Diagnosis, Prevention and Treatment of Bronchopulmonary Dysplasia

NEO Conference
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Case Western Reserve University
Disclosure

- I have no financial conflicts of interest to disclose.
- I will discuss off label use of post-natal steroids, Vitamin A, nitric oxide, and caffeine within this presentation.
OUTLINE

- Diagnosis of BPD in 2014
- Prevention of BPD
- Treatment of Evolving BPD
- Comparison of Effect Sizes
DIAGNOSIS
Diagnosis:

- Oxygen or support at 36 weeks PMA
- NIH consensus definition
  - Adds severity classification
- Physiologic definition
  - Incorporates RA challenge in selected infants.
  - Ensures standard oximeter criteria
Reconciling Definitions: NIH Consensus

<table>
<thead>
<tr>
<th></th>
<th>28 days</th>
<th>36 weeks</th>
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<tr>
<td>No BPD</td>
<td>RA</td>
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</tr>
<tr>
<td>Mild BPD</td>
<td>Support</td>
<td>RA</td>
</tr>
<tr>
<td>Mod BPD</td>
<td>Support</td>
<td>Support  (&lt; 30%)</td>
</tr>
<tr>
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## Reconciling Definitions: Add Physiologic Def to NIH

<table>
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<tr>
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<th>Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mod BPD</td>
<td>Support</td>
<td>Support</td>
<td>Passed = Mild BPD</td>
</tr>
<tr>
<td>Mod BPD</td>
<td>Support</td>
<td>Support</td>
<td>Failed = Mod BPD</td>
</tr>
</tbody>
</table>
Pathophysiology
Saccular Phase - 28 wks
Alveolar Phase - 36 wks - adulthood
What about the Blood Vessels?
Multiple Hits Increase BPD

Antenatal Hits
- Chronic Chorioamnionitis

Hits During Transition
- Initiation of Ventilation

Postnatal Hits
- Ventilation
- Oxygen
- Sepsis

FETAL LUNG

PRETERM LUNG

BPD

CORTICOSTEROID

CPAP, SELECTIVE SURF, XANTHINES

NUTRITION, VITAMIN A

PNS, DIURETIC, BRONCHODILATOR

Jobe 2008
Prevention of BPD

- NonInvasive Ventilation
- Vitamin A
- Methylxanthines
- Nutrition
- Careful oxygen management
- Postnatal corticosteroids
- Inhaled Nitric Oxide
Resuscitation and Lung Injury

Surfactant

Volume (ml/kg)

Age, min

Nml Vol
High Vol

Bjorklund, 1997
Fetal and Neonatal Ventilation creates stretch

A= Control
B= Fetal Ventilation
C= Neonatal Ventilation

Hillman, Ped Research 2010
Limit Volutrauma in Delivery Rm

- Avoid hand bagging
  - Use pressure limited device
  - Use ventilator

- Preserve functional residual volume
  - Nasal CPAP in DR

- Limit chest wall expansion
  - Measure tidal volume (4-5 ml/kg)
  - Aim for just visible chest rise
CPAP decreases lung injury

- Lymphocytes
- Monocytes
- Neutrophils
- H$_2$O$_2$

Jobe et al. 2002
Double Immunofluorescence for Apoptosis

Preterm Surfactant Treated Lambs 3 days IMV or High Frequency Nasal Ventilation

Reyburn, AJRCCM 2008
Alveolarization is disrupted

- Adverse effects of ventilation can be rapid
  - Altered elastin – 1 day (mice)
  - Altered structure, apoptosis and proliferation - 3d (sheep, baboon)
Factors in Alveolarization:

- **Pro-inflammatory:**
  - Hyperoxia or Hypoxia (oxidant stress)
  - Mechanical Ventilation
  - Cytokines - TNFα, TGFα, IL-11, IL-6, IL-13

- **Anti-inflammatory:**
  - Glucocorticoids (Dex > HC)

