The Changing Incidence and Diagnosis of RDS

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What is RDS in 2014?

• How do we diagnose RDS?

• How do we treat and does treatment influence diagnosis?

Mary Ellen Avery
1927-2011
Hyaline Membrane Disease – Pathological Diagnosis

Idiopathic Respiratory Distress of the Newborn (1959 conference)

Avery did not define disease, rather described clinical findings and pathology.

Pathophysiology of RDS

- Surfactant treatment
- Recycling
- Surfactant function
- Surfactant inactivation
- Pulmonary edema
- Severe of RDS
- Lung structure
- Tissue function

Respiratory Mortality for 180,000 Births (2002-2008) in U.S. Adjusted Odds Ratios Relative to Term
What is Problem in Diagnosis of RDS in VLBW Infants

- Symptoms – tachypnea, retractions, flaring, grunting
- Oxygen need – amount and time needed
- Chest x-ray – uniform and granular, lung volume

A diagnosis of exclusion - RDS if the infant does not have infection, pulmonary hypoplasia, TTN.

• The route problem is that RDS is caused primarily by surfactant deficiency –
  - What do we know about surfactant in the preterm lung?
Surfactant Concentration in Alveoli of Humans

<table>
<thead>
<tr>
<th></th>
<th>Surfactant (mg/kg)</th>
<th>Alveolar Fluid (ml/kg)</th>
<th>Surfactant Concentration (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>4</td>
<td>0.4</td>
<td>10 mg/ml</td>
</tr>
<tr>
<td>Term newborn</td>
<td>Assume 100</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Preterm newborn</td>
<td>0-10</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>

P<sub>CO</sub><sub>2</sub> and Surfactant Pool Sizes for Preterm Lambs on CPAP at 2h of Age

 Mulrooney, et al., AJRCCM, 2005

Inhibition of Surfactant Function in RDS

 Nagamii, Jacobs and Jolles, J. Pediatr, 1980
Antenatal Testing for RDS

- Good tests that are no longer available
  - L/S ratio, PG, Lung Profile, TDX
- Poor tests available, but seldom used currently

Obstetricians deliver infants when “clinically indicated”
Antenatal Influences on Lung Maturation/Development

<table>
<thead>
<tr>
<th>Condition</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Delays Maturation</td>
</tr>
<tr>
<td>Maternal Smoking</td>
<td>Interferes with Lung Development</td>
</tr>
<tr>
<td>Fetal Growth Restriction</td>
<td>Abnormal Lung Development</td>
</tr>
<tr>
<td>Corticosteroids – Therapeutic</td>
<td>Induced Lung Maturation</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>Maturation or Injury</td>
</tr>
</tbody>
</table>
Limitations of Meta-Analysis

- Very few infants <28 wks GA
- No assessment of severity of RDS
- Randomized data – before 1990, before surfactant
- Multiple clinical experiences published
Obstetric Precursors to Preterm Birth

Goldenberg, et al., The Lancet, 2008

Spontaneous Preterm Labor

Delivery because of maternal or fetal indications

Premature preterm rupture of the membranes (PPROM)

Preterm labor

Acceleration of Fetal Lung Maturation Following Preterm PROM

<table>
<thead>
<tr>
<th></th>
<th>No PROM</th>
<th>PROM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>42</td>
<td>22</td>
</tr>
<tr>
<td>Mean BW (kg)</td>
<td>1.67</td>
<td>1.44</td>
</tr>
<tr>
<td>Time of ROM</td>
<td>3.9 hr</td>
<td>94 hr</td>
</tr>
<tr>
<td>% RDS</td>
<td>64%</td>
<td>31%</td>
</tr>
<tr>
<td>Deaths from RDS</td>
<td>52%</td>
<td>71%</td>
</tr>
</tbody>
</table>

Richardson, et al., AJObGyn, 1974

Inflammation and Lung Development

Correlation of Chorioamnionitis with RDS and BPD in Ventilated Preterm Infants

<table>
<thead>
<tr>
<th></th>
<th>Chorioamnionitis</th>
<th>No Chorioamnionitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDS</td>
<td>33%</td>
<td>67%</td>
</tr>
<tr>
<td>% BPD</td>
<td>63%</td>
<td>37%</td>
</tr>
</tbody>
</table>

