Bronchopulmonary Dysplasia:
Where did we start?
Where are we now?
Where do we need to go?

Bradley A. Yoder, MD
Professor of Pediatrics
University of Utah
Dr. Yoder has the following conflicts of interest to disclose

Consultant:
Ikaria
Drager
Vapotherm
Fisher & Paykel

“What conflict of interest?! I work here in my spare time.”
Objectives

• Review history & definitions of BPD
• Describe changing epidemiology
  • Review pathophysiology
• Identify successful interventions
• Suggest potential future approaches
Bronchopulmonary Dysplasia

Most common ELGAN morbidity
> 5300 Pub Med citations since 1967
A lot has changed in past ~ 50 years!
## “History” of Neonatal Respiratory Care

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Time Era</th>
<th>Effect on morbidity/mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>1940’s - 1960’s</td>
<td>Too much $\rightarrow$ ROP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Too little $\rightarrow$ increased mortality</td>
</tr>
<tr>
<td>CPAP</td>
<td>1970’s</td>
<td>Improved survival</td>
</tr>
<tr>
<td>Ventilator: IMV</td>
<td>1960’s - 1980’s</td>
<td>Improved survival, but $\rightarrow$ BPD</td>
</tr>
<tr>
<td></td>
<td>1980’s - 2000’s</td>
<td>Extensive RCT’s $\rightarrow$ no clear effect</td>
</tr>
<tr>
<td>Surfactant</td>
<td>1980’s - 1990’s</td>
<td>Extensive RCT’s $\rightarrow$ improved survival &amp; changed BPD</td>
</tr>
<tr>
<td>iNO</td>
<td>1990’s - 2000’s</td>
<td>Extensive RCT’s $\rightarrow$ reduced ECMO, but not BPD in preemies</td>
</tr>
<tr>
<td>Non-Invasive</td>
<td>2000’s - present</td>
<td>Extensive RCT’s $\rightarrow$ ? reduced BPD</td>
</tr>
</tbody>
</table>

Modified from Kamath B et al, Pediatrics 2011
## “History” of Neonatal Respiratory Care

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Time Era</th>
<th>Effect on morbidity/mortality</th>
</tr>
</thead>
</table>
| Oxygen      | 1940’s - 1960’s | Too much $\rightarrow$ ROP  
Too little $\rightarrow$ increased mortality |
| CPAP        | 1970’s       | Improved survival                                                 |
| Ventilator: IMV | 1960’s - 1980’s | Improved survival, but $\rightarrow$ BPD |
| HFV         | 1980’s - 2000’s | Extensive RCT’s $\rightarrow$ no clear effect                   |
| Surfactant  | 1980’s - 1990’s | Extensive RCT’s $\rightarrow$ improved survival & changed BPD  |
| iNO         | 1990’s - 2000’s | Extensive RCT’s $\rightarrow$ reduced ECMO, but not BPD in preemies |
| Non-Invasive | 2000’s - present | Extensive RCT’s $\rightarrow$ ? reduced BPD                    |

Modified from Kamath B et al, Pediatrics 2011
## “History” of Neonatal Respiratory Care

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Time Era</th>
<th>Effect on morbidity/mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>1940’s - 1960’s</td>
<td>Too much → ROP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Too little → increased mortality</td>
</tr>
<tr>
<td>Oxygen</td>
<td>1970’s</td>
<td>Improved survival</td>
</tr>
<tr>
<td>CPAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilator: IMV</td>
<td>1960’s - 1980’s</td>
<td>Improved survival, but → BPD</td>
</tr>
<tr>
<td>Ventilator: HFV</td>
<td>1980’s - 2000’s</td>
<td>Extensive RCT’s → no clear effect</td>
</tr>
<tr>
<td>Surfactant</td>
<td>1980’s - 1990’s</td>
<td>Extensive RCT’s → improved survival &amp; changed BPD</td>
</tr>
<tr>
<td>iNO</td>
<td>1990’s - 2000’s</td>
<td>Extensive RCT’s → reduced ECMO, but not BPD in preemies</td>
</tr>
<tr>
<td>Non-Invasive</td>
<td>2000’s - present</td>
<td>Extensive RCT’s → ? reduced BPD</td>
</tr>
</tbody>
</table>

