Waiting to Inhale: RDS, BPD, and Assisted Ventilation of the Neonate

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A condition that occurs in premature infants with underdeveloped lungs that are surfactant deficient and abnormally permeable.

**Clinical Course**

- Initial improvement with positive-pressure ventilation
- Subsequent decline in lung function over first 24-72 hrs without surfactant
- Diuresis at 24-96 hrs with subsequent improvements in lung function
- Delayed resolution or death in severely affected babies that developed air leaks

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**“Waiting to Inhale” Jeopardy**

<table>
<thead>
<tr>
<th>RDS</th>
<th>Surfactant</th>
<th>BPD</th>
<th>Lung Injury</th>
<th>Interventions</th>
</tr>
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<tbody>
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<td>50</td>
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</tbody>
</table>

What is Neonatal Respiratory Distress Syndrome (RDS)?
What is a hyaline membrane?
Overdistension + collapse of airways
Shear forces in the airway mucosa
Sloughing of the bronchoepithelium
Coalescence with procoagulants
Hyaline membranes

Bronchoepithelial Lesions

What is the typical radiographic appearance of RDS?

“Ground Glass”

Differential Diagnosis for RDS

What are:
- Neonatal pneumonia
- Retained fetal lung fluid (TTN)
- Congenital heart disease with failure
- Meconium aspiration
- Pneumothorax
- Underaerated lungs in weak or anesthetized premature infants
- Choanal atresia
- Pulmonary hemorrhage
Patrick Bouvier Kennedy

A combination of lipids and proteins that lowers surface tension on alveolar surfaces during respiration and stabilizes the alveoli against collapse at end expiration.

What is pulmonary surfactant?

Surfactant Spreading
Impact of Surfactant on Morbidity, Mortality, and Resource Use

Post-Surfactant Introduction in USA
- 20% decrease in odds of RDS
- 30% reduction in odds of death for VLBW infants
- 5% projected nationwide decline in mortality
- 10% decrease in total charges per survivor

Schwartz et al., 1994

Responses to Exogenous Surfactant Therapy
- Improved oxygenation
- Improved lung compliance
- Decreased incidence of air leaks
- Decreased incidence of pulmonary interstitial emphysema
- Decreased death or BPD due to RDS

What are:
- Exosurf, synthetic
- Survanta, modified bovine extract
- Infasurf, calf lung lavage
- Curosurf, pig lung extract

Laplace's Law

Composition of Pulmonary Surfactant

Impact of Surfactant on Morbidity, Mortality, and Resource Use

Responses to Exogenous Surfactant Therapy

What are:

FDA-approved surfactants
- Improved distribution
- Reduced bronchoepithelial lesions
- Decreased leak of serum proteins into the airspaces
- Decreased surfactant inhibition
- Some unnecessary treatments

**What are the advantages of prophylactic treatment at birth?**

**Advantages of Rescue Treatment**

- Allows treatment of only those infants that have RDS
- May allow full stabilization prior to dosing
- Allows for radiographic confirmation of endotracheal tube placement prior to dosing

**Major Precautions during Surfactant Instillation**

- Administer as bolus *not* as infusion
- Ventilate the neonate for at least 30 secs until stable prior to next aliquot
- Never mix air with surfactant in syringe
- Expect to adjust the ventilator during the dosing procedure to maintain adequate oxygenation and ventilation

**Surfactant Distribution**

**Major Precautions following Surfactant Instillation**

- Expect to rapidly wean the FiO₂ after instillation of a modified natural surfactant
- Reduce peak pressures in a timely manner if lung compliance improves in order to avoid pneumothorax
- Observe for evidence of pulmonary hemorrhage
- Watch for mucous/surfactant plugging
Deviations from standard protocol for exogenous surfactant instillation.

What are:
- Lung hypoplasia
- Lung wt not in normal proportion to body wt (e.g. hydrops)
- Retreatment after mainstem instillation or esophageal dosing
- Late retreatment doses
- Revised positioning in unstable infant
- Revised dosing with severe pulmonary edema

Major adverse event that occurs with increased frequency following exogenous surfactant.