Inflammation and Lung Development

Intra-amniotic IL-1α Accelerates Lung Maturation in Fetal Rabbits


Effect of Interval from 20 mg IA Endotoxin to Delivery

Interval to Preterm Delivery

Lung Volume - 40 cmH₂O (ml/kg)

Sat PC - Alveolar Wash (mmol/kg)
Antenatal Inflammation Preceding Antenatal Steroids in Fetal Sheep


- RDS is less frequent now than often appreciated because –
  - Biology of induced lung maturation
    - Antenatal corticosteroids
    - Antenatal exposure to inflammation
  - Clinical care strategies
    - Allowing babies to breathe/adapt
    - Using CPAP to transition
    - Recruiting strategies?/Avoiding injury

Diagnosis of RDS for Infants <28 wks – NICHD Neonatal Research Network

- RDS requires oxygen use from 6-24h of life, respiratory support to 24h, and a chest x-ray consistent with RDS. 1997-2002 (Fanaroff, 2007)
- RDS requires oxygen use or respiratory support for ≥6h only – no requirement for a chest x-ray. 2003-2007 (Stoll, 2010)
### NICHD – Neonatal Research Network

#### Incidence of RDS in VLBW Infants

<table>
<thead>
<tr>
<th>Study</th>
<th>Infants Reported</th>
<th>% RDS</th>
<th>% Treated with Surfactant</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICHD 1997-2002 (Fanaroff – 2007)</td>
<td>500-1000g</td>
<td>63%</td>
<td>62%</td>
</tr>
<tr>
<td>NICHD – 2003-2007 (Stoll, 2010)</td>
<td>22-28 weeks</td>
<td>95%</td>
<td>76%</td>
</tr>
</tbody>
</table>

*Severe RDS is not the rule in VLBW infants.*

### Incidence of RDS in VLBW Infants

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<th>% RDS</th>
<th>% Treated with Surfactant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danish Experience - 1999</td>
<td>27±2 weeks</td>
<td>-</td>
<td>30%</td>
</tr>
<tr>
<td>COIN Trial</td>
<td>950g average</td>
<td>-</td>
<td>38% (CPAP arm)</td>
</tr>
<tr>
<td>NICHD – Support Trial</td>
<td>24-27 weeks</td>
<td>-</td>
<td>67% (CPAP arm)</td>
</tr>
<tr>
<td>Vermont-Oxford CPAP Trial</td>
<td>26-29 weeks</td>
<td>-</td>
<td>15% (CPAP arm)</td>
</tr>
</tbody>
</table>

### A South African Experience where Mechanical Ventilation is Limited (BW-870g, GA – 27.9 weeks, 38% of SGA)

- 309 Infants 0.5-1.0kg, 225 weeks GA
  - 100%
- 212 NCPAP Only
  - 69%
  - 2 Vent
  - 170 Survived to Discharge
    - 80%
- 97 NCPAP + InSurE
  - 31%
  - 15 Vent
  - 61 Survived to Discharge
    - 63%
  - 2 BPD

*Kirsten, et al., Pediatr, 2012*
Incidence of RDS Depends on Diagnostic Criteria and Management Strategy –

Incidence of RDS can be quite low even in VLBW infants

Other Factors that Influence the Incidence of RDS

• Early surfactant treatments
• Other diseases that mimic or occur with RDS
  – Infection/pneumonia
  – Pulmonary hypoplasia
  – Transient tachypnea of newborn
• Clinical management

Infection/Pneumonia

• 50-70% of infants <32wks GA have been exposed to chorioamnionitis/infection (Goldenberg, 2008)

• About 2% of infants <1kg have a positive blood culture/sepsis at birth (Stoll, 2002)

• The diagnosis of “congenital pneumonia” is seldom made in ELBW infants (Stoll, 2010)

• Tracheal aspirates of these infants have indicators of inflammation/infection (Watterberg, 1996; DeDooy, 2003)
Oxygenation Responses of Infants with RDS to a Surfactant Treatment

How Can We Diagnose Lung Inflammation/Diffuse Pneumonia in a ELBW Infant if -

- There is no positive blood culture.
- The organisms are not traditional pathogens (Ureaplasma) or are not culturable.
- The chest x-ray looks like RDS.
- The inflammation/edema inhibits surfactant causing surfactant deficiency.

