The Premature Lung: Respiratory Distress Syndrome and Bronchopulmonary Dysplasia

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Disclosures

- I receive a consult’s fee from the American Academy of Pediatrics for my work with *Pediatrics in Review*.
- I will discuss a specific oxygen delivery device and its off-label use for non-invasive ventilation in preterm infants.
Sweet Little Angel

THE NORMAL LUNG
Normal Lung - 62 weeks PMA
Patrick Kennedy died in 1963.

2016 Limit of viability
Respiratory Distress Syndrome

The Thrill is Gone

Respiratory Distress Syndrome
**Respiratory Distress Syndrome**

RDS- Newborn hypoxemia or increased WOB due to surfactant deficiency or inactivation; generally in preterm infants.

**The Hess Bed**

Oxygen Unit for Premature and Very Young Infants.

Dr. Julius H. Hess, Chicago

American Journal of Disease of Children 47:916-917, 1934

- 147 infants treated with 38-95% O2
- Mortality 41%
Kennedy Baby Dies At Boston Hospital; President at Hand

By The Associated Press

BOSTON, Friday, Aug. 9—The new baby boy of President and Mrs. Kennedy died.

Patrick Kennedy
34 weeks, 2100g
Died of RDS

Treatment
Oxygen infused incubator
Hyperbaric chamber
Respiratory Distress Syndrome

Alveoli 1 and 2 have equal surface tension. 1 has higher pressure (due to smaller radius) and is more likely to collapse and be harder to inflate.

With Surfactant:
1 has less surface tension (more surfactant per area) and 1 and 2 have equal pressure (due to surfactant). 1 will inflate at a faster rate than 2 (until equal in size).
Respiratory Distress Syndrome


Hyaline Membrane Disease

Normal Lung

RDS / HMD Lung

http://www2.sunysuffolk.edu/pickenc/BIO%20132%20Histology.htm
http://library.med.utah.edu/WebPath/jpeg3/PERI129.jpg
Respiratory Distress Syndrome


If Trouble Was Money

BRONCHOPULMONARY DYSPLASIA
Bronchopulmonary Dysplasia

- 1964: Maria Delivoria-Papadopoulos & Paul Swyer described 1st successful mechanical ventilation for a late preterm neonate with RDS (HMD)
  - 17 others in series died

- 1967: Northway, Rosan & Porter described Bronchopulmonary Dysplasia
  - Attributed to mechanical ventilation & high O₂ delivery
Patrick Kennedy died 1963.

2016 Limit of viability.
New BPD

Normal Lung

New BPD Lung

Bronchopulmonary Dysplasia

Supplemental O\textsubscript{2} or mechanical ventilation x28 days

Severity assessment at 36 weeks

- Mild room air
- Moderate <30\% O\textsubscript{2}
- Severe $\geq$30\% and/or positive pressure

2000 NIH Bronchopulmonary Dysplasia (BPD) Workshop Definition of BPD for Infants at Gestational Ages of Less than 32 Weeks
BPD Risk Factors

**Hits to Fetal Lung**
- Chronic Chorioamnionitis

**Hits During Transition**
- Initiation of Ventilation
- Ventilatory Support
- Oxygen
- Sepsis

**Postnatal Hits**

**Proinflammation**
- Preterm Lung
- BPD

**Anti-Inflammation**
- Corticosteroids
- Surfactant
- Corticosteroids

Nutrition
Antenatal Steroids

Molecular effects
  – Upregulates Cholinephosphate cytidyltransferase
  – Increases surfactant production
  – Mesenchymal thinning of fetal lung

Clinical effects
  – Reduced RDS
  – Reduced NEC
  – Reduced Severe IVH & Death
Antenatal Steroids

NIH Consensus Statement, 2000
  – Recommended for anticipated delivery within 7 days for gestational age 24-34 weeks.

