INDICATIONS FOR SURFACTANT REPLACEMENT IN TERM AND PRETERM NEWBORNS

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I have received funds to speak at meetings sponsored by Ross Laboratories, Burroughs Wellcome and Chiesi Farmaceutici and I act as a consultant for the last named
Indications for Surfactant Treatment

• **Treatment of respiratory distress syndrome (RDS)** – Soll 2000: CDSR (2): CD001149

• **Prophylaxis of RDS** – Soll 2000: CDSR: (2): CD000511
Other Potential Indications for Surfactant Treatment

- **Meconium aspiration syndrome** – Findlay et al, Pediatrics, 1996
- **Congenital pneumonia** – Herting et al, Pediatrics 2000
- **Diaphragmatic hernia** – Bos et al, Lancet 1991
- **ECMO** – Lotze et al, J Pediatr 1993
- **Neonatal ARDS** – Khammash et al, Pediatrics 1993
- **Early CLD** - Pandit et al, Pediatrics 1995; Laughon et al, Pediatrics 2009
- **Pulmonary h’age** – Pandit et al, Arch Dis Child 1999
- **Drug delivery** – Yeh et al, Pediatrics, 2008
Natural Surfactant vs Control

Prophylaxis Trials

Treatment Trials

Pneumothorax
IVH
PDA
BPD
Mortality
Death or BPD

Odds ratio

IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia

Synthetic Surfactant vs Control

Prophylaxis Trials

- Pneumothorax
- IVH
- PDA
- BPD
- Mortality
- Death or BPD

Treatment Trials

Odds ratio

IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia

## Results From Systematic Reviews

<table>
<thead>
<tr>
<th>MORTALITY</th>
<th>RR</th>
<th>95% CI</th>
<th>NNT</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple doses</td>
<td>0.63</td>
<td>0.39-1.02</td>
<td>14</td>
<td>7-1000</td>
</tr>
<tr>
<td>Natural surfactant</td>
<td>0.86</td>
<td>0.76-0.98</td>
<td>50</td>
<td>20-1000</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>0.61</td>
<td>0.48-0.77</td>
<td>20</td>
<td>14-50</td>
</tr>
<tr>
<td>Early</td>
<td>0.87</td>
<td>0.77-0.99</td>
<td>33</td>
<td>17-1000</td>
</tr>
<tr>
<td>Early INSURE</td>
<td>0.38</td>
<td>0.08-1.81</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Less air leak and BPD

Data published in the *The Cochrane Database of Systematic Reviews* (Soll RF et al)
Surfactants used in Clinical Trials

**Old Synthetic (Protein-free)**
- Pumactant (ALEC)
- Colfosceril Palmitate (Exosurf)
- Turfsurf (Belfast Surfactant)

**New Synthetic (Protein analogues)**
- Lucinactant (Surfaxin)
- rSP-C Surfactant (Venticute)
- Others in development

**Natural (Minced lung extracts)**
- Surfactant TA (Surfacten)
- Beractant (Survanta)
- Poractant Alfa (Curosurf)

**Natural (Lung lavage extracts)**
- CLSE (bLES)
- Calfactant (Infasurf)
- SF-RI1 (Alveofact)

**Natural (Amniotic fluid)**
- Human Surfactant
Surfactant Preparations Available in Europe and US

Europe

• Beractant
• Bovactant
• Poractant alfa

US

• Beractant
• Calfactant
• Lucinactant
• Poractant alfa
European RDS Guideline Group (December 2012)
European RDS Guidelines - 2013

• 11 neonatologists from 10 countries
• Met at end of 2012 to discuss update
• Evidence from recent Cochrane reviews and medical literature from 2010 onwards
• Levels of evidence and grades (A to D) of recommendations based on GRADE system (Guyatt GH et al: BMJ 2008; 336: 924-926)
US RDS Guideline Team, 2014

Richard A Polin
and Committee on Fetus and Newborn, American Academy of Pediatrics

Wally Carlo
US RDS Guideline Team, 2014

Roger Soll – Consultant to US RDS Guideline Team, 2014
European and US Guidelines for Treatment of RDS


Surfactant – What we knew in 2010

• At least 100 mg/kg phospholipid is required and 200 mg/kg may be better for established RDS

• Administration by bolus results in better distribution (but this requires intubation!)

• Prophylaxis reduces mortality and air leaks, but more babies end up being treated. (No longer true!)