What is pulmonary hemorrhage?

A premature infant with severe lung disease cannot have this disease if he dies at 27 days of life.

What is Bronchopulmonary Dysplasia?
- Classic definition of BPD: supplemental O₂ required beyond 28 days & radiographic abnormalities or
- “chronic lung disease”: O₂ dependency at 36 weeks CGA
New Definitions of BPD Severity following $O_2 > 21\%$ for $> 28$d

- **Mild BPD**: $21\% O_2$ at 36 wks CGA or discharge
- **Moderate BPD**: supplement $< 30\% O_2$
- **Severe BPD**: $\geq 30\% O_2$ and/or PPV or NCPAP

If $> 32$ wks GA at birth replace 36 wks CGA with 56d postnatal age

Pathogenesis

- Related to both underlying susceptibility of the lungs to injury and the iatrogenic contributors that result from subsequent treatment
- Intrauterine stresses that contribute to preterm delivery may also affect subsequent inflammatory and compensatory responses.

What is “Classical BPD”?  

- Hyperoxic baro- &/or volutrauma in surfactant-deficient lungs leading to lung injury with areas of collapse and fibrosis alternating with areas of emphysema.
- RDS, hypoplasia, &/or injury of lungs precede assisted ventilation
- Inflammation & infection
- Immaturity of non-pulmonary organs
- Abnormal repair & regeneration
- Oversimplified terminal airspaces despite exogenous surfactant in micropremies of borderline viability.
What is the “New BPD”? 
- Immaturity, hypoplasia, &/or injury of lungs precede assisted ventilation 
- Disrupted alveolarization 
- Baro- &/or volutrauma 
- Oxygen toxicity 
- Inflammation & infection 
- Immaturity of non-pulmonary organs 
- Abnormal repair & regeneration

Is It Really Injury?
Hussain et al. 
Hum Pathol 29:710, 1998

Preterm Baboon Model of BPD
125d GA fetal baboon 
+ 2 wks in utero 
+ 2 wks vent 
Change in NOS activity +73% -83%
Major obstacle to gas exchange in “New BPD”

What is Abnormal 2° Crest Formation?

Albertine et al. Am J Respir Care Crit Med 159:945, 1999

iNO Modifies Elastin Deposition and Increases the Length of Secondary Crests in Preterm Baboons

McCurnin et al. AJP Lung 288:L450, 2005

Decreased Angiogenesis

What leads to decreased alveolarization?

- Inhibition of pulmonary vascular growth leads to decreased alveolarization
- iNO enhanced pulmonary vascular growth, alveolarization, and lung growth

McCurnin et al. AJP Lung 288:L450, 2005

Decreased Angiogenesis and Abnormal PECAM –1 in Human BPD

Can even occur in preterm neonates receiving mechanical ventilation at “normal tidal volumes”

What is volutrauma?

- Control
- RDS

Volutrauma

- Stretching of capillary endothelium and distal lung epithelium
- ↑ permeability to albumin, procoagulants, and other serum proteins
- further inhibition of inadequate surfactant function

Primary Role of Volutrauma vs. Barotrauma

- Chest wall restriction in young rabbits and newborn lambs prevented microvascular damage at peak inspiratory pressures of 45-55 cm H₂O.
- Permissive hypercapnia in premature rabbits after lower tidal volume ventilation was associated with reduced leak of serum albumin into the lungs.

Chest Wall Restriction Lessens Barotrauma in Young Rabbits

- Leads to bronchoepithelial lesions and hyaline membranes

What is atelectrauma?
- Collapse of airways
- Shear forces in the airway mucosa
- Sloughing of the bronchoepithelium
- Coalescence with procoagulants
- Hyaline membranes

Cytokine cascades lead to inflammation and predispose to this.

What is biotrauma?
- Increased cytokines in amniotic fluid or fetal plasma are associated with imminent preterm delivery.
- Chorioamnionitis and ↑ IL-1β in tracheal lavages on day 1 are associated with ↑ BPD.
- Mechanical ventilation of lungs with volumes above TLC or below FRC causes lung injury and release of proinflammatory cytokines.