ACOG, 2016
  – Not recommended before limits of viability.
  – Considered for anticipated preterm birth for gestational age 34 0/7-36 6/7 weeks.

Carlo et al, JAMA, 2011
BPD Risk Factors

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- Preterm Lung
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- Nutrition

Anti-Inflammation
- Corticosteroids
- Surfactant
- Corticosteroids
Surfactant

Decreases surface tension
Anti-oxidant
Host defense
Anti-inflammatory

Adult 2-3mg/kg
Term neonate 100mg/kg

Surfactant Administration

• Reduces RDS, air leak, and mortality in preterm infants w/ RDS
• CPAP with early rescue (<2 hours) decreases BPD/death compared to prophylaxis
• Improves oxygenation & reduces need for ECMO in meconium aspiration syndrome
• Does not improve outcomes in CDH
Surfactant Administration

AAP Recommendation, 2014

– Preterm infants <30 weeks on mechanical ventilation
– Consider CPAP with selective administration
– Infants with hypoxic respiratory failure due to surfactant deficiency (meconium, pneumonia)

ROH Protocol

– Prophylaxis <26 weeks
– Rescue for any preterm on mechanical ventilation
INSURE

Intubate  
Surfactant  
Extubate

Verder, et al

– 1994: 68 infants on NCPAP, GA 25-35 weeks
  • Rescue INSURE reduced need for MV: 33% vs. 83% (p<0.001)
– 1999: 60 infants with RDS on NCPAP, GA <30 weeks
  • Earlier INSURE improved oxygenation and reduced MV/Death and MV

Insure

Intubate

Surfactant

Extubate

INSURE-treated infants, GA 27-34 weeks, had improved oxygenation from 30 min to 48 hours compared to Surf+MV-treated infants. Implementation of INSURE reduced MV by 50%.

ETT vs LMA Surfactant

• Rescue calfactant
  – 60 preterm infants
  – BW 2031g

<table>
<thead>
<tr>
<th>Intervention Failure</th>
<th>LMA group</th>
<th>ETT group</th>
<th>Comparison between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any failure</td>
<td>9 (30%)</td>
<td>23 (77%)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Early failure</td>
<td>1 (3%)</td>
<td>20 (67%)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Late failure</td>
<td>8 (27%)</td>
<td>3 (10%)</td>
<td>P=0.181</td>
</tr>
<tr>
<td>Other failure</td>
<td>2 (7%)</td>
<td>3 (10%)</td>
<td>P=1.0</td>
</tr>
</tbody>
</table>

Abbreviations: ETT, endotracheal tube; LMA, laryngeal mask airway.
BPD Risk Factors

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**Postnatal Hits**
- Oxygen
- Sepsis

**Proinflammation**
- Fetal Lung
  - Corticosteroids
  - Surfactant

**Anti-Inflammation**
- Preterm Lung
- BPD
- Nutrition
  - Corticosteroids

Jobe A. NeoReviews 2006.
Corticosteroids

Positive
– Decrease inflammation & pulmonary edema

Negative
– Decrease alveolarization & pulmonary vascularization
– Growth impairment
– Poor neurodevelopmental outcomes

Little evidence to balance risk/benefit in individual patients
NICHD Cochrane Reviews

First week dexamethasone not recommended

- Facilitates extubation
- Decreases BPD & PDA
- Adverse events
  - GI bleeding, SIP, Hyperglycemia, Hypertension, Hypertrophic cardiomyopathy, Growth failure
  - Abnormal neuro exam, Cerebral palsy

First week Hydrocortisone

- No respiratory benefit or harmful effects
NICHD Cochrane Reviews

Corticosteroids starting 7-14 days

– Decreases mortality
– Decreases BPD
– Adverse short-term effects
  • Hypertension, Hyperglycaemia, GI bleeding, Hypertrophic cardiomyopathy and infection