Modified from Kamath B et al, Pediatrics 2011
# “History” of Neonatal Respiratory Care

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Time Era</th>
<th>Effect on morbidity/mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>1940’s - 1960’s</td>
<td>Too much → ROP, Too little → increased mortality</td>
</tr>
<tr>
<td>No RCT’s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPAP</td>
<td>1970’s</td>
<td>Improved survival</td>
</tr>
<tr>
<td>No RCT’s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilator: IMV</td>
<td>1960’s - 1980’s</td>
<td>Improved survival, but → BPD</td>
</tr>
<tr>
<td>No RCT’s</td>
<td>1980’s - 2000’s</td>
<td>Extensive RCT’s → no clear effect</td>
</tr>
<tr>
<td>HFV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surfactant</td>
<td>1980’s - 1990’s</td>
<td>Extensive RCT’s → improved survival &amp; changed BPD</td>
</tr>
<tr>
<td>iNO</td>
<td>1990’s - 2000’s</td>
<td>Extensive RCT’s → reduced ECMO, but not BPD in preemies</td>
</tr>
<tr>
<td>Non-Invasive</td>
<td>2000’s - present</td>
<td>Extensive RCT’s → ? reduced BPD</td>
</tr>
</tbody>
</table>

Modified from Kamath B et al, Pediatrics 2011
“History” of Neonatal Respiratory Care

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Time Era</th>
<th>Effect on morbidity/mortality</th>
</tr>
</thead>
</table>
| Oxygen           | 1940’s - 1960’s | Too much → ROP  
Too little → increased mortality                                      |
| CPAP             | 1970’s          | Improved survival                                                  |
| Ventilator: IMV  | 1960’s - 1980’s | Improved survival, but → BPD                                      |
| HFV              | 1980’s - 2000’s | Extensive RCT’s → no clear effect                                  |
| Surfactant       | 1980’s - 1990’s | Extensive RCT’s → improved survival & changed epidemiology of BPD |
| iNO              | 1990’s - 2000’s | Extensive RCT’s → reduced ECMO, but not BPD in preemies            |
| Non-Invasive     | 2000’s - present| Extensive RCT’s → ? reduced BPD                                    |

Modified from Kamath B et al, Pediatrics 2011
# “History” of Neonatal Respiratory Care

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Time Era</th>
<th>Effect on morbidity/mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>1940’s - 1960’s</td>
<td>Too much → ROP&lt;br&gt;Too little → increased mortality</td>
</tr>
<tr>
<td>No RCT’s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPAP</td>
<td>1970’s</td>
<td>Improved survival</td>
</tr>
<tr>
<td>No RCT’s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilator: IMV</td>
<td>1960’s - 1980’s</td>
<td>Improved survival, but → BPD</td>
</tr>
<tr>
<td>No RCT’s</td>
<td>1980’s - 2000’s</td>
<td>Extensive RCT’s → no clear effect</td>
</tr>
<tr>
<td>HFV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surfactant</td>
<td>1980’s - 1990’s</td>
<td>Extensive RCT’s → improved survival &amp; changed epidemiology of BPD</td>
</tr>
<tr>
<td>iNO</td>
<td>1990’s - 2000’s</td>
<td>Extensive RCT’s → reduced ECMO, but not BPD in preemies</td>
</tr>
<tr>
<td>Non-Invasive</td>
<td>2000’s - present</td>
<td>Extensive RCT’s → ? reduced BPD</td>
</tr>
</tbody>
</table>

Modified from Kamath B et al, Pediatrics 2011
BPD: How Has it Changed Over Time?
Mean EGA = 33 wks & Birth Wt 1821 g