The Cytokine Network

Cytokines in Inflammation
- **Early Response Cytokines** (e.g. interleukin-1, tumor necrosis factor)
  - establish cytokine cascades
  - early induction of adhesion molecules
- **Chemokines**
  - enable neutrophil adhesion and migration

Cytokines in Inflammation
- **Cytokines Involved in Pathogen Clearance**
  - IFN-γ is a potent stimulus for clearance of intracellular pathogens and removal of infectious agents.
  - Many interleukins are involved in Ab formation and the removal phase of inflammation.
- **Cytokines Involved in Repair**
  - Growth and angiogenic factors induce proliferation/activation of fibroblasts & ECs
  - Control synthesis of matrix and angiogenesis
Abnormal VEGF in Human BPD

Leads to abnormal ion and lung water transport with decreasing gestational age.

What are:

- β-adrenergic receptors
- numbers of sodium channels
- Na-K ATPase activity
- surface area of absorptive epithelium

All become more deficient with decreasing gestational age and may be further complicated by decreased labor.

Morphometric estimates of surface areas of the airways

Key components of innate immunity present in endogenous surfactant but not in any exogenous surfactants.

What are SP-A and SP-D?
Academic Center that had markedly decreased incidence of BPD

What is Columbia?

Permissive Hypercapnia – Clinical Results

- Associated with ↓ BPD/CLD at Columbia
- Improved survival in adults with ARDS
- Shorter duration of MV and ↓ infections in adult patients with ARDS
- ↓ mean airway pressure and improved oxygenation in adult patients
- ↓ inflammatory mediators

Factors Predisposing to BPD at the Time of Rescue Surfactant

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthwt&lt;1000 gms</td>
<td>5.1 (2.4-10.7)</td>
</tr>
<tr>
<td>C-sxn for fetal distress</td>
<td>4.3 (1.7-11.4)</td>
</tr>
<tr>
<td>VEI&lt;0.15</td>
<td>3.0 (1.3-6.7)</td>
</tr>
<tr>
<td>Lowest pCO₂, mm Hg</td>
<td></td>
</tr>
<tr>
<td>≥40</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>30-39</td>
<td>3.3 (1.3-8.3)</td>
</tr>
<tr>
<td>≤29</td>
<td>5.6 (2.0-15.6)</td>
</tr>
<tr>
<td>≤29 (PIP&gt;30 cm H₂O)</td>
<td>12.5 (1.2-131)</td>
</tr>
</tbody>
</table>


Randomized Trial of Permissive Hypercapnia in Preterm Infants

Standardized clinical practice
- Extubation criteria: PIP<19 cm H₂O, vent rate<10, FiO₂<0.4, pH≥7.25
- Aminophylline loading dose prior to extubation
- Reintubation for pH<7.20, severe apneic spells, or clinical deterioration
- 7d course of dex for vent dependent infants at 10d of age

Mariani et al. Pediatrics 104:1082, 1999

Patient Population

Mariani et al. Pediatrics 104:1082, 1999
**Demographic Data**

<table>
<thead>
<tr>
<th></th>
<th>Hypercapnia</th>
<th>Normocapnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW (gm)</td>
<td>852±156</td>
<td>856±173</td>
</tr>
<tr>
<td>GA (weeks)</td>
<td>26±1</td>
<td>26±2</td>
</tr>
<tr>
<td>Entry age (hrs)</td>
<td>8.5 (5-14)</td>
<td>9 (5-12)</td>
</tr>
<tr>
<td>Antenatal CS</td>
<td>71%</td>
<td>52%</td>
</tr>
<tr>
<td>Black</td>
<td>62%</td>
<td>56%</td>
</tr>
<tr>
<td>Male</td>
<td>46%</td>
<td>44%</td>
</tr>
</tbody>
</table>

