WHAT IS THE ROLE OF SURFACTANT THERAPY IN THE NICU WITH INCREASING USE NON-INVASIVE VENTILATION (NIV)?

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Director of Nurseries, University of Louisville Hospital
Disclosures

- Speakers Bureau: Chiesi-USA, Ikaria, Maquet
- Research Support: NIH, Infacare, Pfizer
- Consultant/Advisory Boards: Ikaria, MedImmune (AZ), Infacare
- AAP Committees: Committee of Fetus and Newborn
Questions for Optimal Respiratory Care

Considerations

• Should caffeine always be used with non-invasive ventilation?
• Which surfactant should be used for non-invasive respiratory support?
• Should there be informed consent (ethical questions)?
• Should permissive hypercapnia to prevent intubation?

Non-Invasive Administration

• Should the surfactant vary according to GA?
• Should the surfactant vary according to chronological age?
• Are there perinatal considerations?
• Which surfactant should be used in your NICU or should there be more than one?
Less Invasive Ventilation: EBM?

- Does avoiding intubation decrease morbidity and/or mortality?
- Does decreasing exposure to invasive support decrease morbidity and mortality?
- Is surfactant given by less or non-invasive routes as effective as that given intratracheally?
- What else can we do to decrease the need for invasive support?
System used to apply continuous positive pressure breathing is diagrammed above. After the trachea has been intubated through the mouth, a mixture of oxygen and air is made to flow through the T-plate and into the bag, or out through the opening tail of the anesthesia bag. Pressure is increased by partially clamping the bag with the screw clamp. Tubing led to a water tank has its exit 30 cm below the water surface and serves as a "pop-off valve" to prevent delivery of excessive pressure.
Alveolar System of a Normal Lung

Lung Morphology in Severe RDS

RDS: Epidemiology

• Nearly 547,000 premature infants were born in the US in 2007 (12.7% of live births)¹

• RDS affects approx. 10% of premature babies:²
  • Approx. 50% of the neonates born at 26-28 weeks of gestation³
  • Approx. 30% of premature neonates born at 30 to 31 weeks of gestation³

• RDS was responsible for 19,000 hospitalizations (first-listed discharges) in 2006 in US⁴

• Between 1996 and 2006, the incidence of RDS declined by approximately 42%⁵

4. NHLBI. 2009 *Chart Book on Cardiovascular, Lung, and Blood Diseases*, 2009:60
5. NHLBI. *Fact Book Fiscal Year 2008*; 2008:42
RDS: Definition

- Respiratory distress syndrome (RDS) is a condition of pulmonary insufficiency.

- RDS is due to a deficiency and immaturity of alveolar surfactant along with structural immaturity of the lung.

- Natural course of RDS commences at birth and increases in severity over the first 2 days of life.

- Neonatal RDS is mainly, but not exclusively, confined to preterm babies.

- If untreated, RDS can lead to death from progressive hypoxia and respiratory failure.

RDS: Epidemiology

- Increased use of *antenatal steroids* to improve pulmonary maturity\(^1\)
- Early postnatal *surfactant therapy* to replace surfactant deficiency\(^1\)
- *Gentler techniques of ventilation* which are likely to minimize damage to the immature lungs\(^2\)

- The major long-term sequela of RDS is the development of bronchopulmonary dysplasia (BPD)\(^1\):
  - Incidence of 30-50% in neonates with birth weights of 700-900 g

RDS: Complications

- Alveolar rupture: air leak (ie, pneumothorax, pneumomediastinum, pneumopericardium, interstitial emphysema)
- Intracranial hemorrhage and/or periventricular leukomalacia (PVL) with associated neurodevelopmental delay
- Septicemia
- Patent ductus arteriosus (PDA)
- Pulmonary hemorrhage
- Necrotizing enterocolitis (NEC)
- Apnea of prematurity (AOP)

- Bronchopulmonary dysplasia (BPD)
- Retinopathy of prematurity (ROP)
- Neurologic impairment