13 infants survived: EGA 30-39 weeks, 1474-3204 g

19 infants died: EGA 23-39 weeks, 900-2466 g
BPD – Changing Demographics

• 1977: Stanford 1962 - 1973
  – Mean: B Wt - 1821 g   EGA - 33.0 wk

  – Mean: B Wt - 1036 g   EGA - 27.5 wk

• 2006: NRN 2006
  – Mean: B Wt - 874g   EGA - 26.7 wk

1977, Edwards, Pediatrics
1998, Yoder, unpublished
2011, Ambalavanan, Pediatrics
**Time related decrease in mortality…**

<table>
<thead>
<tr>
<th># ≤ 1500 g</th>
<th>1976-80 (n=665)</th>
<th>1981-85 (n=834)</th>
<th>1986-90 (n=875)</th>
<th>1991-95 (n=1046)</th>
<th>1996-97 (n=417)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>28%</td>
<td>20%</td>
<td>17%</td>
<td>11%</td>
<td>6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BPD (28d)</td>
<td>11%</td>
<td>22%</td>
<td>33%</td>
<td>30%</td>
<td>27%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Either</td>
<td>35%</td>
<td>37%</td>
<td>45%</td>
<td>38%</td>
<td>31%</td>
<td>0.723</td>
</tr>
</tbody>
</table>

Byrne et al, Semin Perinatol 2002

---

**Start of IMV/CPAP**

**Post-surfactant era**

Vanderbilt U
Time related decrease in mortality... 
...accompanied by increase in BPD

<table>
<thead>
<tr>
<th># ≤ 1500 g</th>
<th>1976-80 (n=665)</th>
<th>1981-85 (n=834)</th>
<th>1986-90 (n=875)</th>
<th>1991-95 (n=1046)</th>
<th>1996-97 (n=417)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>28%</td>
<td>20%</td>
<td>17%</td>
<td>11%</td>
<td>6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BPD (28d)</td>
<td>11%</td>
<td>22%</td>
<td>33%</td>
<td>30%</td>
<td>27%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Either</td>
<td>35%</td>
<td>37%</td>
<td>45%</td>
<td>38%</td>
<td>31%</td>
<td>0.723</td>
</tr>
</tbody>
</table>

Start of IMV/CPAP \[\rightarrow\]
Post-surfactant era

Byrne et al, Semin Perinatol 2002
Vanderbilt U
No change in combined outcome of death and/or BPD

<table>
<thead>
<tr>
<th># &lt; 1500 g</th>
<th>1976-80 (n=665)</th>
<th>1981-85 (n=834)</th>
<th>1986-90 (n=875)</th>
<th>1991-95 (n=1046)</th>
<th>1996-97 (n=417)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>28%</td>
<td>20%</td>
<td>17%</td>
<td>11%</td>
<td>6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BPD (28d)</td>
<td>11%</td>
<td>22%</td>
<td>33%</td>
<td>30%</td>
<td>27%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Either</td>
<td>35%</td>
<td>37%</td>
<td>45%</td>
<td>38%</td>
<td>31%</td>
<td>0.723</td>
</tr>
</tbody>
</table>

Byrne et al, Semin Perinatol 2002

Start of IMV/CPAP

Post-surfactant era
No change in survival or BPD in the decade following surfactant approval

Though BPD unchanged severe BPD appeared to decrease w/ time

Over past decade, BPD rates have increased in Canadian Neo Network

1996-97 v 2006-07
Infants < 29 weeks
17% Decrease in Mortality

Changes noted in face of:
Increased ANS use
Decreased SNAP scores
Trend toward ↑GA
Decreased postnatal steroid

