Adjunct Therapies for Prevention of BPD

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The speaker has signed a disclosure form and indicated he has no significant financial interest or relationship with the companies or the manufacturer(s) of any commercial product and/or service that will be discussed as part of this presentation.

Session Summary

Usual strategies for the prevention of bronchopulmonary dysplasia (BPD) concentrate on the use of “gentle” mechanical ventilation. In this talk the speaker will summarize additional pharmacologic approaches for the prevention and treatment of BPD.

Session Objectives

Upon completion of this presentation, the participant will be able to:

- understand the definition of BPD;
- describe its epidemiology and pathogenesis;
- summarize the evidence basis for pharmacologic prevention strategies.

References


Session Outline

See presentation handout on the following pages.
Bronchopulmonary Dysplasia: Pathogenesis and Strategies for Prevention

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Bronchopulmonary Dysplasia (BPD)
- Definition
- Epidemiology
- Pathogenesis
- Evidence basis for non-ventilatory prevention strategies

Pulmonary Disease Following Respirator Therapy of Hyaline Membrane Disease
- Retrospective Study
- N=32 (34 wks, 2.3 kg)
- Described:
  - History
  - Radiographic Findings
  - Histology - Bronchopulmonary Dysplasia

Neonatology in Evolution
- Antenatal glucocorticoids
  - Less severe RDS
- Exogenous surfactant therapy for respiratory distress syndrome
  - Decreased mortality from RDS
- Survival of smaller and less mature infants
  - Intensive care of infants at earlier stage of lung development

BPD in 21st Century
- Most commonly affects extremely preterm infants
- Usually defined as oxygen requirement or positive pressure support at 36 weeks postmenstrual age
- Physiologic definition (oxygen reduction test)

Public Health Significance of BPD
- ~ 61,000 Annual births in US < 1500g BW
- ~ 23% overall rate of BPD at 36 wks GA (VT-Oxford Network)
- 14,150 new BPD cases annually in US

In infants with BPD:
- Increased mortality, abnormal neurodevelopment, more rehospitalizations, pulmonary hypertension, wheezing and life-long abnormality in pulmonary function
NICHD Neonatal Network
Trends in Neonatal Mortality & BPD


Old BPD
- Focal fibrosis & scarring
- Emphysema
- Mucosal Inflammation
- Fibrosis
- Airway collapse

New BPD
- Fewer & larger alveoli
- ↓ gas exchange surface
- ↓ microvasculature
- Mucosal inflammation
- “arrested” development

Airway and Parenchymal Damage in “Old” and “New” BPD

Arrest in Alveolarization in “New” BPD

Normal Lung
5 months

BPD: Large, simplified alveoli
Biopsy @ 8 months (28 week)

Contributors to Development of “New” BPD

1. Chorioamnionitis and inflammation

Histologic Chorioamnionitis More Frequent at Earlier Gestational Ages

Kallapur S and Jobe A. Arch Dis Child FN 2006
Advanced Chorioamnionitis Associated with More Severe BPD

Contributors to Development of “New” BPD

2. Oxygen Toxicity

Hyperoxia Decreases Lung Microvascularity and Endothelial Progenitor Cells in Mouse Model of BPD

Contributors to Development of “New” BPD

3. Injury due to mechanical ventilation
Summary of Animal Studies

- Volume change causes more lung injury than pressure change in the immature lung
- Even brief overdistention of the surfactant-deficient lung can cause lung injury
- Ventilation at low end-expiratory volume augments lung injury

Effect of Lung Overdistention on Surfactant Response in Preterm Lambs

Preterm lambs: “Bagged” – 6 manual breaths near TLC; Control – routine mechanical ventilation

Ventilation without PEEP Increases Pulmonary Inflammatory Markers in Preterm Lamb Model

Effect of Lung Overdistention on Surfactant Response in Preterm Lambs

Disrupted Alveolarization in Preterm Lamb and Baboon After Mechanical Ventilation

Antenatal & Perinatal Events: Primers of Neonatal Lung Injury

Modified from: Jobe A. J Perinat 2005

<table>
<thead>
<tr>
<th>Hits to Fetal Lung</th>
<th>Hits During Transition</th>
<th>Postnatal Hits</th>
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</thead>
<tbody>
<tr>
<td>Chronic Chorioamnionitis</td>
<td>Initiation of Ventilation</td>
<td>Ventilation</td>
</tr>
<tr>
<td>Fetal Lung</td>
<td>Surfactant</td>
<td>Oxygen</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Inflammation</td>
<td>Sepsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BPD: Inhibition of alveolar and vascular development</td>
</tr>
</tbody>
</table>

Bjorkland, Pediatr Res 1997


Jobe, NeoReviews 2006

Reproduction is not permitted from www.culverstock.com
Weston: 26 weeks

BPD Risks
- Extreme prematurity
- Chorioamnionitis
- Infection/Inflammation
- Mechanical ventilation
- Prolonged oxygen exposure

Estimated 80% risk of developing BPD

Center Variability in Survivors with BPD

<table>
<thead>
<tr>
<th>BW (g)</th>
<th>Affected</th>
<th>Center Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>501 - 1500</td>
<td>17</td>
<td>4 - 26</td>
</tr>
<tr>
<td>501 - 750</td>
<td>42</td>
<td>15 - 61</td>
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<tr>
<td>751 - 1000</td>
<td>25</td>
<td>5 - 42</td>
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<tr>
<td>1001 - 1250</td>
<td>11</td>
<td>1 - 21</td>
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<tr>
<td>1251 - 1500</td>
<td>4</td>
<td>0 - 9</td>
</tr>
</tbody>
</table>