Figure 4-4 Major components in the pathophysiology of RDS. The two main factors contributing to the severity of RDS are lung structural immaturity and the surfactant pool, which both are determined by the stage of development of the lung. Secondary factors such as surfactant treatment and lung injury then modulate the severity of RDS.
Current Strategies Aimed at the Prevention of Early Lung Injury

- Establish and maintain normal functional residual capacity (FRC)
- Avoid high tidal volumes
- Early treatment with surfactant*
- Optimize ventilatory strategies
- Support normal oxygen delivery and reduce oxygen exposure

*In clinical trials, surfactant treatment alone has not demonstrated the ability to significantly reduce the incidence of BPD

Lung Injury: Large Volume Breathes

• Lambs (5 pairs) were delivered by C/S; one lamb in each pair was randomly selected to receive 6 manual inflation of 35-40 ml/kg prior to surfactant therapy

• Hypervolumic breathes inhibited surfactant-induced increase in compliance and lung volume which resulted in more lung injury

• Quote: “a few inflations with volumes that are probably harmless in other circumstances might, when forced into the surfactant deficient lung immediately at birth, compromise the effect of subsequent surfactant rescue treatment”
RDS: Treatment Pillars

- Antenatal Corticosteroids (ANCS)
- Ventilation Techniques
- Surfactant Replacement Therapy

Benefits of Surfactant

- One of the best studied therapies in neonatal medicine with >400 studies evaluating the safety and efficacy
- Prophylactic surfactant (<15 minutes) yields best OR for reduction in major morbidities
- Reduction in ventilator parameters and oxygen levels
- Reduction in mortality by 50%
- Reduction in PAL (pulmonary air leaks) by 30-60%
- May decrease rate of IVH and NEC
- May prevent CLD in infants with GA > 30 weeks
Brief History of Surfactants in U.S.

- Survanta Approved in U.S. 1990
- Infasurf Approved in U.S. 1998
- CUROSURF Approved in U.S. 1991
- Surfaxin Approved in U.S. 2005
- Exosurf Approved in U.S. 1999
- Exosurf Removed From U.S. Market 2012
Bolus Surfactant Administration—Adverse Events

- Desaturations of 25-50%
- Reflux into ETT and circuit
- A/B (reflux or airway obstruction)
- Decreased CBF (cerebral blood flow)
- Decrease in BP
- Hypercapnia
- Reduction in cortical EEG voltage
- Increase in IVH
Effects on EEG: Surfactant/Intubation/Suctioning

- EEG suppression was noted in 18 / 29 (62%) [p=0.008] during surfactant administration
- Despite premedication for intubation, 9 infants had EEG suppression
- Endotracheal suctioning showed EEG suppression during suctioning
- Does this suppression have long-term effects?
Intubation and IVH

• VLBW (n=340); 35 had severe IVH

• Ventilation
  • DR 12
  • DOL #1 10
  • DOL #3 3

• Severe IVH (Grade III and IV) were associated with lower BW, MV in DR, and the duration of MV during the first three days

• Adjusted OR for severe IVH in those intubated in DR was OR=2.7; CI 1.1-6.6, P=0.03
Association of MV and BPD

- OR for the development of BPD is related to need for MV
- Related to timing of initiation of MV
  - DOB: 13.4
  - DOL 1 – 3: 9.6
  - DOL 4 – 7: 6.3
- Max PIP of > 25 cm H20 at birth or > 20 cm H20 at 1-3 days increases risk for BPD
Distribution of infants (%) into respiratory care groups by birth weights

Outcomes Associated with Surfactant Therapy

• Decreased requirements for mechanical ventilation\(^1,2,4\)
• Lower incidence of air leak complications\(^1,2\)
• Reduced mortality\(^1-4\)
• Potential* to reduce BPD when combined with select ventilation techniques\(^1,3\)

*In clinical trials, surfactant treatment alone has not demonstrated the ability to significantly reduce the incidence of BPD

Bronchopulmonary Dysplasia (BPD)

**Epidemiology**
- 30-50% (neonates with birth weight 700-900 g)
- 5% (neonates with birth weight >1250 g)

**Etiopathology**
- Mechanical ventilation (volutrauma, barotrauma, atelectotrauma, oxygen toxicity)

**Clinical findings**
- Tachypnea, tachycardia, cyanosis, chest retraction, wheezing
- Mild or no initial respiratory distress syndrome in the “new BPD”