**Respiratory Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Hypercapnia</th>
<th>Normocapnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days on MV</td>
<td>2.5 (1.5-11)</td>
<td>9.2 (2-22)</td>
</tr>
<tr>
<td>Days on O₂</td>
<td>15 (4-53)</td>
<td>32 (17-50)</td>
</tr>
<tr>
<td>O₂ at 28d</td>
<td>43%</td>
<td>64%</td>
</tr>
<tr>
<td>O₂ at 36 wks</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Reintubation</td>
<td>67%</td>
<td>54%</td>
</tr>
<tr>
<td>Air leaks</td>
<td>8%</td>
<td>16%</td>
</tr>
<tr>
<td>Postnatal Dex</td>
<td>12%</td>
<td>20%</td>
</tr>
</tbody>
</table>

**Non Respiratory Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Hypercapnia</th>
<th>Normocapnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>IVH 3-4</td>
<td>29%</td>
<td>20%</td>
</tr>
<tr>
<td>PVL</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>ROP&gt;Stage II</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>LOS (days)</td>
<td>74±22</td>
<td>76±21</td>
</tr>
</tbody>
</table>
A slower rate usually increases ventilation.

What is High Frequency Oscillatory Ventilation (HFOV)?

Early HFOV vs CMV in VLBW Neonates

- Optimize lung volume
- Maintain FRC
- Most trials since exogenous surfactant have shown no change in BPD incidence.
- Lack of “gold standards” for mechanical ventilation and extubation criteria confuse results.
- Blinding is impossible.

HFOV vs CMV in Preterm Infants: No Effect on Neonatal Mortality

<table>
<thead>
<tr>
<th></th>
<th>HFOV</th>
<th>CMV</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>244</td>
<td>254</td>
</tr>
<tr>
<td>Birth Weight (g)</td>
<td>859 ± 161</td>
<td>848 ± 160</td>
</tr>
<tr>
<td>Age at Randomization (hrs)</td>
<td>2.7 ± 0.9</td>
<td>2.7 ± 0.9</td>
</tr>
<tr>
<td>Antenatal betamethasone</td>
<td>80%</td>
<td>81%</td>
</tr>
<tr>
<td>Median Age at Extubation (d)</td>
<td>13</td>
<td>21*</td>
</tr>
<tr>
<td>Alive/no CLD 36 wk</td>
<td>56%</td>
<td>47%**</td>
</tr>
</tbody>
</table>

*P < 0.001   **P = 0.046
Courtney et al. NEJM 347:643, 2001

Early HFOV vs SIMV in VLBW Infants

- No significant differences in:
  - Mortality
  - IVH
  - Pneumothorax
  - NEC
  - ROP
- More PIE with HFOV (20% vs 13%)
- Less pulm hemorrhage with HFOV (2% vs 7%)

Courtney et al. NEJM 347:643, 2001
HFOV vs CMV for pulmonary dysfunction in preterm infants

Cochrane Database of Systematic Reviews. 1, 2004

No change in:
- neonatal mortality at 1 month
- need for assisted ventilation at 1 month
- need for supp O₂ at 1 month

Borderline benefit of HFOV on:
- CLD at 36 wks CGA

Caveats of Early HFOV in VLBW Infants

- “high lung volume strategy” needed to optimize mean lung volume or no change in BPD and increased PVL
- Unlikely to affect disrupted alveolization
- Must avoid inadvertent overdistension leading to decreased cardiac output and increased CVP
- Overdistension during resuscitation may cause irreversible damage.

What are antenatal maternal corticosteroids (ACS)?

<table>
<thead>
<tr>
<th></th>
<th>+ ACS</th>
<th>- ACS</th>
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</thead>
<tbody>
<tr>
<td>RDS mortality</td>
<td>0%</td>
<td>6.5%</td>
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<tr>
<td>Total mortality</td>
<td>0</td>
<td>15.2</td>
</tr>
<tr>
<td>Air leak</td>
<td>1.7</td>
<td>13.0</td>
</tr>
<tr>
<td>IVH (3 and 4)</td>
<td>6.9</td>
<td>10.9</td>
</tr>
<tr>
<td>PDA</td>
<td>27.6</td>
<td>21.7</td>
</tr>
<tr>
<td>BPD</td>
<td>49.0</td>
<td>55.3</td>
</tr>
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What are Nasal CPAP and High Flow Humidified Nasal Cannula?