Shah et al, J Perinatol 2011
BPD: Change over Time by EGA

BPD rate vs. Year

Year


BPD rate

0%, 10%, 20%, 30%, 40%, 50%, 60%

Courtesy of Reese Clark, MD; Pediatrix
<table>
<thead>
<tr>
<th>“NEW” BPD</th>
<th>“OLD” BPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased alveolarization and surface area</td>
<td>Alternating atelectasis &amp; hyperinflation</td>
</tr>
<tr>
<td>Fewer, larger, and simplified alveoli</td>
<td>Large, simplified alveoli</td>
</tr>
<tr>
<td>Rare fibroproliferative changes</td>
<td>Diffuse fibroproliferation</td>
</tr>
<tr>
<td>Rare epithelial airway lesions</td>
<td>Severe epithelial airway lesions</td>
</tr>
<tr>
<td>Mild airway smooth muscle thickening</td>
<td>Marked airway smooth muscle hyperplasia</td>
</tr>
<tr>
<td>Fewer arteries but “dysmorphic”</td>
<td>Marked remodeling of pulmonary arteries</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>“MILD”</th>
<th>“MODERATE”</th>
<th>“SEVERE”</th>
<th>“CHRONIC-SEVERE”</th>
</tr>
</thead>
</table>
BPD – A Change in Definition

• Initial *radiologic* description - Northway 1967
  – Chronic ventilator & O₂ support

• Revised *clinical* description by Bancalari 1979
  – RDS in neonatal period w/ O₂ need at 28 days
  – *Plus* respiratory symptoms & abnormal CXR

• Updated by Shennan in 1988
  – Supplemental FiO₂ at 36 weeks PMA w/
  – Persistent abnml CXR +/- resp. symptoms
BPD – A Change in Definition

• NICHD Consensus Definitions in 2000
  – Stratification was needed
  – 3-tiers = mild, moderate, & severe
  – Different pathologies & different populations

• “Physiologic” definitions
  – O2 Reduction Test – Walsh 2003
  – V/Q mismatch quantification – Stenson 2009
## NICHD Consensus Definitions

<table>
<thead>
<tr>
<th></th>
<th>EGA - birth</th>
<th>&lt; 32 weeks</th>
<th>≥ 32 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild</strong></td>
<td>O2 @ 28d but RA @ 36 wks or D/C</td>
<td>RA by 8 wks or D/C</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>&lt; 30% O2 @ 36 wks/DC</td>
<td>&lt; 30% O2 by 8 wks/DC</td>
<td></td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td>≥ 30% O2 or any PPS</td>
<td>≥ 30% O2 or any PPS</td>
<td></td>
</tr>
</tbody>
</table>
# Modified NIH Definitions

<table>
<thead>
<tr>
<th>EGA - Birth</th>
<th>&lt; 32 weeks</th>
<th>&gt; 32 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment age</td>
<td>36 wks PMA, or D/C to home</td>
<td>&gt; 28 but &lt; 56 d postnatal age, or D/C to home</td>
</tr>
<tr>
<td>“Mild”</td>
<td>In room air at 36 wk, or D/C to home</td>
<td>In room air by 56 days age, or D/C to home</td>
</tr>
<tr>
<td>“Moderate”</td>
<td>FiO2 &gt; 21% but &lt; 30% at 36 wks PMA, or D/C to home</td>
<td>FiO2 &gt; 21% but &lt; 30% at 56 days age, or D/C to home</td>
</tr>
<tr>
<td>“Severe” #</td>
<td>FiO2 &gt;30% ± NIV at 36 wks PMA, or D/C to home</td>
<td>FiO2 &gt;30% ± NIV at 56 days age, or D/C to home</td>
</tr>
<tr>
<td>“Severe-Chronic” #</td>
<td>Need for ventilator support at 36 wks PMA</td>
<td>Need for ventilator support at 56 days age</td>
</tr>
</tbody>
</table>

# NIH Consensus Conference definition only describes “Severe BPD”

This Table differentiates babies continuing to require MV support from those with increased FiO2 need and/or non-invasive support (NIV)
Comparison of Center BPD Rates by “Clinical” and “Physiologic” Definitions

