Reducing Bronchopulmonary Dysplasia – Is This Possible?

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Disclosures

• No relevant financial disclosures
• Multiple drugs used in the preterm newborn (indomethacin, diuretics, vitamin A, azithromycin, inhaled nitric oxide) are not labeled by the FDA for such use, and their use must be considered off-label.
Objectives

- Define clinical outcomes that are important
- Identify which interventions reduce BPD
- Recognize the basis of center variation in rates of BPD
What are we trying to reduce?

- Bronchopulmonary dysplasia:
  - O₂ requirement at 36 weeks PMA
    - What do we mean by “requirement”?
    - Decision to provide oxygen not uniform; definition of acceptable saturation is variable (85-98%)
  - Physiologic BPD definition
    - Standardized testing improves precision of diagnosis of BPD, reduces overall rate of BPD and reduces variation among centers

Comparison of BPD rate by the clinical definition and physiologic definition of BPD at each center.

Infants with BPD do not all have the same phenotype

• Variation in BPD severity
  – Mild, Moderate, Severe BPD

• Variation in BPD pathology
  • “Classic” BPD [airway injury, inflammation, parenchymal fibrosis] vs. “New” BPD [inhibition of alveolar formation and microvascular development]
    [Jobe AH, Bancalari E. Am J Respir Crit Care Med 163:1723, 2001]

• Infants with BPD exist along a continuum, with varying combinations of clinical and pathologic features

• Definition of BPD is an operational definition, and does not specify specific pathophysiology
Variation in BPD Phenotype - 1

3 month old ex-25w 0.7 kg infant with *Ureaplasma* infection at birth
Variation in BPD Phenotype -2

3 month old ex-24w 0.6 kg infant with supra-systemic pulmonary hypertension (RVP > 80 mm Hg; BNP >3000)
What are the implications of the BPD definition and phenotype?

• We need to define what outcome is important!
  – Infants on 35% $O_2$ by nasal cannula at 36 w PMA may not have the same outcomes as intubated infants on high ventilator settings, even though both are defined as having “severe” BPD
  – ELBW infants without a “BPD” diagnosis may also have impaired lung development and long-term abnormalities on lung function
“BPD disease network” – we need quantitation of links, especially of how environmental determinants affect outcome

- **Intermediate phenotypes**
  - Inflammation
  - Apoptosis
  - Atelectasis
  - Long-term impairment of lung function

- **Pathophenotypes**
  - Inhibition of lung development
  - Abnormal lung vascular development

- **Disease –modifying genes**
  - Cytokine & Immunity genes
  - Surfactant genes
  - Lung development genes

- **Environmental determinants**
  - Fluid overload
  - Volutrauma
  - Impaired nutrition
  - Infection
  - Hyperoxia

- **CENTER EFFECTS**
  - Long-term impairment of lung function
Is BPD the outcome we want to reduce?

• Questions to answer:
  – Is BPD the most important outcome? Or severe BPD? Or long-term pulmonary outcome?
  – What about survival or survival without NDI? Would interventions that reduce BPD also improve survival or reduce NDI? (interventions that improve survival alone may increase infants surviving with BPD, due to larger number of surviving smaller infants)
  – Should we always look at the outcome of BPD and the competing outcome of death in combination (BPD and/or death)?
How do we reduce BPD?

• Standard approach
  – Identify potentially best practices (PBPs) based on review of available evidence
  – Implement PBPs using QI methods

• Possible future approach
  – Targeted interventions to individual infants (personalized medicine) based on statistical modeling + genomic/proteomic/metabonomic markers
Standard Approach

• What are the potentially better practices?
  – Antenatal:
    • Antenatal steroids
    • Antimicrobial therapy
  – Postnatal:
    • Ventilator/CPAP/Gas exchange management
    • Surfactant therapy
    • Fluid and Nutrition management
    • Drugs: Vit A, Caffeine, iNO?, Antimicrobials?, Steroids?, Diuretics?
Future Approach

• Step 1: Identification of infants at high risk
  – BPD outcome estimator from NICHD
    (https://neonatal.rti.org/index.cfm?fuseaction=BPDCalculator.start)
Future Approach

• Step 1: Identification of infants at high risk
  – Potential methods:
    • Clinical features and lung function studies
    • Radiological features
    • Biomarkers
      (Proteomic/Genomic/Respiratory microbiome etc)
Temporal profiles of cytokines associated with BPD and/or death among ELBW infants in multivariate logistic regression analyses.