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Bronchopulmonary Dysplasia
NICHD- Network Centers
Years 2003-2007

Stoll B et al, Pediatrics 2010
Bronchopulmonary Dysplasia (BPD)

Traditional definition\(^1\):
Oxygen requirement at 36 weeks post-menstrual age (PMA)

“New” BDP definition for infants < 32wk GA\(^2\):
Treatment with oxygen > 21% concentration for at least 28 days, \textit{plus}:
- mild (breathing room air at 36 wk PMA or discharge)
- moderate (need for < 30% oxygen at 36 wk PMA or discharge)
- severe (need for ≥ 30% oxygen and/or positive pressure at 36 wk PMA or discharge)

Association of MV and BPD

- Many studies have reported an association between duration of MV and BPD (CLD)
- Certainly there are other morbidities associated with prolonged MV such as NDI (neurodevelopmental impairment)
- Statistically there is an association per publication from Serenius (OR 2.71 per 1-week increment in duration; 95% CI 1.76-4.18)
- There was also an association with severe IVH and PVL with MV (OR 1.53 per 1 week increment in duration; 95% CI 1.01-2.33)
Mechanisms of Damage to the Immature Lung

- Overdistension
  - Excessive Vt; PIP - PEEP
  - Prolonged inspiratory times
  - Excessive FRC: PEEP; gas trapping
- Insufficient FRC; Low PEEP
- Infection – Inflammation
- Oxygen toxicity
- Improper conditioning of the inspired gas
  - Temperature and/or Humidity
- Increased pulmonary blood flow - PDA
Current Trends in Respiratory Management of the Premature Infant with RDS

- High Use of Antenatal Corticosteroids
  - Increase in the number of spontaneously breathing extremely preterm infants

- Need to avoid intubation and mechanical ventilation as much as possible

Increased Use of Non-Invasive Ventilation Techniques for the Treatment of Infants with RDS

### Impact of Variations in Respiratory Management on Incidence of BPD

**Columbia Approach**  
*Early nCPAP (65%)*  
(n=100)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median BW</td>
<td>1090g</td>
</tr>
<tr>
<td>% ANCS</td>
<td>52%</td>
</tr>
<tr>
<td>% Requiring MV</td>
<td>29%</td>
</tr>
<tr>
<td>% Requiring Surfactant</td>
<td>10%</td>
</tr>
<tr>
<td>Oxygen at 36 weeks PMA</td>
<td>4%</td>
</tr>
</tbody>
</table>

**Boston Approach**  
*Early MV (75%)*  
(n=100)

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Median BW</td>
<td>1030g</td>
</tr>
<tr>
<td>% ANCS</td>
<td>65%</td>
</tr>
<tr>
<td>% Requiring MV</td>
<td>75%</td>
</tr>
<tr>
<td>% Requiring Surfactant</td>
<td>45%</td>
</tr>
<tr>
<td>Oxygen at 36 weeks PMA</td>
<td>22%</td>
</tr>
</tbody>
</table>

*Note: Primary diagnosis was intracranial white matter disorder*

Approaches to CPAP

- "INSURE"
  - Intubation
  - Surfactant
  - Extubation
  - CPAP

- Columbia Approach
  - CPAP (Bubble)
  - Intubation
  - Surfactant
  - IMV

**Early vs Delayed NCPAP for RDS**

**Review:** Early versus delayed initiation of continuous distending pressure for respiratory distress syndrome in preterm infants  
**Comparison:** 01 Early vs late CDP  
**Outcome:** 01 Use of IPPV