Walsh M et al, Pediatrics 2004

Physiologic “BPD” was lower in every center, sometimes by 50%
Summary # 1

• BPD remains a very common problem

• Epidemiology has changed significantly

• Primarily occurs at < 30 wks & < 1000 g

• Diagnostic criteria continue to be refined
Pathophysiology of BPD

Legend:
- CC10: Clara cell protein
- FGF: fibroblast growth factor
- ICAM-1: intercellular adhesion molecule-1
- IL: interleukin
- MCP: monocyte chemotactic protein
- MMP: matrix metalloproteinase
- O₂⁻·OH: oxygen free radical, hydroxyl radical
- OPN: osteopontin
- TGFβ: transforming growth factor β
- TIMP: tissue inhibitor of metalloproteinase
- TNFα: tumour necrosis factor α
- VEGF: vascular endothelial growth factor

Histological changes in BPD:
- Mild BPD:
  - Decreased airspace septation
  - Less maturation of epithelium (type 2 → type 1)
  - Fewer capillaries
  - Thickened mesenchyme
- Severe BPD:
  - Peri-bronchiolar and septal fibrosis
  - Vascular muscular overgrowth

Pro-/anti-inflammatory cytokines:
- CC10: Clara cell protein
- FGF: fibroblast growth factor
- ICAM-1: intercellular adhesion molecule-1
- IL: interleukin
- MCP: monocyte chemotactic protein
- MMP: matrix metalloproteinase
- O₂⁻·OH: oxygen free radical, hydroxyl radical
- OPN: osteopontin
- TGFβ: transforming growth factor β
- TIMP: tissue inhibitor of metalloproteinase
- TNFα: tumour necrosis factor α
- VEGF: vascular endothelial growth factor

Proteases and oxidative injury:
- Capillary
- Airway
- Proteolytic enzymes
- Oxidative stress
- Air space

Growth factors:
- TGFβ1
- VEGF
- Capillary
- Air space
Developmental Lung Biology in the Primate

Term equivalent = 185 d

Maniscalco et al. AJP Lung Cell Mol Phys 2002
BPD in the Preterm Baboon – 140 d

21 – day model

“Control”                      BPD
Control = PRN FiO2 + HFO x 3 d, then IMV

“Control”                      BPD
BPD = IMV + 100% x 7 d, then 80% FiO2

Coalson J, AJRCCM 1995
Effect of Early Non-Invasive Respiratory Support

125- day baboon model

IMV + 25 wks  Term + 35 wks  CPAP + 33 wks

X 10
Is there more than one model supporting this idea?
Factors Contributing to Neonatal Lung Injury

- Chronic Stress
- Growth Restriction
- Genetic Predisposition
- Chorio
- O2 exposure
- Preterm Birth
- Delivery Room Care
- Mechanical Ventilation
- Hyperoxia
- Postnatal Infection
- Poor Nutrition
- Other PN Therapy
- Good Nutrition
- Fetal lung
- Antenatal Steroids
- Genetic Predisposition
- Surfactant
- CPAP
- Postnatal lung

Pro-inflammatory

Anti-inflammatory

Yoder BA, NeoRev 2008
710 unique genes were differentially expressed during MV as compared to spontaneous breathing.
Non-injurious MV activates a diffuse transcriptional network.

Results in a broad repertoire of pro-inflammatory molecules and immune-mediated pathways.

May augment, or be enhanced by, other “insults”

176 different gene interactions

Gharib SA et al, Physiol Genomics 2009
Multiple “Hit” Hypothesis
335 genes differentially expressed w/ GBS exposure

Striking interaction (↓↑) between inflammatory, angiogenic, & morphogenic pathways

Ryan M. McAdams RM et al, PLOS ONE 2012
Limitations of Animal Models for BPD

Chronic Stress
- Growth Restriction

Growth Restriction
- Chronic Stress

Chorionic O2 exposure
- Hyperoxia

Postnatal Infection
- Poor Nutrition

Postnatal lung
- Other PN Therapy
- Good Nutrition

Fetal lung
- Antenatal Steroids

Preterm Birth

Delivery Room Care

Pro-inflammatory
- CPAP

Anti-inflammatory

Surfactant

McAdams, PLOS ONE 2012
Yoder BA, NeoRev 2008
Summary # 2

BPD has a multi-factorial pathophysiology

But is primarily inflammatory in nature

1º pathology is interrupted alveolization ("New" BPD)

