.7)</td>
<td>32 (91.4)</td>
<td>0.45</td>
</tr>
<tr>
<td>Death or severe BPD at 36 wk</td>
<td>12 (34.3)</td>
<td>16 (45.7)</td>
<td>0.33</td>
</tr>
<tr>
<td>Death or home with O(_2)</td>
<td>18 (51.4)</td>
<td>21 (60)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

BPD: bronchopulmonary dysplasia

****Among those who survived to 36 weeks.
DART

- Considered to have failed extubation over the 10-day treatment if they remained intubated throughout, died or were withdrawn from the study.

- Other complications that occurred at any time after randomization were documented and included infections, NEC, PDA, ROP, GI hemorrhage/perforation, cardiac hypertrophy and HUS abnormalities.

- Enrollment had to stop due to poor recruitment.

<table>
<thead>
<tr>
<th></th>
<th>Dexamethasone (n=35)</th>
<th>Placebo (n=35)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors assessed for CP</td>
<td>29/31 (93.5)</td>
<td>27/28 (96.4)</td>
<td>0.32</td>
</tr>
<tr>
<td>Impairments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP, n/N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild, n</td>
<td>4/29 (13.8)</td>
<td>6/27 (22.2)</td>
<td>0.5</td>
</tr>
<tr>
<td>Moderate, n</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Severe, n</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Severe, n</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Developmental Scores, mean (SD); n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDI</td>
<td>79.3 (24.7); 27</td>
<td>83.8 (22); 24</td>
<td>0.5</td>
</tr>
<tr>
<td>PDI</td>
<td>84.1 (20.3); 26</td>
<td>79.1 (23.6); 24</td>
<td>0.43</td>
</tr>
<tr>
<td>Major (moderate or severe) disability, n/N (%) assessed</td>
<td>12/29 (41.4)</td>
<td>8/26 (30.8)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

CP: cerebral palsy, MDI: mental developmental index, PDI: psychomotor developmental index
2010 AAP Recommendations

Objectives: review data published since the 2002 AAP statement and to re-examine previous recommendations for the use of glucocorticoid therapy in the view of this new information.
### TABLE 1  RCTs of Dexamethasone to Prevent or Treat BPD Reported Since 2001

<table>
<thead>
<tr>
<th>Study, No. of Centers</th>
<th>n</th>
<th>Eligibility Criteria (All on Mechanical Ventilation)</th>
<th>Dexamethasone Dosing Regimen</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>McEvoy et al, 17</td>
<td>62</td>
<td>500–1500 g BW; ≤32 wk gestation; 7–21 postnatal days</td>
<td>5 mg/kg per d tapered over 7 d vs 0.2 mg/kg tapered over 7 d</td>
<td>Rate of survival without BPD* 78% vs 79% (NS); no benefit to higher dose</td>
</tr>
<tr>
<td>Odd et al, 18</td>
<td>33</td>
<td>≤1250 g BW; 1–3 wk of age</td>
<td>0.5 mg/kg per d tapered over 42 d vs “individualized” (same dose, shorter course)</td>
<td>Rate of survival without BPD: 24% vs 30% (NS); no difference in 18-mo outcomes</td>
</tr>
<tr>
<td>Malloy et al, 19</td>
<td>16a</td>
<td>&lt;1501 g BW; &lt;34 wk gestation; &lt;28 postnatal days</td>
<td>0.5 mg/kg per d tapered over 7 d vs 0.08 mg/kg per d for 7 d</td>
<td>Rate of survival without BPD: 11% vs 38% (NS); higher dose had more adverse effects, no apparent benefit</td>
</tr>
<tr>
<td>Walther et al, 20</td>
<td>36</td>
<td>≥600 g BW; 24–32 wk gestation; 7–14 d postnatal age</td>
<td>0.2 mg/kg per d tapered over 14 d vs placebo</td>
<td>Rate of survival without BPD: 65% vs 47% (NS); extubation: 78% vs 42% (P &lt; .05)</td>
</tr>
<tr>
<td>Anttila et al, 21</td>
<td>109b</td>
<td>500–999 g BW; ≤31 wk gestation; eligible at 4 h of age</td>
<td>0.25 mg/kg every 12 h × 4 doses vs placebo</td>
<td>Rate of survival without BPD: 58% vs 52% (NS)</td>
</tr>
<tr>
<td>Doyle et al, 22</td>
<td>70b</td>
<td>&lt;1000 g BW; &lt;28 wk gestation; &gt;1 wk postnatal age</td>
<td>0.15 mg/kg per d tapered over 10 d vs placebo</td>
<td>Rate of survival without BPD: 14% vs 9% (NS); extubation: 80% vs 12% (odds ratio: 11.2 [95% confidence interval: 3.2–39.0])</td>
</tr>
<tr>
<td>Rozycki et al, 23</td>
<td>61</td>
<td>650–2000 g BW; ≥14 d postnatal age</td>
<td>0.5 mg/kg per d tapered over 42 d vs inhaled beclomethasone at 3 different doses for 7 d followed by above-listed dexamethasone course, if still mechanically ventilated</td>
<td>Rate of survival without BPD: 53% vs 48% (NS); extubation by 7 d: 7 of 15 vs 6 of 46 (P &lt; .01)</td>
</tr>
</tbody>
</table>

* BW indicates birth weight; NS, not significant.
* BPD defined as receiving supplemental oxygen at 36 weeks postmenstrual age.
* Patient enrollment terminated early.
TABLE 2 Neurodevelopmental Follow-up of Dexamethasone RCTs Reported After 2001