<table>
<thead>
<tr>
<th>Study</th>
<th>Early CDP n/N</th>
<th>Delayed CDP n/N</th>
<th>Relative Risk (Fixed) 95% CI</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 CPAP</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Allen 1977</td>
<td>4/12</td>
<td>7/12</td>
<td>0.57 [0.22, 1.45]</td>
<td>25.4</td>
<td></td>
</tr>
<tr>
<td>Hegyi 1981</td>
<td>0/13</td>
<td>5/25</td>
<td>0.17 [0.01, 2.84]</td>
<td>14.0</td>
<td></td>
</tr>
<tr>
<td>Krouskop 1975</td>
<td>3/10</td>
<td>3/11</td>
<td>1.10 [0.28, 4.25]</td>
<td>10.4</td>
<td></td>
</tr>
<tr>
<td>Rowe 1978</td>
<td>6/17</td>
<td>5/19</td>
<td>1.34 [0.50, 3.61]</td>
<td>17.1</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>13/52</td>
<td>20/67</td>
<td>0.77 [0.43, 1.38]</td>
<td>66.8</td>
<td></td>
</tr>
</tbody>
</table>
| Test for heterogeneity chi-square=2.99 df=3 p=0.3937  
Test for overall effect=-0.89 p=0.4
| 02 CNP   |               |                 |                             |            |                             |
| Gerard 1975 | 0/11 | 4/12            | 0.12 [0.01, 2.01]           | 15.7       |                             |
| Mockrin 1975 | 0/10  | 5/13            | 0.12 [0.01, 1.87]           | 17.5       |                             |
| Subtotal (95% CI) | 0/21 | 9/25         | 0.12 [0.02, 0.85]           | 33.2       |                             |
| Test for heterogeneity chi-square=0.00 df=1 p=0.9844  
Test for overall effect=-2.12 p=0.03
| Total (95% CI) | 13/73 | 29/92        | 0.55 [0.32, 0.96]           | 100.0      |                             |
| Test for heterogeneity chi-square=7.11 df=6 p=0.2124  
Test for overall effect=-2.11 p=0.04

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The Cochrane Library
Need for Less Invasive RDS Treatment Strategies

- Bronchopulmonary Dysplasia (BPD), a complication of RDS, is a major cause of mortality and morbidity in very preterm infants.

- Despite the relevant improvements in the management of RDS with the use of antenatal steroids and surfactant therapy, outcomes such as BPD has not substantially decreased.

- Duration of mechanical ventilation via the endotracheal tube has a direct correlation with the potential development of BPD.

- Use of continuous positive airway pressure (CPAP) ventilation and other types of non-invasive ventilation can reduce need for MV and potentially the incidence of BPD in neonates with RDS.

Non-Invasive Ventilation Techniques

Continuous Positive Airway Pressure (CPAP)

Many devices/methods available that share the same principle: continuous administration of a constant positive pressure to the lungs

Nasal Intermittent Positive Pressure Ventilation (NIPPV)

Intermittent ventilator inflations are superimposed on the constant positive pressure of CPAP. This technique may further improve the rates of successful extubation

- Davis et al. Seminars in Fetal & Neonatal Medicine 2009; 14:14
Permissive Hypercapnia

- No overall benefit of a permissive hypercapnia compared to MV
- No reduction in mortality, neurodevelopmental impairment (NDI), or BPD
- Ventilation strategies which target high levels of PCO$_2$ > 55 mmHg probably should only be undertaken in RCTs
Permissive Hypercapnia

- Review of 425 ventilated VLBW who survived until 36 weeks found that PaCO$_2$ > 50 mmHg was associated with a greater incidence of BPD (p=0.024)
- This increase in BPD was found in those infants when the MAP < 8 cms
- Retrospective data suggest that acceptance of higher PaCO2 was safe but associated with IVH in the presence of a low APGAR
Use of Caffeine—CAP Trial

• Major findings
  • Alive at 36 weeks 350 (963)
  • Receiving supplemental oxygen 447 (954)
    • Adjusted OR 0.63; 95%CI 0.52-0.76; p<0.001)

• PAP was discontinued 1 week earlier in the infants assigned to the caffeine than in the placebo, therefore decreasing BPD

• Long-term survival did not show any differences but NDI was improved
Failure of CPAP—Need for Surfactant

• Initially defined as a need for an FiO2 > .3 in the first few hours of life

• CPAP failure was associated with a higher risk of death or BPD at 25-28 weeks (CPAP Failure 53% vs CPAP Success 14%; relative risk was 3.8 with 95% CI 1.6 – 9.3) and a substantially higher risk of pneumothorax at 29 – 32 weeks
Open Issues in Ventilation of Infants with RDS