- Other: Poor Nutrition, deficient Vitamin A
**SUPPORT TRIAL: Antenatal Rand**

<table>
<thead>
<tr>
<th>CPAP Arm</th>
<th>Surfactant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delivery Room</strong></td>
<td></td>
</tr>
<tr>
<td>• 5 cm H20</td>
<td></td>
</tr>
<tr>
<td>• Intubation per NRP</td>
<td></td>
</tr>
<tr>
<td>• If intubated, surfactant</td>
<td></td>
</tr>
<tr>
<td><strong>Intubation/Surfactant</strong></td>
<td>Prior to 1 hour</td>
</tr>
<tr>
<td>□ Required if:</td>
<td></td>
</tr>
<tr>
<td>□ FiO2 &gt; 0.5</td>
<td></td>
</tr>
<tr>
<td>□ PaCO2 &gt; 65</td>
<td></td>
</tr>
<tr>
<td>□ Hemodynamic instability</td>
<td></td>
</tr>
</tbody>
</table>
# Results – Primary Outcome

<table>
<thead>
<tr>
<th></th>
<th>CPAP N=663</th>
<th>Surfactant N=653</th>
<th>Adjusted Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or BPD</td>
<td>47.8%</td>
<td>51.0%</td>
<td>0.95 (0.85, 1.05)</td>
</tr>
<tr>
<td>(Physiologic)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPD - Physiologic</td>
<td>39.2%</td>
<td>40.6%</td>
<td>0.99 (0.87, 1.14)</td>
</tr>
<tr>
<td>Death by 36 wks PMA</td>
<td>14.2%</td>
<td>17.5%</td>
<td>0.81 (0.63, 1.03)</td>
</tr>
</tbody>
</table>
### Results – Delivery Room

<table>
<thead>
<tr>
<th>Variable</th>
<th>CPAP (N=663)</th>
<th>Surfactant (N=653)</th>
<th>Relative Risk for CPAP vs. Surfactant (95% CI)</th>
<th>Adjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 min Apgar &lt;3</td>
<td>23.3%</td>
<td>25.6%</td>
<td>0.92 (0.76, 1.11)</td>
<td>0.38</td>
</tr>
<tr>
<td>5 min Apgar &lt;3</td>
<td>3.9%</td>
<td>4.9%</td>
<td>0.82 (0.5, 1.34)</td>
<td>0.43</td>
</tr>
<tr>
<td>PPV in the DR</td>
<td>65.7%</td>
<td>92.9%</td>
<td>0.71 (0.67, 0.75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intubated in DR</td>
<td>34.4%</td>
<td>93.4%</td>
<td>0.37 (0.34, 0.42)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DR intubation for resuscitation</td>
<td>32.6%</td>
<td>27.0%</td>
<td>1.21 (1.02, 1.43)</td>
<td>0.02</td>
</tr>
<tr>
<td>Surfactant in DR or NICU</td>
<td>67.1%</td>
<td>98.9%</td>
<td>0.67 (0.64, 0.71)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Epinephrine in DR</td>
<td>2.0%</td>
<td>4.1%</td>
<td>0.48 (0.25, 0.91)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Metanalyses:

- 4 trials:
  - COIN
  - SUPPORT
  - CURPAP
  - DR Management
- 2782 infants
- Favors CPAP
- Borderline significant for BPD alone. (10% reduction)

Mortality or BPD

RR 1.12 (1.02-1.24)

Rojas-Reyes, Cochrane. 2012
Strategy 2: Limit Volutrauma

- Preserve functional residual volume
  - Timely surfactant-prophylactic or early (<2hr)
  - Nasal CPAP

- Limit chest wall expansion
  - Newer ventilators: measure and display tidal volume (<6ml/kg)
  - Older Ventilators: Aim for just visible chest rise
Prevention of BPD