Non-invasive respiratory support for extubated neonates with residual lung disease
Benefits of Nasal CPAP

- Stabilizes compliant chest wall (aka pectus)
- Decreases upper airway resistance
- Improves spontaneous tidal volumes
- Increases FRC

CPAP as “Policy”

*de Klerk. J Paediatr Child Health 2001*

- Columbia respiratory approach
  - Early Nasal CPAP for any signs of RDS
  - Minimize leaks w/ snug prongs and chin straps
  - Intubation criteria
    - FiO2 > 60% w/ pO2 < 50 (a/A – 0.14)
    - PCO2 > 65
    - Marked retractions (distress)
    - Intractable metabolic acidosis (BE < -10)
  - Target pCO2 range = 50-60 mm Hg

Features of Successful nCPAP

- Proper prong size & fit
- Warm humidification
- Maintainance of clear nasal passage
- Proper positioning
- Adequate distending pressure
- Maximize nutrition

High Flow Humidified Nasal Cannula

- Delivers flows between 1-8Lpm via Nasal Cannula
- Temperature between 33-43°C
- 95-100% constant humidity delivered to patient
- Interfaces with Premie (<700 grams), Neonate (700-1100 grams), and Infant (>1100 grams) cannulas
- Prevents potential facial trauma or other contraindications associated with NCPAP
- Shortens weaning cycle for spontaneously breathing infants who are not tolerating NCPAP
**High Flow Humidified Nasal Cannula**

- **Flush Dead Space**
  - CO₂ Ventilation
  - Oxygen Efficiency
- **Support Inspiration**
  - Cannula Flow > Inspiratory
  - Work of Breathing
- **Humidity / Warm Airways**
  - Nasal comfort
  - Airway Reactivity

**Delivery Room Use of Nasal or “bubble” CPAP**

- ↓ RDS when efforts made to ↓ rates of intubation and MV
- High TV breaths with PPV may rapidly injure lung during delivery room resuscitation.
- Delayed intubation may delay use of surfactant to prevent lung injury

**Potential pharmacologic interventions to ameliorate BPD**

- Glucocorticoids
- Vitamin A
- Antioxidants
- PDE III and V inhibitors
- Prostacyclin
- ET receptor blockers

**RCT of Vitamin A in ELBW Infants – CLD or Death at 36 Weeks**

<table>
<thead>
<tr>
<th></th>
<th>Vitamin A</th>
<th>Control</th>
<th>p value</th>
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<tbody>
<tr>
<td>n</td>
<td>405</td>
<td>402</td>
<td></td>
</tr>
<tr>
<td>BW (gm)</td>
<td>770+35</td>
<td>769+138</td>
<td></td>
</tr>
<tr>
<td>CLD or Death</td>
<td>55%</td>
<td>62%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>CLD in survivors</td>
<td>47%</td>
<td>56%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Death by 36 wks</td>
<td>15%</td>
<td>14%</td>
<td>0.72</td>
</tr>
<tr>
<td>MV at 36 wks</td>
<td>7%</td>
<td>6%</td>
<td>0.76</td>
</tr>
<tr>
<td>LOS (survivors)</td>
<td>94 (58, 174)</td>
<td>92 (54, 173)</td>
<td>0.44</td>
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<tr>
<td>(median 5th, 95th percentile)</td>
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*Tyson et al. NEJM 340:1962, 1999*

**Normal Fetus**

- low O₂ environment
- liquid-filled lungs with low TV FBMs
- good nutrition
- free range of motion
- growth balanced with maturation
- synchronized lung development
- negligible protein permeability

**Ventilated Micropremie**

- higher O₂ environment
- air breathing with high TVs
- inadequate nutrition
- immobilization/sedation
- maturation at expense of growth
- heterogeneous stages of distal lung epithelium
- significant pulmonary-systemic translocation of proteins