Respiratory Distress
Clinical Signs of Respiratory Distress

- Tachypnea
- Grunting
- Nasal flaring
- Retractions
- Cyanosis

Tachypnea and Retractions

- Tachypnea and retractions result from the need to increase intrathoracic pressure to achieve the necessary volume for adequate minute ventilation.

\[ C = \frac{\Delta V}{\Delta P} \]
Oxygenation

- Ventilation perfusion mismatch
- Right to left shunt
- Diffusion block
- Alveolar hypoventilation
- High altitude

Ventilation

\[ \dot{V} \leftrightarrow (f) \times (TV-DS) \]
Effect of Shunt on $pO_2$ and $pCO_2$

Response to Oxygen

![Graphs showing the effect of shunt on $pO_2$ and $pCO_2$.](image)
Oxygenation: Alveolar Gas Exchange Equation

\[
\text{PiO}_2 = 0.21 \times (760-47) \text{ mm Hg} = 149
\]

\[
\text{PAO}_2 = \text{PiO}_2 - \frac{\text{PACO}_2}{R}, \text{ where } R = \text{resp quotient} = 0.8
\]
Evaluation of Respiratory Distress in the Newborn Infant

- Arterial blood gas measurement
- Electrolytes, Ca, glucose
- Hemoglobin/hematocrit
- Sepsis evaluation
- Chest x-ray
Arterial Blood Gases in the Term Infant in the First Two Hours of Age
Normal Neonatal Chest
RDS: Radiologic Findings
Radiologic Staging of BPD

Stage I

Stage II

Stage III

Stage IV
Congenital Diaphragmatic Hernia
PDA
Phrenic Nerve Paralysis
Pneumothorax
Prominent Skin Folds
Pneumomediastinum

Pneumopericardium
Pneumonia

Aspiration

Chlamydia

Group B Strep

Meconium
Pulmonary Interstitial Emphysema
Grunting

- Grunting is a physiological response to an abnormal reduction in alveolar volume or to the presence of fluid within the alveolus = CPAP.
Benefits of CPAP (1)

- Reduces upper airway occlusion by decreasing upper airway resistance and increasing the pharyngeal cross sectional area.
- Reduces obstructive apneas.
- Increases the FRC.
- Reduces inspiratory resistance by dilating the airways.
- Increases the compliance and tidal volume of stiff lungs with a low FRC by stabilizing the chest wall and counteracting the paradoxical movements.
- Regularizes and slows the respiratory rate.
Benefits of CPAP (2)

• Reduces the incidence of apnea.
• Increases the mean airway pressure and improves ventilation perfusion mismatch.
• Conserves surfactant on the alveolar surface.
• Diminishes alveolar edema.
• The increased pressure helps overcome the inspiratory resistance of an endotracheal tube.
• After extubation, reduces the proportion of babies requiring reventilation.
• Oxygenation is related to the surface area and carbon dioxide elimination is related to the minute ventilation. Normalizing lung volume improves oxygenation and carbon dioxide elimination.
Indications for CPAP

- At birth, in a spontaneously breathing baby who has respiratory difficulty.
- When there is increased work of breathing indicated by: recession, grunting, nasal flaring, increased oxygen requirements or increased respiratory rate.
- Poorly expanded or infiltrated lung fields on chest x-ray picture.
- Atelectasis.
- Pulmonary edema.
- Pulmonary hemorrhage.
- Apnea of prematurity.
- Recent extubation.
- Tracheomalacia or other abnormalities of the airways, predisposing to airway collapse.
- Phrenic nerve palsy.
**Conventional Ventilation**

- PIP
- PEEP
- Rate (f)
- FiO2
- Inspiratory time
  - Time Constant = \( R \times C \)
  - DISEASE-SPECIFIC SETTINGS

**Oxygenation** \( \alpha \) MAP

**CO_2** \( \alpha \) ventilation \( \alpha \) \( f \times (TV - DS) \)
Critical Opening Pressure
Critical Closing Pressure
Critical Opening Pressure
Set Pressures
Critical Closing Pressure