“Old” BPD occurs, but much less common
Major Risk Factors Contributing to BPD

Invasive Mechanical Ventilation
- Supplemental O2
- Early & late onset sepsis, pneumonia, viral

“Chorio”
- Poor fetal growth
- Extra-uterine growth retardation

Preterm Birth

Post-menstrual Age
- ANS
- Surfactant
- Caffeine
- Vitamin A
- Late low dose steroids
- Avoid Hyperoxia / Anti-oxidants

Early, sustained non-invasive support
- Aggressive nutritional support; protein
- Prevent infection

Important Treatment Options to Prevent/Manage BPD

Adapted from Schulzke & Pillow, Ped Resp Rev 2010
Studied Interventions

Surfactant
Inhaled NO
Non-invasive support
Vitamin A
SOD
Caffeine
Steroids
Azithromycin
Nutritional adjuncts
Prevention of VAP
Of the multiple interventions tested, very few have had a positive impact on BPD.
### Systematic review of randomized controlled drug trials for BPD prevention

Beam KS et al, J Perinatol 2014

Either small #'s or very few RCTs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total infants enrolled</th>
<th>Infants enrolled in RCTs</th>
<th>Preliminary data</th>
<th>Prevents BPD</th>
<th>Favorable RCTs, N/total (%)</th>
<th>No. of IND/RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>947</td>
<td>856</td>
<td>Y</td>
<td>Y</td>
<td>1/2 (50)</td>
<td>0/2</td>
</tr>
<tr>
<td>Caffeine</td>
<td>2006</td>
<td>2006</td>
<td>Y</td>
<td>Y</td>
<td>1/1 (100)</td>
<td>0/1</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>1671</td>
<td>1631</td>
<td>Y</td>
<td>Y</td>
<td>4/10 (40)</td>
<td>0/10</td>
</tr>
<tr>
<td>Inositol</td>
<td>233</td>
<td>233</td>
<td>Y</td>
<td>Y</td>
<td>1/1 (100)</td>
<td>0/1</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>68</td>
<td>68</td>
<td>Y</td>
<td>Y</td>
<td>1/1 (100)</td>
<td>0/1</td>
</tr>
<tr>
<td>Surfactant</td>
<td>10128</td>
<td>1647</td>
<td>Y</td>
<td>N</td>
<td>4/8 (50)</td>
<td>0/8</td>
</tr>
<tr>
<td>Inhaled nitric oxide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0/7</td>
</tr>
<tr>
<td>Selenium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0/1</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0/3</td>
</tr>
<tr>
<td>Allopurinol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0/1</td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>391</td>
<td>391</td>
<td>Y</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Inhaled beclomethasone</td>
<td>352</td>
<td>313</td>
<td>Y</td>
<td>N</td>
<td>0/2 (0)</td>
<td>0/2</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>255</td>
<td>220</td>
<td>Y</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Estrogen/progesterone</td>
<td>115</td>
<td>85</td>
<td>Y</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>α-1-Antitrypsin</td>
<td>106</td>
<td>106</td>
<td>N</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Inhaled salbutamol</td>
<td>87</td>
<td>87</td>
<td>Y</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Superoxide dismutase</td>
<td>59</td>
<td>33</td>
<td>Y</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Cromolyn sodium</td>
<td>55</td>
<td>26</td>
<td>Y</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Inhaled fluticasone</td>
<td>53</td>
<td>53</td>
<td>Y</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Thyroxine</td>
<td>49</td>
<td>49</td>
<td>N</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Zinc</td>
<td>97</td>
<td>97</td>
<td>Y</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>21 176</strong></td>
<td><strong>11 953</strong></td>
<td><strong>17</strong></td>
<td><strong>5</strong></td>
<td><strong>14/47 (30%)</strong></td>
<td><strong>0/47</strong></td>
</tr>
</tbody>
</table>
Systematic review of randomized controlled drug trials for BPD prevention