Higher cytokine concentrations associated with BPD/death (IL-8, IL-10, IL-6, IL-1β, IFN-γ)

Lower cytokine concentrations associated with BPD/death (RANTES, IL-17, TNF-β)

Future approach

• Step 2: Targeted intervention
  – To whom?
    • Based on higher-risk profile based on biomarkers or statistical modeling: What risk threshold?
  – Which interventions?
    • Interventions targeted to genomic/proteomic biomarker
    • Interventions based on lung function/radiology (e.g. for tracheomalacia, airway reactivity)
    • Interventions based on risk (better benefit: risk ratio for intervention)
  – When? How much?
Potentially Better Practices
Antenatal steroids

- 21 studies (3885 women, 4269 infants)
- Reduction in RDS: RR 0.66 (0.59-0.73)
- Reduction in neonatal death: RR 0.69 (0.58-0.81)
- But no reduction in BPD! : RR 0.86 (0.61-1.22)

Roberts D, Dlaziel S. Cochrane Database Syst Rev 2006

Does a “Left shift” maintain survivors with BPD constant?

Need analysis of survivors without BPD!
Antimicrobial therapy

- Preterm birth often complicated by PPROM, chorioamnionitis
- Antibiotics following PROM
  - Reduction in chorioamnionitis, birth <48h or <7d, neonatal infection, use of surfactant, oxygen therapy
  - Reduction in oxygen use at 28 days:

  Kenyon S et al. Cochrane Database Syst Rev 2010
Ventilator/CPAP/Gas exchange

- Recent large trials with current practice (frequent AN steroids, more CPAP) indicate benefits of early stabilization on CPAP with selective use of surfactant to infants needing intubation
  - Increased BPD/death with prophylactic surfactant vs. CPAP and selective surfactant:
    RR 1.12 (1.02-1.24); RD 0.06 [0.01-0.1], NNTH 17

Plot of Survival to 36 Weeks' Postmenstrual Age in 3631 Infants in the SUPPORT and BOOST II Trials According to the Calibration Algorithm Used.

<table>
<thead>
<tr>
<th>Study</th>
<th>Lower SpO$_2$</th>
<th>Higher SpO$_2$</th>
<th>Relative Risk (99.73% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old algorithm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUPPORT 2010</td>
<td>114/654</td>
<td>94/662</td>
<td>1.23 (0.84–1.80)</td>
</tr>
<tr>
<td>BOOST II UK</td>
<td>18/113</td>
<td>26/115</td>
<td>0.70 (0.31–1.62)</td>
</tr>
<tr>
<td>BOOST II Australia/New Zealand</td>
<td>67/516</td>
<td>72/516</td>
<td>0.93 (0.58–1.49)</td>
</tr>
<tr>
<td>Pooled result</td>
<td>199/1283</td>
<td>192/1293</td>
<td>1.04 (0.79–1.38)</td>
</tr>
<tr>
<td>New algorithm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BOOST II UK</td>
<td>79/333</td>
<td>50/334</td>
<td>1.58 (0.97–2.59)</td>
</tr>
<tr>
<td>BOOST II Australia/New Zealand</td>
<td>36/194</td>
<td>20/194</td>
<td>1.80 (0.83–3.92)</td>
</tr>
<tr>
<td>Pooled result</td>
<td>115/527</td>
<td>70/528</td>
<td>1.65 (1.09–2.49)</td>
</tr>
<tr>
<td>Overall pooled result</td>
<td>314/1810</td>
<td>262/1821</td>
<td>1.21 (0.96–1.52)</td>
</tr>
</tbody>
</table>

Ventilator/CPAP/Gas exchange

- Evidence supports early CPAP; surfactant if infant needs intubation
- Target oxygen saturation: 90-95%
- Target PaCO2: 45-55 mm Hg (avoid >60 mm Hg in first week)
  - Ventilator support at 36w: 1% in minimal ventilation [target PaCO2 >52] vs. 16% in routine group [target PaCO2 <48] (p<0.01) [Carlo WA et al. J Pediatr 2002; 141:370]
- No strong evidence supporting elective high-frequency ventilation [Cools F et al. Cochrane Database Syst Rev 2009]
- No large RCT supporting volume-targeted ventilation; Systematic review of small studies indicate possible reduction in BPD/death [Wheeler K. Cochrane Database Syst Rev 2010]
Surfactant therapy