- How to combine at best non-invasive ventilation and surfactant replacement therapy?
- How to address the risk of extubation failure?
- Which is the non-invasive technique to be used?
REVIEW OF RECENT TRIALS
Summary of Recent CPAP Literature

Three recently published studies suggest use of early nCPAP in very preterm infants may be a safe alternative to elective intubation and ventilation:


## Summary of CPAP Literature: Design

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>GA</th>
<th>% ANCS</th>
<th>Comparison</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COIN (2008)</strong></td>
<td>610</td>
<td>25 – 28⁶/⁷</td>
<td>Early nCPAP (94%)</td>
<td>Early nCPAP vs. Intubation and MV</td>
<td>Death or BPD at 36 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intubation (94%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SUPPORT (2010)</strong></td>
<td>1316</td>
<td>24 – 27⁶/⁷</td>
<td>Early nCPAP (Any – 96.8%)</td>
<td>Early nCPAP vs. Intubation (MV and selective surfactant)</td>
<td>Death or BPD at 36 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intubation (Any – 95.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VON DRM (2011)</strong></td>
<td>656</td>
<td>26 – 29⁶/⁷</td>
<td>Early nCPAP (Any – 98.7%)</td>
<td>Early nCPAP vs. Intubation (MV, early surfactant, rapid extubation – ISX) vs. Intubation (prophylactic surfactant and MV for 6 hrs. - PS)</td>
<td>Death or moderate to severe BPD at 36 wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intubation (ISX) (Any – 98.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intubation (PS) (Any - 98.6%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Summary of CPAP Literature: Need for MV

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Secondary Outcomes: Need for MV</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COIN (2008)</td>
<td>Early nCPAP vs. Intubation (MV and very late surfactant)</td>
<td>There were significantly fewer days on MV for the early nCPAP group (Median 3 days vs. 4 days)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SUPPORT (2010)</td>
<td>Early nCPAP vs. Intubation (MV and early surfactant)</td>
<td>There were significantly fewer days on MV for the early nCPAP group (Adjusted Mean Days 24.8±1.0 vs. 27.7±1.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>VON DRM (2011)</td>
<td>Early nCPAP vs. Intubation (MV, early surfactant, rapid extubation – INSURE) vs. Intubation (prophylactic surfactant and MV – 6 hrs.)</td>
<td>There was a reduction in the need for any mode of ventilation between nCPAP and ISX groups vs. PS and MV group (52.3% and 59.3% vs. 95.7%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

## Summary of CPAP Literature: Death or BPD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Death or O₂ requirement at 36 weeks PMA</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COIN (2008)</td>
<td>Early nCPAP vs. Intubation (MV and very late surfactant)</td>
<td>nCPAP did not significantly reduce rate of death or BPD compared to intubation (33.9% vs. 38.9%, p=0.19)</td>
<td>0.80 (0.58, 1.12)</td>
</tr>
<tr>
<td>SUPPORT (2010)</td>
<td>Early nCPAP vs. Intubation (MV and early surfactant)</td>
<td>nCPAP did not significantly reduce rate of death or BPD compared to intubation (48.7% vs. 54.1%, p=0.07)</td>
<td>0.91 (0.83, 1.01)</td>
</tr>
</tbody>
</table>
| VON DRM (2011)| Early nCPAP vs. Intubation (MV, early surfactant, rapid extubation – ISX) vs. Intubation (prophylactic surfactant and MV for 6 hrs. - PS) | No significant difference in the rates of death or BPD among groups (30.5% vs. 28.5% vs. 36.5%) | **CPAP vs. PS 0.83** (0.64, 1.09)  
**ISX vs. PS 0.78** (0.59,1.03) |

The “InSurE” Technique

• Early intubation (FiO₂ requirement < 0.45), surfactant administration and rapid extubation

• Alternative to giving late rescue surfactant when RDS has worsened – causing respiratory insufficiency necessitating MV¹