Beam KS et al, J Perinatol 2014

At best there is no more than a 10% decrease in BPD w/ any single approach

Table 1. Summary of RCTs (n = 47) and early-phase studies (n = 19) included in review, by drugs studied

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total infants enrolled</th>
<th>Infants enrolled in RCTs</th>
<th>Preliminary data</th>
<th>Prevents BPD</th>
<th>Favorable RCTs, N/total (%)</th>
<th>No. of IND/RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>947</td>
<td>856</td>
<td>Y</td>
<td>Y</td>
<td>1/2 (50)</td>
<td>0/2</td>
</tr>
<tr>
<td>Caffeine</td>
<td>2006</td>
<td>2006</td>
<td>Y</td>
<td>Y</td>
<td>1/1 (100)</td>
<td>0/1</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>1671</td>
<td>1631</td>
<td>Y</td>
<td>Y</td>
<td>4/10 (40)</td>
<td>0/10</td>
</tr>
<tr>
<td>Inositol</td>
<td>233</td>
<td>233</td>
<td>Y</td>
<td>Y</td>
<td>1/1 (100)</td>
<td>0/1</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>68</td>
<td>68</td>
<td>Y</td>
<td>Y</td>
<td>1/1 (100)</td>
<td>0/1</td>
</tr>
<tr>
<td>Surfactant</td>
<td>10 128</td>
<td>10 128</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>0/1</td>
</tr>
<tr>
<td>Inhaled nitric oxide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4/8 (50)</td>
<td>0/8</td>
</tr>
<tr>
<td>Selenium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2/7 (28)</td>
<td>0/7</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0/1 (0)</td>
<td>0/3</td>
</tr>
<tr>
<td>Allopurinol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0/3 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Inhaled beclomethasone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Azithromycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Estrogen/progesterone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>α-1-Antitrypsin</td>
<td>108</td>
<td>108</td>
<td>N</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Inhaled salbutamol</td>
<td>87</td>
<td>87</td>
<td>Y</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Superoxide dismutase</td>
<td>59</td>
<td>33</td>
<td>Y</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Cromolyn sodium</td>
<td>55</td>
<td>26</td>
<td>Y</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Inhaled fluticasone</td>
<td>53</td>
<td>53</td>
<td>Y</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Thryoxine</td>
<td>49</td>
<td>49</td>
<td>N</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Zinc</td>
<td>97</td>
<td>97</td>
<td>Y</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Total</td>
<td>21 176</td>
<td>11 953</td>
<td>17</td>
<td>5</td>
<td>14/47 (30%)</td>
<td>0/47</td>
</tr>
</tbody>
</table>
Can’t you guys figure this out..... you’re giving me a headache!
Key Issues in Trial Design

• **Access** to highest-risk population
  – Competing studies, limited #’s per center

• **Study design**
  – Single therapy vs multiple therapies vs “BDP”

• **Regulatory** issues
  – Limited pK data for most drugs
  – FDA IND oversight – “deaf” leading the “blind”

• **Definition** of critical outcome
What Outcome Should We Use?

• O2 use at discharge?

• O2 + meds at 36 wks? 40 wks? D/C?

• Level of respiratory support at 36-40 wks?

• Post d/c respiratory illnesses, subsequent hospitalization, chronic lung medications?

• Lung function as child, teen or adult?
Effect of Preterm Birth & BPD on FEV₁

Kotecha SJ et al
Thorax 2013
1964-2000
5-23 years
24-36 wks

No BPD
“BPD” @ 28 d
“BPD” @ 36 wks
Effect of Preterm Birth & BPD on FEV$_1$

Vollsaeter M et al, Thorax 2013

- Infants < 29 wks or 1000 g
- Teens 1991-92
- Adults 1982-85
Why Do We Limit Ourselves to Mono-therapeutic Trials?
Why Do We Limit Ourselves to Mono-therapeutic Trials?