Critical Opening Pressure
High Frequency Ventilation
HFJV PIP vs CV PIP
CO$_2$ Removal

Exhaled gas swirls out along airway walls, facilitating CO$_2$ removal.
Eliminating CO$_2$

$CV \rightarrow \dot{V}_{CO_2} \propto f, V_T$

$HFJV \rightarrow \dot{V}_{CO_2} \propto f, V_T^2$
Oxygenation

• \( \text{PaO}_2 \propto \) mean airway pressure

• \( \text{PaO}_2 \) sensitive to atelectasis
  
  • PEEP to stabilize alveoli
  
  • Role of conventional rate to prevent atelectasis and during recruitment phase
  
  • Wean CV rate when alveoli stable

  • Airleak syndromes 0-3 bpm, atelectasis 5-10 bpm

• Wean FiO\(_2\) whenever possible—it only masks the problem.
Surfactant
Respiratory Distress Syndrome (RDS)

- Developmental disorder typically associated with premature birth
  - Affects 20,000 to 30,000 infants each year in the USA
  - Approximately 50% of infants born between 26 and 28 weeks develop RDS
  - 20-30% of infants born at 30-31 weeks have the disorder

Avery et al, 1994
Respiratory Distress Syndrome
Clinical Signs

• Clinical signs may include tachypnea, grunting, retractions, and cyanosis

• Physical findings may include rales, poor air exchange, nasal flaring, use of accessory muscles, and episodes of apnea

• Radiographic findings often include reticular-granular opacification, air bronchograms, and decreased lung volumes

Avery et al, 1994
Surfactant Function

Normal Inspiration

Normal Expiration
Surfactant Function

Abnormal Respiration Without Surfactant

Exogenous Surfactant
Biophysical Properties of Endogenous Surfactant

- Reduces surface tension
- Rapid adsorption
- Rapid spreading
- Forms stable film
Pressure is greater in the smaller alveolus.

**Law of LaPlace**

\[ P = \frac{2T}{r} \]

- \( P \) = pressure \( (\text{dynes/cm}^2) \)
- \( T \) = surface tension \( (\text{dynes/cm}) \)
- \( r \) = radius \( (\text{cm}) \)

**Larger alveolus**
- \( r = 2 \)
- \( T = 3 \)
- \( P = \frac{(2 \times 3)}{2} = 3 \)

**Smaller alveolus**
- \( r = 1 \)
- \( T = 3 \)
- \( P = \frac{(2 \times 3)}{1} = 6 \)

Air flows into larger alveolus.
Radiographic Changes With Exogenous Surfactant Treatment

Before Surfactant Treatment

45 Minutes Post-Treatment
Composition of Mammalian Pulmonary Surfactant

- Phospholipids 80%
  - Saturated Phosphatidylcholine 60%
  - Unsaturated Phosphatidylcholine 25%
  - Phosphatidylglycerol and Phosphatidylinositol 15%
- Protein 12%
- Neutral Lipids 8%

King, 1984
Functions of Surfactant Associated Proteins

- **Hydrophilic**
  - SP-A: tubular myelin, host defense
  - SP-D: surfactant lipid homeostasis, host defense, antioxidant

- **Hydrophobic**
  - SP-B: surface tension reduction, tubular myelin, type II cell functions
  - SP-C: surface tension reduction, film stability

LeVine et al, 2001
Surfactant Metabolism in the Lung

Whitsett, 2001
Surfactant Metabolism
## Prophylaxis of RDS with Natural Surfactant Extracts

<table>
<thead>
<tr>
<th>Outcome (# of Studies)</th>
<th>Typical Risk Difference (95% CI)</th>
<th>Typical Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumothorax (11)</td>
<td>-0.15 (-0.20, -0.11)</td>
<td></td>
</tr>
<tr>
<td>Patent Ductus Arteriosus (12)</td>
<td>0.03 (-0.03, 0.09)</td>
<td></td>
</tr>
<tr>
<td>Intraventricular Hemorrhage (10)</td>
<td>-0.01 (-0.07, 0.05)</td>
<td></td>
</tr>
<tr>
<td>Bronchopulmonary Dysplasia (10)</td>
<td>-0.03 (-0.09, 0.03)</td>
<td></td>
</tr>
<tr>
<td>Mortality (11)</td>
<td>-0.07 (-0.12, -0.03)</td>
<td></td>
</tr>
<tr>
<td>BPD or Mortality (11)</td>
<td>-0.10 (-0.16, -0.04)</td>
<td></td>
</tr>
</tbody>
</table>