- NonInvasive Ventilation
- **Vitamin A**
- Methylxanthines
- Nutrition
- Careful oxygen management
- Postnatal corticosteroids
- Inhaled Nitric Oxide
Vitamin A

1.5 Chronic lung disease (oxygen use at 36 weeks' postmenstrual age in survivors)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Vitamin A</th>
<th>Control</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.5.1 Supplementation via intramuscular injection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ravishankar 2003</td>
<td>4</td>
<td>17</td>
<td>2.3%</td>
<td>0.66 [0.22, 2.00]</td>
</tr>
<tr>
<td>Tyson 1999</td>
<td>163</td>
<td>346</td>
<td>81.4%</td>
<td>0.85 [0.73, 0.98]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>363</td>
<td>361</td>
<td>83.7%</td>
<td><strong>0.84 [0.73, 0.97]</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>167</td>
<td>198</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.33 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.5.2 Supplementation via oral route</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wardle 2001</td>
<td>40</td>
<td>52</td>
<td>16.3%</td>
<td>1.00 [0.81, 1.24]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>52</td>
<td>48</td>
<td>16.3%</td>
<td><strong>1.00 [0.81, 1.24]</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>40</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.02 (P = 0.98)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>415</td>
<td>409</td>
<td>100.0%</td>
<td><strong>0.87 [0.77, 0.98]</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>207</td>
<td>235</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 1.98, df = 2 (P = 0.37); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.23 (P = 0.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 1.66, df = 1 (P = 0.20), I² = 39.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Vitamin A: other doses?

- Three dosing strategies compared
  - Standard dose: 5,000 IU 3 times/wk IM
  - Once weekly dosing: 15,000 IU once IM
  - Higher dose: 10,000 3 times/wk IM

- Once per week worsened Vit A def.

- Higher dose was no better than standard.

Ambalhavananan et al; J Peds 2003
NeoVitaA Trial

- New RCT of IV administration in preterms < 1000g.
- May provide an alternative treatment.
- In pilot study demonstrated borderline improvement in BPD.
Prevention of BPD

- NonInvasive Ventilation
- Vitamin A
- **Methylxanthines**
- Nutrition
- Careful oxygen management
- Postnatal corticosteroids
- Inhaled Nitric Oxide
Caffeine therapy for apnea of prematurity

- RCT of caffeine vs placebo in 2006 infants 500-1250 gms in the first 10 days of life.
- Hypothesized that caffeine treatment might cause CNS injury through adenosine pathway.
- Primary outcome - Neurodevelopment.
- Published early for important benefit of BPD.

Schmidt B et al. NEJM 2006;354:2112
## CAP Trial: Outcomes before Discharge

### Table 3. Outcomes before the First Discharge Home.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Caffeine Group (N = 1006)</th>
<th>Placebo Group (N = 1000)</th>
<th>Unadjusted Odds Ratio</th>
<th>Odds Ratio Adjusted for Center (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death — no. (%)</td>
<td>52 (5.2)</td>
<td>55 (5.5)</td>
<td>0.94</td>
<td>0.93 (0.63–1.38)</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia — no. (%)‡</td>
<td>350 (36.3)</td>
<td>447 (46.9)</td>
<td>0.65</td>
<td>0.63 (0.52–0.76)</td>
</tr>
<tr>
<td>Retinopathy of prematurity — no. (%)¶</td>
<td>322 (39.2)</td>
<td>362 (43.2)</td>
<td>0.84</td>
<td>0.84 (0.68–1.03)</td>
</tr>
<tr>
<td>Brain injury — no. (%)¶</td>
<td>126 (13.0)</td>
<td>138 (14.3)</td>
<td>0.90</td>
<td>0.90 (0.69–1.18)</td>
</tr>
<tr>
<td>Necrotizing enterocolitis — no. (%)</td>
<td>63 (6.3)</td>
<td>67 (6.7)</td>
<td>0.93</td>
<td>0.93 (0.65–1.33)</td>
</tr>
<tr>
<td>Drug therapy only for closure of patent ductus arteriosus — no. (%)¶**</td>
<td>293 (29.3)</td>
<td>381 (38.1)</td>
<td>0.67</td>
<td>0.67 (0.55–0.81)</td>
</tr>
<tr>
<td>Surgical closure of patent ductus arteriosus — no. (%)**</td>
<td>45 (4.5)</td>
<td>126 (12.6)</td>
<td>0.33</td>
<td>0.32 (0.22–0.45)</td>
</tr>
</tbody>
</table>