• Much literature on surfactant therapy:
  – Questions:
    • When to give; How much to give; How many doses
    • Early treatment vs. Later treatment
    • Administration: IT via ETT vs. Nebulized /Pharyngeal/ LMA
    • Preparation: Natural (bovine) vs. Natural (porcine) vs. New Synthetic (e.g. lucinactant, others in development)
**Fluid/Electrolyte/Nutrition Management**

- Restricted fluid intake reduces PDA, NEC, with trends to reduce BPD, IVH, and death.

### BPD: RR 0.85 (0.63-1.14)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Restricted n/N</th>
<th>Liberal n/N</th>
<th>Risk Ratio N-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio N-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell 1980</td>
<td>5/85</td>
<td>8/85</td>
<td>11.9 % 0.63 [0.21, 1.83]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kavvadia 2000</td>
<td>21/84</td>
<td>22/84</td>
<td>32.8 % 0.95 [0.57, 1.60]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorenz 1982</td>
<td>10/44</td>
<td>12/44</td>
<td>17.9 % 0.83 [0.40, 1.73]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tammela 1992</td>
<td>21/50</td>
<td>25/50</td>
<td>37.3 % 0.84 [0.55, 1.29]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI):** 263
Total events: 57 (Restricted), 67 (Liberal)  
Heterogeneity: Chi² = 5.51, df = 3 (P = 0.32); P = 0.05  
Test for overall effect: Z = 1.08 (P = 0.28)

### Death: RR 0.81 (0.54-1.23)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Restricted n/N</th>
<th>Liberal n/N</th>
<th>Risk Ratio N-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio N-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell 1980</td>
<td>6/85</td>
<td>8/85</td>
<td>13.6 % 0.75 [0.27, 2.07]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kavvadia 2000</td>
<td>21/84</td>
<td>16/84</td>
<td>37.2 % 1.31 [0.74, 2.33]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorenz 1982</td>
<td>5/44</td>
<td>7/44</td>
<td>16.3 % 0.71 [0.25, 2.08]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tammela 1992</td>
<td>1/50</td>
<td>11/50</td>
<td>25.6 % 0.09 [0.01, 0.68]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>von Stockhausen 1980</td>
<td>2/28</td>
<td>1/28</td>
<td>2.3 % 2.00 [0.19, 20.82]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI):** 291  
Total events: 35 (Restricted), 42 (Liberal)  
Heterogeneity: Chi² = 7.87, df = 4 (P = 0.10); P = 0.49  
Test for overall effect: Z = 0.96 (P = 0.33)

Bell EF, Acarregui MJ. Cochrane Database Syst Rev 2008
RCT of Vitamin A in ELBW Infants

<table>
<thead>
<tr>
<th></th>
<th>Vit A</th>
<th>Control</th>
<th>RR</th>
<th>CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=405</td>
<td>N=402</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPD/death</td>
<td>55%</td>
<td>62%</td>
<td>0.89</td>
<td>0.80-0.99</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Death</td>
<td>15%</td>
<td>14%</td>
<td>1.07</td>
<td>0.76-1.50</td>
<td>NS</td>
</tr>
<tr>
<td>*NDI/death</td>
<td>55%</td>
<td>60%</td>
<td>0.94</td>
<td>0.80-1.17</td>
<td>NS</td>
</tr>
</tbody>
</table>

Tyson et al.  NEJM 340:1962, 1999
*Ambalavanan et al.  Pediatrics 115:e249, 2005
Caffeine

- **CAP trial** [Schmidt B et al. NEJM 2006; 354: 2112]
  - BPD: 36.3% in caffeine group vs. 46.9% in Placebo group; Adj OR 0.63 (0.52-0.76), p<0.001
  - Death: 5.2% vs 5.5%; Adj OR 0.93 (0.63-1.38), p NS
  - This study restricted the use of open-label methylxanthines (open label use 10%)

- Restricted use of methylxanthines may increase BPD rate

- Higher doses of caffeine may be better: 20 vs. 5 mg/kg/d for 1 yr outcome [Gray PH et al. J Paediatr Child Health 2011]; 30 or 15 vs. 3 mg/kg/d for apnea [Steer PA et al. J Paediatr Child Health 2003]
Other therapies with varying amounts of evidence

- iNO?
- Antimicrobials e.g. Azithromycin?
- Postnatal steroids?
- Diuretics?
- Bronchodilators?
Implementation of PBPs
What are the problems with implementing PBPs?