Soll, 2000
# Mortality in VLBW Infants Before and After the Introduction of Surfactant

<table>
<thead>
<tr>
<th>Birth Weight (g)</th>
<th>Before Surfactant</th>
<th>After Surfactant</th>
<th>Odds Ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>500-749</td>
<td>62%</td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td>750-999</td>
<td>28%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>1000-1249</td>
<td>14%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>1250-1500</td>
<td>7%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>All VLBW Infants</td>
<td>24%</td>
<td>20%</td>
<td></td>
</tr>
</tbody>
</table>

Schwartz, 1994
Timing of Surfactant Administration

- **Prophylaxis**
  - Prophylactic administration in delivery room

- **Treatment**
  - Early treatment
  - Late treatment (rescue)

Kendig et al, 1988
Advantages of Prophylactic Use of Surfactant

- Better distribution
- Avoid lung damage
- Avoid surfactant inactivation due to protein leak

Morley, 1997
Disadvantages of Prophylactic Use of Surfactant

- Potentially unnecessary treatment
- Added expense
- Interference with resuscitation
- Undocumented endotracheal tube placement

Morley, 1997
Timing of Surfactant Administration

• Eight randomized controlled trials evaluated the effect of delivery room surfactant administration compared to selective surfactant treatment
• All eight trials used natural surfactant extracts
## Surfactant: Prophylaxis vs Treatment

Meta-Analysis of 8 Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Outcome (# of Studies)</th>
<th>Risk Difference (95% CI)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumothorax (6)</td>
<td>-0.02 (-0.04, -0.01)</td>
<td></td>
</tr>
<tr>
<td>Bronchopulmonary Dysplasia (8)</td>
<td>-0.01 (-0.03, 0.02)</td>
<td></td>
</tr>
<tr>
<td>Mortality (7)</td>
<td>-0.05 (-0.07, -0.02)</td>
<td></td>
</tr>
<tr>
<td>BPD or Mortality (8)</td>
<td>-0.04 (-0.07, -0.01)</td>
<td></td>
</tr>
</tbody>
</table>

Soll, 2000
Use of Surfactant for RDS: Commercially Available Surfactants

- **Synthetic, Non-Protein Containing Surfactant**
  - Exosurf (1989)

- **Animal-Derived, Protein-Containing Surfactants**
  - Survanta (1991)
  - Infasurf (1998)
  - Curosurf (1999)

- **Synthetic, Protein-Containing Surfactant**
  - Surfaxin (Emerging, 2000)

- **Commercially Available Surfactants**
  - Exosurf (1989)
  - Survanta (1991)
  - Infasurf (1998)
  - Curosurf (1999)
  - Surfaxin (Emerging, 2000)
Use of Surfactant for RDS: “Natural” Surfactants

Mince (or lavage) lungs

- Add organic solvents
- Perform chromatography
- Add extra lipids
- Add palmitic acid and tripalmitin
Use of Surfactant for RDS: Why We Need New Surfactants

- Limited quantities of animal-derived surfactants
  - Only a few select herds of animals
  - 30% to 60% is discarded due to contamination
- Expensive to manufacture, costly to purchase
- May not work in an optimal amount of time
  - Too slow (pneumothorax, more RDS-related deaths?)
  - Too fast (more IVH and PVL?)
- Many neonates fail to respond to therapy
- Potential immunogenicity risk
- Potential infectious risk (eg, bacterial, viral, prion)
Use of Surfactant for RDS: Why We Need New Surfactants (cont)

• Need for more uniform levels of constituents
  – Target protein levels may vary by as much as 50%