Differential Effects:

- Improved outcomes (death/cp) if ventilated either noninvasive or ETT.
  - ETT (0.73) > noninvasive (0.73) > no support (1.32; ns)
- Larger reduction in ventilated days when started earlier:

<table>
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<th>Early (&lt; 3 days)</th>
<th>Later (≥ 3 days)</th>
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<tr>
<td>PPV 1.35 weeks</td>
<td>PPV 0.55 weeks</td>
</tr>
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Davis PG, et al. J Peds 2010
Prevention of BPD

- NonInvasive Ventilation
- Vitamin A
- Methylxanthines

Nutrition
- Careful oxygen management
- Postnatal corticosteroids
- Inhaled Nitric Oxide
Early Nutrition may mediate

Critical illness in the first weeks of life → Later growth and other outcomes

(1)

Early nutritional practices

(2)

Later growth and other outcomes

(3)

Critical illness in the first weeks of life → Later growth and other outcomes

Ehrenkranz, etal. Ped Research 2010
Early Aggressive Nutrition Protects

- As energy and protein intake during the first 7 days increased in critically ill infants, the OR of such adverse outcomes as NEC, late-onset sepsis, BPD, and NDI decreased by about 2% for each increase of 1 kcal/kg/d of total energy intake.

- Early introduction of human milk further protection.

Ehrenkranz, et al. Ped Research 2010
24 Ohio NICUs
Proportion of Infants 22-29 Weeks Gestation Discharged with at least 1 Nosocomial Infection

OPQC Is A Voluntary Organization of Ohio Stakeholders Who Care About Fetal & Infant Health
Prevention of BPD

- NonInvasive Ventilation
- Vitamin A
- Methylxanthines
- Nutrition
- Careful oxygen management
- Postnatal corticosteroids
- Inhaled Nitric Oxide
Mechanisms of Oxygen Toxicity

- Superoxide
- Hydrogen Peroxide
- Hydroxyl free radical
- Singlet Oxygen

Antioxidant Defenses

- Protein: inactivate enzymes
- Lipid: alter cell membranes
- DNA: breakage, cross linkage
- Apoptosis: trigger cell death
Avoidance of Hyperoxia:

- Reduces markers of oxidative stress.

- Metanalysis 5 oxygen trials:
  - No difference in BPD (RR 0.95, 0.86-1.04)
  - Increased mortality low sat (RR 1.41, 1.4-1.74)
  - Increased NEC low sat (RR 1.25, 1.05, 1.49)

- European consensus guidelines:
  - Delivery Room 21-30%
  - Post-natal 90-95%

Saugstad OD, Aune D. Neonatology 2013
Prevention of BPD

- NonInvasive Ventilation
- Vitamin A
- Methylxanthines
- Nutrition
- Careful oxygen management
- Postnatal corticosteroids
- Inhaled Nitric Oxide
Dexamethasone - first week

- To be avoided
- Increased risks of bowel perforation
- Increased risks of later cerebral palsy and neurodevelopmental impairment.
- 5 MDI points lost for every 1 mg/kg.
Dexamethasone > first week

- Trade Offs-
  - Effective in facilitating extubation
  - Modest impact on BPD at 36 wks (19%)
  - No difference in combined outcome of death or CP.
  - Trend to increased CP/NDI.
  - Harm mitigated by lower doses and shorter courses (eg DART protocol)
Hydrocortisone:

- Biologically distinct
- Identical to endogenous cortisol
- Both glucocorticoid and mineralocorticoid
- Metabolized by 11 Beta hydroxylase to an inactive form
- Shorter half life.
- Dex- synthetic; only glucocorticoid. Long half life and lack of metabolic degradation leads to high serum levels.
- Trials in process. Pilot data no adverse neuro effects.
Prevention of BPD

- NonInvasive Ventilation
- Vitamin A
- Methylxanthines
- Nutrition
- Careful oxygen management
- Postnatal corticosteroids
- Inhaled Nitric Oxide
“Taken as a whole the available evidence does not support the routine use of iNO in early rescue, early prevention or later prevention strategies in infants < 34 weeks gestation who require respiratory support.”

“The positive results of one large study which used higher dose and long term exposure should be confirmed.”

# Predicting BPD Risk

<table>
<thead>
<tr>
<th>Day of Life</th>
<th>Support</th>
<th>Death</th>
<th>Severe BPD</th>
<th>Mod BPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HFV 50%</td>
<td>0.31</td>
<td>0.17</td>
<td>0.31</td>
</tr>
<tr>
<td>7</td>
<td>HFV; 100%</td>
<td>0.42</td>
<td>0.20</td>
<td>0.28</td>
</tr>
<tr>
<td>14</td>
<td>CMV; 50%</td>
<td>0.07</td>
<td>0.28</td>
<td>0.36</td>
</tr>
</tbody>
</table>

25 week, 700 gm, white non-hispanic male

Laughon, M. NRN; Am J Respir Crit Care Med Vol 183; 2011
Treatment of BPD

- Bronchodilators
- Diuretics - loop; Furosemide
- Diuretics - distal limb; Chlorothiazides
Bronchodilators:

- No clinical trials in the treatment of BPD.
- Insufficient evidence to recommend use.
Furosemide

- 7 studies, most pre-surfactant
- Short term benefits in pulmonary function test.
- Furosemide administration had no long-term benefits.
- Increased risk for patent ductus arteriosus and for hemodynamic instability.

**AUTHORS' CONCLUSIONS:**

- There are no data to support routine administration of furosemide in preterm infants with RDS.

Thiazide Diuretics

- 6 studies focused on physiologic parameters, not outcomes.
- Single study, thiazide plus spironolactone for 4 weeks, n=43, pre-surfactant.
- Improved PFT, and lower FiO2 at 1 and 4 weeks.
- No difference in days on oxygen.
- BPD not assessed.

Experimental Agents

- Not ready for prime time.
Can Agents that restore Blood Vessels reverse BPD?
Sildenafil Promotes Capillary and Alveolar Growth in Hyperoxia in Rats
Mesenchymal Stem Cells

- Work in several animal species suggest that lung milieu can be restored by transplanting bone marrow derived stem cells.
- Many hurdles to be evaluated and overcome before ready in humans.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>BPD Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>37% reduction; NNT 10</td>
</tr>
<tr>
<td></td>
<td>NNT for CP- 34</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>13% reduction; NNT 12</td>
</tr>
<tr>
<td>NonInvasive Vent</td>
<td>9% reduction; NNT 15</td>
</tr>
<tr>
<td>Postnatal steroids day 7-14</td>
<td>10% reduction; NNT 15</td>
</tr>
<tr>
<td></td>
<td>But NNH for CP- ?14?</td>
</tr>
</tbody>
</table>
Best Practices:

☐ Antenatal Steroids > 95% eligible pts
☐ CPAP in DR, *not interrupted*
☐ CPAP in NICU- ? Until off oxygen?
☐ ?INSURE? If surfactant needed
☐ Avoid hyperoxia
☐ Excellent nutrition with human milk.
☐ Avoid Infection
☐ Stay tuned for rescue treatments