• Surfactant can be given whilst avoiding mechanical ventilation using INSURE technique

• A second (and occasionally a 3rd) dose is sometimes required
# Prophylaxis versus Rescue (Cochrane 2001)

<table>
<thead>
<tr>
<th>EVENT</th>
<th>PROPHYLAXIS</th>
<th>RESCUE</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1420</td>
<td>1396</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>15%</td>
<td>21%</td>
<td>0.02</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>3%</td>
<td>5%</td>
<td>0.01</td>
</tr>
<tr>
<td>PIE</td>
<td>12%</td>
<td>20%</td>
<td>0.003</td>
</tr>
<tr>
<td>BPD</td>
<td>16%</td>
<td>17%</td>
<td>0.57</td>
</tr>
</tbody>
</table>
Why Avoid Prophylaxis?

• Surfactant requires intubation
• Often results in babies being “bagged” and mechanical ventilation being used
• Studies showing benefits of prophylaxis done in an era of low antenatal steroid use and minimal use of CPAP
• Studies showing benefits of prophylaxis only compared outcomes with “late” rescue
Since 2010 Guideline......

CURPAP

- 208 babies 25 to 28 weeks’ gestation
- Randomised to CPAP alone or surfactant followed by extubation to CPAP within 30 min
- 78% of babies survived without BPD in both groups
- Suggests that prophylactic surfactant not superior to early CPAP and rescue surfactant

Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. Sandri F, et al CURPAP Study Group.
And Another Trial ..... 

SUPPORT

• 1316 babies 24-27 weeks’ randomised to intubation and surfactant or CPAP within 1 h

<table>
<thead>
<tr>
<th></th>
<th>CPAP</th>
<th>INTUBATE &amp; SURF</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surfactant</td>
<td>67%</td>
<td>99%</td>
<td></td>
</tr>
<tr>
<td>Vent days</td>
<td>25</td>
<td>28</td>
<td>0.03</td>
</tr>
<tr>
<td>Steroids for BPD</td>
<td>7.2%</td>
<td>13.2%</td>
<td>0.001</td>
</tr>
<tr>
<td>Death/BPD</td>
<td>48%</td>
<td>51%</td>
<td>0.3</td>
</tr>
</tbody>
</table>

However population in both arms did better than non – recruited eligible babies

Finer et al NEJM 2010
And Another Trial .... (26-29 weeks)

- **DUNN et al – Vermont Oxford Network Study**

<table>
<thead>
<tr>
<th></th>
<th>Prophylactic Surfactant and Ventilation</th>
<th>Prophylactic Surfactant and Extubate to CPAP</th>
<th>Initiate CPAP and rescue surfactant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>209</td>
<td>216</td>
<td>223</td>
</tr>
<tr>
<td>Intubated (%)</td>
<td>99</td>
<td>99</td>
<td>18</td>
</tr>
<tr>
<td>Surfactant (%)</td>
<td>99</td>
<td>98</td>
<td>15</td>
</tr>
<tr>
<td>Death (%)</td>
<td>7</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Death or BPD (%)</td>
<td>36</td>
<td>29</td>
<td>30</td>
</tr>
</tbody>
</table>

Dunn et al Pediatrics 2011
Prophylactic Surfactant vs Treatment of Established RDS: CLD or Death

**Analysis 1.6. Comparison 1 Prophylactic surfactant vs. treatment of established respiratory distress in preterm infants, Outcome 6 Chronic lung disease or death.**

Review: Prophylactic versus selective use of surfactant in preventing mortality and mortality in preterm infants.

Comparison: Prophylactic surfactant vs. treatment of established respiratory distress in preterm infants.

Outcome: Chronic lung disease or death.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Prophylactic n/N</th>
<th>Selective n/N</th>
<th>NRI Ratio</th>
<th>Weight</th>
<th>n NI Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dunn 1991</td>
<td>16/42</td>
<td>12/60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>62</td>
<td>60</td>
<td>3.1 %</td>
<td>1.29 [0.67, 2.49]</td>
<td></td>
</tr>
<tr>
<td>Total events: 16 (Prophylactic), 12 (Selective)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 861</td>
<td></td>
<td></td>
<td>96.9 %</td>
<td>1.12 [1.02, 1.24]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>923</td>
<td>943</td>
<td>100.0 %</td>
<td>1.13 [1.02, 1.25]</td>
<td></td>
</tr>
</tbody>
</table>

Rojas-Reyes MX et al: Cochrane 2012: CD000510
Prophylactic Surfactant vs Treatment of Established RDS

Authors’ Conclusions
Although the early trials of prophylactic surfactant for those at risk of RDS compared with selective surfactant in established RDS demonstrated decreased risks of air leak and mortality, recent large trials that reflect current practice (including greater use of maternal steroids and routine post delivery stabilization on CPAP) do not support these differences and demonstrate less risk of CLD or death when using early stabilization on CPAP with selective surfactant administration to infants requiring intubation.