• Current preparations
  – Are subject to inactivation, inhibition, and degradation, with the requirement for repeated administration
  – Do not contain SP-A or SP-D and may have little to no anti-inflammatory or anti-infection action
Use of Surfactant for RDS: Lucinactant SELECT Trial

• **SELECT**: Safety and Efficacy of Lucinactant Versus Exosurf in a Clinical Trial of RDS in Premature Neonates

• **Design**
  – Phase III superiority trial
  – 1,294 neonates (24-32 week gestational age, BW 600-1250 grams) enrolled at 49 international sites

• **Prophylaxis strategy**: randomization (2:2:1)
  – Surfaxin (lucinactant)
  – Exosurf (colfosceril)
  – Survanta (beractant)  

*Moya et al., Pediatrics 115:1018, 2005*
Use of Surfactant for RDS: Lucinactant SELECT Trial (cont)

- Results

Kaplan-Meier Survival Curves

Survival Function (%)

0 0.75 0.80 0.85 0.90 0.95 1.00

Number of Days Alive

0 10 20 30 40 50 60 70 80 90

Survanta, Surfaxin, Exosurf

Moya et al., Pediatrics 115:1018, 2005
At last! Discovery Labs gets Surfaxin approval

Philadelphia Business Journal by John George, Senior Reporter
Date: Tuesday, March 6, 2012, 4:32pm EST

Surfaxin is a synthetic surfactant product developed by the Warrington, Pa., biopharmaceutical company to prevent respiratory distress syndrome (RDS) in premature infants.

Discovery labs (NASDAQ:DSCO) first sought approval from the FDA for the compound in 2004. The company endured four requests for more information from the agency prior to getting the drug approved.

I chronicled the company’s long and arduous path to approval this week in the Philadelphia Business Journal.

“The approval of Surfaxin is an important medical advancement for the neonatology community and parents of preterm infants who will soon have an effective alternative to animal-derived surfactants to prevent the development of RDS,” said W. Thomas Amick, chairman and CEO of Discovery Labs. “This is a significant milestone in our continuing efforts to develop a pipeline of products to further advance the standard of respiratory critical care.”

The company anticipates that Surfaxin will be commercially available in the United States later this year.

About 90,000 premature infants in the United States are treated annually with animal-derived surfactants.

The FDA granted Discovery Labs its first-ever product approval last month when it granted marketing clearance to the company’s Afectair technology developed to simplify delivery of aerosolized medications to patients requiring ventilator support.

Discovery Labs’ stock was trading up 5 percent, to $3.75 per share, Tuesday afternoon before trading was halted pending the announcement of the FDA’s decision on the company’s new drug application for Surfaxin.
Target Oxygen Levels
Can you predict the $\text{PaO}_2$ from measurement of oxygen saturation using pulse oximetry?

The bars show the range of 95% of all measures when the oximeter read 90%, 92%, 94%, 96% & 98%.

*Increased risk of ROP*
Flynn NEJM 1992

Hay, Brockway & Eyzaguirre Pediatr 83:, 717, 1998
What is the Relationship between $\text{PaO}_2$ and Pulse Oxygen Saturation Levels?

Prospective comparison of $\text{PaO}_2$ and $\text{SaO}_2$ levels in 747 neonates receiving supplemental oxygen.

When oxygen saturation levels were 85%-93% the mean $\text{PaO}_2$ was $56 \pm 14.7$ mm Hg. (4% of the $\text{PaO}_2$ values were $> 80$ mmHg & 4.6% were $< 40$ mm Hg)

When the pulse oxygen saturation values were $> 93\%$ the mean $\text{PaO}_2$ was $68.8 \pm 15.9$ mm Hg. (59.5% of the $\text{PaO}_2$ values were $> 80$ mmHg)

1316 infants (24\(^{0}/7\) - 27\(^{6}/7\)) were randomized to a target saturation of 85-89% or 91-95%.