Prevention Strategy:
Limit oxygen exposure

Standard versus High Oxygen Saturation Targets in Preterm Infants
Infants < 30 weeks still in O2 at 32 weeks PMA
(mean BW 920 g, GA 26.5 weeks, N=358)

* P < 0.005


Lower Oxygen Sat Targets Associated with Shorter Duration of Ventilation and O2 Therapy


Oxygen Saturation Targets and Outcomes in Infants < 1250 g

Retrospective comparison 2000 - 2002 v. 2003 - 2004 after change in sat targets

* P < 0.05

Deulofeut, J Perinatol 2006
Oxygen Saturation Targets: Effect on Death and BPD

**Effects on BPD not observed in either COT of BOOST**

* P < 0.05

SUPPORT Study Group, NEJM 2010

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Pilot Trial of Initial Resuscitation with 30% or 90% Oxygen in Infants < 28 weeks

<table>
<thead>
<tr>
<th>Duration O₂ (days)</th>
<th>Duration vent (days)</th>
<th>BPD (%)</th>
<th>Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Oxygen (30%, n=37)</td>
<td>6</td>
<td>13</td>
<td>15.4</td>
</tr>
<tr>
<td>High Oxygen (90%, n=41)</td>
<td>22*</td>
<td>27*</td>
<td>31.7*</td>
</tr>
</tbody>
</table>

* P < 0.01

Babies resuscitated with 30% oxygen had lower serum and urinary markers of oxidative stress and inflammation over first week

Vento, Pediatrics 2009

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Positive Pressure Ventilation in the Delivery Room: Hypocarbia and Hyperoxia

**Prospective Cohort Study**

N=26 preterm infants

23-34 wks (mean: 28wks)

480-4200g (mean: 1180g)

26% hypocarbic (PCO₂ <30 mmHg)

... 20% PCO₂ <25 mmHg

38% hyperoxic (PO₂ >100 mmHg)

20% both hypocarbic & hyperoxic

Clinically determined ventilator settings (i.e. chest wall excursion) in transport from delivery room to NICU frequently results in over-ventilation and hyperoxygenation

Tracy M, Arch Dis Child FN 2004

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Prevention Strategy:
Pharmacologic therapies

- Glucocorticoids
- Vitamin A
- Caffeine

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Use of Steroids to Treat or Prevent BPD

**Reduce inflammation**

- Improve lung mechanics
- Shorten time to extubation

**Treat relative adrenal insufficiency**

- Possible association with BPD

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Effects of Postnatal Steroid (PNS) Therapy

<table>
<thead>
<tr>
<th>36 week outcomes</th>
<th>&lt; 8 days (28 trials)</th>
<th>&gt; 7 days (19 trials)</th>
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<tbody>
<tr>
<td>Mortality/BPD</td>
<td>0.89</td>
<td>0.72</td>
</tr>
<tr>
<td>BPD</td>
<td>0.79</td>
<td>0.72</td>
</tr>
<tr>
<td>Mortality</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Failure to extubate</td>
<td>0.75</td>
<td>0.58</td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>1.75</td>
<td>1.22*</td>
</tr>
<tr>
<td>NDI</td>
<td>1.28</td>
<td>1.13*</td>
</tr>
</tbody>
</table>

* NS

Halliday, Cochrane Reviews, 2009
Reduction in PNS Use in Two Neonatal Networks

Walsh, Pediatrics, 2006

Does Steroid Choice Matter?
Randomized Trial of Early Hydrocortisone

Infants < 1,000 g enrolled @ 12 – 48 hrs; f/u @ 2 yrs

<table>
<thead>
<tr>
<th></th>
<th>HCTZ N=180</th>
<th>Placebo N=180</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Survival w/o BPD</td>
<td>43%</td>
<td>42%</td>
<td>NS</td>
</tr>
<tr>
<td>Death</td>
<td>16</td>
<td>17</td>
<td>NS</td>
</tr>
<tr>
<td>No BPD (chorio)</td>
<td>46</td>
<td>35</td>
<td>0.04</td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>13</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>NDI</td>
<td>39</td>
<td>44</td>
<td>NS</td>
</tr>
</tbody>
</table>


Differential Benefit/Harm of PNS

- Adverse outcomes with PNS may be less with higher risk of BPD
- Early treatment exposes infants at low risk
- Benefit in select infants more than one wk old at highest risk for BPD?
- May be dose related effect
- Dexamethasone may be more toxic to CNS

Doyle, Pediatrics, 2005

Vitamin A Supplementation Reduces BPD in Infants < 1,000 g

- Vitamin A important in lung tissue injury repair and alveolar development
- Preterm infants are deficient in vitamin A
- Randomized trial (N=807) of supplemental vitamin A (5000 IU IM 3x/week x 4): small reduction in BPD
- No short or long term toxicity

Tyson, N Engl J Med 1999

Caffeine for Apnea of Prematurity (CAP) Trial

- Caffeine commonly used for treatment of apnea of prematurity
- Randomized, controlled trial of caffeine in infants < 1250 g BW, started within first 10 days
- Mean BW 960 g, GA 27 weeks; N=2006
- Primary outcome: neurodevelopment at 18 to 22 months


Caffeine Therapy Improves Short and Long Term Outcomes

- *P < 0.008

Conclusions

- BPD is multifactorial
- Early insults may prime the immature lung for accelerated injury from later insults/events
- No silver bullet for prevention – strategies need to address antenatal, perinatal and neonatal contributors