• Interventions that have been shown to work in a multicenter RCT may not work in a single center, due to interaction with other clinical practices

• Interventions that have been shown to work initially may not keep working as clinical practices and patient populations evolve
Variation in BPD_{28d}: Survey of 8 centers

Figure. Shaded areas are percentages of infants in oxygen at 28 days of age; open areas are survivors without added oxygen at 28 days. Note that center 3 has lowest percentage of infants who were dependent on oxygen and among the highest percentage of survivors.

Avery ME et al. Pediatrics 1987; 79:26
Comparison of BPD rate by the clinical definition and physiologic definition of BPD at each center.

Center variation in outcomes

- BPD (and other outcomes) in preterm neonates vary in incidence across neonatal centers even after adjustment for demographic and antenatal characteristics.

- The magnitude of these center variations in BPD is larger than the effect sizes of many clinically proven interventions such as surfactant, CPAP, or vitamin A.
Why are there center differences?

Center differences after adjustment for patient characteristics may possibly be due to:

• Chance
• Residual confounding by unmeasured or poorly measured predictors
• Differences in treatment approaches
The Benchmarking Trial

• A cluster randomized trial of benchmarking and multimodal QI to improve rates of survival free of BPD for infants with BW<1250g*
• Performed in 17 centers of the NRN
• 3 centers with the highest rates of survival free of BPD were identified as the benchmark centers.
• The remaining 14 centers were randomly assigned to control (n=7) or intervention groups (n=7).
• Intervention centers implemented potentially better practices
• BPD (Physiologic) rates compared between study years 1 and 3

Results of Benchmarking Trial

• Benchmarking and multimodal QI changed practices (median rate of success 75%: range 40-100%)
  – Decreased time to first surfactant
  – Increased use of CPAP
  – Decreased IMV in first week
  – Restricted fluid intake
  – Implemented use of high SpO₂ alarms
• but did not reduce survival free of BPD rates
  – Intervention group: 63.3 → 62.2%
  – Control group: 62.7 → 62.8%
Center differences in BPD

- It is therefore important to determine the characteristics of center variation and identify if these variations are amenable to intervention.

- Using data from the Benchmarking trial, we evaluated:
  - The magnitude of clustering of $BPD_{36w}$/death across centers of the NICHD NRN.
  - The infant-level variables associated with outcome and their clustering.
  - The center-specific practices associated with the differences.

Analysis – Stage 1

• Estimate the magnitude of clustering of BPD/death outcome in centers, adjusted and unadjusted for basic demographic factors