Targeting was begun 2 hrs after birth and continued until 36 weeks.
Oxygen Saturation Targets & Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Lower SaO₂</th>
<th>Higher SaO₂</th>
<th>RR (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>BPD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen need at 36 weeks</td>
<td>37.6%</td>
<td>46.7%</td>
<td>0.82 (0.72-0.93)</td>
</tr>
<tr>
<td>Physiological Definition</td>
<td>38.0%</td>
<td>41.7%</td>
<td>0.92 (0.81-1.05)</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before discharge</td>
<td>19.9%</td>
<td>16.2%</td>
<td>1.27 (1.01-1.60)</td>
</tr>
</tbody>
</table>

These data suggest one additional death for two cases of ROP prevented.
Kaplan–Meier Estimate of Survival to Hospital Discharge, Transfer, or 1 Year of Life.
### Plot of Survival to 36 Weeks' Postmenstrual Age in 3631 Infants in the SUPPORT and BOOST II Trials According to the Calibration Algorithm Used.

**No. of deaths/total no. of infants**

<table>
<thead>
<tr>
<th>Study</th>
<th>Lower SpO₂</th>
<th>Higher SpO₂</th>
<th>Relative Risk (99.73% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Old algorithm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUPPORT 2010</td>
<td>114/654</td>
<td>94/662</td>
<td>1.27 (1.01-1.60)</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/N. 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>192/1283</td>
<td>1.04 (0.79-1.38)</td>
</tr>
<tr>
<td><strong>New algorithm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BOOST II UK</td>
<td>79/334</td>
<td>50/334</td>
<td>1.58 (0.97-2.59)</td>
</tr>
<tr>
<td>BOOST II Australia/N. Zealand</td>
<td>36/94</td>
<td>20/194</td>
<td>1.80 (0.83-3.92)</td>
</tr>
<tr>
<td>Pooled result</td>
<td>115/1810</td>
<td>70/528</td>
<td>1.6 (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>

Conclusions

The inspiratory oxygen concentration and target oxygen saturation values should be tailored to the clinical setting and other variables.

Targeting saturation values 85-89% is associated with an increased mortality.

The saturation value range resulting in optimal clinical outcomes is unknown; however, saturation targets > 94% are generally not required.

Saturation values should be monitored immediately after birth and values should be kept within the targeted range for a given nursery (88-94%).
Should We Intubate?
## Table 2. Death or Need for Oxygen Treatment or Respiratory Support at 36 Weeks’ Gestational Age, According to Gestational Age at Birth.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Infants (25 to 28 Weeks’ Gestation)</th>
<th>25 or 26 Weeks’ Gestation</th>
<th>27 or 28 Weeks’ Gestation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CPAP (N=307)</td>
<td>CPAP (N=100)</td>
<td>CPAP (N=207)</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Death or oxygen treatment</td>
<td>33.9</td>
<td>38.9</td>
<td>53.0</td>
</tr>
<tr>
<td>Death, oxygen treatment, or respiratory support</td>
<td>35.2</td>
<td>40.3</td>
<td>55.3</td>
</tr>
<tr>
<td>Death before 36 weeks’ gestation</td>
<td>6.5</td>
<td>5.9</td>
<td>13.0</td>
</tr>
<tr>
<td>Survivors treated with oxygen</td>
<td>29.3</td>
<td>35.1</td>
<td>46.0</td>
</tr>
</tbody>
</table>

* Odds ratios are for the comparison between infants receiving nasal continuous positive airway pressure (CPAP) and those receiving intubation and ventilation.