Late steroids >7 days

– Reduced mortality
– Limited long-term safety evidence
NICHD Cochrane Reviews

Inhaled steroids

– Treatment in first 2 weeks does not decrease BPD
– Treatment after 7 days does not decrease BPD
– Not routinely recommended for prevention or treatment of BPD in ventilated infants
Dexamethasone: A Randomized Trial
DART

70 infants, BW <1000g, >7 days

Low dose dexamethasone
Facilitates extubation
Shortens duration of mechanical ventilation
No increased morbidity at 2 years
BPD Risk Factors

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Hits During Transition
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- Ventilatory Support
- Oxygen
- Sepsis

Preterm Lung
- Corticosteroids
- Surfactant
- Corticosteroids

Postnatal Hits
- BPD
- Nutrition

Proinflammation

Anti-Inflammation

Jobe A. NeoReviews 2006.
Oxygen

Oxygen

Oxygen

Ventilation + Normal $O_2$  
Ventilation + 80-100% $O_2$

Preterm baboons ventilated x21 days, lung biopsy at 33 weeks
BPD Risk Factors

- **Hits to Fetal Lung**
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  - Oxygen
  - Sepsis

**Proinflammation**

**Anti-Inflammation**

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- Corticosteroids

**Preterm Lung**

**BPD**

**Nutrition**

Jobe A. NeoReviews 2006.
Mechanical Ventilation

Fold Increase from Fetal Lung

<table>
<thead>
<tr>
<th></th>
<th>IL-1b</th>
<th>IL-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal Lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEEP 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEEP 4</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

* indicates significant difference.
Mechanical Ventilation

Graph showing the relationship between alveolar number and radial alveolar count across different groups:
- Preterm Lambs ventilated for 3 wks
- 126d Fetus
- 1d Term
- 3wks Post Term

Comparative analysis between R20 and R60.
Mechanical Ventilation
There Must Be a Better World Somewhere

NON-INVASIVE SUPPORT
ETT Ventilation in 1\textsuperscript{st} Week

Infants ≤30 weeks receiving primarily ETT ventilation were at increased risk for BPD or death compared to those receiving non-invasive respiratory support

OR 3.1 (95% CI 1.3-7.8)

Adjusted for gender, BW, Sepsis, PDA, Race, Surfactant, & Time to regain BW.

Effect of avoiding eMV on death or BPD
Preterm infants, GA <30 weeks

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Avoid ventilation</th>
<th>Control group</th>
<th>Weight, %</th>
<th>Odds Ratio</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BPD/death</td>
<td>Total</td>
<td>BPD/death</td>
<td>Total</td>
<td>Random effects model (95% CI)</td>
</tr>
<tr>
<td>COIN (2008)</td>
<td>108</td>
<td>307</td>
<td>122</td>
<td>303</td>
<td>0.81 (0.58–1.12)</td>
</tr>
<tr>
<td>CNRN (2009)</td>
<td>53</td>
<td>74</td>
<td>54</td>
<td>72</td>
<td>0.84 (0.40–1.75)</td>
</tr>
<tr>
<td>SUPPORT (2010)</td>
<td>323</td>
<td>663</td>
<td>353</td>
<td>653</td>
<td>0.81 (0.65–1.00)</td>
</tr>
<tr>
<td>CURPAP (2010)</td>
<td>22</td>
<td>103</td>
<td>23</td>
<td>105</td>
<td>0.97 (0.50–1.87)</td>
</tr>
<tr>
<td>DRM (2011)</td>
<td>68</td>
<td>223</td>
<td>138</td>
<td>425</td>
<td>0.91 (0.64–1.29)</td>
</tr>
<tr>
<td>AMV (2011)</td>
<td>15</td>
<td>108</td>
<td>17</td>
<td>112</td>
<td>0.90 (0.43–1.91)</td>
</tr>
<tr>
<td>Take Care (2013)</td>
<td>25</td>
<td>74</td>
<td>30</td>
<td>67</td>
<td>0.63 (0.32–1.24)</td>
</tr>
<tr>
<td>Total</td>
<td>614</td>
<td>1552</td>
<td>737</td>
<td>1737</td>
<td>0.83 (0.71–0.96)</td>
</tr>
</tbody>
</table>