• Variables associated with survival free of BPD and that also varied by center were identified
  • Alternating logistic regression (ALR) with Pair-Wise Odds Ratio (PWOR) as a measure of clustering
  • ALR is a form of logistic regression in which clustering parameter is calculated in an iterative fashion together with estimates of regression parameters
  • PWOR
    - 1 : no clustering
    - <1.2 : low
    - 1.2-1.9 : moderate
    - >1.9 : high clustering
<table>
<thead>
<tr>
<th>Center</th>
<th>n</th>
<th>BW (g)</th>
<th>BPD/Death %</th>
<th>Raw OR</th>
<th>Adj OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>229</td>
<td>885</td>
<td>39.7</td>
<td>1.18</td>
<td>1.11</td>
<td>0.82-1.51</td>
<td>0.49</td>
</tr>
<tr>
<td>B</td>
<td>266</td>
<td>946</td>
<td>30.1</td>
<td>0.77</td>
<td>0.85</td>
<td>0.63-1.13</td>
<td>0.26</td>
</tr>
<tr>
<td>C</td>
<td>223</td>
<td>910</td>
<td>53.8</td>
<td>2.09</td>
<td>2.86</td>
<td>2.09-3.92</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>D</td>
<td>133</td>
<td>900</td>
<td>31.6</td>
<td>0.83</td>
<td>0.98</td>
<td>0.65-1.47</td>
<td>0.92</td>
</tr>
<tr>
<td>E</td>
<td>189</td>
<td>936</td>
<td>41.8</td>
<td>1.29</td>
<td>1.40</td>
<td>1.01-1.93</td>
<td>0.05</td>
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<tr>
<td>F</td>
<td>158</td>
<td>904</td>
<td>50.0</td>
<td>1.79</td>
<td>1.82</td>
<td>1.29-2.58</td>
<td>0.001</td>
</tr>
<tr>
<td>G</td>
<td>167</td>
<td>888</td>
<td>42.5</td>
<td>1.33</td>
<td>1.01</td>
<td>0.71-1.43</td>
<td>0.96</td>
</tr>
<tr>
<td>H</td>
<td>116</td>
<td>861</td>
<td>38.8</td>
<td>1.14</td>
<td>1.10</td>
<td>0.74-1.66</td>
<td>0.63</td>
</tr>
<tr>
<td>I</td>
<td>287</td>
<td>828</td>
<td>42.2</td>
<td>1.31</td>
<td>1.39</td>
<td>1.06-1.82</td>
<td>0.02</td>
</tr>
<tr>
<td>J</td>
<td>180</td>
<td>896</td>
<td>16.1</td>
<td>0.34</td>
<td>0.25</td>
<td>0.17-0.39</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>K</td>
<td>340</td>
<td>783</td>
<td>32.9</td>
<td>0.88</td>
<td>0.75</td>
<td>0.58-0.97</td>
<td>0.03</td>
</tr>
<tr>
<td>L</td>
<td>219</td>
<td>903</td>
<td>32.0</td>
<td>0.84</td>
<td>1.10</td>
<td>0.80-1.51</td>
<td>0.55</td>
</tr>
<tr>
<td>X</td>
<td>300</td>
<td>936</td>
<td>22.0</td>
<td>0.51</td>
<td>0.46</td>
<td>0.34-0.63</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Clustering: PWOR 1.3, p<0.001
BPD/Death: Overall 35%, Range 16-54%

OR adjusted for BW, gender, race
Stage 2 Analysis

• Logistic regression analysis was done with center indicators as fixed effects; birth weight, gender, and race as control indicators, and the variables of interest from the previous table.

• However, even after addition of all candidate variables, the center variable was still significant ($p<0.001$) and magnitude of clustering was not different (PWOR: 1.42).
## Stage 3 Analysis: Reduced predictive model

(*variables that lose significance when center is added, indicating strong association between center and these practices/variables*)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (per gram)</td>
<td>0.997</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>1.38</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Mother’s age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;17 vs. &gt;35</td>
<td>2.43</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>18-20 vs &gt;35</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>21-28 vs. &gt;35</td>
<td>1.03</td>
<td></td>
</tr>
<tr>
<td>29-34 vs. &gt;35</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Hypertension/Pre-eclampsia/Eclampsia</td>
<td>0.69</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>NICU admission temperature</strong></td>
<td>0.76</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Drug therapy – day 1</strong></td>
<td>0.85</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Indomethacin prophylaxis</strong></td>
<td>1.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Endotracheal intubation</strong></td>
<td>0.63</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Postnatal steroids by day 7</td>
<td>2.95</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Days on conventional ventilation by day 7</td>
<td>1.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days on HFV by day 7</td>
<td>1.32</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Days on supplemental oxygen by day 7</td>
<td>1.12</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Summary

• BPD/death rates demonstrate moderate clustering by center
• Clinical variables associated with BPD/death are also clustered
• Many of these clinical variables may be indicators of illness severity or responses of caregivers (intent to resuscitate or aggressiveness of therapy)
• Center differences after correction of clustered variables indicate presence of as-yet unmeasured center variables
Do centers that have low BPD also do better with other outcomes?