Pulmonary Hypoplasia/Delayed Lung Maturation

- Difficult to diagnose in preterm
- No decrease in RDS for SGA infants
- Animal model data indicate adverse effects on lung growth from –
  - Growth restriction
  - Maternal tobacco exposure
RDS Incidence by Gestational Ages

Chang, et al., AJ Ob/Gyn, 191:1414, 2004

Risk of BPD Relative to Gestational Age Adjusted Birth Weight Percentiles for 4525 Infants Born at 24-31 Weeks Gestation


Confounding Effects of Delivery Room Treatments on RDS

Injury with Mechanical Ventilation  
Epithelial Leaks and Inflammation  
Surfactant Inhibition  
“ARDS”

Use of CPAP  
Recruitment of FRC/Surfactant Secretion  
Minimizing Lung Injury  
No RDS if Enough Surfactant
Hypothetical Stresses to Epithelial Cells of a Small Airway During Reopening (A), or from a Fluid Plug (B)


Bronchoalveolar Lesions in Airways of Preterm Surfactant Deficient Rabbits are Prevented by Surfactant Treatment

Robertson, 1984

Lung mRNA Levels - 3h

Ilbeyat et al., Am J Respir Crit Care Med. 2007 Sep;176(6):575-81.
Early – Delivery Room/within 15 min – Surfactant Treatments –

- Do not know who would have had RDS

  - Persistent RDS – is that surfactant deficiency disease?

  - No RDS after treatment – did treatment correct deficiency or was there no deficiency?

Clinical Trials: Can we demonstrate that we can decrease lung injury by gentle resuscitation (CPAP)?

The Coin Trial

- Assessed 25/0 to 28/6 week infants for ventilatory effort and status with stimulation at 5 min.

- Clinical judgment - is baby breathing but needs help?

- Yes - randomize to N-CPAP or intubate and ventilate (+ surfactant)

Morley, NEJM, 2008
The Coin Trial

<table>
<thead>
<tr>
<th>N</th>
<th>Ventilation</th>
<th>CPAP</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW</td>
<td>303</td>
<td>307</td>
<td></td>
</tr>
<tr>
<td>% Surfactant by 5d</td>
<td>77%</td>
<td>38%</td>
<td>*</td>
</tr>
<tr>
<td>% Intubated by 5d</td>
<td>100%</td>
<td>46%</td>
<td>*</td>
</tr>
<tr>
<td>Ventilation days (median)</td>
<td>4</td>
<td>3</td>
<td>*</td>
</tr>
</tbody>
</table>

Morley, NEJM, 2008

The Coin Trial - 36 Week Outcomes

<table>
<thead>
<tr>
<th>Pneumothorax</th>
<th>Ventilation</th>
<th>CPAP</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>3.0</td>
<td>9.1</td>
<td>*</td>
</tr>
<tr>
<td>BPD - 28d O₂</td>
<td>65%</td>
<td>54%</td>
<td>NS</td>
</tr>
<tr>
<td>BPD - 36d O₂</td>
<td>35%</td>
<td>29%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Morley, NEJM, 2008

Comments on COIN Trial

- Randomization at 5 min excluded “bad” and “good” infants.
- CPAP of 8 cmH₂O used for most infants.
- Pneumothorax occurred after delivery room intervention.
- Median ventilation days were low for both groups.
### Delivery Room CPAP or Intubation + Surfactant for ELBW Infants

- Infants between 24th and 27th wks GA randomized.
- Randomized prior to delivery.
- Protocol limited ventilation strategy.
- Primary outcome – BPD or death

<table>
<thead>
<tr>
<th></th>
<th>CPAP</th>
<th>Intubation and Surfactant</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>663</td>
<td>653</td>
</tr>
<tr>
<td>Gestational Age (wks)</td>
<td>$26.2\pm1.1$</td>
<td>$26.2\pm1$</td>
</tr>
<tr>
<td>Birth Wt. (g)</td>
<td>$835\pm18$</td>
<td>$826\pm198$</td>
</tr>
<tr>
<td>Full course antenatal steroids</td>
<td>74%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Support Trial: NEJM, 2010