Test for overall effect: \( z = 2.55 \) (\( P = .01 \))

Heterogeneity: \( \tau^2 = 0.00; \chi^2 = 1.27; \text{df} = 6 \) (\( P = .97 \)); \( I^2 = 0\%

Favors avoiding ventilation Favors control group

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Non-Invasive Modes

High Flow Nasal Cannula
  HFNC (HHNC)
Nasal Continuous Positive Airway Pressure
  NCPAP
Non-Invasive Positive Pressure Ventilation
  NIPPV (NIV, NC-IMV)
Non-Invasive NAVA
  NIV-NAVA
Gambler’s Blues

HIGH-FLOW NASAL CANNULA
High-Flow Nasal Cannula

Gas source

Pressure relief valve 45cm H2O

Nasal interface

Humidifier

HFNC

12 physiologic studies 1993-2013
  – Pressure delivered is variable and unpredictable
  – Affected by mouth-opening, flow rate, and infant size
12 clinical studies 2005-2013
  – Flow-rates up to 8 lpm without significant morbidity
  – HFNC more effective than low flow NC for preventing intubation
  – Minimal differences verses NCPAP

HFNC vs. NCPAP

303 Preterm infants
GA <32 weeks

Extubated to HFNC 5-6 lpm or NCPAP 7cm

Extubation failure rate was equal
– Most likely due to apnea

HFNC Group
– Decreased nasal trauma compared to nasal prong CPAP
– Increased extubation failure <26 weeks
– Half HFNC failures rescued with NCPAP

HFNC Conclusions

Easy to use
Works fairly well
Pressure delivered is variable but may be excessive
Not as effective as NCPAP for more premature infants
Call It Stormy Monday

NASAL CPAP
Nasal CPAP

- Gas source
- Pressure control system
- Humidifier
- Nasal interface
Nasal CPAP Devices

Nasal Interface
- Long nasopharyngeal tube
- Single nasal prong
- Nose mask
- Short bi-nasal prongs
- Nasal cannula

Pressure Control
- Bubble CPAP
- Variable flow device
- Ventilator
Nasal CPAP Effects

Splints open upper airway
  – Reduces obstruction & apnea
Prevents alveolar collapse
  – Reduces atelectasis
  – Reduces QV mismatch
  – Conserves surfactant
Nasal CPAP Complications

- Leak
- Trauma
CPAP vs. Headbox O2

Cochrane Review, 2003
  – Preterm infants extubated after IPPV

Nasal CPAP reduces
  – Apnea
  – Respiratory acidosis
  – Oxygen requirement

Nasal CPAP is effective in preventing failure of extubation in preterm infants following a period of endotracheal intubation and IPPV

COIN Trial

610 Preterm infants
GA 25-28 6/7 weeks

CPAP vs. Intubation in DR

CPAP Group:
– Decreased use of O₂ at 28 days
– Increased pneumothorax

But...
– ½ CPAP group was intubated
– Initial CPAP was 8cm H₂O

SUPPORT Trial

1316 Preterm infants  
GA 24-27 6/7 weeks

CPAP vs. Intubation in DR

CPAP Group:
- Fewer intubated days
- Decreased need for post-natal steroids for BPD

But...
- ¾ CPAP group was intubated

NCPAP Conclusions

- Easy to use
- Helps prevent extubation failure
- Reduces BPD compared to ETT ventilation
- Commonly used devices can cause pressure injury
(I Got Everything I Need) Almost

NON-INVASIVE PPV
Nasal PPV

Gas source

Pressure control system

Nasal interface

Humidifier
Nasal PPV Devices

Nasal Interface

- Long nasopharyngeal tube
- Single nasal prong
- Nose mask
- Short bi-nasal prongs
- Nasal cannula