- No significant correlation was seen between adjusted center OR of BPD and OR of other outcomes (mortality, ROP, sepsis, NEC etc) in NICHD NRN (unpublished data)
- Centers which have a low incidence of a certain outcome may have higher incidence of other outcomes
It is possible that clinical practices that reduce the risk of a certain outcome may increase the risk of other outcomes. For example,

- Use of lower SpO₂ target range may reduce ROP, but slightly increase mortality
- Use of prophylactic indomethacin may reduce symptomatic PDA, but may also increase risk of spontaneous GI perforation (interaction with postnatal steroids)
Effect of oxygen saturation targets

- Target range of SpO₂ 85-89 % vs. 91-95%
- 1316 infants between 24-27⁶ weeks gestation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lower SpO₂</th>
<th>Higher SpO₂</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe ROP</td>
<td>8.6%</td>
<td>17.9%</td>
<td>0.52 (0.37-0.73)</td>
</tr>
<tr>
<td>Death before discharge</td>
<td>19.9%</td>
<td>16.2%</td>
<td>1.27 (1.01-1.60)</td>
</tr>
<tr>
<td>BPD 36w (suppl O2)</td>
<td>37.6%</td>
<td>46.7%</td>
<td>0.82 (0.72-0.93)</td>
</tr>
<tr>
<td>BPD 36w (Physiol)</td>
<td>38%</td>
<td>41.7%</td>
<td>0.92 (0.81-1.05)</td>
</tr>
<tr>
<td>BPD (Physiol) or Death</td>
<td>48.8%</td>
<td>50%</td>
<td>0.99 (0.90-1.10)</td>
</tr>
</tbody>
</table>

SUPPORT Study Group: NEJM 2010; 362:1959
# Effect of indomethacin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Indomethacin group</th>
<th>Placebo group</th>
<th>Odds Ratio (Adj; 95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDA</td>
<td>24%</td>
<td>50%</td>
<td>0.3 (0.2-0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PDA surgery</td>
<td>7%</td>
<td>12%</td>
<td>0.5 (0.3-0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BPD 36w (suppl O2)</td>
<td>45%</td>
<td>43%</td>
<td>1.2 (0.9-1.5)</td>
<td>0.26</td>
</tr>
<tr>
<td>Gl perforation</td>
<td>6%</td>
<td>5%</td>
<td>1.2 (0.7-1.9)</td>
<td>0.56</td>
</tr>
<tr>
<td>Severe IVH</td>
<td>9%</td>
<td>13%</td>
<td>0.6 (0.4-0.9)</td>
<td>0.02</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Treatment</th>
<th>All infants (n)</th>
<th>Infants with Gl perforation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dex + Indomethacin</td>
<td>70</td>
<td>13 (19%)</td>
</tr>
<tr>
<td>Dex alone</td>
<td>41</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Placebo + Indomethacin</td>
<td>82</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Placebo alone</td>
<td>27</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Stark AR et al: NEJM 2001; 344:95
Clinical practices and outcomes

• It is possible that it is not just the presence or absence of a certain clinical practice that is important, but how exactly the practice is performed in a given center. For example,
  – TPN with light protection vs. exposed
    • TPN exposure to light and risk of BPD (OR 9.3 [1.2-73], p=0.03)
  – Antenatal steroid timing
  – Resuscitation in delivery room (interns vs. fellows/faculty)
  – Antenatal antimicrobials – Ampicillin vs. Azithromycin

• We collect much data on patient characteristics and outcomes, but little on details of care practices and processes of care
How can we improve analysis of center variation?

• More targeted data collection is necessary for better center comparisons:
  – Known measured variables:
    • Known to be associated with outcome, measured
    • Antenatal steroids, IMV days, FiO₂
  – Known unmeasured variables:
    • Known to be possibly associated with outcome, not usually measured
    • Tidal volumes, blood gas variables, blood cytokine concentrations
    • Clinician intent underlying decisions
  – Unknown variables:
    • “Unknown unknowns”
    • Unknown markers of illness severity, physician expertise, nursing skills, staffing patterns, medico-legal environment, moral and ethical beliefs of parents and caregivers
Conclusion

• BPD is a complex multifactorial disorder

• Reduction of BPD is possible, but:
  – Proven interventions need to be implemented (caffeine, vitamin A)
  – We need more evidence on common interventions – RCTs on diuretics, bronchodilators, azithromycin
  – Analysis of center practices is important
  – Careful QI processes and monitoring of outcomes is important to ensure that outcomes are not worse after initiating an intervention