• Cochrane meta-analysis suggests “InSurE” may help reduce need for MV, air leaks and BPD vs. late selective surfactant treatment¹

• A lower treatment threshold (FiO₂ < 0.45) confers greater treatment advantage vs. a higher treatment threshold¹

## Success with nCPAP

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Gestational Age</th>
<th>Ventilation Strategy</th>
<th>Indication for MV</th>
<th>Success with nCPAP†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verder H, et al. 1994¹ (pilot)</td>
<td>73</td>
<td>25-35 weeks</td>
<td>NCPAP vs. NCPAP + surfactant</td>
<td>a/APO$_2$ ≤ 0.15</td>
<td>57% of infants treated with CUROSURF did not require subsequent MV</td>
</tr>
<tr>
<td>Verder H, et al. 1999²</td>
<td>60</td>
<td>25-29 weeks</td>
<td>NCPAP + early surfactant administration vs. NCPAP + late surfactant administration</td>
<td>a/APO$_2$ ≤ 0.21 to 0.15</td>
<td>79% of infants treated with early administration of CUROSURF did not require subsequent MV</td>
</tr>
</tbody>
</table>
| Dani C, et al. 2004³          | 27 | Early surfactant administration + rapid extubation to NCPAP (INSURE): 29.0 ± 2.2 weeks | INSURE vs. MV + surfactant | FiO$_2$ > 0.50                                           | 100% of infants treated with early CUROSURF administration followed by rapid extubation did not require subsequent MV  
|                              |    | MV+ surfactant: 28.3 ± 1.32 weeks |                      |                                                            | 0% of infants in INSURE group required more than 1 dose of CUROSURF |
| Bohlin K, et al. 2007⁴ (retrospective) (INSURE group) | 420 | 27-34 weeks     | INSURE vs. MV + surfactant                               | a/APO$_2$ ≤ 0.22           | 81% of infants treated with early CUROSURF administration followed by rapid extubation did not require subsequent MV  
|                              |    |                 |                                                          |                                                            | 17% of infants in INSURE group required more than 1 dose of CUROSURF |

†Success with NCPAP is defined as no further need to reintubate for subsequent MV  
‡Late surfactant administration was defined as after FiO$_2$ has risen to 0.57–0.77.¹⁴
## Success with NIPPV

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Gestational Age</th>
<th>Ventilation Strategy</th>
<th>Indication for MV</th>
<th>Success with NIPPV†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramanathan R, et al. 2012</td>
<td>110</td>
<td>26-30 weeks</td>
<td>NIPPV vs. SIMV with extubation to nCPAP</td>
<td>FiO$_2$&gt;0.60</td>
<td>83% of infants treated with CUROSURF did not require subsequent surfactant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>NIPPV (n=53)</th>
<th>SIMV (n=57)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV @ 7 days of Age (Primary Endpoint)</td>
<td>17 %</td>
<td>42 %</td>
<td>0.005</td>
</tr>
<tr>
<td>Oxygen @ 36 weeks PMA (BPD)</td>
<td>21 %</td>
<td>39 %</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Early CPAP vs. IPPV in extremely low gestational age newborns

<table>
<thead>
<tr>
<th></th>
<th>Death/BPD</th>
<th>IPPV</th>
<th>Surfactant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CPAP</td>
<td>MV-Surf</td>
<td>CPAP</td>
</tr>
<tr>
<td><strong>COIN</strong></td>
<td>34%</td>
<td>39%</td>
<td>58.7%</td>
</tr>
<tr>
<td>25-28 wks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SUPPORT</strong></td>
<td>49%</td>
<td>54%</td>
<td>83.1%</td>
</tr>
<tr>
<td>24-28 wks</td>
<td></td>
<td></td>
<td>24.8 d</td>
</tr>
<tr>
<td><strong>VON (CPAP)</strong></td>
<td>31%</td>
<td>37%</td>
<td>52%</td>
</tr>
<tr>
<td>26-30 wks</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>VON (ISX)</strong></td>
<td>29%</td>
<td>37%</td>
<td>59%</td>
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</tbody>
</table>
Early CPAP vs. ventilation trials in extremely low gestational age newborns - complications.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Pneumothorax</th>
<th></th>
<th>Severe IVH</th>
<th></th>
<th>PVL</th>
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<tbody>
<tr>
<td></td>
<td>CPAP</td>
<td>Surfactant</td>
<td>CPAP</td>
<td>Surfactant</td>
<td>CPAP</td>
</tr>
<tr>
<td>COIN</td>
<td>9%</td>
<td>3%</td>
<td>9%</td>
<td>9%</td>
<td>3%</td>
</tr>
<tr>
<td>SUPPORT</td>
<td>7%</td>
<td>7%</td>
<td>14%</td>
<td>11%</td>
<td>--</td>
</tr>
<tr>
<td>VON</td>
<td>5%</td>
<td>3%</td>
<td>3%</td>
<td>4%</td>
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</tr>
</tbody>
</table>