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CPAP</th>
<th>Intubation and Surfactant</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome – Death or BPD</td>
<td>47.8%</td>
<td>51.0%</td>
<td>0.30</td>
</tr>
<tr>
<td>Death</td>
<td>14.2%</td>
<td>17.5%</td>
<td>0.09</td>
</tr>
<tr>
<td>Survival without mechanical ventilation</td>
<td>55.3%</td>
<td>48.8%</td>
<td>0.01</td>
</tr>
<tr>
<td>Any air leak</td>
<td>6.8%</td>
<td>7.4%</td>
<td>0.56</td>
</tr>
<tr>
<td>Postnatal Steroids</td>
<td>7.2%</td>
<td>13.2%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Support Trial: NEJM, 2010

### Comment on Support Trial

- Infants randomized prior to birth – include “good” and “bad” infants.
- Outcomes in general favor CPAP.
Comparison of CPAP Alone, CPAP + Surfactant, or Prophylactic Surfactant + Ventilation in Delivery Room (26-29 wks GA)

<table>
<thead>
<tr>
<th></th>
<th>Intubation + Surfactant and Ventilation</th>
<th>Intubation + Surfactant and CPAP</th>
<th>CPAP and Selective Surfactant</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>209</td>
<td>216</td>
<td>223</td>
</tr>
<tr>
<td>Death or BPD</td>
<td>36.5%</td>
<td>28.5%</td>
<td>30.5%</td>
</tr>
<tr>
<td>Death</td>
<td>7.2%</td>
<td>7.0%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Received Surfactant – first 7d</td>
<td>99.5%</td>
<td>99.1%</td>
<td>46.3%*</td>
</tr>
<tr>
<td>ETT – first 7d</td>
<td>95.7%</td>
<td>51.4%*</td>
<td>45.5%*</td>
</tr>
</tbody>
</table>

*p<0.05

Dunn, et al., Pediat., 2010

Multicenter Randomization of Spontaneous Breathing 800-1500g Infants at 5 min after Birth to:
- CPAP + Surfactant for >35% O₂
- Oxygen + IMV and Surfactant for >35% O₂

<table>
<thead>
<tr>
<th></th>
<th>CPAP/Insure</th>
<th>O₂/MV-Surfactant</th>
<th>P&lt;0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>131</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>Mean GA</td>
<td>29.9 wks</td>
<td>29.5 wks</td>
<td></td>
</tr>
<tr>
<td>RDS</td>
<td>50%</td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
<td>30%</td>
<td>50%</td>
<td>*</td>
</tr>
<tr>
<td>Surfactant Rx</td>
<td>28%</td>
<td>46%</td>
<td>*</td>
</tr>
<tr>
<td>BPD</td>
<td>7%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>8%</td>
<td>10%</td>
<td></td>
</tr>
</tbody>
</table>

Tapia, et al., J. Pediat., 2012

Early CPAP (Treatment) vs Early Surfactant – ELBW Infants All Studies – Death or BPD

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Randomized</th>
<th>Center</th>
<th>CG/CG.wks</th>
<th>COC/CG.cmg</th>
<th>COC/CG.cmg</th>
<th>CG/CG.cmg</th>
<th>CG/CG.cmg</th>
<th>CG/CG.cmg</th>
<th>CG/CG.cmg</th>
<th>CG/CG.cmg</th>
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<th>CG/CG.cmg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen et al.</td>
<td>CG/CG</td>
<td>129/129</td>
<td></td>
<td>120/95</td>
<td>5.00 (5.00, 5.00)</td>
<td>5.00 (5.00, 5.00)</td>
<td>5.00 (5.00, 5.00)</td>
<td>5.00 (5.00, 5.00)</td>
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<td>5.00 (5.00, 5.00)</td>
<td>5.00 (5.00, 5.00)</td>
</tr>
<tr>
<td>Total N (CG/CG)</td>
<td>258</td>
<td>258</td>
<td></td>
<td>120/95</td>
<td>5.00 (5.00, 5.00)</td>
<td>5.00 (5.00, 5.00)</td>
<td>5.00 (5.00, 5.00)</td>
<td>5.00 (5.00, 5.00)</td>
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</tr>
</tbody>
</table>

Mediation analysis of CPAP vs Surfactant Trials – New Topics 2016 with permission of Dr. Neil Finer
What is RDS in 2013?

- A disease that seldom is the primary cause of death
  - Antenatal corticosteroids

- Can be decreased by delivery room management

- Can be effectively treated with surfactant

But: A specific diagnosis is difficult to make.

Mortality of Preterm Infants in the US Due to Respiratory Distress Syndrome

Modified from Lee, et al., J. Pediatr, 1999 by Smith & Hansen, with permission