Rojas-Reyes MX et al: Cochrane 2012: CD000510
Surfactant Therapy - Recommendations

• Babies with RDS should be given a natural surfactant preparation as early as possible (A).
• A policy of early rescue rather than prophylaxis should be standard, with the caveat that some babies may need “rescue” in the delivery suite (A).
• Babies should be treated with rescue surfactant early in the course of disease. Suggested protocol is to treat babies ≤ 26 wk when FiO\textsubscript{2} > 0.30 and > 26 wk when FiO\textsubscript{2} > 0.40 (B).
• Poractant alfa 200 mg/kg is better than 100 mg/kg of poractant or beractant for rescue therapy (A).
• Aim where possible to use INSURE technique (B).
• A 2\textsuperscript{nd}/ 3\textsuperscript{rd} dose should be given if ongoing evidence of RDS such as persistent oxygen or MV need (A).
## Porcine versus Bovine Surfactants:
Meta-analysis and Systematic Review

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>Poractant 100 or 200 mg/kg vs Beractant 100 mg/kg</th>
<th>Poractant 200 vs Beractant 100 mg/kg</th>
<th>Poractant 100 vs Beractant 100 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD</td>
<td>0.98 (0.75 to 1.29)</td>
<td>0.99 (0.74 to 1.33)</td>
<td>0.96 (0.66 to 1.41)</td>
</tr>
<tr>
<td>Redosing</td>
<td>0.71 (0.57 to 0.88)*</td>
<td>0.64 (0.53 to 0.83)*</td>
<td>0.81 (0.59 to 1.11)</td>
</tr>
<tr>
<td>Death</td>
<td>0.51 (0.30 to 0.89)*</td>
<td>0.29 (0.12 to 0.66)*</td>
<td>0.89 (0.46 to 1.74)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1.69 (0.88 to 3.24)**</td>
<td>1.69 (0.88 to 3.24)**</td>
<td></td>
</tr>
</tbody>
</table>

* p<0.05; ** significant test of heterogeneity

Durations of oxygen treatment, ventilation and hospital stay – all significantly reduced with poractant alfa (p<0.0001) although heterogeneity present

Singh N et al; Pediatrics 2011; 128: e1588-e1595
# INSURE – CPAP and Early Rescue

## Surfactant (Cochrane)

<table>
<thead>
<tr>
<th></th>
<th>INSURE (surf &amp; CPAP)</th>
<th>RESCUE &amp; VENT</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>355</td>
<td>329</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1.5%</td>
<td>3.5%</td>
<td>0.84</td>
</tr>
<tr>
<td>Need for Vent</td>
<td>35%</td>
<td>55%</td>
<td>0.009</td>
</tr>
<tr>
<td>Use of surfactant</td>
<td>99%</td>
<td>61%</td>
<td>0.001</td>
</tr>
<tr>
<td>Airleak</td>
<td>4%</td>
<td>8%</td>
<td>0.03</td>
</tr>
<tr>
<td>BPD 28 days</td>
<td>7.5%</td>
<td>15%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Stevens & Blennow Cochrane 2008
**CPAP Recommendations**

- CPAP should be started from birth in all babies at risk of RDS, such as those < 30 wk not needing MV, until clinical status can be assessed (A).
- The system delivering CPAP is of little importance. Short binasal prongs should be used rather than a single prong and a pressure of at least 6 cm water should be used (A).
- CPAP with early rescue surfactant should be considered in babies with RDS (A).
- A trial of NIPPV can be considered in babies failing on CPAP, but may not offer any significant long term advantages (A).
PULMONARY SURFACTANTS: BRITISH NATIONAL FORMULARY: 2012

- **Pulmonary surfactants** derived from animal lungs, *beractant* and *poractant alfa* are used to prevent and treat respiratory distress syndrome (hyaline membrane disease) in preterm neonates. Prophylactic use of a pulmonary surfactant may reduce the need for mechanical ventilation and is more effective than ‘rescue treatment’ in preterm neonates of 29 weeks or less post-menstrual age.

- **Pulmonary surfactants** may also be of benefit in neonates with meconium aspiration syndrome or intrapartum streptococcal infection.

- Pulmonary immaturity with surfactant deficit is the commonest reason for respiratory failure in the neonate, especially those of less than 30 weeks post-menstrual age. *Betamethasone* given to the mother (at least 12 hours but preferably 48 hours) before delivery substantially enhances pulmonary maturity in the neonate.
Pulmonary Surfactants: British National Formulary: 2012

- **Beractant**: licensed for use in respiratory distress syndrome in newborn premature infants, birthweight over 700 g, and as prophylaxis in neonates less than 32 weeks post-menstrual age.