Pressure Control

- Ventilator
- Variable flow device
Nasal PPV Effects

Splints open upper airway
  – Reduces obstruction & apnea
Prevents alveolar collapse
  – Reduces atelectasis
  – Reduces QV mismatch
  – Conserves surfactant
Causes lung expansion during apnea
  – Assists alveolar recruitment
  – Increases respiratory drive
Nasal PPV Complications

Trauma

Leak
NIPPV vs. NCPAP

Cochrane Review, 2014

– Preterm infants after extubation

NIPPV reduces extubation failure

Device and synchronization may be important variables

NIPPV vs. NCPAP

1009 Preterm infants
GA <30 weeks, BW <1000g, Age <28 days

No difference in death or BPD

But...

– No standardization of NIPPV practice
– ½ had prolonged intubation in 1st week
  Median ~3.5 days (IQR ~2-7 days)
NIPPV vs. NCPAP

200 Preterm infants
GA 26-33 6/7 weeks

No difference in BPD

NIPPV Group:
  – Fewer failures 24-72hrs
  – Fewer failures >1000g

But...
  – Initial NIPPV rate was 20-30
  – NIPPV weaned to NCPAP after 72hrs

sNIPPV vs. NCPAP

41 Preterm infants
GA <32 weeks, BW 600-1250g

sNIPPV Group
– Decreased BPD
– Decreased BPD/Death

Extubated <90min after surfactant

sNIPPV vs. NCPAP

469 Preterm infants
Retrospective - BW <1250g

sNIPPV Group

– Decreased BPD
– Decreased BPD/Death
– Due to effect of 500-750g sub-group

Blood-gas values of Pco2 in infants in the SNIPPV versus no-SNIPPV groups on postnatal days 1, 3, 7, 14, 21, and 28.

NIPPV vs. NCPAP

110 Preterm infants
GA 26-29 6/7 weeks

NIPPV Group:
- Fewer extubation failures
- Fewer days with supplemental O₂

Primary and secondary outcomes. †Logistic regression to control for potentially confounding effects of GA, gender, center, antenatal steroid use and multiple births was done; *P=0.005, **P=0.001, ***P=0.04, MVET, mechanical ventilation via endotracheal tube; BPD, bronchopulmonary dysplasia; PMA, postmenstrual age.

Neotech RAM Cannula

Developed by a Neonatologist for Babies and Clinicians

http://www.ramcannula.com/
RAM Pressure Delivery

Post-operative Safety

“Does continuous positive airway pressure for extubation in congenital tracheoesophageal fistula increase the risk of anastomotic leak? A retrospective cohort study.”

- 51 neonates extubated after TEF repair
  - CPAP: 0/10 with anastomotic leak
  - No CPAP: 4/41 with leak
JUST EXTUBATE.
Rate = 40  iTime = 0.5

Rate = 20  iT ime = 0.35

Contraindications

Absolute

– Choanal atresia
– Cleft lip/palate
– Paralysis or persistent apnea

Relative

– NIPPV FiO2 >60% or ETT FiO2 >40%
– Frequent apnea
  • >4/hour with stimulation
  • >2/hour with bag/mask ventilation
Nutrition

- Other factors that can interfere with lung development are corticosteroids and starvation. Newborn rabbits that are fed less calories have increased sensitivity to oxidant damage, and adult rodents that are starved develop an emphysematous lung, which returns to normal with refeeding. (18) There is no information in newborn humans about the effects of low calorie intake on lung development. However, nutritional status may be an important and underappreciated variable on the pathway to BPD.
Surfactant

\[ P = \frac{2 \text{ ST}}{r} \]

A. With Surfactant
B. Without Surfactant

Wall or Surface Tension (ST)

"Pneumatic Splint"

Large Radius

Small Radius