**FIGURE 10.** Are two antidepressant mechanisms better than one?

Single selective mechanisms = loss of side effects
loss of efficacy?

Multiple mechanisms = side effects

Multiple therapeutic mechanisms = improved
efficacy

TCA=tricyclic antidepressant; SSRI=selective serotonin reuptake inhibitor; 
SNRI=serotonin-norepinephrine reuptake inhibitor.

Why Do We Limit Ourselves to Mono-therapeutic Trials?

**Figure 10.** Are two antidepressant mechanisms better than one?

- Single selective mechanisms = less of side effects, less of efficacy
- Multiple mechanisms = more of side effects, more of efficacy

TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor.

Why Do We Limit Ourselves to Mono-therapeutic Trials?
Clarithromycin, montelukast, & pentoxifylline combination Rx ameliorates experimental neonatal hyperoxic lung injury

Demir K et al, *J Mat-Fetal Neo Med*, 2008

Multi-targeted treatments may be effective when single Rx appears not to be
Single v Multiple Therapy v “BDP”

• BDP = “Best Demonstrated Practice”
  • How do we find BDP?
  • How do we study this?
Variation in BPD by Center
Walsh M et al, Pediatrics 2004

Even w/ defined criteria BPD rates vary widely

Physiologic

Percent
Variation in BPD by Center

Walsh M et al, Pediatrics 2004

What are they doing different?
Comprehensive Approach

- DR or NICU
- Intubation
  - Surfactant
  - Immediate extubation
    - Extubate per guidelines
    - Selective PN steroids
- INSURE approach
  - Caffeine
  - Nutrition
  - Vitamin A?
- Nasal Respiratory Support
  - Nasal Ventilation
  - Spontaneous Unsupported breathing
- CPAP
- Targeted O2 SAT’s
- Permissive hypercapnia

Kugelman A, Peds Pulm 2011
Multi-Pronged Protocol to Assist ELGANs in Transition to Extrauterine Life
Mehler K et al, Acta Paeds 2012

1. Delayed cord clamping
2. Only sxn mouth/airway if blood or MSAF
3. **Immediate** CPAP @ 8 cm H2O & 30%
4. CPAP &/or SI (30 sec) if poor response
5. MIST: Distress / FiO2 > 30% / CPAP > 8
6. HFV if intubated
7. Early PDA screen & treatment
Multiple Changes in Care Accompanied by Improved Survival & Less Morbidity

Survival

BPD

Mehler K et al, Acta Paeds 2012
Only 40 more slides to go!
Challenges are what make life interesting …..

…… overcoming them is what makes life meaningful

Joshua J. Marine
The Future in BPD?

• Better identification of at-risk population

• Incorporating “best practices” into multi-center trial design

• Multi-targeted interventional studies
On-going / Future Approaches to BPD

- SLI +/- MIST
- Surfactant-based medications
- Stem cell therapy
- Enhanced NIV
- HA-bCPAP
- HFNV
- CLARA CELL 10
- IGF-1
- RX of Antenatal Inflammation
- HDAC inhibitors
- Nutrition/Growth
COURAGE
Do One Brave Thing Today.....Then Run Like Hell!
"Just Tell Me How It Works."

"Yes, it is the new printer ... and yes, it works by magic."

IS NEWER ALWAYS BETTER?
Varying the angle of the underwater tube markedly alters oscillatory amplitude.
Oscillatory $\Delta V$ during HFB-CPAP is optimal at 135 degree angle

DiBlasi RM et al, Pediatr Res 2010
Small but significant increase in PaO₂ & slight insignificant decrease in PaCO₂

135° HAB-CPAP associated with marked reduction in work of breathing (PRP)
Human Umbilical Cord Blood-Derived Mesenchymal Stem Cells Attenuate Hyperoxia-Induced Lung Injury in Neonatal Rats

Chang YS et al, *Cell Transpl* 2009