<table>
<thead>
<tr>
<th>Study, Planned Age at Follow-up</th>
<th>Follow-up, % (No. of Infants Seen)</th>
<th>Treatment Start Time</th>
<th>Dexamethasone Dosing Regimen</th>
<th>Primary Neurodevelopmental Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>McEvoy et al,\textsuperscript{20} 1 y</td>
<td>66 (59)</td>
<td>At 7–21 d</td>
<td>High vs low dose; 7-d taper from 0.5 mg/kg per d vs 0.2 mg/kg per d</td>
<td>MDI &lt; 70: 24% (high) vs 17% (low) (NS); CP: 10% vs 11% (NS)</td>
</tr>
<tr>
<td>Armstrong et al,\textsuperscript{26} 18 mo chronological age</td>
<td>98 (64)</td>
<td>On day 7</td>
<td>42-d taper vs 3-d pulse</td>
<td>No difference in 18-mo outcomes No disability: 34% vs 31% (NS)</td>
</tr>
<tr>
<td>Doyle et al,\textsuperscript{26} 2 y corrected age</td>
<td>98 (58)</td>
<td>After 7 d</td>
<td>0.15 mg/kg per d tapered over 10 d</td>
<td>Death or major disability: 46% vs 43% (NS); death or CP: 25% vs 37% (NS); CP: 14% vs 22% (NS); major disability 41% vs 31% (NS)</td>
</tr>
<tr>
<td>Stark et al,\textsuperscript{26} 18–22 mo corrected age</td>
<td>74 (123)</td>
<td>On day 1</td>
<td>0.15 mg/kg per d tapered over 7 d</td>
<td>MDI &lt; 70: 51% vs 43% (NS); PDI &lt; 70: 30% vs 35% (NS); abnormal neurologic exam: 25% each group</td>
</tr>
<tr>
<td>Romagnoli et al,\textsuperscript{27} 3 y</td>
<td>100 (50)</td>
<td>On day 4</td>
<td>0.5 mg/kg per d tapered over 1 wk</td>
<td>No differences in any parameter; CP: 9% vs 14% (NS)</td>
</tr>
<tr>
<td>Wilson et al,\textsuperscript{28} 7 y</td>
<td>84 (127)</td>
<td>Before 3 d</td>
<td>4 groups: 0.5 mg/kg per d tapered over 12 d vs late (15 d) selective, vs inhaled early or late selective</td>
<td>No difference in cognitive, behavioral, CP, or combined outcomes</td>
</tr>
<tr>
<td>Yeh et al,\textsuperscript{29} school age (mean: 8 y)</td>
<td>92 (146)</td>
<td>On day 1</td>
<td>0.5 mg/kg per d for 1 wk, then tapered for a total of 28 d</td>
<td>Treated children were shorter (P = .03), had smaller head circumference (P = .04), lower IQ scores (P = .008), and more significant disabilities (CP, IQ &lt; 5th percentile, vision or hearing impairment): 39% vs 22% (P = .04)</td>
</tr>
<tr>
<td>O'Shea et al,\textsuperscript{30} 4–11 y</td>
<td>89 (84)</td>
<td>On day 15–25</td>
<td>0.5 mg/kg per d tapered over 42 d vs placebo</td>
<td>Death or major NDI+: 47% vs 41% (NS); major NDI alone: 38% vs 14% (P = .01)</td>
</tr>
<tr>
<td>Gross et al,\textsuperscript{31} 15 y</td>
<td>100 (22)</td>
<td>On day 14</td>
<td>0.5 mg/kg per d tapered over 42 d vs 18-d taper vs placebo</td>
<td>Intact survival (IQ &gt; 70, normal neurologic exam, regular classroom): 69% vs 25% (18-d course) vs 18% (placebo) (P &lt; .05)</td>
</tr>
<tr>
<td>Jones and the Collaborative Dexamethasone Trial Follow-up Group,\textsuperscript{32} 15–17 y</td>
<td>95 (150)</td>
<td>At 2–12 wk</td>
<td>0.5 mg/kg per d for 7 d</td>
<td>No difference in moderate/severe disability (defined as IQ &gt; 2 SDs &lt; mean, CP, hearing or vision loss); CP: 24% vs 15% (relative risk: 1.58 [95% confidence interval: 0.81–3.07])</td>
</tr>
</tbody>
</table>

MDI indicates Bayley Mental Developmental Index, NS, not significant. PDI, Bayley Psychomotor Developmental Index, NDI, neurodevelopmental impairment.
* Major neurodevelopmental impairment included CP and/or an IQ score of <70.
2010 Summary and Recommendations

- Additional RCTs of postnatal glucocorticoids are warranted to optimize therapy and improve outcomes for these infants

- Minimize use of open-label glucocorticoids

- Include assessment of long-term pulmonary and neurodevelopmental outcomes

*Pediatrics. 2010;126:800-808.*
In the absence of randomized trial results showing improved short- and long-term outcomes, therapy with high-dose dexamethasone cannot be recommended.

There is insufficient evidence to make a recommendation regarding treatment with low-dose dexamethasone.
Early hydrocortisone treatment may be beneficial in a specific population of patients; however, there is insufficient evidence to recommend its use for all infants at risk of BPD.

Existing data are insufficient to make a recommendation regarding treatment with high-dose hydrocortisone.
Implications for Practice

Clinicians must use clinical judgment to balance adverse effects of BPD with the potential adverse effects of treatments for each individual patient

Decision should be made in conjunction with the infant’s parents
Wrapping it all up…

‘With great power comes great responsibility…’
Uncle Ben to Peter Parker in Spiderman

“Let’s be careful out there…”
Hill Street Blues
Steroids: What’s the Rage???

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May 14, 2014