- Increase in Vt and Ve
- Upper airway stimulation may reduce apnea
- Higher mean airway pressure (MAP) may lead more lung stability and better gas exchange
- Reduction of dead space—clearing exhaled gas from proximal airway
Physiologic Effects of NIV

- Improves ventilation with improvement in gas exchange
- Lung volumes are enhanced
- Improves oxygenation
- Reduction in respiratory effort with less chest wall distortion leading to better synchrony
NCPAP versus Nasal Cannula

- This study randomized VLBW (n=303) to either HFNC at 5 -6 LPM or nasal CPAP at 7 cms H2O pressure after extubation
- Treatment failure
  - Nasal cannula 34.2%
  - NCPAP 25.8%
- Approximately ½ of the VLBWs whom were treated with HFNC who failed were successfully treated with CPAP without reintubation
- Incidence of nasal trauma was significantly lower in the NC group than in the CPAP group (P=0.01)
Non-Invasive Ventilation Decrease Death / BPD

• Compared to NIPPV and NCPAP with >1000 patients
• Compared these two methods of non-invasive ventilation at the time of the first use of noninvasive respiratory support during the first 28 days of life
• NIPPV (n=497)
  • Died/Survived with BPD 191 (38.4%)
• NCPAP (n=490)
  • Died/Survived with BPD 180 (36.7%)
• No real differences
How Can We Keep Babies Off MV?

• Do not initiate ventilation unless clearly justified
  • Strict indications for intubation
• Discontinue ventilation as soon as possible
  • Aggressive weaning to less invasive respiratory support
In Summary

• Clinical outcomes for infants with RDS have improved due to increased use of antenatal steroids, early postnatal surfactant therapy and gentler techniques of ventilation

• Despite these advances in perinatal management, BPD continues to be a significant morbidity

• Clinical trials suggest early management with nCPAP may be a viable alternative to intubation, surfactant and mechanical ventilation
CONCLUSIONS

• NCPAP is effective in the initial management of RDS and can be used starting in the delivery room to avoid PPV in infants with good respiratory effort
• Administer early caffeine
• NCPAP is more successful in infants over 26-27 weeks
• NCPAP is successful after extubation to prevent respiratory deterioration and apnea
• There is no conclusive evidence that early CPAP instead of IPPV improves survival or long-term outcomes
CONCLUSIONS

• If the infant reaches NCPAP Failure criteria (probably an FiO2 >0.35, consider the least invasive approach for surfactant administration

• Consider different methods of non-invasive administration (INSURE Technique): MIST, aerosol, fine catheter or angiocath (#16 g)

• NIPPV not conclusively proven by EBM
CONCLUSIONS

• Early nCPAP in very preterm infants seems to be safe and might lead to improved outcomes compared with elective intubation and ventilation\(^1\)

• A significant number of infants stabilized with nCPAP shortly after birth can avoid intubation, ventilation and surfactant treatment all together\(^1\)

• If early nCPAP used to stabilize at birth, it is likely to be optimal if selective surfactant treatment is provided early (FiO\(_2\) < 0.45) using techniques such as “InSuRE”\(^1,2\)

• While trends are promising, there is no conclusive evidence that early CPAP instead of IPPV reduces BPD, improves survival or long term outcomes