*Morley et al., NEJM 358:700, 2008*
# CPAP vs Ventilator

## Table 3. Selected Prespecified Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CPAP (N=663)</th>
<th>Surfactant (N=653)</th>
<th>Relative Risk with CPAP (95% CI)</th>
<th>Difference in Means (95% CI)</th>
<th>Adjusted P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD or death by 36 wk of postmenstrual age — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiological definition of BPD†</td>
<td>317 (47.8)</td>
<td>333 (51.0)</td>
<td>0.95 (0.85 to 1.05)</td>
<td></td>
<td>0.30</td>
</tr>
<tr>
<td>BPD defined by need for supplemental oxygen</td>
<td>323 (48.7)</td>
<td>333 (54.1)</td>
<td>0.91 (0.83 to 1.00)</td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>BPD by 36 wk of postmenstrual age — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiological definition of BPD†</td>
<td>223/569 (39.2)</td>
<td>219/539 (40.6)</td>
<td>0.99 (0.87 to 1.14)</td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>BPD defined by need for supplemental oxygen</td>
<td>229/569 (40.2)</td>
<td>239/539 (44.3)</td>
<td>0.94 (0.82 to 1.06)</td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>Death by 36 wk of postmenstrual age — no. (%)</td>
<td>94 (14.2)</td>
<td>114 (17.5)</td>
<td>0.82 (0.63 to 1.03)</td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>Need for supplemental oxygen — no. of days†‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted mean</td>
<td>62.2±16.0</td>
<td>65.3±16.0</td>
<td>-3.1 (-7.1 to 0.8)</td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Unadjusted median</td>
<td>52</td>
<td>56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>20 to 86</td>
<td>27 to 91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Need for mechanical ventilation — no. of days¶</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted mean</td>
<td>24.8±10.0</td>
<td>27.7±11.1</td>
<td>-3.0 (-5.8 to -0.3)</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Unadjusted median</td>
<td>10</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>2 to 32</td>
<td>2 to 36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival without need for high-frequency or conventional ventilation at 7 days — no./total no. (%)</td>
<td>362/655 (55.3)</td>
<td>318/652 (48.8)</td>
<td>1.14 (1.03 to 1.25)</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Any air leak in first 14 days — no. (%)</td>
<td>45 (6.8)</td>
<td>48 (7.4)</td>
<td>0.89 (0.6 to 1.32)</td>
<td></td>
<td>0.56</td>
</tr>
<tr>
<td>Necrotizing enterocolitis requiring medical or surgical treatment — no./total no. (%)</td>
<td>83/654 (12.7)</td>
<td>63/636 (9.9)</td>
<td>1.25 (0.92 to 1.71)</td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>Intraventricular hemorrhage grade 3 or 4 — no./total no. (%)¶</td>
<td>92/642 (14.3)</td>
<td>72/628 (11.5)</td>
<td>1.26 (0.94 to 1.68)</td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Postnatal corticosteroid therapy for BPD — no./total no. (%)</td>
<td>47/649 (7.2)</td>
<td>83/631 (13.2)</td>
<td>0.57 (0.41 to 0.78)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe retinopathy of prematurity among survivors — no./total no. (%)</td>
<td>67/511 (13.1)</td>
<td>65/473 (13.7)</td>
<td>0.94 (0.69 to 1.28)</td>
<td></td>
<td>0.71</td>
</tr>
</tbody>
</table>

*NEJM 362:1970, 2010*
<table>
<thead>
<tr>
<th>COIN trial</th>
<th>SUPPORT trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-29 wks, randomized at birth</td>
<td>24-28 wks, randomized before birth</td>
</tr>
<tr>
<td>CPAP 8, intubated @ 60% O₂</td>
<td>CPAP 5, intubated at 50%</td>
</tr>
<tr>
<td>Surfactant: 38% of CPAP group, 77% of intubated</td>
<td>Surfactant: 67% of CPAP group, 99% of intubated</td>
</tr>
<tr>
<td>Pneumothorax: 9% in CPAP group, 3% of intubated</td>
<td>Pneumothorax: 6.8% CPAP, 7.4% intubated</td>
</tr>
</tbody>
</table>
No difference in primary outcome (or secondary)
CPAP failure at 40% FiO₂
50 (48.5%) in nCPAP group needed intubation/surfactant at median age of 6 hrs.

Sandri et al., Pediatrics 125:6, 2010
Other Issues and Future

• Role of early nasal IMV?
• Patient-triggered ventilation: AC
• Volume-targeted/volume-guaranteed neonatal ventilation
• Nebulized surfaxin
• BPD prevention: steroids, anti-oxidants, anti-inflammatory