- **Poractant alfa**: licensed for use in respiratory distress syndrome in newborn premature infants, birthweight over 700 g, and as prophylaxis in neonates 24-32 weeks post-menstrual age.

Preterm Infants

1. Preterm infants born at < 30 wk of gestation who need mechanical ventilation because of severe RDS should be given surfactant after initial stabilization (Level 1).

2. Using CPAP immediately after birth with subsequent selective surfactant administration should be considered as an alternative to routine intubation with prophylactic or early surfactant administration in preterm infants (Level 1).

Polin RA et al; Pediatrics 2014; 133: 156-163
European Guidelines, 2013

Preterm Infants

1. Babies with RDS should be given a natural surfactant preparation (A).

2. A policy of early rescue surfactant should be standard but there are occasions when surfactant should be administered in the delivery suite, such as extremely preterm infants in whom the mother has not had antenatal steroids or those who require intubation for stabilization (A).

3. Babies with RDS should be given rescue surfactant early in the course of the disease. A suggested protocol would be to treat babies <26 weeks’ gestation when FiO2 requirements >0.30 and babies >26 weeks when FiO2 requirements >0.40 (B).

4. Poractant alfa in an initial dose of 200 mg/kg is better than 100 mg/kg of poractant alfa or beractant for treatment of RDS (A).

5. Consider the INSURE technique. More mature babies can often be extubated to CPAP or NIPPV immediately following surfactant, and a clinical judgement needs to be made as to whether an individual baby will tolerate this (B).

6. A second, and sometimes a third, dose of surfactant should be administered if there is evidence of ongoing RDS such as persistent oxygen requirement and need for MV (A).

Sweet DG et al; Neonatology 2013; 103: 353-368
Additional Information from US Guidelines, 2014

Preterm and term neonates who are receiving surfactant should be managed by nursery and transport personnel with the technical and clinical expertise to administer surfactant safely and deal with multisystem illness. Therefore, pediatric providers who are without expertise or who are inexperienced or uncomfortable with surfactant administration or managing an infant who has received surfactant should wait for the transport team to arrive.

Polin RA et al; Pediatrics 2014; 133: 156-163
Additional Information from European Guidelines, 2013

The 2013 European guidelines make additional recommendations in the following specific areas: prenatal care, delivery room stabilization, oxygen supplementation beyond stabilization, non-invasive respiratory support, mechanical ventilation strategies, prophylactic treatment for sepsis, supportive care and miscellaneous considerations.

Sweet DG et al; Neonatology 2013; 103: 353-368
US Guidelines, 2014

Term Infants
Rescue surfactant may be considered for infants with hypoxic respiratory failure attributable to secondary surfactant deficiency (eg. meconium aspiration syndrome or sepsis/pneumonia) (Level 2).

Polin RA et al; Pediatrics 2014; 133: 156-163
European Guidelines, 2013

Term (and Preterm) Infants

• Surfactant therapy can be used to improve oxygenation following pulmonary haemorrhage but there may be no long-term benefits (C).

• Surfactant replacement for evolving BPD leads to only short-term benefits and cannot be recommended (C).

Sweet DG et al; Neonatology 2013; 103: 353-368
Additional Information from US Guidelines, 2014

Term Infants

• Surfactant treatment improves oxygenation and reduces the need for ECMO without an increase in morbidity in neonates with meconium aspiration syndrome (Level 2).

• Surfactant treatment of infants with congenital diaphragmatic hernia does not improve clinical outcomes (Level 2).

Polin RA et al; Pediatrics 2014; 133: 156-163
Additional Information from European Guidelines, 2014

Term Infants

- Although RDS is primarily a disease of preterm babies, it can occur in those born close to or at term. RDS should be considered as a differential diagnosis in any baby with early respiratory distress, and surfactant therapy considered as part of management.

- In rare cases, babies with RDS may suffer from genetic conditions such as surfactant protein-B or ABCA3 deficiency which are difficult to manage and beyond the scope of these guidelines.

Sweet DG et al; Neonatology 2013; 103: 353-368
Benefits of Surfactant

- First drug developed solely for neonates – a major breakthrough
- Improved neonatal survival
- Reduced pulmonary air leaks
- Increased survival without CLD
- Cost effective
- Immediate 6% reduction in IMR
Problems Still to be Solved

1. Prevention and management of CLD
2. Limits of viability – survival without disability
3. Neonatal care in the developing world
4. Putting the patient (family) first
Indications for Surfactant Replacement in Term and Preterm Newborns

Conclusions

• Treatment of RDS
• Prophylaxis of RDS but early CPAP is probably just as effective
• May help in MAS or pneumonia improving oxygenation and reducing need for ECMO
• Other indications are largely experimental